Supplemental Material

Personalized monitoring of electrical remodelling during atrial fibrillation progression via remote transmissions from implantable devices

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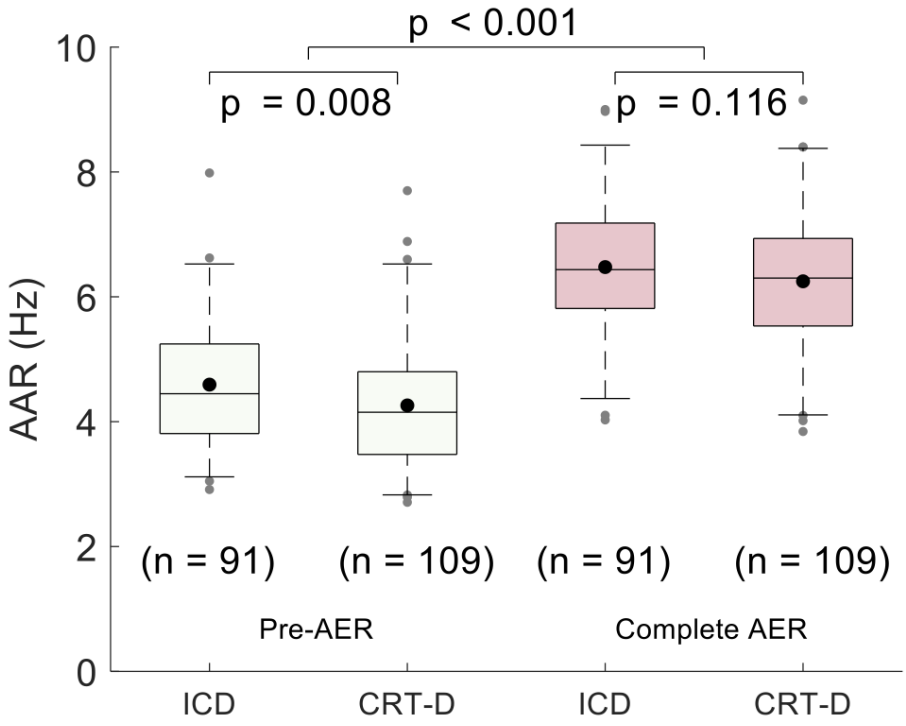
Supplemental Material

ICD/CRT-D database

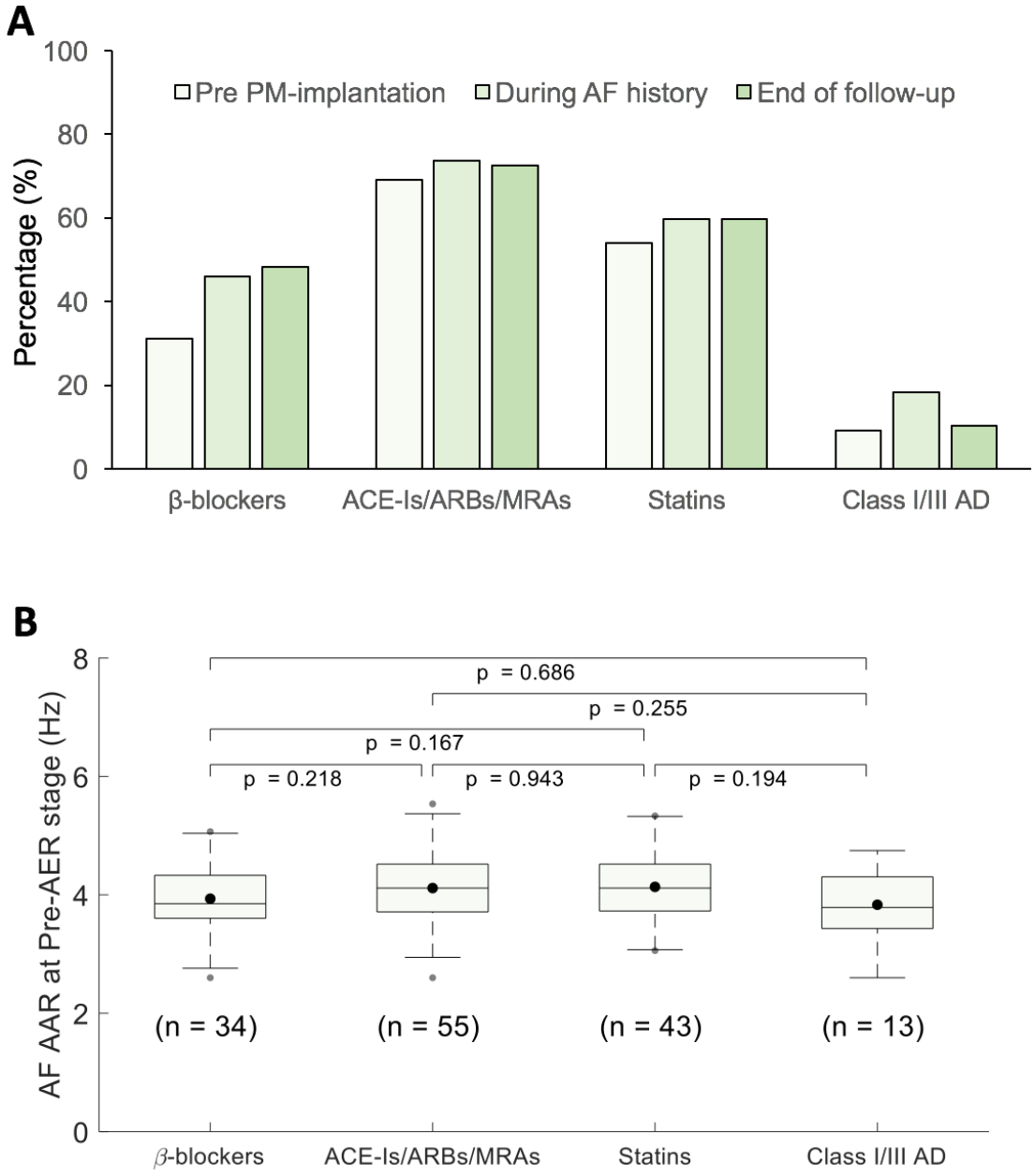
The Scientific COOperation Platform (SCOOP) is a Spanish cloud based big-data tool for generating cooperative knowledge in the field of cardiac implantable devices.[1, 2] The main property of SCOOP is its capability for remote monitoring and digital signal acquisition. The follow-up of each patient was incorporated into a database within an observational research study (UMBRELLA), ensuring the legal, normative, and scientific data exploitation. Clinical baseline and demographic data were retrospectively collected at the time of device implantation using the official data collection sheet from the Spanish Society of Cardiology: "http://secardiologia.es/images/stories/file/arritmias/registros-arritmias-hoja-datos-dai.pdf".

In this study we included 4618 patients undergoing a Medtronic implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy plus defibrillator (CRT-D) implantation, from August 2011 to November 2017. The following Spanish hospitals participated in the study:

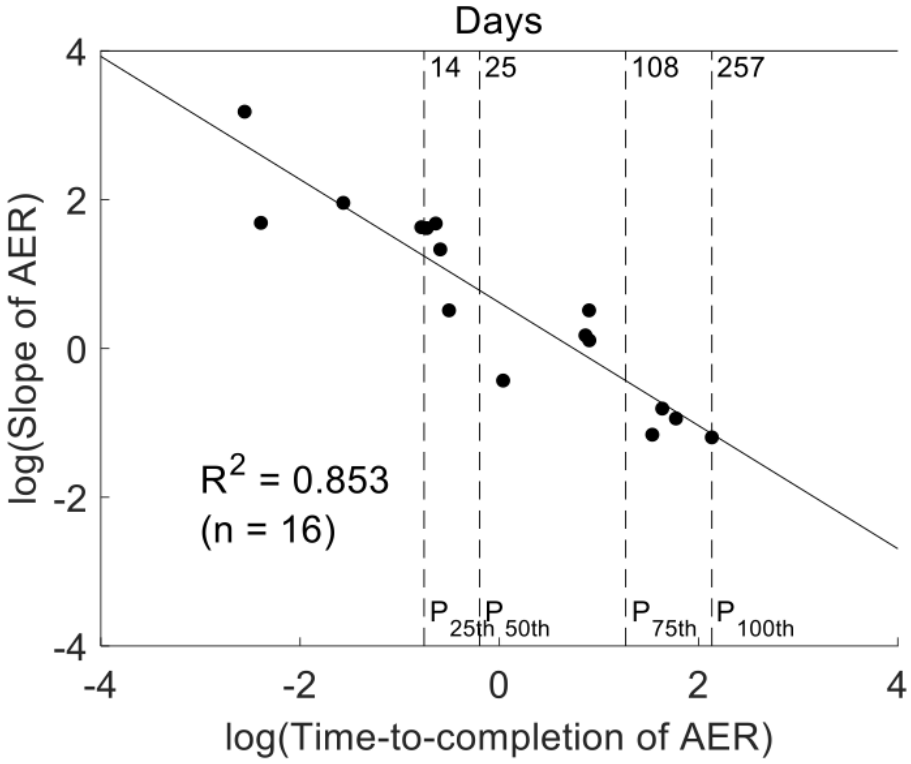
Hospital Clínico Universitario San Carlos, Hospital General Universitario de Ciudad Real, Hospital Universitario Puerta de Hierro-Majadahonda, Hospital Universitario de la Fe, Hospital de la Santa Creu i Sant Pau, Hospital General Universitario Guadalajara, Hospital General Universitario Alicante, Hospital Universitario Virgen de la Arrixaca, Hospital Virgen de la Victoria, Hospital Infanta Cristina, Hospital Universitario de Canarias, Hospital Virgen de las Nieves, Hospital Universitario Insular de las Palmas, Hospital Ntra. Señora de la Candelaria, Hospital Clínic de Barcelona, Hospital Universitario la Paz, Hospital San Juan de Alicante, Hospital de Cruces, Hospital Reina Sofía de Córdoba, Hospital Universitario Marqués de Valdecilla, Hospital Universitario Araba, Hospital Ntra. Señora de Valme, Hospital Universitario 12 de Octubre, Hospital de Donostia, Hospital General Universitario Gregorio Marañón, Hospital Infanta Leonor, Hospital San Pedro de Alcántara, Hospital Son Llátzer, Hospital Universitario Central de Asturias, Hospital de Basurto, Hospital Galdakao-Usansolo, Hospital Universitario Joan XXIII, Hospital General de Valencia, Hospital Universitario Virgen Macarena, Hospital Clínico de Valladolid, Hospital de Elche, Complejo Hospitalario Torrecárdenas, Hospital Universitario Burgos, Complejo Hospitalario Universitario de A Coruña, Hospital de Navarra, Hospital de Bellvitge, Hospital Trias i Pujol, Complejo Hospitalario Universitario de Vigo, Hospital Ramón y Cajal, Hospital del Ribera-Alzira, Complejo Universitario Asistencial de León, Hospital General Universitario Reina Sofía de Murcia, Hospital Ramón Méndez, Hospital Virgen de la Salud de Toledo, Hospital Clínico Universitario de Santiago de Compostela.



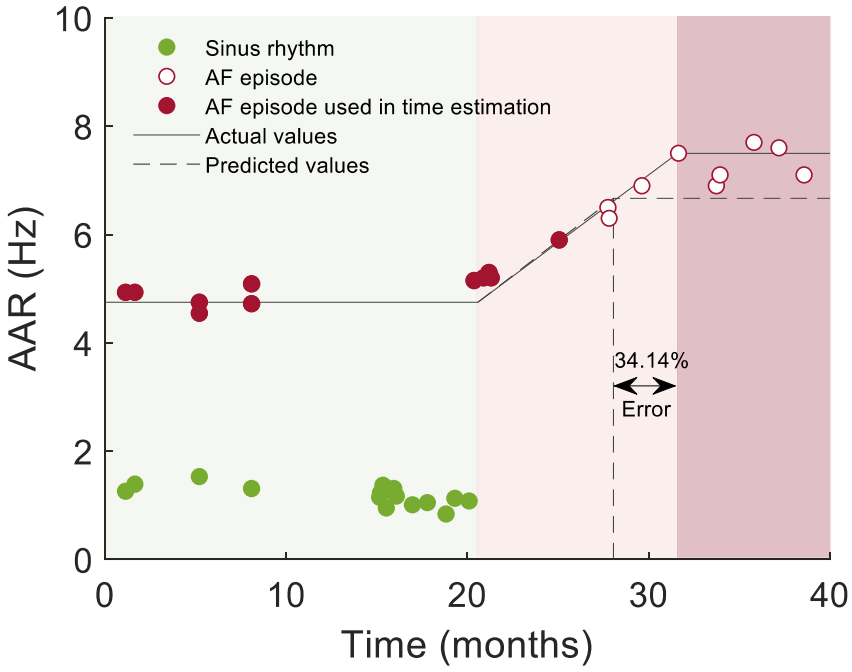
Supplemental Figure 1. Atrial activation rate comparisons among specific subsets of the study. Blox plots and comparisons of atrial activation rate (AAR) between patients with ICD and CRT-D devices. ICD/CRT-D: implantable cardioverter defibrillator+/- resynchronization therapy.



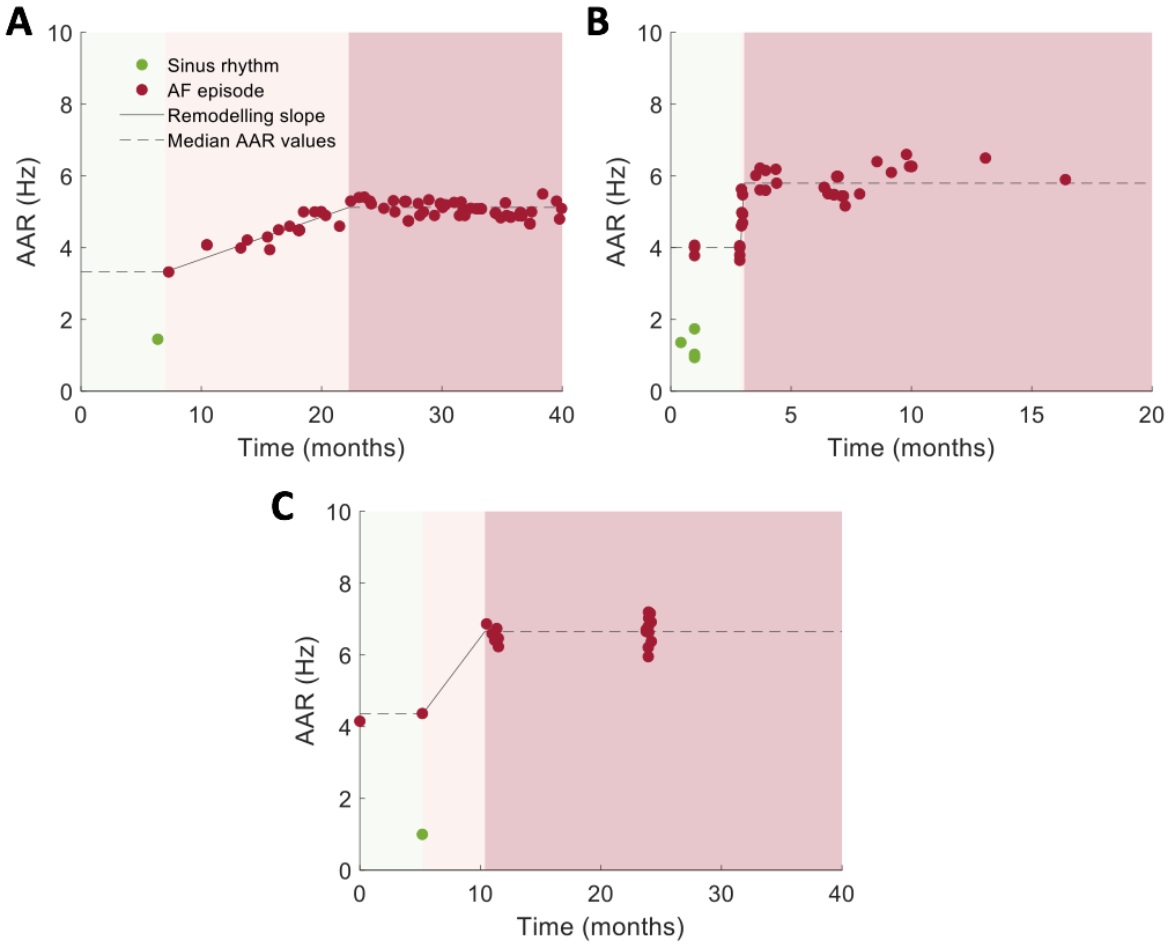
Supplemental Figure 2. Pharmacological therapy in patients with pacemaker and effects on atrial activation rate. A, Percentage of patients with upstream therapies and antiarrhythmic drugs (AD) in the pacemaker (PM) population (N=87). **B,** Blox plots and comparisons of atrial activation rate (AAR) among different pharmacological therapies. ACE-Is: angiotensin-converting-enzyme inhibitors. AER: atrial electrical remodelling. AF: atrial fibrillation. ARB: angiotensin-receptor blockers. MRAs: mineralocorticoid receptor antagonists.



Supplemental Figure 3. Log(slope) correlation with log(time-to-completion AER) in patients with pacemaker. AER: atrial electrical remodelling.



Supplemental Figure 4. Sample case with estimation of time-to-completion of atrial electrical remodelling. Estimation of time-to-completion of atrial electrical remodelling (AER) requires: (1) the median atrial activation rate (AAR) during paroxysmal AF episodes (early stages of AER), (2) the predicted AAR after completion of the electrical remodelling process, and (3) the computed slope at 25% of the expected change in AAR from paroxysmal AF to complete AER in persistent AF. In this case the actual progression of AER is represented with the continuous line. The oblique and horizontal dashed lines show the estimated progression of AER. Red dots indicate median AAR values during the AF episodes used to estimate the time-to-completion of AER. White dots indicate actual AAR values during AF episodes that are not used to estimate the time-course of AER. Green dots indicate AAR during sinus rhythm. Error quantifications of the predicted and actual time-to-completion of AER are shown between the vertical dashed line and the actual completion of AER (end of the pink light background colour). Early stages of AER are indicated with a light green background colour. Complete AER in persistent AF episodes is indicated with a red light background colour. AF: atrial fibrillation.



Supplemental Figure 5. Representative cases of atrial electrical remodelling progression as atrial fibrillation evolves. A and **B,** Sample cases from the ICD/CRT-D population using stored atrial fibrillation (AF) episodes and remote transmissions. In **A,** Time-course of atrial activation rate (AAR, red dots) during AF progression from early stages of electrical remodelling in paroxysmal AF (light green background colour), to completion of atrial electrical remodelling (AER) in persistent AF (red light background colour). Pink light background indicates the electrical remodelling period, which was gradual at 0.11 Hz/moth. In **B,** Representative case of fast progression (12.02 Hz/month) of AER. C, Sample case from the pacemaker population using only stored AF episodes. In patients with pacemakers is also evident the differences in AAR from paroxysmal to persistent AF episodes after completion of AER. Green dots indicate the AAR of sinus rhythm tracings. ICD/CRT-D: implantable cardioverter defibrillatosr+/- resynchronization therapy.

Supplemental Table 1. Univariate analysis of variables potentially associated with time-to-completion of atrial electrical remodelling.

Clinical characteristics	No	Yes	p-value / R^2
Age			0.248 / 0.007
Male, n (months)	22 (1.84)	178 (3.35)	0.152 / -
Cardiomyopathy, n (months)			0.394 / -
ICM		101 (3.63)	
DCM		68 (2.13)	
Other SCM: HCM, ARVC, VHD, or		29 (3.39)	
Non-structural arrhythmogenic disease		2 (3.99)	
LBBB, n (months)	116 (3.61)	84 (2.13)	**0.036** / -
LVEF (≤35%), n (months)	53 (3.21)	147 (2.98)	0.757 / -
Functional class, n (months)			0.782 / -
NYHA I		30 (3.76)	
NYHA II		80 (3.50)	
NYHA III		67 (2.21)	
NYHA IV		2 (2.78)	
Clinical history, n (months)			
Hypertension	76 (2.49)	120 (3.44)	0.259 / -
Diabetes mellitus	143 (3.01)	57 (3.24)	0.871 / -
Hyperlipidaemia	90 (3.19)	110 (2.95)	0.864 / -
Current smoking	131 (3.14)	53 (3.48)	0.614 / -
Chronic renal failure	151 (3.01)	44 (3.57)	0.449 / -
Previous stroke or TIA	167 (3.40)	16 (1.55)	0.064 / -
Clinical presentation, n (months)			
Asymptomatic	106 (3.72)	92 (2.26)	0.123 / -
Syncope	166 (3.30)	32 (2.35)	0.731 / -
Sudden cardiac death	183 (3.14)	15 (3.72)	0.931 / -
Primary prevention, n (months)	57 (3.75)	143 (2.49)	0.112 / -
Device type (ICD), n (months)	109 (2.79)	91 (3.24)	0.929 /-
AAR during Paroxysmal AF			0.002 / 0.584

Data are shown as the number of patients (n) and the median time-to-completion of atrial electrical remodeling (in months). AAR: atrial activation rate. AF: atrial fibrillation. ARVC: arrhythmogenic right ventricular cardiomyopathy. CHD: congenital heart disease. DCM: non-ischemic dilated cardiomyopathy. ICD: implantable cardioverter defibrillator. ICM: ischemic cardiomyopathy. HCM: hypertrophic cardiomyopathy. LBBB: left bundle branch block. LVEF: left ventricular ejection fraction. SCM: structural cardiomyopathy. TIA: transient ischemic attack. VHD: valvular heart disease.

Supplemental References

[1]Lillo-Castellano JM, Marina-Breysse M, Gomez-Gallanti A, Martinez-Ferrer JB, Alzueta J, Perez-Alvarez L, et al. Safety threshold of R-wave amplitudes in patients with implantable cardioverter defibrillator. *Heart* 2016; 102: 1662-70.
[2]Fontenla A, Lopez Gil M, Martinez Ferrer J, Alzueta J, Fernandez Lozano I, Vinolas X, et al. Clinical profile and incidence of ventricular arrhythmia in patients undergoing defibrillator generator replacement in Spain. *Rev Esp Cardiol* 2014; 67: 986-92.