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Electrocardiographic alternans as an additional criterion for cardioverter defibrillator implantation in primary prevention of sudden cardiac death

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ABSTRACT

The current Guidelines recommend implantable cardioverter defibrillator (ICD) for primary prevention of sudden cardiac death (SCD) when left ventricular ejection fraction (LVEF) is reduced. Nevertheless, LVEF lacks sensitivity and specificity as a risk index, meaning that additional risk indexes are needed. Electrocardiographic alternans (ECGA) is the every-other-beat morphology oscillation in either ECG wave: P-wave/QRS-complex/T-wave alternans (PWA/QRSA/TWA, respectively). This study aims to investigate ECGA as an additional criterion to decide for ICD implantation for primary prevention of SCD.

ECGs were acquired during a bicycle-ergometer test in a heart-failure population having ICDs for primary prevention. During follow-up, patients were classified into cases, if device therapy was administered, and controls, if no device therapy occurred. Resting and exercise ECGs were analyzed using the enhanced adaptive matched filter method (EAMFM) to identify ECGA.

Unlike the exercise condition, the resting condition showed a statistically significant difference in PWA and QRSA between cases and controls. Thus, to classify them, rest-related ECGA features were used to feed a support vector machine (SVM), validated by a leave-one-out cross-validation algorithm. SVM yielded a sensitivity, specificity, and F1 score of 98.49%, 83.33%, and 95.61%, respectively. These results suggest that EAMFM-derived ECGA may act as a further useful feature to stratify the arrhythmia risk, overcoming the insufficient sensitivity and specificity of LVEF only. Thus, the main contribution of this study is the proposal of an additional ECGA-based criterion for identifying patients who may benefit from primary prevention ICD implantation paving the way for a conceivable revision of the current Guidelines.

1. Introduction

The implantable cardioverter defibrillator (ICD) is a cornerstone in the treatment of patients at risk of sudden cardiac death (SCD). These devices are effective by applying anti-tachycardia pacing/ventricular defibrillation when sensing potentially lethal arrhythmias. In primary prevention of SCD, it remains a major challenge to identify the patients who may benefit from ICD implantation. The MADIT II (Multicenter Automated Defibrillator Implantation Trial II) and SCD HeFT (Sudden Cardiac Death in Heart Failure Trial) trials have proved the efficacy of ICD therapy in subjects with severely depressed left ventricular systolic function, and showed similar survival benefits in ischemic and non-ischemic patients [1–5]. These trials represent the foundation of guidelines and recommendations across different geographic regions regarding the primary prevention of SCD in reduced ejection fraction heart failure [4,6]. A reduced left ventricular ejection fraction (LVEF $<$ 35 % or higher in the presence of concomitant critical conditions) is already more than two decades in the Guidelines as an indication for ICD implantation in primary prevention of SCD [7].

However, LVEF has some limitations in stratifying SCD risk. Indeed, as a parameter of mechanical heart function, it likely reflects only partially the electrophysiological substrate that induces arrhythmias. In the report on SCD prevention published in 2010 by the Heart, Lung and Blood Institute and Heart Rhythm Society [8], LVEF shows to lack sensitivity in stratifying the arrhythmia risk. Sensitivity is insufficient because many SCD events occur in patients with mildly impaired or even preserved LVEF [7,9–12]. LVEF shows to lack also specificity in

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Nomenclature

ACE	angiotensin converting enzyme
AMP	amplitude
AR	area
AT	angiotensin
AUC	area under the curve
BMI	body mass index
CHF	congestive heart failure
CI	confidence interval
CRT-D	cardiac resynchronization therapy
DUR	duration
EAMFM	enhanced adaptive matched filter method
ECG	electrocardiogram
ECGA	electrocardiographic alternans
F	female
FN	false negatives
FP	false positives
HR	heart rate
ICD	implantable cardioverter defibrillator
LSB	least significant beat
LVEF	left ventricular ejection fraction
M	male
MAG	magnitude
MAX AMP	maximum amplitude
MAX DUR	maximum duration
MAX MAG	maximum magnitude
NYHA	New York heart association
NS	nephrotic syndrome
PWA	P-wave alternans
QRSA	QRS-complex alternans
ROC	receiver operating characteristic
SCD	sudden cardiac death
SE	sensitivity
SP	specificity
SVM	support vector machine
TN	true negatives
TP	true positives
TWA	T-wave alternans

stratifying the arrhythmia risk. Specificity is insufficient because among patients with reduced LVEF who are assumed as good candidates for primary prevention ICD therapy, only a small percentage will experience a ventricular arrhythmia resulting in SCD and requiring the ICD shock [10]. Such limitations contribute to reducing the ICD clinical benefits. [13]. Thus, it appears to be crucial to go beyond the consideration of a single risk criterion, such as LVEF, when assessing the need for an ICD implantation [4]. In this context, noninvasive parameters have been proposed as SCD risk predictors in addition to LVEF. Some of them are electrocardiogram (ECG)-derived, like ECG alternans (ECGA).

ECGA is an electrophysiological phenomenon that manifests in the ECG as the every-other-beat fluctuation (ABAB pattern) in the morphology (amplitude, polarity and/or shape) of ECG waves [14]. ECGA may occur in the P wave, resulting in P-wave alternans (PWA); in the QRS complex, resulting in QRS-complex alternans (QRSA); and in the T wave, resulting in T-wave alternans (TWA); these forms may concur [15–18]. ECGA has been recognized as a cardiac risk index for arrhythmia predisposition. Indeed, ECGA is associated with various cardiac pathologies affecting both atria and ventricles, and is able to unmask cardiac instabilities that can lead to malignant ventricular arrhythmias and SCD [14–20]. Among the possible forms of ECGA, TWA is the most investigated by researchers in the literature and, even if recognized as an efficient risk index, TWA testing has a class IIa indication in the current Guidelines, released in 2022 by the European Society of Cardiology [7]. Probably, among the reasons for still marginal TWA consideration is the necessity of high heart rates for a more reliable detection by most of the automated TWA-measurement methods proposed in the literature, and this condition may not be applicable for some patients, thus making TWA testing not always feasible. Specifically, the need to accelerate heart rates is based mainly on two factors: (1) the amplitude of TWA is known to increase at high heart rates, thereby enhancing its detectability through automated methods; (2) the methods, in their technical approach and rationale for quantifying TWA, may be less reliable in the case of heart rate variability, a confounding factor that is negated at high heart rates. However, the enhanced adaptive matched filter method (EAMFM), introduced in 2021, showed the ability to detect all forms of ECGA at any heart rate, hence in resting conditions (low heart rates) as well [14]. Thus, this heart rate-based limitation may be overcome by the application of the EAMFM. Moreover, ECGA detection through this method has been shown to be reliable because, differently from the other existing ones, it considers and avoids possible biased ECGA interpretation when different ECGA forms affect concurrently the ECG [14,21]. In addition, the method is very robust against noise, being based on filtering in a very narrow band of frequencies (the band of relevance to ECGA), and this implies a minimal preprocessing before its application.

Evaluation of the role of ECGA as an independent predictor of cardiac events in primary prevention needs exclusion of the possible contribution of other risk factors, such as sex, age, body mass index (BMI), LVEF, and resting heart rate (HR). Indeed, peculiar sex-related manifestations of cardiovascular diseases have been shown by several studies in the literature, which also underline the sex-related differences in the response to risk factors and treatments [22]. Age is a known risk factor for the development of cardiovascular diseases (considering the unavoidable process of cardiovascular disease development in old age), as well as BMI (the lowest all-cause mortality is associated with BMI 20–25 kg/m^2) [23]. As stated, LVEF has an important role in the Guidelines, actually being the primary criterion for implantation decisions in clinical practice [24]. Eventually, also HR at rest acts as an independent risk factor for major adverse cardiac events, as cardiovascular mortality is observed to increase by 30 % to 50 % for every 20-bpm increase in resting HR [25–27].

The literature lacks studies that comprehensively evaluate all possible forms of ECGA in ICD patients. Rather, only the prognostic value of TWA in ICD populations has been evaluated. However, studies that have examined TWA in ICD patients differ from the present study in one key aspect: they do not compare ICD patients who benefitted from ICD implantation with those who did not. Indeed, rather than defining ICD subgroups, they assessed alternans across the entire ICD patient population to evaluate the overall survival benefit of the device [28,29], at most comparing the whole ICD patient population with healthy controls [30].

Summarizing the state of the art: the current Guidelines recommend ICD implantation if LVEF is reduced, while it is recognized that the specificity of this single criterion is insufficient, and clinicians often need to rely on additional clinical factors. Moreover, while acknowledging TWA has a high negative predictive value, Guidelines suggest but do not strongly recommend its testing for arrhythmia risk assessment, and do not even mention PWA and QRSA. In line with this approach, the methods usually used, and sometimes even integrated in ECG machines, consider TWA as the only form of ECGA to be examined as risk index, even if several studies suggest that PWA and QRSA also deserve consideration [16,17]. In addition, methods usually applied for TWA testing need the subject to be at high heart rates, and this might be inadvisable or prohibitive in some patients. In this context, trying to fill these gaps, our study aims to investigate the potential role of EAMFM-derived ECGA as an additional criterion for ICD implantation in

primary prevention of SCD. More in detail, we intend to evaluate the ability of ECGA in all possible forms of manifestation to classify patients who benefitted from ICD implantation and patients who did not need it. To do so, an ICD heart failure population is analyzed through the EAMFM to characterize ECGA, both at low (resting) and high (exercise) heart rates. Application of the EAMFM is one of the innovative aspects of this work, since to our knowledge it is the first and only existing method introduced in the literature that detects all ECGA forms, and not TWA only.

2. Materials and methods

2.1. Study population and enrollment criteria

The population analyzed in the present study comes from the Leiden University Medical Center Database. The database was recorded from August 2006 to September 2010. It consists of a set of routine clinical data acquired from 266 heart failure patients who had an ICD implantation for primary prevention of SCD because of a low LVEF [31]. Starting from ICD implantation, all patients had a 4-year-lasting follow-up during which they received standard care. It consisted of regular visits and tests, including bicycle-ergometer tests with concurrent ECG acquisition. ECGs (lead I, II, V_1–V_6) were acquired by a CASE 8000 stress-test recorder (GE Healthcare, Freiburg, Germany), using 3 M Red Dot ECG Electrode Soft Cloth 2271 electrodes, suitable for particular skin conditions as in the case of stress testing. Before application, the skin was cleaned with alcohol and lightly abraded to improve electrode/skin contact. The electrodes were applied according to the Mason-Likar configuration [32]. Sampling frequency and amplitude resolution were 500 Hz and 4.88 μV/LSB, respectively.

The bicycle-ergometer test consisted of 2 phases: (1) the exercise phase, an approximately 10-min bicycle exercise phase with a regular increment (approximately 10 % of the expected maximal exercise capacity, applied every minute) of the workload from zero (no-workload period) to the patient's maximal exercise capacity (maximum workload period), and (2) a recovery phase of about 2–5 min bicycle exercise with a regular decrement of the workload until the patient's heart rate returned close to that of the no-workload period. As a consequence, ECG recordings are about 20 min long and are characterized by a period of increasing heart rate during the exercise phase and a period of decreasing heart rate during the recovery phase [31]. ECG annotations in the database contained the following ECG fiducial points: onset of QRS complex, end of QRS complex, peak position of T wave, end of T wave, and a QRS-related reference point not coincident with the R peak but reflecting its periodicity in time.

At the end of the follow-up, patients were classified into cases and controls. Cases were the patients who developed ventricular tachycardia or ventricular fibrillation requiring ICD therapy during the follow-up period. Controls were the patients who did not develop any ICD-triggering arrhythmia during follow-up. This classification criterion yielded a total of 76 cases and 190 controls.

Patients had at least one but sometimes also multiple ECGs from the bicycle ergometer test, but only one ECG per patient was included in the database. If cases experienced a major cardiac event between the bicycle ergometer test and the ventricular tachycardia/fibrillation episode, the associated acquired data was excluded. Indeed, such events (e.g., infarction) and/or the clinical interventions to address them (e.g., ventricular tachycardia ablation, coronary artery bypass graft) might modify the arrhythmogenic substrate with respect to the state in which it was when the ICD was implanted. For cases, if more than one ergometry test remained available, the one closest in time to the ventricular tachycardia/fibrillation episode was included in the database, so that the electrophysiological properties of the arrhythmogenic substrate during the stress test would be as close as possible to those just preceding the ventricular arrhythmia requiring ICD therapy. For controls, if more than one bicycle ergometer test was eligible, only the earliest was included in the database.

Patients in whom the ICD was also functioning as a CRT-D dual-chamber pacemaker to deliver cardiac resynchronization therapy (36 cases and 100 controls) were not considered, resulting in 40 cases and 90 controls. Patients' identities remained anonymous, and no informed consent was considered necessary for enrollment in the database, according to "Guideline for Good Clinical Practice" (European Medicines Agency, CPMP/ICH/135/95) and the data privacy law in the Netherlands [31]. This study is retrospective, observational, and based on standard clinical data. The clinical features characterizing cases and controls are reported in Table 1.

Additional enrollment criteria were applied to controls. Specifically, only controls with age (years), BMI (kg/m^2), LVEF (%), and HR (bpm) at rest within case ranges were included in the study in order to obtain a uniform clinical condition of the study group.

2.2. Enhanced adaptive matched filter and feature extraction

Two segments (lasting about 60 s each) of the entire ECG tracing were considered for analysis: one in the no-workload period, which we called resting stage and one after HR reached the value of 120 bpm, called the maximal exercise stage. If HR remained below this value throughout the exercise phase, the exercise stage was defined as the one around the maximal HR. In this study, ECGA detection and quantification was performed by EAMFM. The details of the originally published method, including the related block diagram, can be found in reference [14].

The EAMFM is designed to provide ECGA measurement in ECG windows that include a limited number of heartbeats and are extracted overlapping consecutively along the entire ECG considered, for each available ECG tracing representing a different lead. Thus, we analyzed all the available 12 ECG leads (lead III, aVR, aVL, aVF were derived retrospectively from the acquired ones). ECG windowing was performed by extracting 10 windows of 64 heartbeats every second, in the resting and exercise stages. Specifically, the resting stage included the first 10 ECG windows, while the exercise stage included the 10 windows after HR had reached the value of 120 bpm, or around the maximum value of HR.

Table 1
Clinical features expressed as median [25th, 75th percentile] for continuous parameters and number of occurrences (percentage) for the categorical ones.

	CONTROLS (not receiving ICD therapy during follow-up)	CASES (receiving ICD therapy during follow-up)
General:		
NUMBER OF PATIENTS	90	40
SEX	76 M (84 %), 14 F (16 %)	34 M (85 %), 6 F (15 %)
AGE (years)	61[50,67]	56[48,67]
BMI (kg/m^2)	25[24,29]	26[24,28]
LVEF (%)	41[32,50]	32*[22,39]
HR at rest (bpm)	70[60,75]	70[65,77]
NYHA functional class:		
I-II	79(88 %)	32(80 %)
III-IV	11(12 %)	8(20 %)
Medications:		
Beta-blocker	72(80 %)	37(90 %)
Amiodarone	5(6 %)	8*(20 %)
Calcium antagonists	10(11 %)	2(5 %)
Flecainide	0(0 %)	1(3 %)
Digoxin	3(3 %)	4(10 %)
ACE inhibitor / AT antagonist	78(87 %)	37(93 %)
NS Diuretics for CHF	47(52 %)	27(68 %)
Statins	65(72 %)	29(73 %)

* $p < 0.05$; ACE: angiotensin converting enzyme; AT: angiotensin; CHF: congestive heart failure; F: female; M: male; NYHA: New York Heart Association; NS: nephrotic syndrome.

2.2.1. Preprocessing phase

Each ECG window was resampled to 200 Hz and low-pass filtered using a 6th-order bidirectional Butterworth filter at 35 Hz. Then, heartbeats have been segmented according to the following fiducial points: the onset of P wave (Pon), the onset of QRS complex (Qon), the ending of QRS complex (J), the ending of T wave (Tend). Qon, J, and Tend were available as annotations in the database (as explained in 2.1), thus the only fiducial point that was not available as annotation in the database was Pon. The sequence of annotated reference points was used to compute the mean RR interval duration (mRR, ms) and its standard deviation (sdRR, ms) for each ECG window, and Pon was defined according to mRR, as expressed in (1):

$$\begin{cases} Pon = Qon - 180\ ms,\ mRR < 750\ ms \\ Pon = Qon - 200\ ms,\ 750\ ms \le mRR < 1100\ ms \\ Pon = Qon - 220\ ms,\ mRR \ge 1100\ ms \end{cases} \quad (1)$$

The heartbeat segmentation divided it into three adjoining sections: the section including the P wave (from Pon to Qon, P section), the section including the QRS complex (from Qon to J, QRS section), the section including the T wave (from J to Tend, T section), as expressed in (2–4):

$$P\ section = ECG(Pon : Qon) \quad (2)$$

$$QRS\ section = ECG(Qon : J) \quad (3)$$

$$T\ section = ECG(J : Tend) \quad (4)$$

where *ECG* is the window tracing considered, and P, QRS, and T sections define the three sections in which PWA, QRSA, and TWA are detected, respectively.

For this purpose, two steps follows: the suitability test and the signal enhancement. In order to perform the suitability test, a heartbeat template was created as the median heartbeat over all heartbeats in the ECG window. The waveforms of the heartbeat template served as a reference to which the corresponding ECG waveforms included in the QRS, and T sections of each heartbeat were compared by correlation (computing Pearson's correlation coefficient). If the QRS and T correlations were both greater than 0.85, the heartbeat was considered a regular sinus beat and free of artifacts; vice versa, the heartbeat was considered ectopic or affected by artifact and replaced by the template. The overall number of replaced heartbeats (N_{rep}) was computed along the ECG window. The ECG window was considered suitable for the analysis if it satisfied both of the following suitability criteria (5)-(6):

$$N_{rep} \le 5 \quad (5)$$

$$stdRR \le 0.1 \bullet mRR \quad (6)$$

thus, if either criterion was not met, the ECG window was rejected and did not undergo the signal enhancement step [14]. For each stage, leads were considered suitable if at least one ECG window met the suitability criteria, otherwise the lead was rejected from the analysis.

The signal enhancement step consists in setting the ECG amplitude to the baseline value except for the section where alternans is being assessed, as expressed in (7)-(9). This implies that three signals come from enhancement: the signal obtained by forcing the whole ECG window amplitude except the P section to the baseline value (P signal), the signal obtained by forcing the whole ECG window amplitude except the QRS section to the baseline value (QRS signal), the signal obtained by forcing the whole ECG window amplitude except the T section to the baseline value (T signal).

$$P\ signal = \begin{cases} ECG(x) = ECG(x),\ Pon \le x < Qon \\ ECG(x) = 0,\ x < Pon,\ x \ge Qon \end{cases} \quad (7)$$

$$QRS\ signal = \begin{cases} ECG(x) = ECG(x),\ Qon \le x \le J \\ ECG(x) = 0,\ x < Qon,\ x > J \end{cases} \quad (8)$$

$$T\ signal = \begin{cases} ECG(x) = ECG(x),\ J < x \le Tend \\ ECG(x) = 0,\ x \le J,\ x > Tend \end{cases} \quad (9)$$

where *ECG* is the window tracing considered and *x* is the generic sample inside ECG.

2.2.2. Detection and quantification of electrocardiographic alternans

Then, PWA, QRSA, and TWA were quantified and characterized on the P signal, QRS signal, and T signal, respectively. These signals were band-pass filtered around the alternans-related frequency, using a narrow passing band of 0.12 Hz, defined as in (10):

$$PB = [f_H = f_A - 0.06\ Hz;\ f_L = f_A + 0.06\ Hz] \quad (10)$$

where *PB* is the passing band and f_A is the alternans-related frequency, which equals half the heart rate ($f_A = mRR/2$). The filter applied was a 6th-order bidirectional Butterworth band-pass filter. The transfer function of the filter can be found in [14] and is as in (11):

$$|H(f)|^2 = |H_L(f)|^2 \bullet |H_H(f)|^2 = \frac{1}{1 + (\frac{f}{f_L})^6} \bullet \frac{(\frac{f}{f_H})^6}{1 + (\frac{f}{f_H})^6} \quad (11)$$

Being a narrow passing band filter, the outputs were pseudo-sinusoidal signals, namely the PWA signal (related to the P signal as input), the QRSA signal (related to the QRS signal as input), and the TWA signal (related to the T signal as input), having their maxima and minima in the P, QRS, and T sections, respectively.

The EAMFM provided two heartbeat-related features (in other words 2·64 values for each window and each form of alternans): the alternans amplitude, defined as the difference between the maximum and the minimum of the alternans signal, and the alternans area, defined as the product of alternans amplitude and the indicative time duration (expressed in ms) of the wave under examination (fixed to 100 ms for P wave, 80 ms for QRS complex, 200 ms for T wave) [14].

Eventually, each ECG window of each ECG lead was characterized in terms of alternans according to the following features:

- amplitude (AMP, μV), defined as the median amplitude of PWA/QRSA/TWA over all heartbeats, including also the non-fluctuating heartbeats (for which amplitude was 0 μV);
- area (AR, μV·ms), defined as the median area of PWA/QRSA/TWA over all heartbeats, including also the non-fluctuating heartbeats;
- duration (DUR, beats), defined as the number of heartbeats presenting PWA/QRSA/TWA;
- magnitude (MAG, μV·beats), computed as the product of PWA/QRSA/TWA median amplitude over the fluctuating heartbeats (for which amplitude was different from 0 μV) and DUR.

2.3. Statistics

Patients having no suitable windows in one of the two stages were excluded, and this could determine a different number of cases and controls with respect to the study group, as well as between resting and maximal exercise stages. According to the canonical division of the lead groups into bipolar limb leads (I-II-III), augmented unipolar limb leads (aVF-aVR-aVL), and unipolar precordial leads (V1-V6), the frequency of suitable leads was computed in each group, and only the most frequent one was selected and considered in the following.

For both the resting and maximal exercise stages, ECGA features (*i.e.*, AMP, AR, DUR, MAG) were averaged (median) over the extracted ECG windows, for each patient and each lead of the selected lead group. The same was performed for RR intervals. In turn, the median values of the ECGA features computed over the ECG windows (for each stage, each patient, and each lead) were further pooled over the leads or selected according to a criterion applied to the leads to obtain ECGA values representative of all the considered leads for each patient. Specifically,

the lead pooling was performed by computing the median and the mode, while the lead selection was performed considering the maximum ECGA amplitude, duration, and magnitude, respectively. The block diagram related to the analysis at the single-patient level is reported in Fig. 1.

The area under the receiver operating characteristic (ROC) curve (AUC), together with the confidence interval (CI), was computed in each of the lead pooling/selection procedures, considering cases and controls of the study group. Then, the statistics providing the best discriminant power was used in the following. Distributions of ECGA features related to both cases and controls of the study group were further characterized in terms of median, 25th, and 75th percentiles, and were compared through the Wilcoxon rank-sum test, setting the statistical significance p at 0.05 in both the resting and maximal exercise stages. Cohen's d effect size values were also computed for each ECGA feature and interpreted as recommended by Cohen: small effect size if between 0.20 and 0.49, moderate effect size if between 0.50 and 0.79, large effect size if $\geq$ 0.80 [33].

2.3.1. Classification

ECGA features related to the most frequent suitable lead group and to the stage (resting or maximal exercise) providing the strongest statistical difference between cases and controls were retained for classification. Indeed, in order to evaluate their ability in classifying cases and controls, these ECGA features were used to feed a support vector machine (SVM), using a leave-one-out cross-validation algorithm. In both training and validation, classification performance was evaluated by computing sensitivity (SE), specificity (SP), and F1 score from the confusion matrix, computed as in (12)-(14):

$$SE = TP/(TP + FN) \tag{12}$$

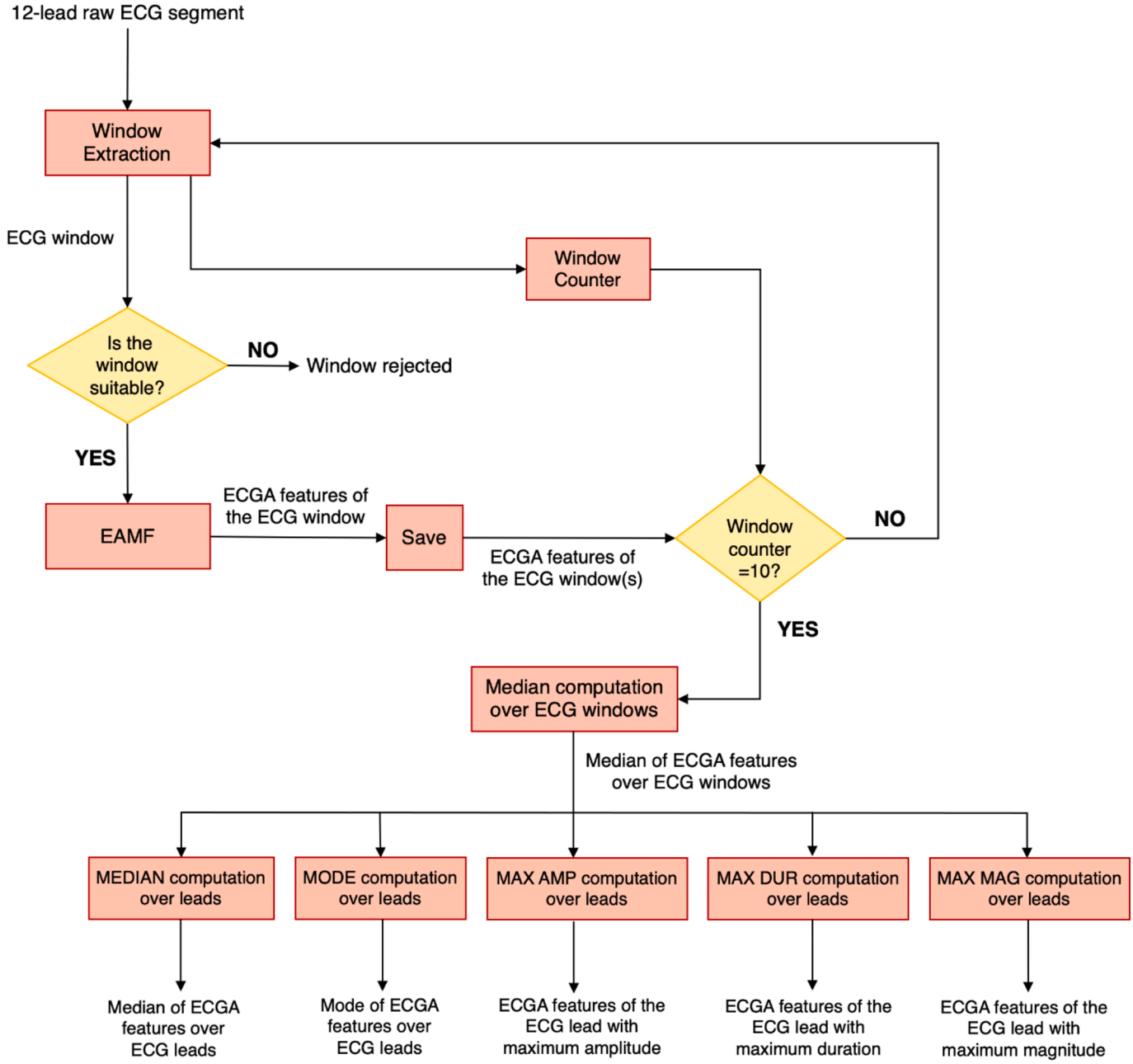

Fig. 1. Block diagram of the electrocardiographic alternans (ECGA) analysis at single-patient level: application of the enhanced adaptive matched filter method (EAMFM) and intra-subject statistics. The input is the segment (lasting about 60 s) of the electrocardiogram (ECG) tracing from which the 10 windows were extracted; the procedure is the same for the resting and maximal exercise stages (abbreviations used in the blocks: MAX AMP – maximum amplitude; MAX DUR – maximum duration; MAX MAG – maximum magnitude).

$$SP = TN/(TN + FP) \quad (13)$$

$$F1 = (2 \bullet TP)/(2 \bullet TP + FN + FP) \quad (14)$$

where TP is the number of true positives (number of correctly classified cases), TN is the number of true negatives (number of correctly classified controls), FN is the number of false negatives (number of incorrectly classified cases), and FP is the number of false positives (number of incorrectly classified controls).

3. Results

After applying the study enrollment criteria (section 2.1 of this paper), 82 controls and 40 cases formed the study group of the research described here. Clinical features characterizing the study group are reported in Table 2. Due to EAMFM suitability criteria, 15 controls/10 cases and 16 controls/6 cases were further excluded from the resting stage and maximal exercise stage distributions, respectively. Further details regarding the patients excluded from the study group can be found in Table A.1 of Appendix A.

The frequency of suitable lead groups was:

- 30 % and 25 % for the three bipolar limb leads
- 31 % and 25 % for three unipolar augmented limb leads
- 59 % and 60 % for the six unipolar precordial leads

in the resting and maximal exercise stages, respectively. As a result, the precordial leads were selected for further interpretation of the results.

Referring only to the precordial lead group, results related to the AUC and CI computed in each of the lead pooling/selection procedure are reported in Table 3. The statistics of the median showed the best discriminant power. Thus, median ECGA features were further characterized over both cases and controls and were used to feed the SVM. Specifically, distributions of ECGA features related to cases and controls belonging to the study group are shown in Fig. 2, where outcomes from the Wilcoxon rank-sum test are also indicated. ECGA features that resulted to be statistically different between cases and controls were also characterized by a moderate to large effect size. Resting stage showed to provide the strongest statistical difference between cases and controls. Thus, rest-related ECGA features were used to feed the SVM. Results of the SVM classification performance in both training and validation are reported in Table 4.

Table 2
Clinical features expressed as median [25th, 75th percentile] for continuous parameters and number of occurrences (percentage) for the categorical ones, related to the study group.

	CONTROLS (not receiving ICD therapy during follow-up)	CASES (receiving ICD therapy during follow-up)
General:		
NUMBER OF PATIENTS	82	40
SEX	71 M (86 %), 11 F (14 %)	34 M (85 %), 6 F (15 %)
AGE (years)	61[52,66]	56[48,67]
BMI (kg/m^2)	26[24,29]	26[24,28]
LVEF (%)	41[33,50]	32*[22,39]
HR at rest (bpm)	70[60,75]	70[65,77]
NYHA functional class:		
I-II	72(88 %)	32(80 %)
III-IV	10(12 %)	8(20 %)
Medications:		
Beta-blocker	66(80 %)	37(90 %)
Amiodarone	4(5 %)	8*(20 %)
Calcium antagonists	10(12 %)	2(5 %)
Flecainide	0(0 %)	1(3 %)
Digoxin	3(4 %)	4(10 %)
ACE inhibitor / AT antagonist	71(87 %)	37(93 %)
NS Diuretics for CHF	43(52 %)	27(68 %)
Statins	61(74 %)	29(73 %)

* $p < 0.05$; ACE: angiotensin converting enzyme; AT: angiotensin; CHF: congestive heart failure; F: female; M: male; NYHA: New York Heart Association; NS: nephrotic syndrome.

4. Discussion

The results of this study are intended to further investigate and possibly confirm the preliminary outcomes observed in the pilot study by Iammarino et al. [34] using the same database here analyzed, *i.e.*, the Leiden University Medical Center database. Patients belonging to this database were identified during follow-up into those who benefited from ICD therapy and those who did not. This makes it a proper database to demonstrate whether ECGA is able to improve the discrimination of cases and controls' clinical profile. Moreover, being the ECGs acquired during a bicycle ergometer test, and knowing the dependence of ECGA on heart rate, the option to study the electrophysiological phenomenon at different heart rates represented a relevant aspect of the study. The database included only one ECG per patient, and whenever controls had more than one acquisition, only the earliest in time was included in the

Table 3
Area under the curve (AUC) of the receiver operating characteristic curve (ROC) and [confidence interval (CI)] of electrocardiographic alternans (ECGA) features, where, for each patient, the median over leads in the selected lead group (MEDIAN), the mode over leads in the selected lead group (MODE), the maximum amplitude lead in the selected lead group (MAX AMP), the maximum duration lead in the selected lead group (MAX DUR), and the maximum magnitude lead in the selected lead group (MAX MAG) were considered. The best performance reached by the three forms of ECGA in discriminating between cases and controls is in bold.

Features		AMP	DUR	AR	MAG
MEDIAN	**PWA**	**65.92 [53.73;78.11]**	**66.72 [54.59;78.84]**	**65.67 [53.47;77.88]**	**62.21 [49.81;74.62]**
	QRSA	**71.84 [60.21;83.47]**	**71.59 [59.94;83.25]**	**72.14 [60.55;83.73]**	**70.22 [58.42;82.03]**
	TWA	**50.97 [38.45;63.49]**	**51.17 [38.64;63.69]**	**50.90 [38.38;63.41]**	**52.11 [39.57;64.66]**
MODE	**PWA**	58.48 [45.95;71.02]	63.71 [51.38;76.04]	58.51 [45.97;71.04]	63.68 [51.35;76.01]
	QRSA	66.87 [54.75;78.98]	67.96 [55.94;79.98]	66.82 [54.70;78.94]	70.22 [58.42;82.03]
	TWA	55.57 [43.00;68.14]	53.83 [41.26;66.40]	55.62 [43.05;68.19]	58.71 [46.18;71.24]
MAX AMP	**PWA**	53.48 [40.92;66.05]	53.46 [40.89;66.02]	53.71 [41.14;66.27]	54.68 [42.1;67.25]
	QRSA	64.28 [51.98;76.58]	61.32 [48.87;73.77]	64.68 [52.40;76.95]	61.07 [48.61;73.53]
	TWA	48.03 [35.62;60.45]	40.37 [28.47;52.28]	47.81 [35.40;60.22]	46.97 [34.60;59.33]
MAX DUR	**PWA**	53.08 [40.52;65.65]	54.30 [41.73;66.87]	53.01 [40.45;65.57]	55.20 [42.63;67.77]
	QRSA	63.96 [51.64;76.27]	65.15 [52.91;77.39]	64.20 [51.9;76.51]	61.99 [49.57;74.41]
	TWA	45.02 [32.76;57.29]	46.79 [34.43;59.15]	44.93 [32.67;57.18]	42.94 [30.82;55.05]
MAX MAG	**PWA**	53.03 [40.47;65.59]	57.44 [44.88;69.99]	53.01 [40.45;65.57]	55.22 [42.65;67.80]
	QRSA	62.41 [50.01;74.81]	61.47 [49.03;73.91]	62.46 [50.07;74.86]	62.29 [49.88;74.69]
	TWA	47.99 [35.57;60.40]	38.68 [26.94;50.43]	47.94 [35.52;60.35]	47.39 [35.00;59.78]

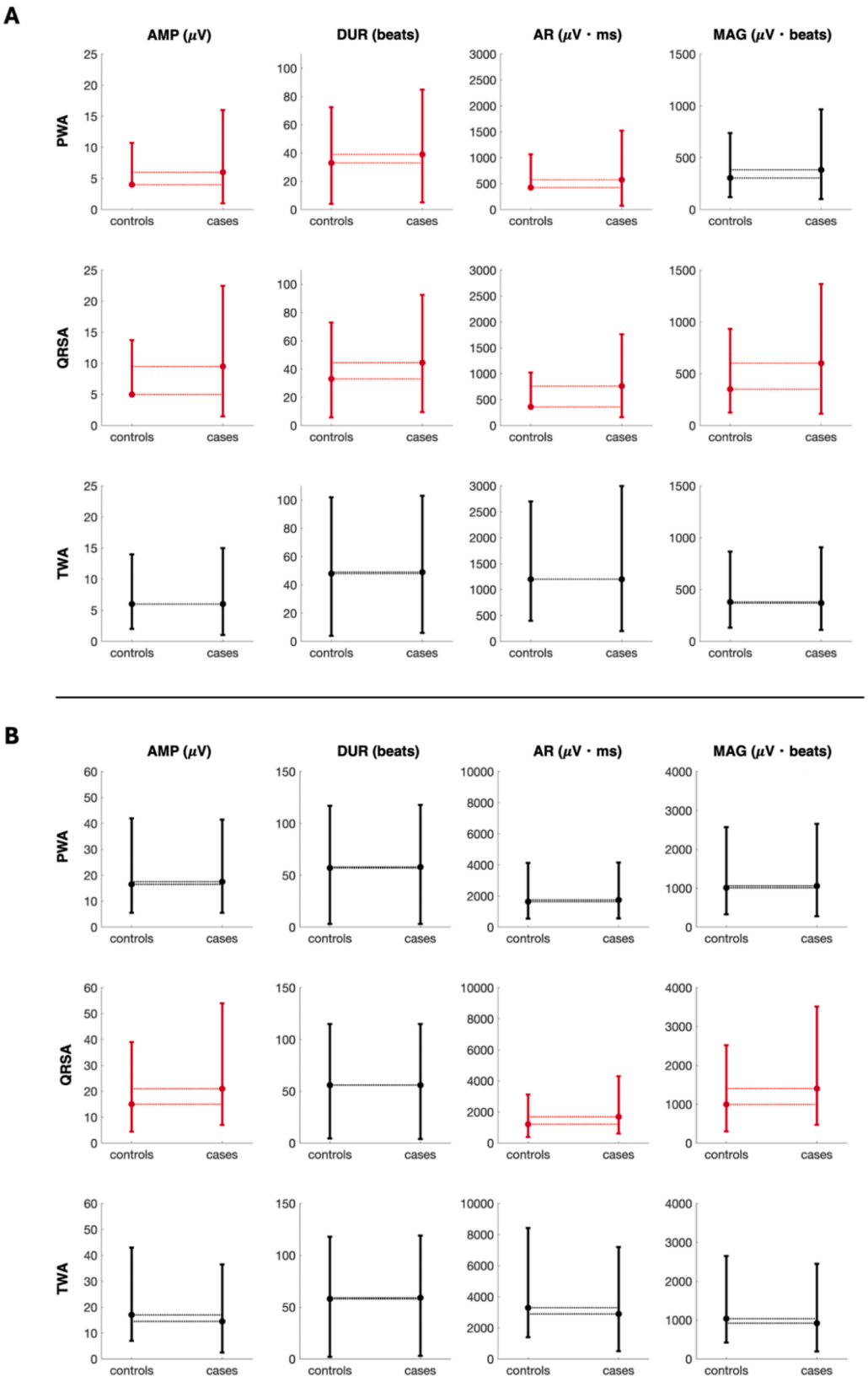

Fig. 2. Distributions of P-wave, QRS-complex, and T-wave alternans (PWA, QRSA, and TWA, respectively) features: amplitude (AMP) in the first column, duration (DUR) in the second column, area (AR) in the third column and magnitude (MAG) in the last column. Panel A refers to the resting stage and panel B refers to the maximal exercise stage. In each figurine, the median (dot) and the 25th and 75th percentiles (bar ends), for controls (on the left) and cases (on the right) are shown. The statistically significant difference between controls and cases is highlighted in red.

Table 4
Support vector machine (SVM) classification performance in terms of sensitivity (SE), specificity (SP), and F1 score, in both training and validation. Results are expressed as median [25th percentile;75th percentile] in training.

	Training	Validation
SE	100.00 [100.00;100.00] %	98.49 %
SP	96.33 [96.32;96.33] %	83.33 %
F1	99.18 [99.17;99.19] %	95.61 %

database, so evaluation of ECGA feature variability across ECG recordings for the same patient was not feasible. Patients with CRT-D dual-chamber pacemaker were excluded because the morphology of the P wave and/or QRS complex, as predicted and preliminarily verified by visual inspection, could be not physiological. Therefore, the results related to ECGA detection, particularly PWA and/or QRSA, would have been biased and inevitably artificial. Moreover, further enrollment criteria on the controls were applied, specifically considering sex, age, BMI, LVEF, and HR at rest. Indeed, evaluating the prognostic value of ECGA in primary prevention of SCD in heart failure required balancing the possible contribution of these general clinical features recognized as risk factors for arrhythmic events. Thus, we matched the clinical features of the two populations of cases and controls so that they were comparable to avoid confounding factors and ensure a faithful ECGA comparison between cases and controls.

The database was analyzed by the EAMFM. An extensive comparison of the method with the other existing ones cannot be performed, being the first automated method implemented to reliably identify and measure ECGA in all its possible single or combined forms as PWA, QRSA and/or TWA. Nevertheless, a comparison may be performed considering the method of which the EAMFM is the enhancement, the adaptive match filter method [20] that shares the core approach and was originally implemented to identify TWA, as the other methods in the literature. Focusing on the most used classic procedures to detect TWA, such as the fast-Fourier-transform spectral method, or the modified-moving-average method, which are both included in modern medical equipment, we can affirm that the fast-Fourier-transform spectral method showed its major limitation in the poor ability to recognize non-stationary features of TWA phenomena [35], the modified-moving-average method tends to provide false-positive TWA [35], while the adaptive match filter method proved to achieve often a good compromise between avoiding false-positive manifestations of the phenomenon and identifying its rapid changes [35], and the EAMFM inherited these advantages.

In this work, the onset and ending of each ECG wave were considered, and most of them (except for the onset of the P wave) were available as annotations in the database considered. In general, if annotations are not available, they should be identified in the pre-processing phase before applying the EAMFM. In this case, baseline wandering should be removed. A cubic spline interpolation is suggested to reconstruct the baseline based on the position of fiducial points that are known to be at the baseline level. This approach to remove the baseline is the one originally associated with the method, and used when it has been tested, but the suitability of other methods, such as the two-stage median filter [36], may be also considered.

The approach of filtering in a very narrow band centered around the ECGA frequency, which was maintained in common with the adaptive match filter [37], has already demonstrated the great advantage of robustness against artifacts and interferences, in particular the ones affecting the ECG frequency band outside the narrow one pertaining to ECGA. In addition, the suitability criteria ensure the rejection of ECG portions still affected by artifacts, or including ectopic heartbeats, or characterized by high heart-rate variability, all factors that would bias ECGA interpretation. In the worst scenarios, this may imply rejection of the entire ECG, as happened in the present study with the exclusion of 15 controls/10 cases and 16 controls/6 cases from the resting stage and maximal exercise stage distributions, respectively. This could be seen as a limit of the method, but it actually makes the analysis more reliable.

It was important to compute the four features (*i.e.*, AMP, DUR, AR, and MAG) for ECGA characterization. Indeed, besides the amplitude, which is the basic feature considered by all the methods existent in the literature, the area takes into account if the alternans is affecting a short wave or a long wave, resulting in a lower or higher area, respectively. This is particularly important if PWA and QRSA are considered besides TWA only. The duration of the wave is different from the duration of the alternans, which instead refers to the number of heartbeats that are affected by the phenomenon. Thus, an alternans characterized by a small amplitude but affecting many heartbeats may be as worrisome as a high alternans affecting fewer beats, and this is overall reflected in the magnitude.

When considering the ECGA value representative of the precordial leads, we decided to take into account the lead pooling, particularly computing the median because it resulted in being the statistical metric giving the best results in terms of AUC and CI (Table 3). Moreover, the available ECG leads here considered were the standard ones (*i.e.*, I-III, aVR, aVL, aVF, V1-V6) and, among them, the unipolar precordial leads resulted to be the most representative of the alternans electrophysiological phenomenon, as earlier observed [38]. Indeed, the statistical difference increased, and also the evaluation of AUC performed in [34] showed a better ECGA ability to discriminate between cases and controls when considering precordial leads only rather than all leads. Thus, this information confirmed and expanded the results of previous studies considering TWA [31,38,39], and it could be very useful in the perspective of reducing the computational burden of automatic detection methods without changing the derived outcomes. The computational load reduction is also helped by reducing the sampling frequency to 200 Hz, which is the minimum suggested by EAMFM [14]. These aspects are important in view of embedding EAMFM into ECG machines for real-time ECGA monitoring.

If possible (retrospectively speaking, it was always possible), the exercise stage was defined by the applied procedure around a predefined HR (*i.e.*, 120 bpm, section 2.3) and not around the maximal HR reached during the test. This choice is due to a phenomenon observed about TWA, which we assume reflecting in general on ECGA [31]. Specifically, ECGA is known to be HR dependent, but this dependence does not mean a one-to-one correspondence, but rather a HR-dependent hysteresis. Indeed, it was observed that TWA (and more in general ECGA) increases linearly with HR until HR reaches the value of 120–125 bpm. Then, TWA falls to initial values, even in case HR keeps increasing [31]. In our view, this implies that the maximum evidence of ECGA should occur when HR is around 120–125 bpm (regardless of whether this occurs at the end of the exercise or during the exercise). Thus, we have decided to consider two conditions: one in which ECGA appears minimized (resting HR) and one in which it appears maximized (HR equal to 120–125 bpm), both for cases and controls.

Our results confirmed that the difference between cases and controls in terms of ECGA is more evident in resting HR conditions, where we found that PWA and, in particular, QRSA features related to cases were statistically different than those related to controls. Specifically, during the resting stage, PWA and QRSA amplitudes (where amplitude is mostly the only feature considered in the literature to quantify ECGA [40]) were about 50 % and 90 % higher in cases than in controls, respectively. In contrast, during the maximal exercise stage, they were about 6 % and 40 % higher in cases than in controls, respectively. Despite being the only form of ECGA that has been considered by the literature as an index of SCD risk, this study showed that TWA seems to behave differently from the other ECGA forms since, at resting HR, TWA values were almost the same in both cases and controls, while they were 15 % higher in controls than in cases during the maximal exercise stage.

Additionally, during exercise, when HR increases, a kind of amplitude saturation was observed in the study group. Indeed, higher ECGA values in cases than in controls were observed in the resting stage, when

HR values were around 70 bpm, but these differences became less evident in the maximal exercise stage, when HR values were around 120 bpm, despite the known ECGA dependency from HR. Specifically, from resting to exercise stages, PWA amplitude increased by 191 % in cases and by 313 % in controls, QRSA amplitude increased by 121 % in cases and by 200 % in controls, and TWA amplitude increased by 142 % in cases and by 183 % in controls. Therefore, differences between cases and controls resulted smoothed during the exercise stage, and this translates into a reduced discriminant power of ECGA.

These observations were confirmed by the classification performance achieved by the SVM implemented to classify cases and controls. SVM was selected based on the characteristics of our study, such as population size. In addition, preliminary evaluation considering various classifiers (decision tree, logistic regression, Naïve Bayes, and linear discriminant analysis) was performed and it confirmed that SVM was the most suitable. Indeed, this supervised machine learning model demonstrated that rest-related ECGA features were able to correctly identify ICD patients who actually needed device intervention since the classification performance computation showed a sensitivity that was higher than 98 % in validation. On the other hand, the classification performance showed a specificity that was higher than 83 % in validation. This means that their ability to identify ICD patients who did not need device intervention was not excellent but still high. Indeed, the percentage of patients incorrectly identified as not needing ICD implantation is significantly lower than the percentage of patients who received the ICD according to the Guidelines but never required its therapy during their lifetime (approximately 30 %) [41–43]. The reliability of the model used to perform the classification was also demonstrated. The accuracy of the model assessed through the F1 score overcame 95 %. Statistically, a classifier should present equal values of sensitivity, specificity, and F1 score, but this ideal situation is unrealistic in a clinical environment, due to physiological inter- and intra-subject variability. In view of this, higher sensitivity/lower specificity situation has to be considered preferable in order to limit the clinically most dangerous situation for the patient. Furthermore, the idea behind our study is that the key solution to identify patients who will benefit from ICD implantation is not the use of ECGA alone or LVEF alone. This study examined the reasonableness of the possibility of a combined approach involving consideration of ECGA in addition to LVEF. From this perspective, the results obtained are promising and this might be a reasonable way to reconsider the current Guidelines. Further investigation in this direction seems conceivable.

Among the considered forms of ECGA, QRSA features appeared to be the most suitable for distinguishing between cases and controls. Thus, QRSA-related features extracted from precordial leads seem to be the best solution in identifying heart failure patients who should benefit from primary prevention ICD implantation. As a result, this study suggests the possibility of shifting the focus from TWA, the only form of ECGA considered by current Guidelines for SCD prevention, to QRSA.

More evidence to support ECGA (especially QRSA form) introduction in clinical practice is needed, since so far studies on the assessment of TWA in patients with an ICD are conflicting, and a consensus is desirable. In the recent study by Pelli et al. [44], TWA was investigated in its possible role associated with the benefit of ICD implantation in primary prevention. The main differences between this study and that of Pelli et al. are based on the method applied to detect and measure TWA, which is different in that they used the modified-moving-average method instead of the EAMFM, the assessment of TWA alone instead of the concomitant assessment of PWA, QRSA, and TWA, and the goal of evaluating the role of TWA in predicting death or appropriate shocks in patients with ICDs instead of the role of ECGA in identifying patients who need ICD intervention. In [44], TWA was recognized as non-prognostic of death or appropriate ICD intervention both in patients with reduced LVEF with ICD and in patients with reduced LVEF without ICD and undergoing appropriate medical treatment.

The novelty of our study relies on the following four aspects:

1. A new strategy for deciding on ICD implantation
   While current Guidelines mainly recommend LVEF testing among the criteria for identifying patients who may benefit from primary prevention ICD implantation, confining TWA testing to a suggestion, we have proposed the inclusion of an ECGA-based strategy, paving the way for a conceivable revision of the current Guidelines. To this aim, we tested the ability of ECGA to identify patients who will benefit from ICD implantation, where the device can intervene through shock therapy (for SCD prevention) or antitachycardia pacing (for ventricular arrhythmia treatment).
2. The use of a comprehensive ECGA detection method (instead of the usual TWA) in ICD patients
   We have detected ECGA using the EAMFM, which is the only (as far as we know) automated method implemented to reliably identify and measure all ECGA forms, while the other methods proposed in the literature are dedicated to TWA identification only. This study represents the first application of the EAMFM on an ICD population for testing its ability to discriminate patients who benefited from the device implantation from those who did not.
3. The investigation of two forms of alternans not considered by the current ICD implantation guidelines
   No other study in the literature investigated PWA and QRSA as features to be detected to support the decision of an ICD implantation. Indeed, TWA is the only form mentioned by the current Guidelines as a class IIa indication. ECGA ability to predict SCD was confirmed by our investigation. Indeed, this is a topic that has already been widely debated in the literature, even if mostly focusing on TWA since PWA and QRSA were left almost out of consideration. Instead, in our investigation, we observed the statistical difference between cases and controls precisely in PWA and QRSA, which appeared to be more informative than TWA. Thus, our results represent a contribution to the body of evidence that also ECGA, and in particular PWA and QRSA, should be considered to decide for ICD implantation.
4. Evidence that the resting condition is more informative than the exercise condition in ECGA studies
   TWA testing usually needs the subject to be at high heart rates, condition required for the application of most TWA detection methods described in the literature. In addition to being an unfeasible condition in some diseases, our preliminary evaluation considering (and comparing) ECGA at resting heart rates vs. higher heart rates (120 bpm) showed that the best discrimination is obtained under resting conditions and not during exercise.

Future studies should evaluate classification algorithms considering only QRSA-related features to possibly confirm the outcomes observed in the present study suggesting a possible significant role of this form of ECGA in clinical practice. Moreover, future studies should evaluate whether the discriminant ability of ECGA further improves if it is quantified at heart rate during the recovery phase rather than heart rate at rest because, according to previous results on the same database, but analyzed with the adaptive match filter, it seemed to provide additional information to identify patients at higher risk of arrhythmic events [31]. Possibly, this evidence may be confirmed by the use of the EAMFM.

5. Conclusions

This study investigated the ability of ECGA to identify heart failure patients who could benefit from primary prevention ICD implantation. Our results, albeit preliminary, suggest evaluating ECGA as a possible additional criterion in association with LVEF, promoting consistency between clinical and technical literature and paving the way for a possible revision of the current Guidelines with a view to greater consideration of ECGA. Further studies are needed to confirm our hypothesis.

CRediT authorship contribution statement

Ilaria Marcantoni: Writing – original draft, Data curation, Methodology, Conceptualization, Software. **Erica Iammarino:** Visualization, Writing – original draft, Formal analysis. **Agnese Sbrollini:** Writing – review & editing, Formal analysis. **Micaela Morettini:** Writing – review & editing, Formal analysis. **Cees A. Swenne:** Writing – review & editing, Data curation, Supervision. **Laura Burattini:** Writing – review & editing, Project administration, Supervision, Methodology, Validation.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A

Table A1
Additional information about patients excluded from the study group.

Exclusion Criterion	Motivation	Number of excluded patients	
CRT-D dual-chamber pacemaker	To avoid non-physiological ECG wave morphologies	36 cases	100 controls
Clinical features	To obtain a uniform clinical profile	0 cases	8 controls
EAMFM suitability criteria:	To avoid unreliable quantifications of ECGA		
all windows rejected in resting stage		10 cases	15 controls
all windows rejected in maximal exercise stage		6 cases	16 controls

Data availability

The authors do not have permission to share data.

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