# The electrocardiogram as a predictor of successful pharmacological cardioversion and progression of atrial fibrillation

# The ECG as a Predictor of Successful Pharmacological Cardioversion and Progression of Atrial Fibrillation

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## INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia that progresses over time. As demonstrated by both invasive(1) and non-invasive(2) assessment of the electrophysiological properties of AF, the incidence of local conduction heterogeneities or conduction block and the number of fibrillation waves increases with the duration of AF episodes. AF is classified as paroxysmal or persistent, depending on AF episode duration and cardioversion attempts undertaken.(3) A decision on rhythm control strategy is based on this classification, the patient's symptoms, and physician's and patient's preference. Whether a patient will respond to rhythm control therapy is difficult to predict. Moreover, any kind of rhythm control strategy is associated with considerable risks, such as ventricular pro-arrhythmia in case of anti-arrhythmic drug therapy or procedural risks caused by AF ablation. Predicting acute and long-term success of AF treatment at any stage of the disease is therefore desirable and subject to extensive research.(4)

Progression of AF is characterized by an increase in number of fibrillation waves, caused by increasing incidence of conduction block in the atria as a consequence of a progressive structural remodelling.(1) The standard 12-lead ECG is an attractive choice for non-invasive assessment of the level of AF complexity because of its widespread use in daily clinical practice. However, whether AF complexity quantified from the surface ECG can be employed in a clinical setting to predict treatment outcome and ultimately guide management of AF, still has to be established. In the recent past, many complexity parameters derived from the 12-lead ECG have been proposed.(4,5) Although several studies report encouraging results in either classifying AF or predicting treatment outcome, it is not a straightforward task to compare and interpret these results, because of large differences in patient populations, the parameters computed on the ECG, and the specific clinical setting.

There is a clear need for standardization of ECG-based AF complexity analysis to predict response to therapy and develop an individualised treatment strategy.(5,6) To address these issues, we investigated a large set of ECG-derived AF complexity parameters and their ability to predict successful outcome of pharmacological cardioversion (PCV) using flecainide in patients with recent onset AF. Long-term implications of observed AF complexity were investigated by associating AF complexity prior to cardioversion to progression to persistent AF. Our study shows that ECG parameters outperform commonly used clinical predictors in the setting of PCV and in the prediction of long-term progression to persistent AF.

## METHODS

### Patient database

Patient data were retrieved from a database at Maastricht University Medical Center, Maastricht, the Netherlands, of consecutive patients with short lasting episodes of AF (< 48h, recurrent or new onset AF) undergoing first time cardioversion with the anti-arrhythmic drug flecainide between the years 2008 and 2012. Exclusion criteria were the use of anti-arrhythmic drugs (AAD) less than 5 half-lives prior to the PCV attempt, use of additional medication during the PCV procedure, and a missing or poor quality ECG (assessed visually). A total of 221 patients were included in this study. Patient characteristics are listed in Table 1.

Echocardiographic parameters were included if echocardiography was recorded within one year before or after the PCV attempt (available in 139 patients). A 10-second 12-lead ECG was recorded during AF for each patient before the PCV attempt, using a GE MAC® 5500 resting ECG recording device (sampling frequency 250Hz). PCV success was defined as restoration of sinus rhythm within one hour after starting the flecainide infusion. Flecainide was dosed at 2 mg/kg with a

maximum dose of 150 mg intravenously. Follow-up data on progression to persistent AF within the period January 2008-March 2015 was available for 201 patients. Progression was defined as occurrence of an AF episode with a duration > 7 days, as derived from Holter ECG or 2 consecutive ECGs at least 7 days apart with symptomatic AF.

**Non-invasive AF complexity parameters**

The list of non-invasive AF complexity parameters included in this study was composed of parameters that appeared frequently in the last decade of non-invasive AF complexity literature. See Supplementary Materials for detailed parameter definitions and interpretation. Parameters were computed with algorithms provided by the original author(s) or otherwise as described in the original publication. An overview of parameters and their domain is shown in Figure 1.

Before parameter computation, ECGs were filtered with a 1-100Hz band-pass filter (3$^{rd}$ order Chebyshev, 20dB stop-band attenuation). To enable analysis of TQ-segments, the end of the T-wave and onset of the Q-wave were detected in unfiltered signals using Woody's improved method.(7) Ventricular QRST complexes were removed by a single lead cancellation method based on singular value decomposition of QRST windows.(8) The extracted atrial signals were filtered with a 3Hz high-pass filter to remove any remaining T-wave residues. Finally, the first and last second were truncated to avoid the border effect of filtering procedures, leaving 8 seconds available for analysis.

**Prediction models and statistical analysis**

PCV prediction models were built by logistic regression. In multivariate analyses parameters were selected by combing the selected parameters from both stepwise

and sparse logistic regression, a method that can identify dominant predictors from a large set of candidate predictors while also accounting for parameter correlation.(9) The optimal model was then found by iterating over all possible combinations of this subset of parameters. See Supplementary Materials for a detailed description of the parameter selection procedure.

Prediction performance was measured as the area under the receiver operating characteristic (ROC) curve (AUC). Complexity parameters were first individually scored in terms of predictive performance. Then, parameters were divided into 4 groups, based on their electrophysiological interpretation (in the time or frequency domain) and the number of leads involved in the computation (one lead or multiple leads). Best predicting parameter models were compared to the prediction performance obtained by conventional clinical and echocardiographic predictors. Model prediction performance was cross-validated using 5-fold data partitioning with repeated (20 times) random subsampling. Differences in model performance were assessed with a Student's t-test with a significance level alpha = 0.05.

The association between parameters and the risk of progression to persistent AF was investigated using Cox proportional hazards models. Hazard models were estimated for each parameter individually, unadjusted and adjusted for age and sex, and for combinations of parameters, again applying a sparse technique to select dominant predictors.(10) Differences in hazard model fit quality were assessed using a likelihood ratio test with a significance level alpha =0.05.

All computations were performed in MATLAB (MATLAB and Statistics Toolbox Release 2014a, The MathWorks, Inc., Natick, Massachusetts, United States), using custom made software and the Glmnet for MATLAB toolbox(11) for elastic net regression.

## RESULTS

### Prediction using one parameter derived from one lead

Single lead ECG parameter results are listed in Supplementary Table 1.

The best predictor for successful PCV was lower dominant frequency (DF, computed from Welch's power spectral density estimate), with maximum AUC at lead II (0.66, 95% confidence interval [0.64-0.67], sensitivity 78[76-79]%, specificity 45[43-48]%). All other significant predictors in the frequency domain obtained lower performance with an AUC below 0.60. Best predictor in the time-domain was sample entropy (SAE) at lead II (AUC 0.63 [0.62-0.65], sensitivity 86[85-87]%, specificity 33[31-35]%)).

### Prediction using one parameter derived from multiple leads

Results for ECG parameters derived from multiple leads, so-called multidimensional parameters, are listed in Supplementary Table 2. This analysis focused on the parameters that were computed using information derived from multiple leads, but expressed the complexity of those multiple leads as a single parameter value. Maximum predictive power was observed using multidimensional DF (MDF) (AUC 0.64 [0.62-0.66], derived from leads $V_{(1,2,4,5,6)}$, sensitivity 84[82-86]%, specificity 37[35-39]%) and spectral variability (SV) (AUC 0.64 [0.62-0.66], all leads, sensitivity 77[76-79]%, specificity 48[45-50]%).

### Prediction using a combination of ECG parameters

Results are listed in Table 2. The best model containing a combination of frequency-domain parameters computed on a single lead improved performance from an AUC of 0.66 [0.64-0.67] to 0.72 [0.70-0.73], sensitivity 75[73-77]%, specificity 54[52-57]% ($p<0.001$), by adding organization index (OI, lead III) and spectral entropy (SE, lead

I) to the best single lead parameter DF (lead II). In the time-domain prediction improved by extending the best performing single lead parameter SAE (lead II) with fibrillation wave amplitude (FWA, lead aVF and $V_1$) and fibrillation wave power (FWP MAW, lead $V_2$), from an AUC of 0.63 [0.62-0.65] to 0.72 [71-74], sensitivity 83[81-84]%, specificity 48[46-51]% ($p<0.001$).

Combining multidimensional parameters produced similar results in the frequency-domain, with a 6-parameter model increasing the AUC from 0.64 [0.62-0.66] to 0.71 [0.69-0.72], sensitivity 95[94-96]%, specificity 29[27-31]% ($p<0.001$). Combining multidimensional time-domain parameter did not improve predictive performance. Combining the best predicting parameters of each group into a single model further improved prediction performance (AUC 0.78 [0.76-0.79], sensitivity 80[79-82]%, specificity 60[57-62]%). A selection of cross-validated ROC curves is depicted in Figure 2a. Supplemental Figure 1 shows the effect of combining parameters within each parameter group on prediction performance.

**Prediction using clinical parameters and ECG parameters**

An overview of the performance of a combination of clinical patient characteristics with ECG parameters can be found in Figure 2b and Supplementary Table 3. The predictive capability of clinical parameters alone was limited, with the best results obtained using weight and right atrial volume (RAV) (0.68 [0.66-0.70], sensitivity 87[86-89]%, specificity 35[32-37]%). Predictive performance of optimized ECG parameter models was superior, except for the multidimensional time-domain parameter model. Combining these ECG parameter models with the optimized clinical parameter model significantly enhanced predictive performance in all cases, again except for the multidimensional time-domain parameter model. The best predictive model was obtained by combining clinical and single lead frequency-

domain parameters DF(II), OI(III) and SE(I) (AUC 0.81 [0.79-0.82], sensitivity 83[81-85]%, specificity 64[61-67]%).

**Risk of progression to persistent AF**

Out of the 201 patients for whom follow-up was available, 38 (19%) developed persistent AF between the moment of PCV and March 2015 (median time to persistent AF: 408 days, interquartile range (IQR): 171-822 days, median follow-up 49 months). Table 3 contains the significant hazard ratios (HR) of individual clinical and ECG complexity parameters for AF progression. Age, BMI, left atrial diameter (LAD), RAV, left ventricular end systolic diameter (LVESD) and ejection fraction (LVEF) showed small, but significant hazard ratios. Unsuccessful PCV was not a significant hazard (HR 1.58, 95% confidence interval (CI) 0.82-3.06, p=0.17). The ECG complexity parameters DF and FWA obtained significant HRs, with both a higher DF and – surprisingly - a higher FWA associated with a larger risk of developing persistent AF.

Figure 3 depicts Kaplan-Meier curves for four dichotomized parameters, showing that obesity (BMI>30 kg/m$^2$), an enlarged left atrium (LAD>41 mm), faster atrial rate (DF>5.7 Hz), and higher fibrillation wave amplitude (FWA>0.06 mV) were associated with an increased risk of AF progression. As expected from previous studies, an elevated HATCH score indicated a significantly higher risk for progression to persistent AF.(12) However, FWA ($V_1$) was a better predictor than the HATCH score in predicting progression within 2 years (AUC 0.72 [0.70-0.74] vs. 0.60 [0.57-0.62] p<0.001, n=184, 22 persistent AF). Combining FWA and the HATCH score did not improve prediction performance.

Multivariate analysis showed that the risk of progression to persistent AF is best explained by LAD, when considering only clinical parameters. ECG complexity

parameters modelled progression best using a combination of DF (lead aVL) and FWA (lead $V_1$) (n=201, DF(aVL): HR 1.45, CI 1.08-1.94, p=0.01; FWA($V_1$): HR 1.16, CI 1.05-1.27, p<0.01). Adding DF(avL) or FWA ($V_1$) to the best model containing only clinical parameters both improved the model fit (p=0.05 or 0.02 respectively).

## DISCUSSION

### EGC parameters as predictors of pharmacological cardioversion outcome

The results of the ECG parameter analysis demonstrate that characteristics of 12-lead ECGs can predict successful PCV of recent onset AF and progression from paroxysmal to persistent AF. Patients with a lower DF were more likely to respond to treatment, which is in line with the observation by Choudhary et al. who showed that recent onset AF with a lower DF was more likely to spontaneously terminate.(13) Also in patients with persistent AF a lower DF was found to predict successful electrical CV outcome.(14) Moreover, single lead measures of organization of atrial rate (OI and SE) indicate that a higher degree of organization favours successful PCV. Overall, differences between successful and unsuccessful PCV were subtle, but plausible given the interpretation of DF as a surrogate parameter for the AF cycle length. In the patients investigated in this study, undergoing their first cardioversion, the process of electrical remodelling is still on-going and may have an important effect on the success of PCV. The degree of electrical remodelling increases with AF duration. Although precise AF duration is difficult to assess in the majority of recent onset AF patients, DF may reflect action potential duration shortening associated with the degree of electrical remodelling and - indirectly - the duration of AF in these patients.(15)

Multidimensional parameters that compute one complexity indicator from multiple leads are a logical extension of single lead analysis. Incorporating spatial differences

among leads and capturing inter-lead variability as an additional measure of complexity, could lead to a more sophisticated estimate of AF complexity. The results from the multidimensional parameter analysis partially confirm this. While DF computed on one of the precordial leads only gave a significant result on lead $V_1$, the multidimensional extension MDF performed better, with significant results for many combinations of precordial leads. Maximum performance of MDF was however still lower than the performance of single lead DF on limb lead II (AUC 0.64 vs. 0.66). We did not notice an important role of left atrial content in this patient population as indicated by Uldry et al. in their study on discriminating persistent and long-standing persistent AF.(16) Most significant multidimensional parameter differences were observed in a mix of right- and left-oriented precordial leads. Overall, predictive performance of a single parameter was moderate, even when calculated from multiple leads. More importantly, combining several complexity parameters in a prediction model significantly improved prediction, regardless of whether these different parameter values were calculated from single lead or multiple leads.

**Added predictive value of ECG parameters compared to clinical information**

The ability of clinical parameters, including echocardiographic parameters, to predict successful outcome of PCV was limited. Combinations of ECG parameters performed better on the subset of patients with complete clinical and echocardiographic data records. Combining ECG and clinical parameters further improved prediction. This implies that features extracted from the ECG contain complementary information to the available clinical characteristics in this patient population. Worthwhile noting is that the best overall predictive performance was obtained by combining a small number of frequency-domain parameters computed on a single lead with the clinical parameters RAV and weight. The 3 ECG parameters

in this model were all computed in limb leads I, II and III, with a strong role of DF at lead II, again suggesting the need to include leads that contain both right and left atrial activity.

**Non-invasive complexity and risk of progression to persistent AF**

Interestingly, both clinical as well as ECG complexity parameters were associated with risk of progression to persistent AF. Clinical parameters like age, BMI and HATCH score, and echocardiographic parameters like LAD, RAV and LVEF were indicators for an increased risk of progression to persistent AF, which is in line with previous findings.(12,17) From the set of ECG parameters only parameters computed on a single lead showed significant hazard ratios, namely DF and FWA. The threshold of 5.7 Hz computed for DF to produce the survival curve in Figure 3c is very comparable to the AFR threshold of <350 fibrillations per minute (5.8 Hz) found by Choudhary et al.(13) associated with a significant increase in the likelihood of spontaneous cardioversion of recent onset AF within 18 hours. One could argue that patients that are not likely to spontaneously convert to sinus rhythm have a higher risk to develop persistent AF, due to more electrical and, eventually, structural remodelling caused by prolonged episodes of AF. On the other hand, Mochalina et al.(18) reported no predictive value of DF in a comparable cohort of patients undergoing PCV with vernakalant. A possible explanation for this discrepancy is that in their study only lead $V_1$ was analyzed, as opposed to all 12 ECG leads in the present study. Alternatively, differences in the anti-arrhythmic mechanism of flecainide and vernakalant may affect the predictive performance of complexity parameters.

The role of FWA on $V_1$ in the development of persistent AF in this patient cohort is more challenging to interpret: a higher FWA was associated with a higher risk for

persistent AF, while the inverse relation was found for FWA in the prediction of successful PCV. Moreover, a higher FWA on $V_1$ attained better predictive value than an elevated HATCH score, an established predictor of progression to persistent AF. The relatively low HATCH scores in this cohort may limit its predictive power. The amplitude of fibrillation waves that are visible on an ECG is influenced by both the atrial mass and the degree of complexity of AF. On the one hand, patients with an organised AF pattern have a larger simultaneously activated atrial mass and therefore larger vectors in a certain direction.(19) Larger electrical vectors are expected to produce larger f-waves, potentially explaining higher success rates of PCV. On the other hand, patients with atrial dilatation have more atrial mass and therefore could produce larger f-waves. Patients with atrial dilatation are known to be more likely to progress into persistent AF, as also indicated by our results.(12) Certainly, the implications of FWA for long-term rhythm outcome warrant further investigation.

**ECG parameters in clinical decision-making**

We showed that non-invasive atrial complexity parameters, automatically derived from a standard 12-lead ECG improve prediction of successful PCV in patients with recent onset AF. Correctly predicting patients in whom AF is likely to terminate using drugs is certainly of relevance in the emergency department. In patients with low complexity, one could wait for spontaneous CV or restore of SR (for example using intravenously administered AADs) but refrain from continuous anti-arrhythmic drug treatment for rhythm control, thereby minimizing drug-related adverse effects.(3) For patients reporting at the emergency department with a complex AF pattern, a more aggressive rhythm control strategy may be necessary to prevent recurrences and reduce the risk of progression to persistent AF, by either continuous AAD treatment

or early catheter ablation. Early identification of these patients with early treatment might result in improved success percentages and prevent future cardiovascular complications.(20) Implementation of algorithms capable of extracting atrial activity and computing non-invasive complexity parameters into commercially available ECG acquisition systems is an important prerequisite to enable individualized AF therapy.

## LIMITATIONS

The retrospective nature of this study had implications for the availability and quality of clinical information and ECG signals. Echocardiography was not recorded at the same time as the ECG, but selecting an available echocardiography within a year produced similar results compared to a narrower timeframe (see Supplementary Materials). Our institutional protocol for PCV introduced a weight-dosage dependency for patients with a weight above 75kg. This dependency is most likely partially responsible for the inclusion of weight in the final clinical prediction model of successful PCV. ECG signals were not recorded with the intention to analyse AF complexity but rather to diagnose the arrhythmia, meaning that quality was varying and recording duration was limited to 10 seconds. This does however reflect everyday clinical practice.

## CONCLUSIONS

AF complexity parameters determined from 12-lead ECGs are superior to common clinical predictors in predicting successful PCV in patients with recent onset AF. Combining ECG and clinical parameters generally improved prediction, especially by including single lead frequency-domain parameters. Notably, both clinical characteristics as well as ECG complexity parameters can predict progression to persistent AF, which may guide individualized rhythm control strategies in the future.

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**CONFLICT OF INTEREST**

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## FIGURE LEGENDS

**Figure 1.** Overview of ECG signal processing and complexity parameter computation. In the time-domain, multidimensional parameters derived from multiple leads can be computed on both the extracted atrial activity (AA), as well as on the TQ-segments of the original ECG. In the frequency-domain, complexity can be quantified based on spectra computed from a single lead or multiple leads.

DF: Dominant Frequency; OI: Organization Index; SE: Spectral Entropy; RHE: Relative Harmonic Energy; MDF/MOI/MSE: Multidimensional DF/OI/SE; SC: Spectral Concentration; SV: Spectral Variability; SAE: Sample Entropy; FWA: Fibrillation Wave Amplitude; FWP MAW: Fibrillation Wave Power of the Main Atrial Wave; $K_{0.95}$, C: spatial complexity parameters; NMSE, CV: Variability of spatial complexity; MFWA: Multidimensional FWA

**Figure 2.** Cross-validated receiver operating characteristics (ROC) curves of various prediction models. The band around each curve indicates the 95% confidence interval of the sensitivity for a given specificity. Depicted are the ROC curves for **a)** the best prediction performance of a single parameter computed on 1 lead (Dominant Frequency (DF) on lead II, area under the ROC curve (AUC) 0.66), the best performance for a single multidimensional parameter (Spectral Variance (SV) derived from all leads, AUC 0.64), the best performing combination of parameters computed on 1 lead (DF (II), Organization Index (OI) (III) and Spectral Entropy (SE) (I), AUC 0.72), and the best combination of all ECG parameters (DF (II), SE (I), Fibrillation Wave Amplitude (FWA) (aVF, $V_1$), Multidimensional OI (MOI) ($V_{(3,4)}$, $V_{(3,5)}$), SV, and Multidimensional FWA (MFWA), AUC 0.78). In **b)** the ROC curves are shown for the

453 best model consisting only of clinical parameters (Right Atrial Volume (RAV) and
454 weight, AUC 0.68), only of parameters computed on the ECG (best ECG parameter
455 model derived from the full data set, AUC 0.78), and a combination clinical and ECG
456 parameters (weight, RAV and the best single lead frequency-domain parameter
457 model, AUC 0.81).

458

459 **Figure 3.** Kaplan-Meier curves for the risk of progression to persistent AF after the
460 PCV attempt for patients with a) Body Mass Index (BMI)>30 kg/m$^2$ (Hazard ratio (HR)
461 2.97), b) Left Atrial Diameter (LAD)>41 mm (HR 2.65), c) Dominant Frequency
462 (DF)>5.7 Hz on lead aVL (HR 4.16), and d) Fibrillation Wave Amplitude (FWA)>0.06
463 mV (HR 3.25). All HRs $p<0.01$.

464 **TABLES**

465

466 **Table 1.** Patient characteristics.

| **Characteristic** | **Successful PCV** n=157 (71%) | **Unsuccessful PCV** n=64 (29%) | **P-value** |
|---|---|---|---|
| Sex (Male \ Female) | 93\64 | 52\12 | 0.002 |
| Age (years) | 61±13 | 57±15 | 0.170 |
| Height (cm) | 174±10 (116) | 179±12 (51) | 0.004 |
| Weight (kg) | 81±14 (116) | 91±19 (51) | 0.001 |
| BMI (kg/m$^2$) | 26.9±3.9 (116) | 28.1±5.3 (51) | 0.305 |
| Diabetes | 11 (141) | 5 (61) | 0.924 |
| Hypertension | 66 (141) | 29 (62) | 0.996 |
| COPD | 8 (141) | 2 (61) | 0.471 |
| PVI in history | 2 (141) | 5 (60) | 0.014 |
| Left atrial diameter (mm) | 40.3±5.1 (113) | 43.1±6.0 (49) | 0.003 |
| Left atrial volume (ml) | 74.2±20.8 (111) | 80.8±19.6 (48) | 0.067 |
| Right atrial volume (ml) | 56.3±18.0 (99) | 69.9±23.3 (47) | <0.001 |
| LVEDD (mm) | 49.4±5.4 (117) | 51.5±6.0 (51) | 0.127 |
| LVESD (mm) | 33.6±4.5 (116) | 36.3±7.3 (50) | 0.064 |
| LVEF (%) | 60.1±5.6 (117) | 57.0±10.0 (51) | 0.171 |
| $CHA_2DS_2$-VASc | 2[0-3] (140) | 1[0-3] (61) | 0.159 |
| HATCH | 1[0-1] (140) | 1[0-1] (61) | 0.621 |

467 Numbers are given as mean±SD, median [25th-75th percentile] or count. Between

468 brackets is the number of observations for each parameter if lower than n=221.

469 Binary variables were tested using a Chi-square-test for proportions.

470 BMI: body mass index; COPD: chronic obstructive pulmonary disease;

471 LVEDD/LVESD: left ventricular end diastolic/systolic diameter; LVEF: left ventricular

472 ejection fraction; PVI: pulmonary vein isolation

473

474 **Table 2.** Best performing parameter models for single and multidimensional ECG

475 parameters in the frequency- and time-domain.

| Group | Parameters | Leads or signal | AUC [95%CI] |
|---|---|---|---|
| Single lead | DF | II | |
| Frequency domain | OI | III | 0.72 [0.70-0.73] |
| | SE | I | |
| Single lead | SAE | II | |
| Time domain | FWA | aVF, $V_1$ | 0.72 [0.71-0.74] |
| | FWP MAW | $V_2$ | |
| Multiple leads | MDF | $V_{(1,2,4,5)}$, $V_{(1,2,4,5,6)}$ | |
| Frequency domain | MOI | $V_{(3,4)}$, $V_{(3,5)}$, $V_{(2,4,5,6)}$ | 0.71 [0.69-0.72] |
| | SV | All leads | |
| Multiple leads | MFWA | AA | 0.61 [0.60-0.63] |
| Time domain | CV | AA | |
| Combined | DF (II), SE (I), FWA (aVF, $V_1$), MOI ($V_{(3,4)}$, $V_{(3,5)}$), SV, MFWA | | 0.78 [0.76-0.79] |

476 AUC: Area under the Receiver Operator Characteristics Curve; CI: Confidence

477 Interval; AA: Atrial Activity

478 DF: Dominant Frequency; OI: Organization Index; SE: Spectral Entropy; SAE:

479 Sample Entropy; FWA: Fibrillation Wave Amplitude; FWP MAW: Fibrillation Wave

480 Power of the Main Atrial Wave; MDF/MOI: Multidimensional DF/OI; SV: Spectral

481 Variability; MFWA: Multidimensional FWA; CV: Variability of spatial complexity

482

**Table 3.** Significant hazard ratios for risk of progression to persistent AF.

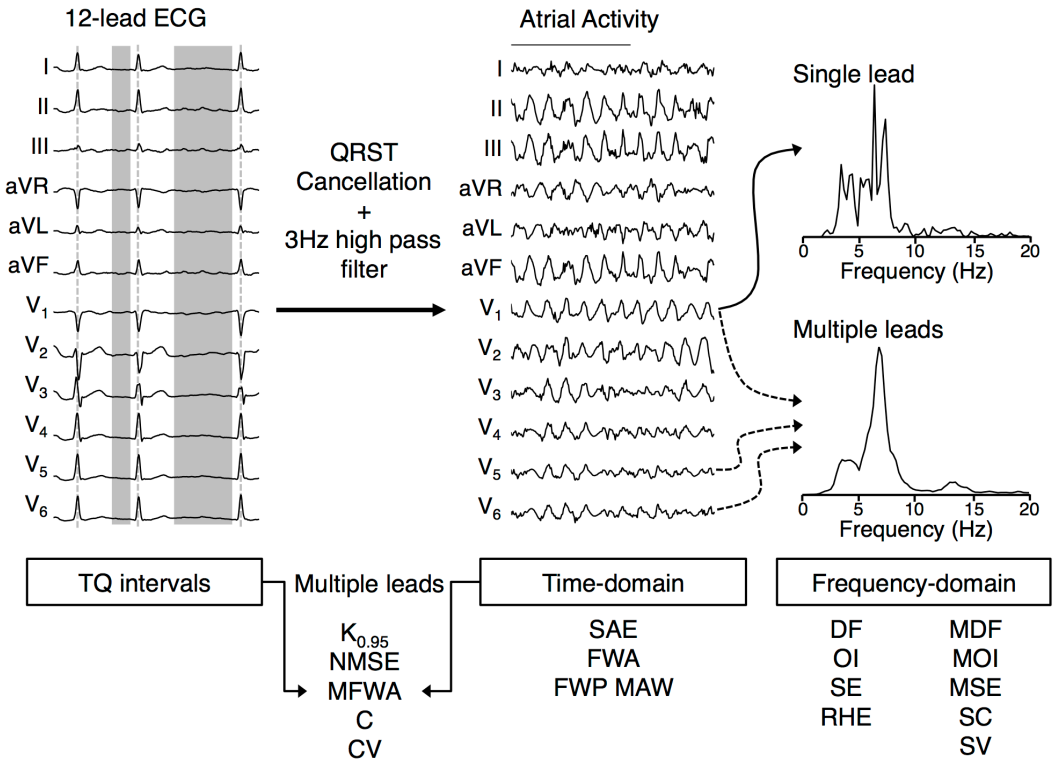
| Parameter | Increment | Hazard ratios (95% CI) | |
|---|---|---|---|
| | | **Unadjusted** | **Adjusted for Sex and Age** |
| Age | 1 year | 1.03 (1.01-1.06) † | N/A |
| BMI (n=159) | 1 kg/m$^2$ | 1.09 (1.03-1.17) ‡ | 1.10 (1.03-1.18) ‡ |
| LAD (n=155) | 1 mm | 1.12 (1.05-1.19) ‡ | 1.11 (1.04-1.18) ‡ |
| RAV (n=141) | 5 ml | 1.11 (1.03-1.21) † | 1.12 (1.02-1.22) † |
| LVESD (n=158) | 1 mm | 1.06 (1.00-1.11) † | 1.08 (1.02-1.14) ‡ |
| LVEF (n=160) | -1 % | 1.06 (1.02-1.11) ‡ | 1.06 (1.02-1.10) ‡ |
| HATCH (n=184) | 1 point | 1.43 (1.10-1.86) ‡ | 1.27 (0.92-1.76) |
| DF (III) | 1 Hz | 1.57 (1.17-2.10) † | 1.65 (1.24-2.19) ‡ |
| DF (aVL) | 1 Hz | 1.50 (1.14-1.99) ‡ | 1.64 (1.24-2.16) ‡ |
| DF (aVF) | 1 Hz | 1.46 (1.11-1.92) ‡ | 1.53 (1.17-2.00) † |
| DF ($V_4$) | 1 Hz | 1.37 (1.03-1.87) † | 1.34 (0.99-1.83) |
| FWA ($V_1$) | 0.01 mV | 1.17 (1.07-1.29) ‡ | 1.16 (1.06-1.27) ‡ |

CI: Confidence interval; † $p<0.05$, ‡ $p<0.01$

BMI: body mass index; LAD: left atrial diameter; RAV: right atrial volumn; LVESD: left ventricular end systolic diameter; LVEF: left ventricular ejection fraction; DF: Dominant Frequency; FWA: Fibrillation wave amplitude

## FIGURES

### Figure 1



494 **Figure 2**

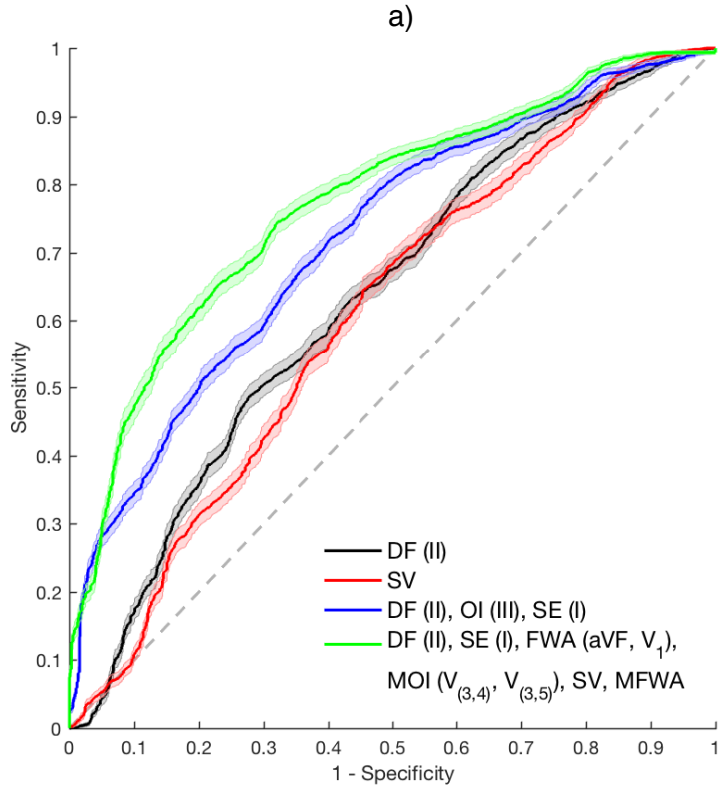



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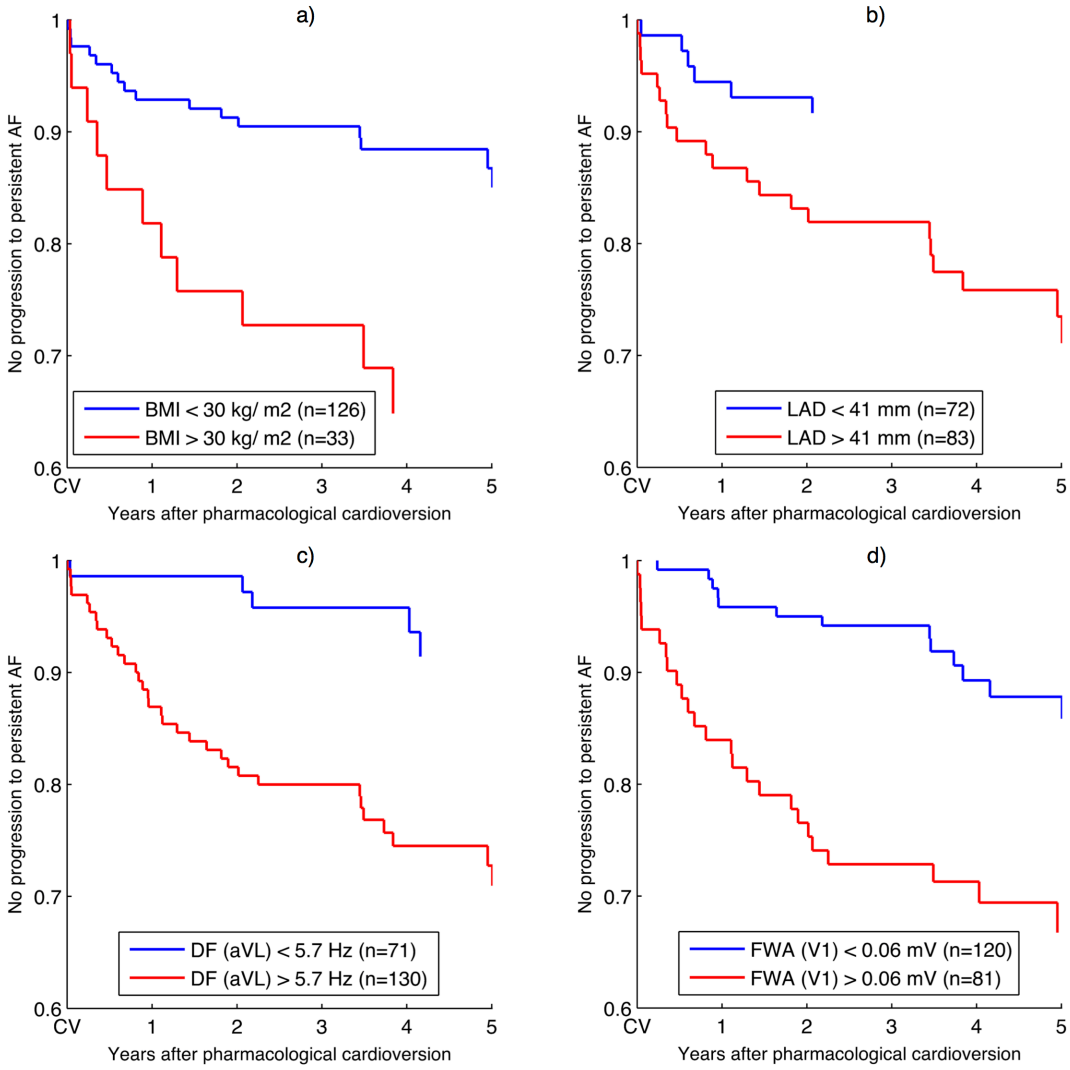
**Figure 3**


a)
b)
c)
d)
No progression to persistent AF
Years after pharmacological cardioversion
CV
BMI < 30 kg/ m2 (n=126)
BMI > 30 kg/ m2 (n=33)
LAD < 41 mm (n=72)
LAD > 41 mm (n=83)
DF (aVL) < 5.7 Hz (n=71)
DF (aVL) > 5.7 Hz (n=130)
FWA (V1) < 0.06 mV (n=120)
FWA (V1) > 0.06 mV (n=81)

# SUPPLEMENTAL MATERIALS

## METHODS

### Non-invasive AF Complexity parameters

*Spectral parameters*

Frequency-domain parameters are parameters that derive a complexity score from the frequency content of the atrial signal. The frequency content of each lead was determined by computing the spectrum using 1) the (fast) Fourier transform of the extracted atrial signal, 2) Welch's power spectral density estimate (3 segments, 1024 points, 50% overlap), and 3) the compressed spectrum (CS)(1) using the original ECG signal.

The dominant atrial frequency (DF) was defined as the frequency with the largest power within the 3-12Hz band. The organization index (OI) of the spectrum was defined as the relative contribution of the 2 largest peaks to the total spectral power. OI reflects the relative strength of the 2 dominant frequencies compared to other frequencies present in the atrial activity as a measure of the number of competing fibrillatory processes present in the atria. A low value of OI indicates high complexity.

Spectral entropy (SE) is the application of Shannon's entropy to the frequency distribution and can be interpreted as a measure of uniformity of the fibrillatory frequencies present in the atria. A high value of SE indicates high complexity.

Single lead spectral analysis can be extended to a multidimensional analysis that incorporates spectral information from multiple leads using the so-called spectral envelope. The spectral envelope describes the shared spectral characteristics of a multidimensional signal.(2) This means that the spectral information from multiple leads is represented in a single spectrum. From the spectral envelope, the same three spectral parameters were derived: multidimensional dominant frequency

(MDF), multidimensional spectral organization index (MOI) and multidimensional spectral entropy (MSE).(3) MDF, MOI and MSE were computed on the spectral envelope of all possible combinations of 2 or more precordial leads, as opposed to only pairs of leads in Uldry et al.(3)

*Fibrillation wave amplitude*

The amplitude of fibrillation waves was determined in two ways: automatic annotation of f-waves in a single lead by peak detection, followed by amplitude computation (FWA), comparable to the manual annotation method used by Nault et al. (4), and – analogous to the computation of spectral complexity – a signal envelope approach that computes a multidimensional f-wave amplitude on multiple leads (MFWA).(5) MFWA was computed on both the AA signal and TQ segments. A low value of FWA or MFWA indicates high complexity.

*Sample entropy*

Sample entropy (SAE) is a time-domain parameter that quantifies the irregularity of a signal by searching for similar segments of a certain length. It can be interpreted as a measure of repetitiveness and predictability of the atrial activity. As proposed by Alcaraz et al.(6) SAE was computed on the main atrial wave (MAW) of each lead. The MAW is the signal resulting from filtering the atrial signal centred around the dominant frequency with a 3Hz bandwidth. A high value of SAE indicates high complexity. Additional parameters related to the MAW are the f-wave power of the MAW (FWP MAW), with similar interpretation as FWA, and the relative sub-band energy (RHE)(6), computed as the relative energy present in the first and second harmonics of the MAW. A low value of RHE indicates high complexity as it indicates a less dominant role of the main atrial wave.

*Principal component analysis*

Another multidimensional approach to AF complexity quantification is principal component analysis (PCA), which expresses the information from all 12 leads in a number of linearly uncorrelated components that essentially describe the amount of variance between the leads. Complexity measures based on PCA included were spatial complexity $k_{0.95}$, the number of components required to describe 95% of the variance in all 12 leads, and spatio-temporal stationarity (NMSE), the degree in which the three major signal components vary over time.(7) A high value of $k_{0.95}$ and NMSE indicates high complexity, as they indicate that there is a large amount of variation in the atrial activity between leads and in time. Additional measures of spatial complexity C and variability of spatial complexity CV were also included. C defines spatial complexity as the relative signal variance, excluding the three major components.(8) Also here, a high value of C indicates high complexity as it means that the variance between lead activity is higher. Frequency domain parameters derived from PCA were spectral concentration SC and spectral variability SV(8), where SC quantifies the concentration of the spectral power around the dominant frequency and SV the temporal variation of the SC. A low value of SC or a high value of SV indicates high complexity. PCA parameters were computed on both the AA signal and the TQ segments.

**Parameter selection via elastic net logistic regression**

In several cases, the number of candidate parameters in the logistic regression model makes it infeasible to iterate over all possible parameter combinations to select the overall best performing model. Parameter selection using stepwise logistic regression has the disadvantage that it is dependent on the order in which

parameters are added or removed from the prediction model. Stepwise parameter selection is also affected by parameter correlation. To select dominant parameters from a large set of candidate parameters, and to overcome the limitations of stepwise methods we applied an approach that combines information from classical stepwise logistic regression and elastic net logistic regression. Elastic net regression is based on mixed $\ell_1/\ell_2$-norm regularization of the parameter coefficients in the criterion function of the regression model at hand. This regularization aims to minimize the number of non-zero parameter coefficients in the estimated model. Given a certain output data *y* of length *N*, in the case of logistic regression the objective is to minimize the model deviance $D(y,\theta) = -2\big(\log\big(p(y|\theta)\big) - \log\left(p(y|\theta_s)\right)\big)$, where the vector $\theta$ contains the parameter coefficients and $\theta_s$ denotes the parameter vector of the saturated model. The formulation for the elastic net logistic regression problem is

$$\min_{\theta}\left(\frac{1}{N}D(y,\theta) + \lambda P_\alpha(\theta)\right), \text{ with}$$

$$P_\alpha(\theta) = \frac{(1-\alpha)}{2}\|\theta\|_2^2 + \alpha\|\theta\|_1.$$

The two regression tuning parameters are lambda ($\lambda$) and alpha (α). Lambda determines the strength of the regularization of the parameter coefficients, while alpha (a value between 0 and 1) controls the balance between penalizing either the $\ell_2$- and/or the $\ell_1$-norm of the coefficient vector(9).

Several steps of the parameter selection procedure are outlined in Figure 2. In the analysis shown there the set of parameters under investigation was the group of parameters computed on 1 lead in the frequency domain (DF, OI, SE and RHE). Figure 2a) and b) show the elastic net estimation result for a fixed value of alpha (alpha = 0.5). The choice of lambda influences the estimated parameter coefficients and the deviance of the estimated model. A commonly accepted choice for lambda is the value that corresponds to a model deviation that lies within 1 standard deviation

of the cross-validated minimum deviation. These lambda values are indicated with a green (minimum deviation) and a blue line (minimum deviation + 1 standard deviation). The choice of alpha also determines the number of parameters that are selected. For alpha = 1 the algorithm corresponds the Lasso algorithm, which tends to select one parameter from a group of correlated parameters, but for alpha values between 0 and 1, the elastic net algorithm will include more correlated parameters. Therefore a range of alpha (between 0.1 and 1) was investigated and for each value of alpha the non-zero parameter coefficients were stored (see Figure 2c)). Parameters that appeared in any of the models computed with this range of alpha were considered potential candidates for the final logistic regression model. In this case the parameters DF (on leads II, aVR and $V_4$), OI (leads I and III) and RHE (lead I) were selected. As an additional step, parameters were also selected through forward stepwise logistic regression ($P < 0.05$ for significant deviance improvement by adding a parameter). In this case selected parameters were DF (lead II), OI (III) and SE (I). The union of the parameters selected by the two regression methods was then taken to iterate over all possible combinations of parameters to find the model with the best prediction performance. Figure 2d) shows the result of this last step. The model performance increased by adding more parameters, but reached a maximum at a model containing 3 parameters (DF (II), OI (III) and SE(I)).

## Results

### Effect of time interval between echocardiography and CV attempt

In our analysis we included echocardiographic data that was collected within a year (365 days) of the date of the CV attempt. In this analysis we also included patients without an ECG or a poor quality ECG before the CV attempt (n=198). Results are

130 shown in Figure 3. From Figure 3a it becomes clear that the number of patients that
131 can be included in the analysis based on their echocardiographic data, initially
132 decreases slowly when we move from 365 days to a narrower timeframe. This
133 decrease accelerates when we reach 100 days as a cut-off value. The performance
134 of the best model containing only clinical parameters (weight and right atrial volume
135 (RAV)), shown in Figure 3b, remains relatively stable until 100 days, and then starts
136 to increase, but also becomes more irregular, due to the lower number of patients
137 included in the analysis. This observation is supported by examining the evolution of
138 the two clinical parameters forming the best performing model, as shown in Figure 3c
139 and 3d.

## Tables

**Table 1.** Significant single lead parameter differences and prediction AUC**.** Parameter values are reported as mean ± SD or median (interquartile range). AUC values are given as mean [95% confidence interval]. Parameter differences between patients with a successful and patients with an unsuccessful PCV were tested for normality (Lilliefors test) and compared using a standard 2-tailed unpaired t-test or a Mann-Whitney U-test if the test for normality failed.

| Parameter | Lead | Successful PCV | Unsuccessful PCV | P-value | AUC |
|---|---|---|---|---|---|
| Frequency domain | | | | | |
| DF (Hz) | II | 5.9 (1.0) | 6.3 (1.1) | < 0.001 | 0.66 [0.64-0.67] |
| Welch | III | 6.1 (0.7) | 6.3 (1.2) | 0.009 | 0.60 [0.58-0.62] |
| | aVR | 5.9 (1.2) | 6.3 (1.2) | 0.008 | 0.61 [0.59-0.62] |
| | aVF | 5.9 (1.0) | 6.3 (1.5) | 0.007 | 0.60 [0.59-0.62] |
| | $V_1$ | 6.3 (1.2) | 6.6 (1.6) | 0.027 | 0.59 [0.57-0.60] |
| RHE | I | 0.201 (0.155) | 0.166 (0.106) | 0.043 | 0.58 [0.56-0.60] |
| OI (%) | III | 57.8±17.7 | 53.1±19.7 | 0.020 | 0.59 [0.58-0.61] |
| SE | $V_6$ | 5.67 (0.67) | 5.83 (0.55) | 0.043 | 0.58 [0.56-0.59] |
| Time domain | | | | | |
| SAE | II | 0.317±0.046 | 0.341±0.055 | 0.001 | 0.63 [0.62-0.65] |
| | aVF | 0.323±0.060 | 0.345±0.061 | 0.010 | 0.60 [0.58-0.61] |
| FWP MAW | aVL | 0.0064±0.0018 | 0.0058±0.0018 | 0.021 | 0.59 [0.57-0.60] |
| FWA (mV) | II | 0.055 (0.024) | 0.051 (0.017) | 0.044 | 0.58 [0.56-0.60] |
| | III | 0.059 (0.024) | 0.053 (0.021) | 0.007 | 0.61 [0.59-0.62] |
| | aVL | 0.044 (0.016) | 0.040 (0.015) | 0.023 | 0.58 [0.57-0.60] |
| | aVF | 0.053 (0.024) | 0.048 (0.016) | 0.016 | 0.60 [0.58-0.61] |
| | $V_6$ | 0.038 (0.012) | 0.034 (0.010) | 0.018 | 0.59 [0.58-0.61] |

DF: Dominant Frequency; RHE: Relative Harmonic Energy; OI: Organization Index; SE: Spectral Entropy; SAE: Sample Entropy; FWA: Fibrillation Wave Amplitude; FWP MAW: Fibrillation Wave Power of the Main Atrial Wave;

**Table 2.** Significant multidimensional parameter differences and prediction AUC**.** Parameter values are reported as mean ± SD or median (interquartile range). AUC values are given as mean [95% confidence interval]

| Parameter | Leads or Signal | Successful PCV | Unsuccessful PCV | P-value | AUC |
|---|---|---|---|---|---|
| Frequency domain | | | | | |
| MDF (Hz) | $V_{(2,5)}$ | 6.0(1.0) | 6.3(1.3) | 0.008 | 0.61 [0.59-0.62] |
| Top 4 | $V_{(1,4,5)}$ | 6.0(1.3) | 6.8(1.5) | 0.003 | 0.62 [0.60-0.64] |
| (of 42) | $V_{(1,2,4,6)}$ | 6.0(1.3) | 6.5(1.4) | 0.001 | 0.63 [0.61-0.65] |
| | $V_{(1,2,4,5,6)}$ | 6.0(1.3) | 6.5(1.3) | 0.001 | 0.64 [0.62-0.66] |
| MOI (%) | $V_{(3,4)}$ | 50.6±8.7 | 47.6±6.9 | 0.015 | 0.60 [0.58-0.61] |
| Top 3 | $V_{(1,2,4)}$ | 53.8(10.2) | 51.2(10.0) | 0.005 | 0.61 [0.59-0.63] |
| (of 22) | $V_{(2,4,5,6)}$ | 41.6(8.0) | 38.9(6.2) | 0.005 | 0.61 [0.60-0.63] |
| MSE | $V_{(3,4)}$ | 6.37±0.39 | 6.49(0.34) | 0.046 | 0.59 [0.57-0.61] |
| SC (%) | All leads | 23.8(1.4) | 23.5(1.5) | 0.031 | 0.58 [0.56-0.60] |
| SV | All leads | 0.51(0.26) | 0.66(0.37) | 0.001 | 0.64 [0.62-0.66] |
| Time domain | | | | | |
| $k_{0.95}$ | AA | 4.8(0.8) | 5.0(0.8) | 0.033 | 0.58 [0.56-0.60] |
| | TQ | 3.2(0.6) | 3.4(0.4) | 0.050 | 0.57 [0.55-0.59] |
| MFWA | AA | 0.049(0.037) | 0.040(0.031) | 0.025 | 0.59 [0.57-0.60] |
| C | AA | 9.4(3.5) | 10.7(4.3) | 0.021 | 0.59 [0.57-0.61] |
| | TQ | 4.6±1.8 | 5.2±2.0 | 0.050 | 0.57 [0.55-0.59] |
| CV | AA | 2.5±1.0 | 3.0±1.5 | 0.005 | 0.58 [0.56-0.60] |
| | TQ | 2.8±1.2 | 3.2±1.3 | 0.076 | 0.57 [0.55-0.58] |

MDF/MOI/MSE: Multidimensional DF/OI/SE; SC: Spectral Concentration; SV: Spectral Variability; $K_{0.95}$, C: spatial complexity parameters; CV: Variability of spatial complexity; MFWA: Multidimensional FWA

158 **Table 3.** Predictive performance of clinical parameters and the added value of the
159 best performing single lead and multidimensional ECG parameters models, as
160 determined on the full data set (see Table 2).

| Parameter model | AUC on subset (n=139) | AUC Clinical & ECG Parameters | P-value (vs. combined) |
|---|---|---|---|
| Clinical parameters (Weight, RAV) | 0.68 [0.66-0.70] | N/A | N/A |
| Single lead Frequency domain | 0.75 [0.73-0.77] | 0.81 [0.79-0.82] | <0.001 (<0.001) |
| Single lead Time domain | 0.73 [0.71-0.74] | 0.77 [0.75-0.78] | <0.001 (<0.001) |
| Multiple leads Frequency domain | 0.73 [0.71-0.74] | 0.77 [0.75-0.78] | <0.001 (<0.001) |
| Multiple leads Time domain | 0.59 [0.57-0.61] | 0.67 [0.65-0.68] | 0.289 (<0.001) |
| Best ECG model | 0.78 [0.76-0.79] | 0.78 [0.76-0.80] | <0.001 (0.473) |

161 P-values denote the comparison between the area under the receiver operating
162 characteristics curve (AUC) of the model consisting of only clinical parameters and
163 the specific combination. P-values between brackets signify the difference between
164 the model consisting of ECG parameters and the combined model of clinical (weight
165 and right atrial volume (RAV)) and ECG parameters.

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## Figures

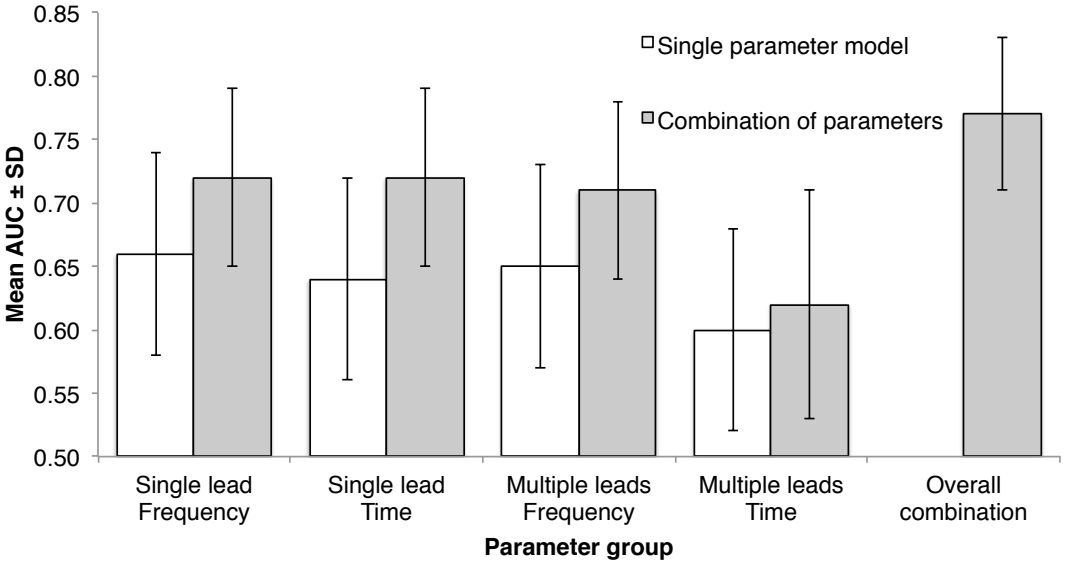


Figure 1. Prediction performance of different types of complexity parameters computed on one lead and multiple leads, in the frequency-domain and the time-domain. Performance is expressed as the mean area under the receiver operating characteristic curve (AUC)± standard deviation (SD) for each of the 4 groups (parameter computed in the frequency/time-domain and on one/multiple leads). For every group the best performing single parameter model AUC is given, as well as AUC of the best combination of parameters belonging to the same group.

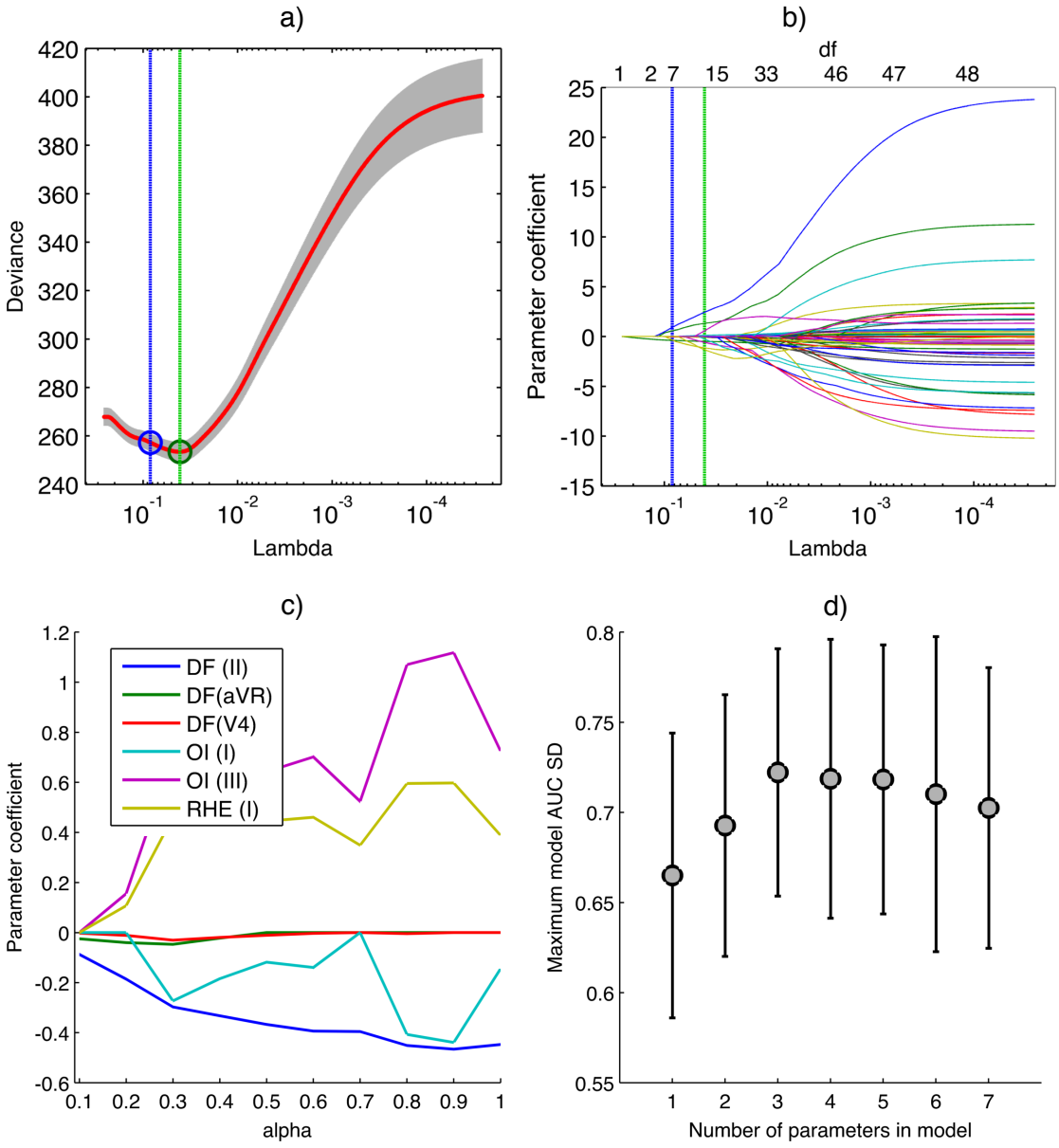


Figure 2. Parameter selection via elastic net logistic regression (parameters computed on a single lead, frequency-domain). The upper plots show the result of the analysis for alpha=0.5, with in a) the cross-validated deviance as a function of lambda and in b) the parameters coefficients (df indicates the number of non-zero parameter coefficients). The green line/circle marks the choice of lambda that minimizes the deviance, the blue line/circle marks the solution that is within 1 standard deviation. Panel c) shows the non-zero parameters coefficients selected by the elastic net regression as a function of alpha. Panel d) contains the result for the cross-validated maximum AUC for models composed of a specific number of

candidate parameters, defined by union of the stepwise regression and elastic net parameter selection.

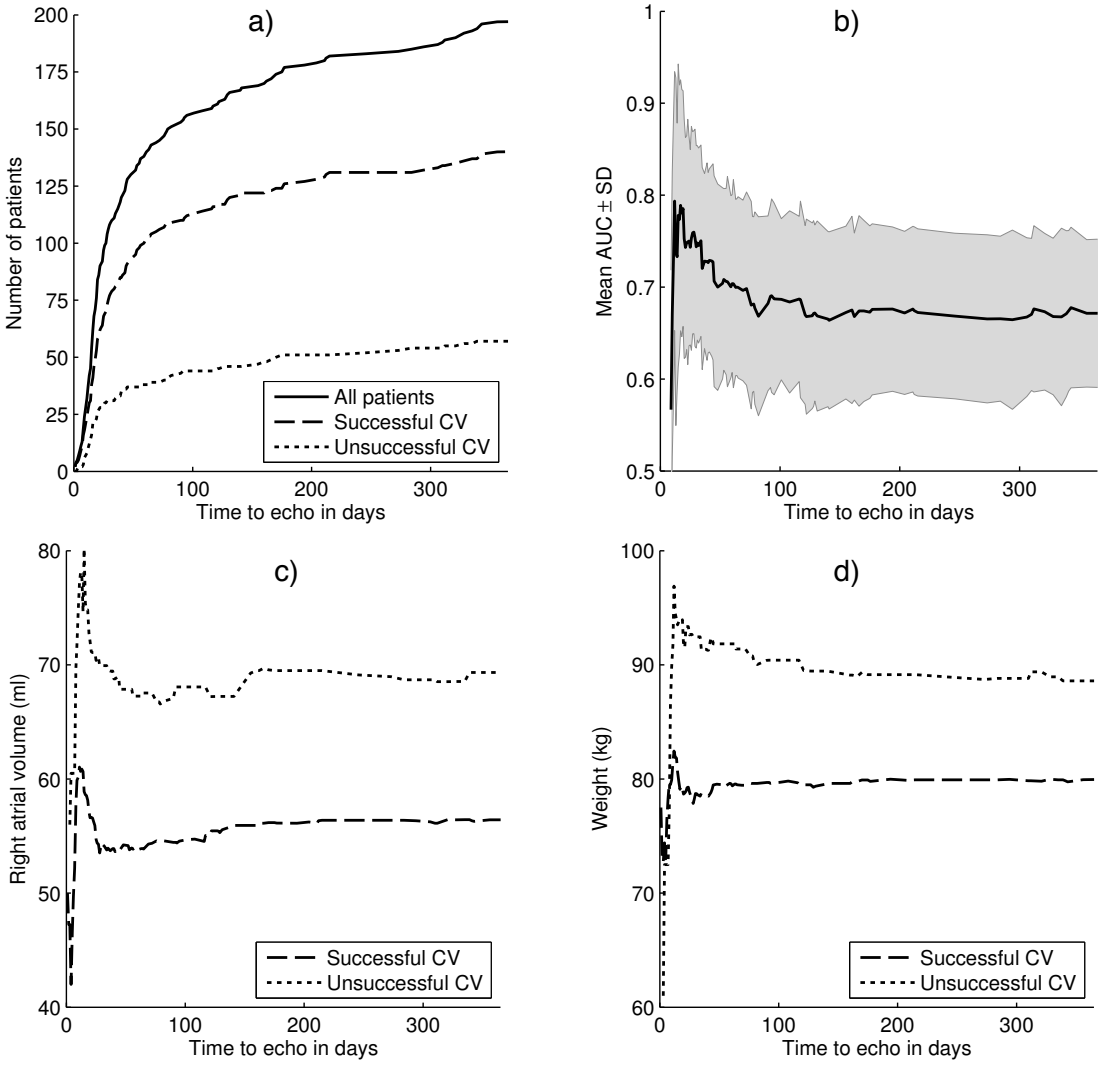


Figure 3. The effect of maximum allowed time difference between the date of cardioversion and the closest date of an echocardiography on (a) the number of patients included in the analysis, (b) prediction performance of the best performing model containing clinical parameters weight and right atrial volume (RAV), (c) differences in patient RAV (successful and unsuccessful CV), and (d) differences in patient weight.

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