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Original article

Clinical value of ECG-derived markers for risk stratification in sudden cardiac arrest due to Chagas cardiomyopathy

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ABSTRACT

Introduction and objectives: Sudden cardiac arrest (SCA) is a significant complication in the spectrum of Chagas cardiomyopathy (CC) among infected individuals. Although the Rassi score (RS) is the most established tool for predicting mortality, a nonnegligible proportion of low- or intermediate-risk CC patients still experience SCA. This study aimed to evaluate whether electrocardiogram (ECG)-derived ventricular repolarization indices, when combined with the RS, improve SCA risk stratification in low- or intermediate-risk CC patients.

Methods: We analyzed 24-hour ECGs from 144 chronic CC patients to derive QT ($\Delta\alpha^{QT}$), T-peak-to-end ($\Delta\alpha^{Tpe}$), T-wave morphology (TMR), and T-peak-to-end morphology (TpeMR) restitution indices. Cox regression models, adjusted for RS, assessed the independent predictive value of each index for SCA. A combined risk model was developed by combining the strongest predictors with RS.

Results: $\Delta\alpha^{Tpe}$ showed the strongest association with SCA ($P < .001$) and remained an independent predictor alongside RS and hypertension (HR, 13.6; $P = .020$). The combined risk model improved sensitivity, balanced accuracy, and negative predictive value for identifying high-risk patients compared with RS alone, although it showed a reduction in specificity and positive predictive value. Moreover, the combined risk model maintained overall discrimination (HR, 23.1 vs RS alone HR, 17.8; both $P < .001$), providing complementary prognostic information.

Conclusions: $\Delta\alpha^{Tpe}$ was independently associated with SCA risk in CC. Its combination with the RS improved the identification of high-risk patients but was less effective at detecting low-risk individuals, suggesting a complementary rather than superior role to the RS.

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Valor clínico de marcadores derivados del ECG para la estratificación de riesgo de parada súbita cardiaca en la miocardiopatía chagásica

Palabras clave:
Chagas
Súbita
Electrocardiografía
Biomarcadores

RESUMEN

Introducción y objetivos: La parada súbita cardiaca (PSC) es una complicación en la miocardiopatía chagásica (MC). Aunque la puntuación de Rassi (PR) es un predictor consolidado de mortalidad, una proporción de pacientes clasificados como riesgo bajo o intermedio sigue presentando PSC. El objetivo fue evaluar si los índices de repolarización ventricular derivados del ECG, junto con la PR, mejoran la estratificación del riesgo de PSC en estos pacientes.

Métodos: Se analizaron registros de ECG de 24 horas de 144 pacientes con MC crónica para obtener los índices de restitución de QT ($\Delta\alpha^{QT}$), T-pico-fin ($\Delta\alpha^{Tpe}$), morfología de la onda T (TMR) y T-pico-fin (TpeMR). Se evaluó su valor predictivo independiente mediante modelos de Cox ajustados por PR y se propuso un modelo de riesgo combinando los predictores más relevantes junto con la PR.

Resultados: El $\Delta\alpha^{Tpe}$ mostró la asociación más sólida con la PSC ($p < 0{,}001$) y fue un predictor independiente junto a la PR e hipertensión (HR = 13,6; p = 0,020). El modelo de riesgo combinado de hipertensión, $\Delta\alpha^{Tpe}$ y PR mejoró la sensibilidad, precisión y valor predictivo negativo en comparación con la PR, aunque se redujeron la especificidad y el valor predictivo positivo. Mantuvo la capacidad discriminativa global (HR = 23,1 frente a HR de PR = 17,8; $p < 0{,}001$), lo que proporcionó información pronóstica complementaria.

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Conclusiones: El $\Delta\alpha^{Tpe}$ se asoció independientemente al riesgo de PSC en MC. Su combinación con la PR mejoró la identificación de pacientes de alto riesgo, pero mostró menor capacidad para detectar a pacientes de bajo riesgo, lo que respalda un papel complementario, no superior, a la PR.
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Abbreviations

CC: Chagas cardiomyopathy
CRM: combined risk model
ECG: electrocardiogram
HR: hazard ratio
RS: Rassi score
SCA: sudden cardiac arrest

INTRODUCTION

Chagas cardiomyopathy (CC) is strongly associated with sudden cardiac death (SCD), which occurs in approximately 65% of affected individuals.[1] Originally confined to Latin America,[1] CC has become a global health concern due to migratory flows.[2] Current clinical risk stratification for CC relies primarily on the Rassi score (RS),[3] which stratifies patients into low-, intermediate- and high-risk groups according to their 10-year mortality risk. Although the use of RS is well established for predicting mortality, there is still a nonnegligible proportion of CC patients with low- or intermediate-RS risk who still experience sudden cardiac arrest (SCA).[4] This suggests that the RS may not capture all the underlying electrophysiological mechanisms responsible for SCA.

CC predominantly affects the left ventricle, leading to fibrotic remodeling and pathological restitution of ventricular repolarization.[2,5] While electrocardiogram (ECG)-derived markers of T-wave morphology[6] have demonstrated the predictive value of ventricular arrhythmias and SCD in other cardiomyopathies,[7–9] their utility in CC remains unexplored.

In this study, we aimed to evaluate whether integrating ECG-derived ventricular repolarization restitution indices with the RS improves SCA prediction in a cohort of low- and intermediate-RS risk CC patients.

METHODS

Study population, primary endpoint and exclusion criteria

The original study population consisted of 315 patients with chronic CC enrolled in the protocol-based clinical follow-up program of patients from the CC outpatient clinic of the Clementino Fraga Filho University Hospital of the Federal University of Rio de Janeiro (HUCFF-UFRJ) between 1992 and 2017.[10] Patients were excluded if they showed malignancy or severe noncardiac comorbidities (including psychiatric disorders, advanced liver disease, or renal disease), if they were lost to follow-up, or had prior cardiac resynchronization therapy, resulting in a screened population of 220 participants (figure 1).

In each patient, a single 24-hour ECG Holter recording (sampling frequency 128 Hz) was selected. When multiple recordings were available (52 patients, median inter-recording interval, 3.5 [4.9] years), the most recent recording before the primary endpoint was considered.

The primary endpoint included SCA, appropriate implantable cardioverter-defibrillator therapies or ablation procedures, as these interventions address similar electrophysiological and arrhythmogenic mechanisms and may represent prevented SCA events.[11,12] SCA was defined as sudden cessation of cardiac activity with unresponsiveness, absence of normal breathing, and absence of signs of circulation.[13] All CC patients who experienced SCA were referred for interventions (implantable cardioverter-defibrillator therapies or ablation procedures) within the framework of the Brazilian Unified Health System.[13] Patients were excluded if they had a prior pacemaker, implantable cardioverter-defibrillator or ablation procedures before ECG-Holter monitoring, had ECG analog-to-digital conversion anomalies, or were classified as high risk by the RS (figure 1).

All patients received treatment that followed protocols previously established by the National Health Surveillance Secretariat/Ministry of Health for Chagas heart disease in Brazil. This study was approved by the institutional ethics committee of the Federal University of Rio de Janeiro (CEP-HUCFF-UFRJ) and written informed consent was obtained from all participants.[10] Detailed information on the clinical setting and patient management can be found in the methods section of the supplementary data.

Rassi score calculation

The RS[3] was calculated for each patient at each medical evaluation (1 week before ECG-Holter acquisition) to estimate the risk of mortality. This score (0-20 points) is based on New York Heart Association functional class III or IV (5 points), cardiomegaly on chest radiography (5 points), left ventricular systolic dysfunction on echocardiography (3 points), nonsustained ventricular

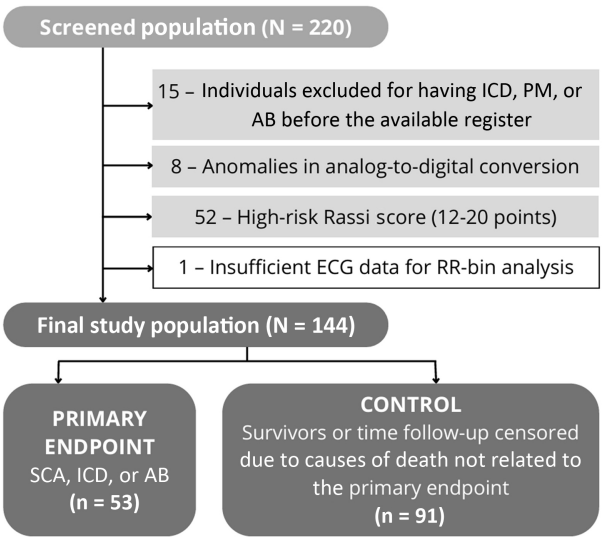


Figure 1. Flowchart of the study population. AB, ablation surgery; ICD, implantable cardioverter-defibrillator; PM, pacemaker; SCA, sudden cardiac arrest.

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tachycardia on 24-hour Holter monitoring (3 points), low QRS voltage (2 points), and male sex (2 points). Patients were stratified into low- (0-6 points), intermediate- (7-11 points), and high-risk (12-20 points) categories.

Quantification of the ECG-based indices of ventricular restitution

Quantification of the 4 ventricular restitution indices was performed on each ECG recording following previously described methodology.[14] First, a standard ECG preprocessing was applied (see the methods of the supplementary data). Then, an RR interval (RR) histogram was derived from each individual 24-hour recording using 10-msec-wide bins (figure 2A) and only those RR bins with more than 75 occurrences were included. This approach favors highly recurrent RR intervals and minimizes the influence of rhythm irregularities. Next, the 2 most distant RR bins from the median (RR_1 and RR_2) (figure 2A, green, red, and blue bins, respectively), distributed symmetrically around this median, were chosen as those defining the maximum intraparticipant RR range, ΔRR, ie, $\Delta RR = RR_2\text{-}RR_1$. Then, the beats associated with the RR interval within these 2 bins were used for the computation of the 4 ECG-based indices, which can be divided into 2 groups:

Temporal ECG indices of ventricular restitution

The indices $\Delta\alpha^{QT}$ and $\Delta\alpha^{Tpe}$ were defined as:

$$\Delta\alpha^{QT} = \frac{|QT^m_{RR1} - QT^m_{RR2}|}{\Delta RR}$$

$$\Delta\alpha^{Tpe} = \frac{|Tpe^m_{RR1} - Tpe^m_{RR2}|}{\Delta RR}$$

where QT^m_{RR1} and QT^m_{RR2}, and Tpe^m_{RR1} and Tpe^m_{RR2} measure the median duration of the QT and Tpe intervals, respectively, of the beats measured at bins with RR intervals of RRI_1 or RRI_2 (figure 2B).

Morphological ECG indices of ventricular restitution

Two mean warped T-waves, representing the average T-wave morphology at RR1 and RR2, respectively, were computed using a previously described warping method[15] (figure 2C). To quantify the morphological differences between the 2 T-waves, we used the index d_w, which quantifies the level of warping required to align any 2 T-waves[15]:

$$d_w = \frac{1}{N_r}\sum_{n=1}^{Nr}|\gamma^*(t^r(n)) - t^r(n)|$$

where the warping function $\gamma^*(t^r)$ optimally relates the temporal sample values of each T-wave (figure 2C, center).

The T-wave morphology restitution (TMR) index was calculated by dividing d_w, here renamed as d_w^{TW}, by ΔRR (figure 2C, above):

The T-peak-to-T-end-wave morphology restitution (TpeMR) index is obtained by estimating d_w restricted to the interval from the T peak to the end, d_w^{Tpe} (figure 2C, below):

$$TpeMR = \frac{|d_w^{Tpe}|}{\Delta RR}$$

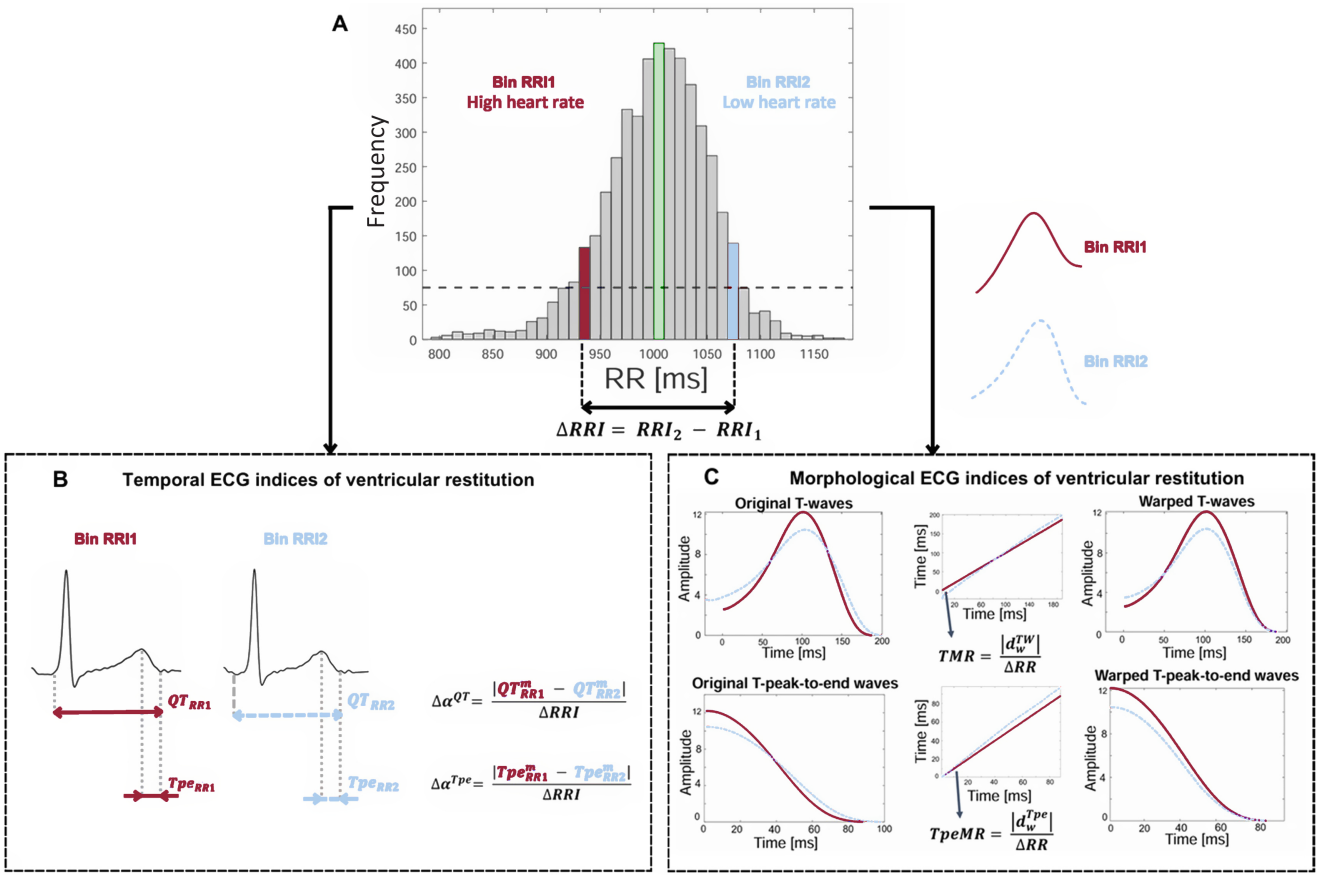


Figure 2. Quantification of the ECG indices of ventricular restitution. A: RR histogram, showing the median RR interval (green) and the maximum intraparticipant range, ΔRRI (red and blue). B: quantification of the temporal ECG indices of ventricular restitution. C: quantification of the morphological ECG indices of ventricular restitution.

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Independent association of clinical and ECG indices with the primary endpoint

The Wilcoxon test (2-tailed Mann-Whitney U test) was used for continuous variables, and the chi-square test was used for categorical variables to evaluate the association of clinical (age, body mass index, RS, type 2 diabetes mellitus, hypertension, amiodarone intake, dyslipidemia, coronary artery disease, and thyroid-stimulating hormone) and ECG variables ($\Delta\alpha^{QT}$, $\Delta\alpha^{Tpe}$, TMR and TpeMR) with the primary endpoint. Clinical variables were selected based on an a priori knowledge of their role in cardiovascular risk[1] and their independence from the RS. Variables with no significant association with the primary endpoint were not included in subsequent analyses. No imputation for missing data was required, as complete information was available for all variables.

Pairwise correlations among covariates were calculated, and in high correlation ($|r| > 0.8$) cases, 1 variable from each correlated pair was excluded.[16] Univariate Cox regression analyses were performed to determine the relationship between each clinical or ECG-based variable and the time to the primary endpoint. Hazard ratios (HRs) were calculated using the low-risk groups as the reference for categorical variables. Only the ECG-based index most significantly associated with the primary endpoint was included in the multivariate Cox regression analysis, which was performed by adjusting for the RS and all clinical variables that were significant in the univariate analysis. The proportional hazards assumption was assessed using Schoenfeld residuals, and model discrimination was evaluated using the C-index.

A value of $P < .05$ was considered statistically significant. Statistical analyses were performed using RStudio version 2024.12.0 (Posit PBC, United States).

Kaplan-Meier curves were derived for each variable, with a comparison of cumulative events performed using log-rank tests. For this, we dichotomized each variable by setting the optimal cutoff point as the value that jointly maximized sensitivity and specificity for risk stratification.[14] From this optimal cutoff point, patients were dichotomized into 2 groups: high, if the value was above the optimal threshold, and low, if it was below the optimal threshold. Specifically for the RS, patients were stratified into risk groups based on the original publication[3] as high (H), intermediate (I) and low (L) risk.

Calculation and evaluation of a combined risk model

We developed a combined risk model (CRM) as the weighted sum of the RS with the variables that remained statistically significant in the multivariate Cox regression analysis, where the weights were the respective β-coefficients from the multivariate Cox model[17] (see methods of the supplementary data). Then, patients were dichotomized into 2 CRM risk groups according to the optimal cutoff point and the association between the 2 risk groups and the primary endpoint was evaluated using Kaplan-Meier survival curves, the log-rank test, and univariate Cox regression analyses. Classification performance metrics, including balanced accuracy, positive and negative predictive value (PPV and NPV, respectively), sensitivity, and specificity, as well as confusion matrices, were calculated and compared between the RS and the CRM. Net reclassification improvement quantified the added predictive value of the CRM, using risk categories aligned with the primary endpoint event rate.

Sex-specific and sensitivity analyses

Sex-specific associations of the ECG-based indices in CC for risk stratification were assessed by repeating the main analysis separately in male and female patients. In addition, a sensitivity analysis was performed excluding patients receiving amiodarone treatment to assess whether its use influenced the main findings.

Finally, time-to-event analyses were explored to assess whether the predictive value of the ECG indices varied during the follow-up.

RESULTS

Population description

Figure 1 shows the flow diagram of the inclusion and exclusion criteria, leading to the final study population, which consisted of 144 patients with chronic CC, of whom 53 were male and 91 were female, aged 23 to 62 years. A total of 53 patients (36.8%) met the primary endpoint (21 men and 32 women) within a median follow-up period of 10.9 years. The detailed characteristics of the study population are shown in table 1.

Association of clinical and ECG-based indices with the primary endpoint

Patients in the primary endpoint group showed higher values of RS ($P < .0001$) and a higher proportion of hypertension ($P = .002$) and amiodarone intake ($P < .0001$), while age, sex, body mass index, diabetes mellitus type 2, dyslipidemia, coronary artery disease and thyroid-stimulating hormone showed no significant variations. Upon comparison of ECG variables between the primary endpoint and control groups, both $\Delta\alpha^{Tpe}$ and TpeMR were significantly higher in the primary endpoint group ($P < .001$ and $P = .005$, respectively). Clinical variables and ECG-derived indices that were not associated with the primary endpoint were not included in subsequent analyses (table 1). The AUC for RS, $\Delta\alpha^{Tpe}$ and TpeMR was 0.913 (95% confidence interval [95%CI], 0.864-0.962), 0.693 (95%CI, 0.599-0.786), and 0.640 (95%CI, 0.541-0.738), respectively (figure S1).

Selection of predictors of sudden cardiac arrest risk

Univariate Cox analysis revealed that hypertension, amiodarone intake, RS, $\Delta\alpha^{Tpe}$ and TpeMR were all significantly associated with the primary endpoint (table 2).

Figure 3 shows the correlation coefficients among amiodarone intake, ECG-derived parameters, the RS, and hypertension. Amiodarone intake was not associated with ECG parameters, but was strongly correlated with the RS and was therefore excluded from the multivariable analysis to avoid collinearity, while the low correlations between the RS and ECG-derived parameters support their complementary and nonredundant value. Multivariate Cox analysis was then performed including $\Delta\alpha^{Tpe}$, as the most significant ECG-based index in the univariate analysis, hypertension and RS, all remaining significantly associated with the primary endpoint, with an HR of 13.6 ($P = .020$), 2.80 ($P = .014$), and 1.46 ($P < .0001$), respectively (table 2). The proportional hazards assumption was not violated for any covariates (methods of the supplementary data), and the model showed good discrimination (*C-index* = 0.859).

In line with the original publication,[3] the RS was stratified as low risk, or RS(L), from 0 to 6 points, and intermediate risk, or RS(I), from 7 to 11 points. The optimal thresholds were 0.036 for $\Delta\alpha^{Tpe}$ and 0.021 for TpeMR. Of the 144 patients studied, 95 (66%) were included in the RS(L) group and 49 (34%) in the RS(I) group. Likewise, 89 (61.8%) were included in the $\Delta\alpha^{Tpe}$(L) group and 55 (38.2%) in the $\Delta\alpha^{Tpe}$(H) group; similarly, 90 (62.5%) were included

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Table 1
Patient characteristics

Variables	Overall population (N = 144)	Primary endpoint group (n = 53)	Control group (n = 91)	*P*
Clinical variables				
Age, y	43.9 [13.3]	43.4 [10.8]	44.0 [14.0]	.991
Sex, male[a]	53 (36.8)	21 (39.6)	32 (35.1)	.722
BMI (kg/m^2)	28 [2.25]	28 [3]	28 [3]	.071
Rassi score, points	5 [9]	11 [3]	3 [3]	<.0001[b]
LVEF, %[a]	57 [26]	42 [5]	67 [13]	<.0001
DM2	20 (13.8)	10 (18.8)	10 (11)	.285
Hypertension	102 (70.8)	46 (86.8)	56 (61.5)	.002[b]
Amiodarone intake	44 (30.5)	38 (71.7)	6 (6.59)	<.0001[b]
Dyslipidemia	63 (43.7)	29 (54.7)	34 (37.3)	.064
CAD	5 (3.5)	2 (3.7)	3 (3.3)	.999
TSH, mUI/L	2.25 [0.9]	2.1 [0.8]	2.3 [0.9]	.245
ECG variables				
$\Delta\alpha^{QT}$, a.u.	0.148 [0.098]	0.166 [0.179]	0.141 [0.089]	.177
$\Delta\alpha^{Tpe}$, a.u.	0.024 [0.049]	0.044 [0.089]	0.019 [0.026]	<.001[b]
TMR, a.u.	0.035 [0.025]	0.036 [0.033]	0.034 [0.023]	.434
TpeMR, a.u.	0.014 [0.025]	0.026 [0.040]	0.012 [0.016]	.005[b]

a.u., arbitrary units; BMI, body mass index; CAD, coronary artery disease; DM2, diabetes mellitus type 2; ECG, electrocardiogram; LVEF, left ventricle ejection fraction; TMR, T-wave morphology restitution; TpeMR, T-peak-to-end morphology restitution; TSH, thyroid-stimulating hormone.
The data are presented as No. (%) or median [interquartile range].
[a] Sex and LVEF were included in Rassi score.
[b] Statistical significance was set at a $P \leq .05$.

Table 2
Univariate and multivariate Cox analysis

Variables	Univariate		Multivariate[a]		
	HR (95%CI)	*P*	HR (95%CI)	β	*P*
ECG variables					
$\Delta\alpha^{Tpe}$ (per unit increment)	65.6 (7.86-547.7)	<.001[b]	13.6 (1.49-124.6)	2.612	.020[b]
TpeMR (per unit increment)	9412.9 (26.7-3.3e6)	.002[b]	N.A.	N.A.	N.A.
Clinical variables					
Hypertension	3.36 (1.51-7.46)	.002[b]	2.80 (1.23-6.39)	1.032	.014[b]
Amiodarone intake	12.5 (6.74-23.2)	P <.0001[b]	N.A.	N.A.	N.A.
Rassi score (per unit increment)	1.47 (1.34-1.62)	P <.0001[b]	1.46 (1.33-1.61)	0.382	<.0001[b]

95%CI, 95% confidence interval; ECG, electrocardiogram; H, high; HR, hazard ratio; I, intermediate; N.A., not applicable; TpeMR, T peak-to-end morphology restitution. Only covariates specified in this table were included in the analyses. The overall population consisted of 144 participants, of whom 53 (36.8%) met the primary endpoint within the follow-up period and the remaining were controls.
[a] Multivariate analysis included only the most significant ECG variable in the univariate analysis and excluded amiodarone intake to avoid multicollinearity.
[b] Statistical significance was set at a $P \leq .05$.

in the TpeMR(L) group and 54 (37.5%) in the TpeMR(H) group. figure 4 shows Kaplan-Meier survival curves for the low- and high-risk groups defined for $\Delta\alpha^{Tpe}$ (figure 4A), TpeMR (figure 4B), and RS (figure 4C).

Sudden cardiac arrest predictive value of the combined risk model

The CRM was constructed by combining hypertension, RS, and $\Delta\alpha^{Tpe}$ (methods of the supplementary data). The AUC for the CRM was 0.930 (95%CI, 0.886-0.974, figure S1). Although the CRM showed a numerically higher area under the curve (AUC) and slightly narrower CI compared with the RS, the difference was not statistically significant according to the DeLong test ($P = 0.15$). Of the 144 patients studied, 63 (43.8%) were included in the high risk group [CRM(H)] and 81 (56.2%) in the low risk group [CRM(L)] (table S1).

Individuals classified in the CRM(H) group had a significantly higher risk of experiencing the primary endpoint (HR = 23.1; $P = < .0001$) than those in the CRM(L) group (table 3). For reference, the HR value for participants in the RS (I) group compared with those in the RS (L) group was 17.8 ($P < .0001$). Kaplan-Meier survival curves for the CRM (L) and (H) risk groups are shown in figure 4D.

Figure 5A shows that the CRM correctly classified more true positives than the RS (48 vs 42) but also had more false positives (15 vs 7). figure 5B shows that the CRM had higher sensitivity (0.906 vs 0.792), and NPV (0.938 vs 0.884), while specificity (0.835 vs 0.923) and PPV (0.762 vs 0.857) were reduced, with a slight

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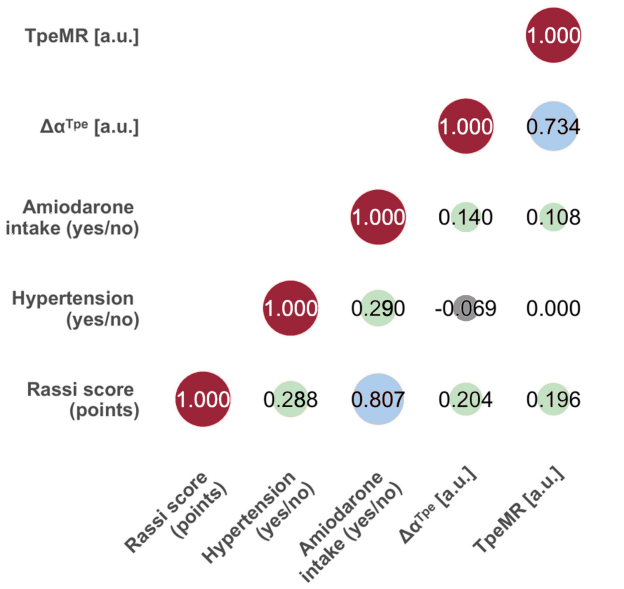


Figure 3. Matrix of correlation coefficients. The normality of continuous variables was assessed using the Shapiro-Wilk test. Spearman's rank correlation was used for nonnormally distributed continuous variables, the Phi coefficient for binary categorical variables, and the point-biserial correlation for continuous-binary associations. Coefficients were calculated based on 144 complete cases.

Table 3
Univariate Cox analysis for the Rassi score and combined risk model

Scores	HR (95%CI)	*P*
Current clinical score		
Rassi score (I)	17.8 (8.88-35.6)	<.0001*
Our proposal		
CRM (I)	23.1 (9.12-58.6)	<.0001*

Hazard ratios were calculated using the low-risk groups as reference. Distribution of Rassi score and CRM categories according to the primary endpoint is shown in table S1.
95%CI, 95%confidence interval; CRM, combined risk model; I, intermediate.
* Significant differences.

global improvement in balanced accuracy (0.870 vs 0.858). The mean net reclassification improvement for CRM vs RS was 0.542 (0.280-0.805, $P < .001$; see table S2).

Influence of sex and amiodarone intake

Sex-stratified analyses showed that $\Delta\alpha^{Tpe}$ predicted SCA-related events in both sexes, while $\Delta\alpha^{QT}$ showed an association only in male patients and TpeMR only in female patients. However, these associations did not persist after multivariable adjustment,

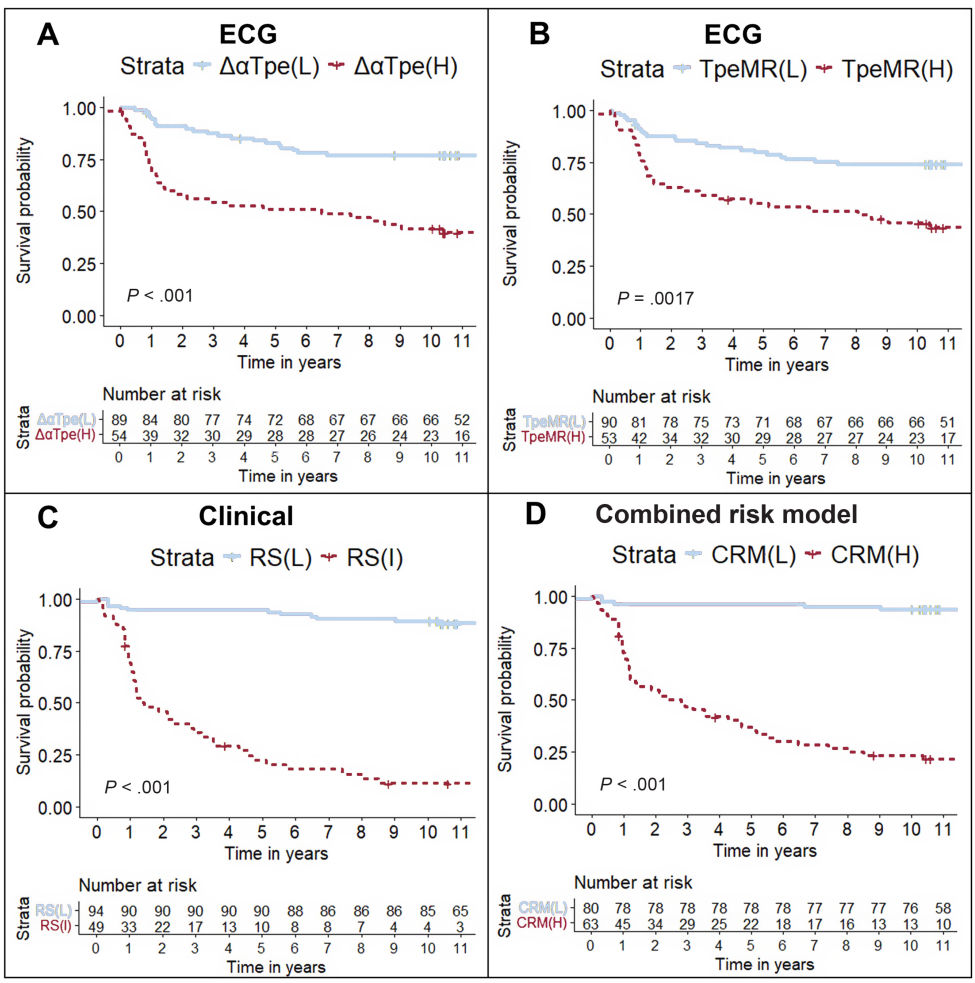


Figure 4. Kaplan-Meier survival curves. Cumulative survival rates of individuals stratified by A: $\Delta\alpha^{Tpe} \geq 0.036$ ($\Delta\alpha^{Tpe}$(H)), B: TpeMR ≥ 0.021 (TpeMR(H)), C: RS between 7 and 11 points (RS(I)), and D: by the 2 risk groups defined in the combined specific risk model for sudden cardial arrest. CRM, combined risk model; H, high; I, intermediate; L, low; TpeMR, T peak-to-end morphology restitution; RS, Rassi score.

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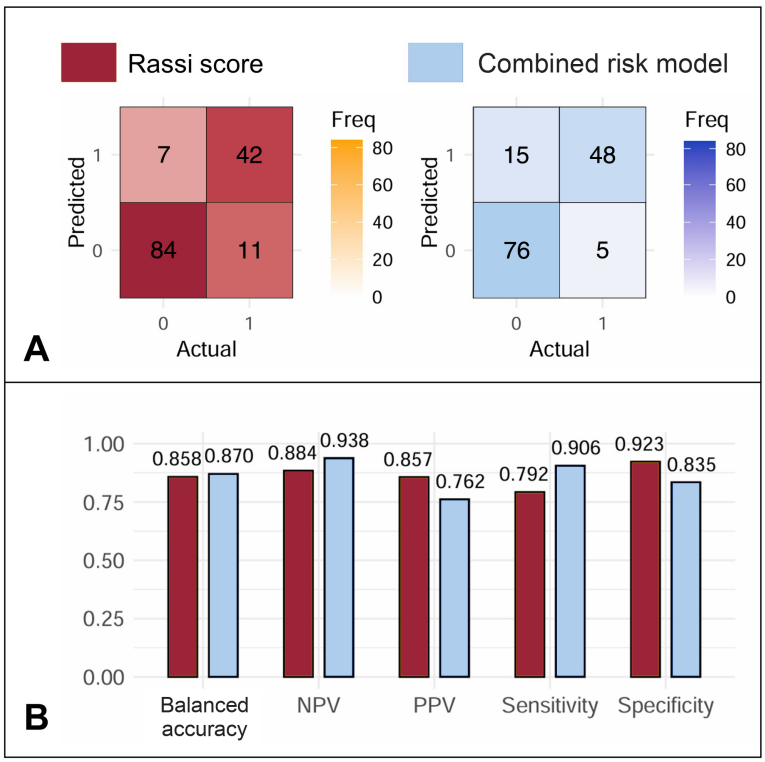


Figure 5. Confusion matrices (A) and classification performance metrics (B) for the current Rassi score (red) and the proposed combined risk model (CRM, blue). NPV, negative predictive value; PPV, positive predictive value.

and no sex-specific CRMs were supported. Similarly, in the amiodarone-free population, ECG-derived variables did not show an independent association with the primary endpoint after adjustment, whereas the RS remained the only significant predictor. Finally, a predictive performance analysis across fixed follow-up periods identified the 3-year time point as showing the best discrimination. Detailed results are provided in the methods of the supplementary data, tables S4-S8, and figure S2.

DISCUSSION

We evaluated the SCA-related predictive value of 4 ECG indices of ventricular restitution, $\Delta\alpha^{QT}$, $\Delta\alpha^{Tpe}$, TMR, and TpeMR in patients with chronic CC. The main result of this study is that $\Delta\alpha^{Tpe}$ is strongly associated with an increased risk of SCA-related outcomes. $\Delta\alpha^{Tpe}$ showed the strongest primary endpoint predictive value and remained associated after adjustment for the RS.

The low correlations observed between the RS and ECG-derived variables further support their complementary and nonredundant contribution. Moreover, both $\Delta\alpha^{Tpe}$ and TpeMR showed low correlation with amiodarone intake, despite the strong association between the latter and the RS. This suggests that the prognostic value of these ECG markers is not driven by treatment status and may provide complementary information to clinical risk stratification. Importantly, our sensitivity analyses excluding patients receiving amiodarone showed attenuation of the predictive value of ECG-derived variables, which may indicate that $\Delta\alpha^{Tpe}$ provides a stronger contribution to SCA risk stratification in patients at intermediate RS risk, who are also more likely to receive this treatment.

By incorporating $\Delta\alpha^{Tpe}$, a marker of ventricular repolarization heterogeneity associated with arrhythmic risk, and hypertension in addition to the RS, the proposed CRM increased sensitivity, balanced accuracy, and NPV when identifying high-risk patients compared with the RS alone (figure 6). However, these results were accompanied by a reduction in specificity and PPV. These findings indicate that the CRM is more sensitive in detecting high-risk patients at low and intermediate RS, whereas the RS alone better identifies low-risk individuals, highlighting the complementary strengths of the 2 models. Nonetheless, the clinical benefit of the CRM requires further evaluation in larger populations before clinical translation.[18]

Increased values of $\Delta\alpha^{QT}$, related to arrhythmic risk,[19] and TMR, associated with SCA risk,[14] have been observed in chronic heart failure patients who had an SCA. In our study, $\Delta\alpha^{QT}$ and TMR were not associated with SCA in CC patients. This result points to a possible mechanism in which CC may have an SCA-unrelated effect on the early phase of ventricular repolarization, masking the arrhythmogenic substrate specifically linked to SCA. The electrophysiological basis of these findings is discussed in the supplementary methods.

While the RS[3] remains the strongest overall predictor of mortality in CC, the FIOCRUZ score[20] has been proposed specifically for SCD and incorporates variables such as the QT interval dispersion. However, its calculation requires a full 12-lead ECG, which was not available in our study, and it reflects a static, global measure of ventricular repolarization heterogeneity. In contrast, $\Delta\alpha^{Tpe}$ can be derived from a single ECG-Holter lead long enough to capture heart rhythm changes, making it simple, noninvasive, and clinically practical.

Limitations

A key limitation of this study is the inability to compare results with the FIOCRUZ score[20] due to the lack of multilead ECG data

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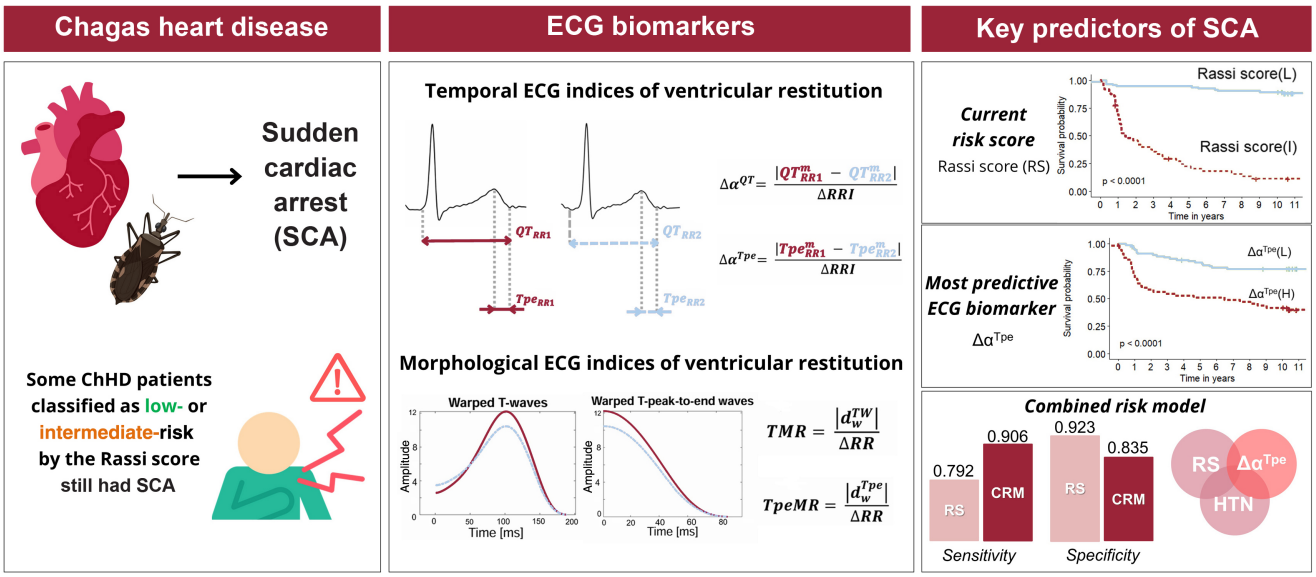


Figure 6. Central Illustration. Overview of ECG biomarkers evaluated as predictors of sudden cardiac death in Chagas heart disease (ChHD). HTN, hypertension.

needed to calculate QT interval dispersion. This restricts alignment with established models and highlights the need for more comprehensive ECG data in future research. Moreover, a limitation of the CRM is that the gain in sensitivity, balanced accuracy, and NPV comes at the expense of a loss of specificity and PPV, limiting its clinical benefits. While the increased sensitivity, balanced accuracy, and NPV indicate the enhanced ability of CRM to identify patients who have been categorized as low or intermediate risk using the RS but are, nevertheless, still at high risk of SCA, this comes at the expense of reduced specificity and PPV, which can result in unnecessary monitoring or interventions in clinical practice.

Consequently, our findings need to be validated in larger populations to strengthen the reliability of our conclusions and provide insights into the adaptability of the model to diverse patient populations and clinical settings. It should be noted that this study was not blinded. In addition, interobserver reproducibility was not performed, as the measurement procedure was fully automated, ensuring observer independence and repeatability. Moreover, only a single Holter recording per patient was analyzed. When multiple recordings were available (n = 52), and in view of the large mean time between recordings (3.5 ± 4.9 years), the recording closest to the primary endpoint was selected, as it likely contained the most relevant information about the arrhythmogenic substrate leading to the event. Consequently, intraparticipant reproducibility was considered underpowered and was therefore not assessed. Future well-powered studies with repeated ECG recordings are needed to evaluate the intraparticipant reproducibility of our results.

CONCLUSIONS

This study suggests that $\Delta\alpha^{Tpe}$, an ECG-derived biomarker quantifying late-phase ventricular restitution, is associated with an increased risk of SCA-related events in patients with chronic CC independently of the RS. Moreover, its addition to a CRM, alongside hypertension, improved the identification of patients at higher risk, but the RS alone remained better at detecting low-risk individuals, indicating the complementary strengths of the 2 models.

WHAT IS KNOWN ABOUT THE TOPIC?

- SCA is a frequent endpoint in CC patients.
- Although the RS is the most established tool for predicting mortality, a nonnegligible proportion of CC patients, classified as low- or intermediate-risk, still experience an SCA.

WHAT DOES THIS STUDY ADD?

- $\Delta\alpha^{Tpe}$, an ECG index of ventricular restitution, provides prognostic information beyond the RS, increasing sensitivity in identifying patients at higher risk, but with a concomitant reduction in specificity and precision, suggesting a complementary role to the RS.

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ETHICAL CONSIDERATIONS

For the acquisition and use of the information in this research, the authorization process was approved by the institutional ethics committee of the Federal University of Rio de Janeiro, CEP-HUCFF-UFRJ, which waived the need for written informed consent under

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the protocol CAAE: 45360915.1.1001.5262 in accordance with the standards currently applied by the Brazilian National Committee for Research Ethics and the principles outlined in the Declaration of Helsinki. All patients received treatment following norms and protocols previously established by the National Health Surveillance Secretariat/Ministry of Health for Chagas Heart Disease in Brazil. SAGER guidelines regarding potential sex/gender biases have been followed.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tools were used in applying the methodology or obtaining the results in this article.

AUTHORS' CONTRIBUTIONS

Conceptualization: Á. Hernández, J. Ramírez, P. Laguna. Data acquisition: J. P. Madeiro, R. C. Pedrosa. Data curation: Á. Hernández. Formal analysis: Á. Hernández, J. Ramírez. Funding acquisition: J. Ramírez, R. C. Pedrosa. Methodology: J. Ramírez, P. Laguna. Software: Á. Hernández. Writing–original draft: Á. Hernández. All authors contributed to the interpretation of results, revised the manuscript, and approved the final version for publication.

CONFLICTS OF INTEREST

None of the authors has anything to declare in relation to the content of this article.

APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.rec.2026.05.005.

REFERENCES

1. Marin-Neto JA, Rassi A, Oliveira GMM, et al. SBC Guideline on the Diagnosis and Treatment of Patients with Cardiomyopathy of Chagas Disease – 2023. *Arq Bras Cardiol.* 2023;120:e20230269.
2. Carlos Pinto Dias J, Novaes Ramos A, Dias Gontijo E, et al. II Consenso Brasileiro em Doença de Chagas, 2015. *Epidemiologia e Serviços de Saúde.* 2016;25:1–10.
3. Rassi AJR, Rassi A, Little WC, et al. Development and Validation of a Risk Score for Predicting Death in Chagas' Heart Disease. *N Engl J Med.* 2006;355:799–808.
4. Pedrosa RC, Paulo do Vale Madeiro J, Alberto AC, et al. Risk stratifier for sudden cardiac death beyond the left ventricular ejection fraction in Chagas cardiomyopathy. *Pacing Clin Electrophysiol.* 2024;47:312–320.
5. Nunes MCP, Beaton A, Acquatella H, et al. Chagas Cardiomyopathy: An Update of Current Clinical Knowledge and Management: A Scientific Statement From the American Heart Association. *Circulation.* 2018;138:e169–e209.
6. Chugh SS, Reinier K, Uy-Evanado A, et al. Prediction of Sudden Cardiac Death Manifesting With Documented Ventricular Fibrillation or Pulseless Ventricular Tachycardia. *JACC Clin Electrophysiol.* 2022;8:411–423.
7. Panikkath R, Reinier K, Uy-Evanado A, et al. Prolonged Tpeak-to-Tend Interval on the Resting ECG is associated with increased risk of Sudden Cardiac Death. *Circ Arrhythm Electrophysiol.* 2011;4:441–447.
8. Ramírez J, Orini M, Pueyo E, Laguna P. Comparison of ECG T-wave Duration and morphology restitution markers for sudden cardiac death prediction in chronic heart Failure. *CinC.* 2017;44:224–267.
9. Ramírez J, Kiviniemi A, van Duijvenboden S, et al. ECG T-Wave Morphologic Variations Predict Ventricular Arrhythmic Risk in Low-and Moderate-Risk Populations. *J Am Heart Assoc.* 2022;11:e025897.
10. Cavalcante CHL, Primo PEO, Sales CAF, et al. Sudden cardiac death multiparametric classification system for Chagas heart disease's patients based on clinical data and 24-hours ECG monitoring. *Math Biosci Eng.* 2023;20:9159–9178.
11. Moss AJ, Zareba W, Jackson Hall W, et al. Prophylactic Implantation of a Defibrillator in Patients with Myocardial Infarction and Reduced Ejection Fraction. *N Engl J Med.* 2002;346:877–883.
12. Sapp JL, Wells GA, Parkash R, et al. Ventricular Tachycardia Ablation versus Escalation of Antiarrhythmic Drugs. *N Engl J Med.* 2016;375:111–121.
13. Buxton AE, Calkins H, Callans DJ, et al. ACC/AHA/HRS 2006 key data elements and definitions for electrophysiological studies and procedures: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (ACC/AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology). *Circulation.* 2006;114:2534–2570.
14. Ramírez J, Orini M, Mincholé A, et al. T-Wave Morphology Restitution Predicts Sudden Cardiac Death in Patients With Chronic Heart Failure. *J Am Heart Assoc.* 2017;6:e005310.
15. Ramírez J, van Duijvenboden S, Aung N, et al. Cardiovascular Predictive Value and Genetic Basis of Ventricular Repolarization Dynamics. *Circ Arrhythm Electrophysiol.* 2019;12:e007549.
16. Vatcheva P, Lee KM. Multicollinearity in Regression Analyses Conducted in Epidemiologic Studies. *Epidemiology (Sunnyvale).* 2016;6:227.
17. Ramírez J, Van Duijvenboden S, Young WJ, et al. Prediction of Coronary Artery Disease and Major Adverse Cardiovascular Events Using Clinical and Genetic Risk Scores for Cardiovascular Risk Factors. *Circ Genom Precis Med.* 2022;15:444–452.
18. Carrion-Arias JC, Grüne de Souza e Silva C, de Bragança Pereira B, Matos do Nascimento E, Coury Pedrosa R. Cardioverter-defibrillator implantation in chronic Chagas cardiomyopathy: the Rassi death risk score for decision-making. *Rev Esp Cardiol.* 2025;78:485–486.
19. Iacoviello M, Forleo C, Guida P, et al. Ventricular Repolarization Dynamicity Provides Independent Prognostic Information Toward Major Arrhythmic Events in Patients With Idiopathic Dilated Cardiomyopathy. *J Am Coll Cardiol.* 2007;50:225–231.
20. De Souza ACJ, Salles G, Hasslocher-Moreno AM, et al. Development of a risk score to predict sudden death in patients with Chaga's heart disease. *Int J Cardiol.* 2015;187:700–704.

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