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PROMISE

IMPACT OF REMOTE MONITORING AND ATRIAL HIGH RATE EPISODES ON OUTCOME OF PATIENTS WITH CARDIAC IMPLANTABLE ELECTRONIC DEVICES (SSD MED/11)

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1. INTRODUCTION

The prevalence of heart failure (HF) is continuously increasing in Western countries and it is estimated to reach eight million people in the United States by 2030.

The natural history of the disease implies the occurrence of frequent hospitalizations due to episodes of heart failure with a considerable and continuously growing economic-health cost (1-2).

For this reason, several attempts have been made over the years to improve the monitoring of these patients in order to immediately intercept the phases of decompensation through an early diagnosis of signs and symptoms of worsening, reducing the need for any hospitalization. (3-4).

In this context, the possibility of transmitting data remotely via telemedicine systems represents one of the most innovative technologies for the management and treatment of these patients.

Telemonitoring options range from the simple transmission to an operations center (usually a cardiology department) of some vital parameters such as body weight, blood pressure and heart rate, to the most advanced chest impedance measurement systems integrated in

modern cardiac implantable electronic device (CIEDs) such as pacemakers and defibrillators (5-6).

Studies supporting this new approach have been developed over the last few years and have shown significant benefits in terms of reducing the frequency of new hospitalizations, with a significant impact on quality of life, morbidity and mortality (7).

According to these results, these strategies have proven to be effective and economical, but their diffusion is still burdened by logistical problems that require a new integrated approach to the clinical evaluation of patients with HF, still based on periodic visits (8).

Moreover, nowadays, many parameters can be collected by remote monitoring (RM) systems and all of them can provide different information to clinician.

The role of this PhD project is therefore to evaluate the effective advantage of telemedicine in the follow-up of patients with HF in terms of outcome and management, focalizing the attention on particular events that can be recorder by CIEDs and defined as atrial high rate episodes (AHRE).

1.1 HEART FAILURE

Heart failure is a complex clinical syndrome resulting from impairment of ventricular filling or ejection of blood associated with symptoms of dyspnoea, fatigue, and peripheral and/or pulmonary oedema. (9) Although significant innovations in medical and device treatments in recent decades, the incidence of heart failure is increasing with an estimation of more than 23 million people worldwide (10-11). This condition impact on quoad vitam and quoad valetudinem prognosis, imposing heavy costs on the health care system.

The syndrome of heart failure is commonly divided into 2 categories: heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Although past literature and guidelines have proposed different definitions of HFrEF, (9-12-13) the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Task Force currently defines it as heart failure with an ejection fraction (EF) of no more than 40%.

The clinical course of heart failure is progressive but nonlinear, characterized by worsening quality of life despite increasing levels of care (14) (Fig. 2). Early in the syndrome, the diagnosis of heart failure

is established, and there is a period of initiation and titration of evidence-based pharmacologic and, when appropriate, implantation of electrical therapies to prevent sudden death and resynchronize ventricular contraction. Following this stage, there is often improvement leading to a stage of stability lasting months to years. However, as the disease progresses, functional status declines, resulting in multiple admissions for heart failure, which originally responds to therapy but ultimately becomes advanced and refractory to treatment (Figure 1).

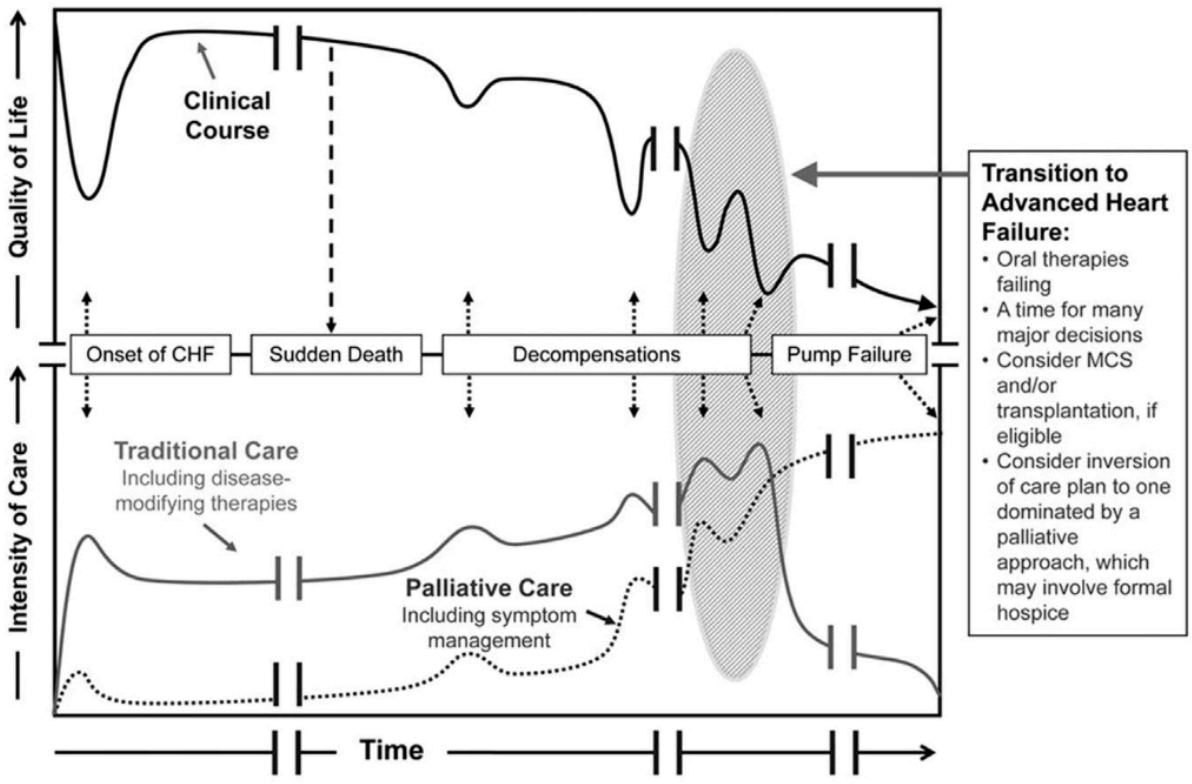

Figure 1. Natural history of Heart Failure

Before clinical symptoms become evident, patients may present with asymptomatic cardiac abnormalities, both structural and functional (left ventricular systolic and / or diastolic dysfunction), precursors of HF. The recognition of these precursors is important because they are related to bad prognosis and because they allow an early therapy. Most patients have a history of hypertension, coronary artery disease, cardiomyopathy, or valvular heart disease.

Ischemic heart disease is considered the most important risk factor for HF.

It is estimated that in the 7-8 years following an MI, more than a third of patients will develop the disease, especially those who showed left ventricular dysfunction at the time of the ischemic attack.

Considering pathophysiology, the deleterious action of the various risk factors on the myocardium progressively leads to an alteration of cardiac function, with important consequential haemodynamic modifications. The biomechanical principle governing cardiac function is the relationship between the degree of pressure present in the cardiac cavities, myocardial contractility and circulating blood volume. Reduced contraction of the left ventricle initially causes a reduction in stroke volume and incomplete filling of the ventricle. As a consequence, the end-diastolic volume increases and muscle fibers

stretch which, according to the Frank-Starling principle, lead to a more energetic contraction with an increase in stroke volume. The Frank-Starling mechanism is the most immediate mechanism to act, but it is also destined to fail over time, with a consequent reduction in systolic stroke and ejection fraction.

The reduction in EF is the parameter that most correlates with mortality and in particular with sudden cardiac death (SCD) that represents the most frequent cause of death in this population and occurs 6 to 9 times more frequently in this population than in the general one. Sudden cardiac death is the cause of death in 30%–50% of people with heart failure.

Regarding therapy, in patients with HF associated with systolic dysfunction (LVEF ≤35-40%) the use of ACE inhibitors (or ARBs in case of intolerance), beta-blockers and mineralocorticoid receptor antagonist (MRA) are the gold standard of treatment considering that these drugs reduce all-cause mortality and SCD. ACE inhibitors result in a 15-25% reduction in all-cause mortality and are recommended in all patients with reduced LVEF. Beta-blockers reduce mortality by about 35%, possess anti-ischemic properties that translate into specific antiarrhythmic effects and, in particular, reduce the incidence of sudden death. MRAs not only reduce mortality but also reduce the

incidence of sudden death in patients with HF being treated with ACE inhibitors and beta-blockers. In the most recent trial evaluating the use of eplerenone, 20% of patients were also carriers of an implantable device (ICD or CRT), but the drug was equally effective in patients who received or did not receive device therapy. . The favourable effects of MRAs on the incidence of SCD in patients with LV systolic dysfunction were confirmed by a meta-analysis of 6 studies, in which patients treated with MRA showed a 23% lower risk of SCD than control subjects. Diuretics and digoxin are still used in many patients with HF, although they are not associated with a reduction in all-cause mortality or SCD rates. The addition of ivabradine is indicated in those patients with heart rate persistently above 70 bpm despite maximal therapy with beta-blockers. Amiodarone has no effect on the outcome of patients with HF and, given its high toxicity, it is not generally recommended in this population. However, in the case of patients with HF who develop symptomatic ventricular tachyarrhythmia (e.g. those receiving recurrent ICD shocks or suffering from symptomatic unsustained VA), amiodarone is the preferred antiarrhythmic agent. Other antiarrhythmic drugs are not recommended in patients with HF due to concerns about their safety. An important innovation in the field of drug therapy for HF was the

recent introduction in the guidelines of ARNI (angiotensin receptor neprilysin inhibitor), a new class of drugs that act at the level of the RAAS and on the neutral endopeptidase system, combining an ARB (valsartan) and a neprilysin inhibitor (sacubitril). Administration of this drug is recommended as a replacement for an ACE-I or ARB in symptomatic patients despite optimized therapy and EF ≤ 35%.

Patients treated pharmacologically are however exposed to the risk of SCD on an arrhythmic basis. The implantation of a cardiac defibrillator (ICD) in association with optimized medical therapy reduces the risk of SCD in patients with reduced EF regardless of the etiological basis, as it is capable of delivering electrical therapies on sustained, potentially fatal, ventricular arrhythmias. The guidelines recommend the implantation of this device in both secondary and primary prevention, especially in symptomatic patients in NYHA II-III class and EF ≤ 35% after at least 3 months of optimized medical therapy.

Resynchronization therapy (CRT) is recommended in symptomatic patients, with a QRS ≥ 130 ms, left bundle bundle block morphology, and an EF ≤ 35% despite optimized medical therapy. CRT has been shown in responding patients to improve cardiac performance,

promote reverse remodelling and reduce symptoms, morbidity and mortality.

Two large trials have provided data on the use of the ICD for the primary prevention of SCD in patients with HFrEF: the SCDHeFT (Sudden Cardiac Death in Heart Failure Trial) and the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II). In the SCD-HeFT, the use of the ICD was associated with a reduction in the risk of death of 23% and an absolute reduction in mortality of 7% at 5 years (from 29% to 22%). A 60% reduction in sudden death events was documented in the ICD implant arm. The effects on all-cause mortality based on the ischemic or non-ischemic aetiology of HF were similar, while differences emerged in relation to NYHA class, where ICD therapy proved extremely effective in class II patients but not resulted in apparent benefits in terms of mortality in class III patients.

In MADIT-II, a 31% reduction in all-cause mortality was observed in patients who received an ICD, and at a later study review, the favourable effects of ICD therapy were time-dependent, with greater benefit in patients who had experienced a first myocardial infarction longer after randomization. In the DEFINITE (Defibrillator in Non-Ischemic Cardiomyopathy Treatment Evaluation) study, a reduction in mortality was observed in the ICD therapy group, accompanied by a

significant reduction in SCD. Similarly, in a meta-analysis conducted by Desai et al., which included 5 primary prevention studies for a total of 1,854 patients with HF of non-ischemic origin, the use of the ICD was associated with a reduction in total mortality of 31%. ICD therapy is not recommended in patients with terminal HF (NYHA class IV) and in those with a life expectancy of <1 year. There are currently no randomized controlled clinical trials that have demonstrated the utility of the ICD in asymptomatic patients (NYHA class I) with systolic dysfunction (LVEF ≤35-40%) or in patients with HFpEF (LVEF> 40-45%)therefore, primary prevention ICD therapy is not recommended in these categories of patients. There are no data from randomized studies to support the use of the ICD in NYHA class IV patients, but it is generally agreed that ICD therapy is not recommended in patients with severe and refractory symptoms, candidates for CRT, ventricular assist device implantation or heart transplant.

However, the situation may be different for NYHA IV outpatients who are on the list for heart transplant, as waiting times are often at least 1 year and the risk of sudden death is high.

Two large randomized controlled trials [COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) and CARE-HF (Cardiac Resynchronization - Heart Failure)], conducted in

patients with moderate-to-severe HF (NYHA III-IV) in sinus rhythm, have shown that CRT is effective in reducing morbidity and mortality in this population. The COMPANION enrolled patients with HFrEF and a duration of QRS ≥120 ms; compared to patients on optimized medical therapy, those treated with CRTP showed a trend towards a reduction in all-cause mortality, while a 36% reduction was observed in those undergoing CRT with function of defibrillator (CRT-D). In this study, CRT-D treatment also resulted in a reduction in SCD.

In CARE-HF, that also involved patient with a QRS duration ≥120 ms, CRT-P therapy was associated with a 36% reduction in all-cause mortality. In a report with long-term CARE-HF data (mean follow-up of 37 months), CRT-P also resulted in a 46% reduction in sudden death, accompanied by a 40% reduction in total mortality. COMPANION and CARE-HF both provided solid evidence to support the use of CRT (both CRT-P and CRTD) in patients with HFrEF and moderate-severe symptoms with enlarged QRS, particularly in those with BBS morphology. Several other studies and registries, as well as a meta-analysis, have evaluated the response to CRT based on QRS morphology, almost always concluding that a QRS morphology to BBS identifies a category of patients who benefit most from this therapy. In the Medicare ICD Registry, which included

14,946 patients, CRT-D therapy was not effective in patients with right bundle branch block (BBD), as evidenced by an increase in 3-year mortality in patients with BBD compared to those with BBS. The REVERSE study (Resynchronization Reverses Remodelling in Systolic Left Ventricular Dysfunction) confirmed a reduction in the incidence of the composite clinical endpoint only in patients with BBS, reporting a lack of benefit in patients with non-BBS QRS morphology. Similarly, the MADIT-CRT study showed a reduction in the primary endpoint in patients with QRS morphology to BBS but not in those with non-BBS morphology. It should also be noted that the risk of VT / VF and mortality was significantly lower only in patients with BBS.

A recent long-term analysis conducted in patients enrolled in MADIT-CRT confirmed at a follow-up of 7 years that the survival benefit of CRT-D was found in patients with BBS morphology but not in those with non-BBS morphology in which, on the contrary, CRTD had been shown to be harmful in some cases. From the analysis of RAFT study (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial), CRT was found to be more effective in patients with BBS-type morphology than in non-BBS. In a recent and extensive meta-analysis of 6 RCTs [COMPANION, CARE-HF, MADIT-CRT, MIRACLE

(Multicentre InSync Randomized Clinical Evaluation), RAFT and REVERSE], which included a total number of 6,914 participants (of which 1,683 with QRS non-BBS), CRT was not associated with a reduction in mortality and / or hospitalizations for HF in patients with non-BBS morphology. The presence of wide QRS with non-BBS morphology therefore remains an area of uncertainty in the context of CRT. As for patients with atrial fibrillation, the success of CRT depends mainly on the effectiveness of biventricular stimulation, which in many patients is achieved only by ablation of the AV junction. In summary, CRT can be considered in patients with HF, permanent AF and LVEF ≤35% when (a) ventricular pacing is required or otherwise the patient meets the selection criteria for CRT and (b) CRT in association ablation of the AV junction or rhythm control drug therapy allows obtaining a biventricular stimulation close to 100%. Ablation of the AV junction must be considered in the case of incomplete biventricular pacing.

Two controlled trials randomized 3,618 patients with mild HF to optimized medical therapy associated with ICD or CRT-D. The MADIT-CRT study enrolled 1,820 patients with mild symptoms (NYHA class I / II), LVEF ≤30%, and a QRS duration ≥130 ms. In the first report, a 34% reduction in the primary endpoint of death from all

causes or events of HF was documented; in a subsequent long-term analysis (mean follow-up of 7 years), treatment with CRT-D was associated with a significant reduction in mortality compared to therapy with ICD alone, however limited only to patients with BBS in baseline conditions, while no benefit was observed in those without BBS. The RAFT study enrolled 1,798 patients with mild-to-moderate HF (NYHA class II / III), LVEF ≤30%, and a QRS duration ≥120 ms (or ≥200 ms if electro-induced). Compared to patients randomized to ICD only, the CRT-D group showed a 25% reduction in the risk of mortality from any cause, thus providing for the systematic use of CRT in patients with mildly symptomatic HFrEF.

1.2 ATRIAL HIGH RATE EPISODES

Atrial high rate episodes (AHRE) are a form of atrial tachyarrhythmia. Over the years, they have aroused increasing interest from the scientific community and several studies have tried to understand the mechanisms that determine them and their prognostic role. The AHRE do not have official guidelines that give a universally recognized definition, therefore they still represent a reality to be defined in a complete and exhaustive way. However, many studies have led to an enrichment of the scientific literature in this regard, bringing us ever closer to a more precise definition from an epidemiological, prognostic point of view and any indications on their management. The studies on AHREs concern their possible association with thromboembolic events, as well as with atrial fibrillation. The correlation of AHRE with different clinical outcomes has been studied in several clinical trials over the last few years.

AHREs are "episodes of tachyarrhythmia of atrial origin characterized by a frequency of at least 190 beats per minute and identified by means of an implantable cardiac device" (15).

The definition reported is one of the most complete, and was developed by the European Heart Rhythm Association (EHRA) and

published in 2017, and was approved by the Heart Rhythm Association (HRS), the Asia Pacific Heart Rhythm Society (APHRS) and the Sociedad Latinoamericana de Estimulatìon Cardìaca y Electofisiologìa (SOLEACE).

AHREs are an asymptomatic phenomenon in most cases, they are identified and diagnosed only by means of implantable cardiac devices such as: pacemakers (PM), implantable cardiac defibrillators (ICD Implantable Cardioverter-Defibrillator) and devices for Cardiac Resynchronization therapy (Cardiac Implantable Electronic Device, CIED). For the recording of the event, the presence of an electrode in the atrium is required. The implantable devices continuously record the heart rhythm, and are able to memorize spontaneous episodes of tachyarrhythmia according to specific programmable algorithms, making it possible for the clinician to view the arrhythmia, the latter necessary in order to exclude false positives. The algorithm often varies in relation to the manufacturer of the device, this is due to the fact that even today there is no definitive and unambiguous definition of AHRE. The majority of devices are set to record an arrhythmia when the heart rate exceeds a threshold value of 175-220 bpm, moreover the event must have a duration equal to a minimum of

consecutive beats, or must be maintained for a certain time period (16).

AHREs represent a large and heterogeneous entity not totally similar to atrial fibrillation. In order to clarify the reported definition of AHRE, it is necessary to highlight the differences between the latter and atrial fibrillation in its clinical, subclinical and silent form.

AHREs are episodes of high atrial rate, so the term AHRE includes several types of atrial tachycardia such as flutter, subclinical atrial fibrillation, and atrial tachycardia (17).

Clinical atrial fibrillation has a much higher burden than AHRE and therefore can be diagnosed using less sensitive methods such as ECG. The AHREs have a much lower burden, from a few minutes to a few hours per year: the longest episode lasted only 3.6 hours (18), and was recorded through continuous and prolonged monitoring of patients enrolled in the ASSERT trial.

Furthermore, it should be noted that not all the episodes recorded by the device are really AHRE, because the episodes recorded automatically by the device in 20% of cases turn out to be false positives. Only manual review of the ECGs recorded by the device allows us to diagnose specific arrhythmias.

Furthermore, AHREs differ from atrial fibrillation also as regards the prognosis and the risk of thromboembolic events associated with them.

AHREs involve an increased thromboembolic risk that is 2-2.5 times higher in subjects with AHRE compared to those who do not have them. The absolute risk associated with them is however much lower than what is instead determined by atrial fibrillation (19).

Subclinical atrial fibrillation consists of high-frequency atrial episodes lasting a minimum of 6 minutes and a maximum of 24 hours. It is asymptomatic and is evidenced by the implantable cardiac device. Patients diagnosed with subclinical atrial fibrillation generally do not have a previous diagnosis of atrial fibrillation. AHREs lasting more than 24 hours should be considered as "otherwise documented" atrial tachyarrhythmia (TA / FLA / AF) episodes (15).

Silent atrial fibrillation (SAF) is instead given by those episodes of AF documented in the absence of any symptoms or previous diagnosis. It manifests itself with a complication such as ischemic stroke, heart failure, etc.

Defining the actual prevalence of AHRE is currently difficult.

One of the main reasons that make the prevalence underestimated is the fact that AHREs are asymptomatic in almost all cases.

Furthermore, the diagnosis is mainly made only in subjects with an implantable cardiac device and therefore they cannot be found and diagnosed in the rest of the population.

The real incidence is variable in relation to various factors such as clinical profile of the population studied, specific algorithm used to identify them, duration, indication of the device's implant and follow up.

For this reason it is not possible to identify a stable incidence, but we can say that this fluctuates between 30-70% in subjects with cardiac devices recruited in the various trials (17).

In any case, the incidence of AHRE is lower than clinical relevant forms of atrial tachyarrhythmia (20)

Several studies have tried to detect the incidence of AHRE: the ASSERT study (a prospective and multicenter study) recruited 2451 patients with an average age of 77 ± 7 years, hypertensive but without a history of atrial fibrillation. Patients were followed up for 2.5 years. It was found that 10.1% of the population studied developed an episode of AHRE during the first 3 months of follow-up following the implantation of the device. 24.5% experienced episodes during the subsequent follow-up period. In this case, AHREs were defined as episodes with a rate ≥190 bpm for at least 6 minutes (18).

One of the most recent studies is the RATE trial which evaluated 5379 patients with pacemakers or ICDs, recruited within 45 days of implantation (20) The AHRE were defined as ≥ 3 successive premature atrial complexes (48% with pacemaker and 52% with ICD) during a mean follow-up of 22.9 months (15).

Study	AHRE Definition	AHRE incidence (n,%)
AIDA (21) (1998)	≥1 min (the AIDA algorithm)	179/354 (50.6)
MOST (20) (2003)	Atrial rate >220 bpm for >5 min	160/312 (51.3)
TRENDS (22) (2009)	Atrial rate >175 bpm for ≥20 s	1,389/2,486 (55.9)
ASSERT (18) (2012)	Atrial rate ≥190 bpm for >6 min; all episodes confirmed by manual expert review of electrocardiograms	261/ 2,451 (10.1) within first 3 months of device implantation; 633/2,437 (24.5) during further follow-up
Healey et al. (23) (2013)	Any PM-detected AF (by manufacturer specific nominal settings for AF detection)	246/445 (55.3)
IMPACT (24) (2015)	≥3 consecutive premature atrial complexes	945/2,718 (34.8)
RATE (25) (2016)	≥3 consecutive premature atrial complexes	50.0 (48.0 in patients with PM; 52.0 in patients with ICD)

Table 1. Principal studies on AHRE

As shown in Table 1, in the various studies the incidence of AHRE has proved to be not very homogeneous. The arithmetic mean of the age of the sample ranges between 70 and 77 years.

By reducing the minimum duration that is attributed to the event in order to identify AHRE, the incidence of it increases. Therefore the incidence varies according to the criteria and the algorithm used to identify them. Also based on the population studied, the incidence varies, for example the incidence tends to be lower in a population in which we exclude subjects with a history of AF, SI or taking antiarrhythmic drugs.

The risk factors of AHRE have not yet been well defined, unlike those of atrial fibrillation.

Healey et al conducted a retrospective analysis that made it possible to identify the possible risk factors of AHRE. The study was done on patients with a dual-chamber pacemaker implanted, capable of recording and memorizing events. 51 AHREs were identified in 55.3% of subjects and in particular in 65.8% of patients with a history of atrial fibrillation prior to pacemaker implantation and in 51.8% of subjects with no previous history of AF.

Patients whose AHREs were identified by the device were of age (74.3 ± 13.7 years vs 71.7 ± 14.4 years, P = 0.046).

Furthermore, they were more likely to have a history of clinical AF (29.7% vs 19.1%, P = 0.01) and also had a greater volume index of the left atrium (34.4 ± 11.8 mL / m2 vs 30.0 ± 9.9mL / m2, P = 0.019) compared to patients in whom AHRE did not occur. Among patients with no history of clinical AF, the volume index of the left atrium was found to be higher in subjects with AHRE (33.7 ± 11.3 mL / m2 vs 29.0 ± 10.1mL / m2, P = 0.034). Anticoagulants were used in 35.3% of patients with AHRE, compared with 21.6% of subjects without (P <0.05) (21). Furthermore, in this group of patients with AHRE who used anticoagulants, the latter were used more in subjects who had additional clinical AF (58.9%) than in those who did not (23.7%, P <0.001).

Thrombogenesis is one of the most frequent and important consequences of supraventricular arrhythmias, especially of permanent and persistent atrial fibrillation. On the other hand, the thromboembolic risk associated with paroxysmal, subclinical atrial fibrillation and the AHRE themselves is less defined and currently still under study. The mechanisms underlying this phenomenon are well studied and identified. Chronic atrial fibrillation involves changes in

atrial structure and endothelial function (26,27) inflammation (27,28) and prothrombotic activity (29,30). Thrombogenesis depends on the alteration of the factors of the Virchow Triad, which are: blood stasis, endothelial damage and a state of hypercoagulability. The factor that seems to be most involved in the case of atrial fibrillation is blood stasis, especially at the level of the left auricle (31)

Still the relationship between the AHRE and the pathophysiological mechanisms of thrombosis is not known. Various studies conducted on AHREs have highlighted the relationship between them and thromboembolic phenomena. What has not yet been defined is the role that AHREs play in the development of thromboembolic events, i.e. it is not yet known whether they represent a causal factor or only a risk factor.

1.2.1 AHRE diagnosis

As mentioned above, AHREs are diagnosed through implantable cardiac devices, the only tools capable of detecting this arrhythmia. On the other hand, it is not possible to diagnose them with ECG, due to their very low burden compared to atrial fibrillation and which therefore does not make them detectable through the surface electrodes, which scan the heart rhythm only for a few seconds. For

the correct diagnosis it is necessary to review the ECGs recorded by the device, to exclude false positives.

It is imperative that an atrial electrode is present, preferably with short bipolar spacing. A high atrial sensitivity is also required, in order to avoid episodes of intermittent undersensing of AF, which can lead to an inappropriate diagnosis of persistent AF through the identification of multiple episodes of short duration. Ventricular farfield oversensing can be avoided by adjusting the post-ventricular blanking time. Furthermore, it is necessary to know some specific causes of false positives, in order to avoid errors of interpretation and of

Management such as repetitive non-reentrant ventriculo-atrial synchrony (RNRVAS) (32).

Many algorithms are used by different manufactures to identify AHRE.

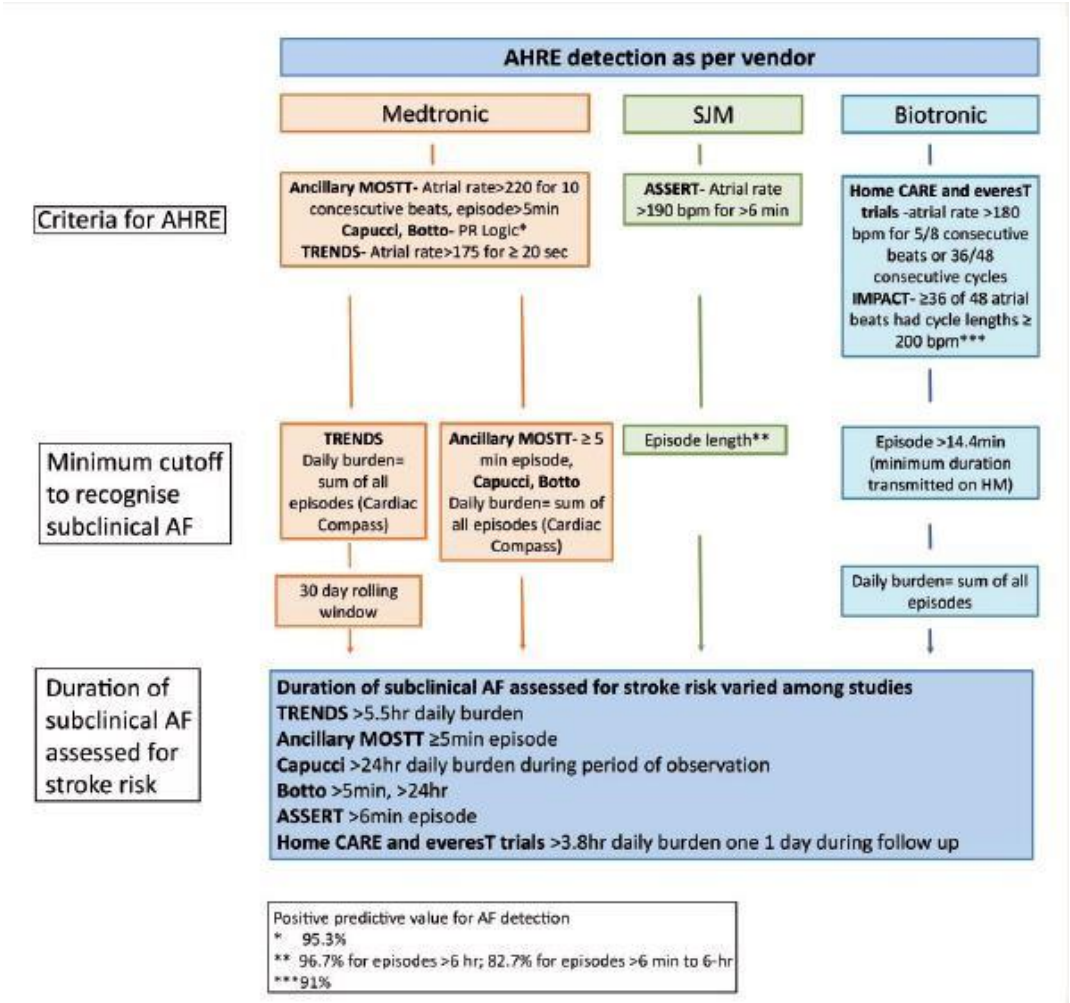

Figure 2. Criteria and cut-offs for the identification of Subclinical Atrial Fibrillation. From: Mahajan R, et al. Eur Heart J. 2018 Apr 21; 39 (16): 1407-1415.

In one of the first studies conducted on AHREs, the ancillary study of the Mode Selection Trial (20) published in 2003, the diagnostic criterion used was the atrial rate> 200bpm for at least 5 minutes. Later, in the TRENDS study (12) published in 2009, an atrial rate>

175bpm for 20 seconds was considered. In the ASSERT trial (18), the criteria were instead represented by atrial rate> 190bpm for> 6min.

More recent is the IMPACT study (24), in which AHREs are defined as episodes with an atrial rate> 200bpm for ≥ 36 of 48 atrial beats.

Given the variability of the criteria used so far, the European Heart Rhythm Society of 2017 through a consensus document defined the AHRE as episodes characterized by a frequency> 190bpm identified with a CIED (33). Episodes lasting> 6 minutes and <24 hours are defined as subclinical atrial fibrillation (SCAF).

Furthermore, since both conditions are asymptomatic, the diagnosis is easy in subjects with implantable devices but, based on the algorithms used, implantable cardiac devices can undergo to inappropriate detection of AHREs, resulting in false positives or false negatives. Consequently we may have an overdiagnosis (due to false positives) or underdiagnosis (due to false negatives) of the AHRE, and this can lead to incorrect patient management, with more or less serious consequences depending on the case. It is necessary to detect how often the AHREs identified by the device underlie an arrhythmia, also determining its positive predictive value.

An analysis of the ASSERT trial showed that the positive predictive value (PPV) of AHRE is only 82.7% for episodes of at least 6

minutes. This PPV value is low, in 1 out of 6 cases there would be an incorrect diagnosis of atrial tachyarrhythmia. Consequently, it is necessary to review the episodes by the physician. In any case, the PPV of the AHRE varies in relation to the duration of the episode and its frequency. In fact, as the duration of the episodes increases, the PPV increases, passing to 93.2%, 96.7% and 98.2% with a duration of 30 minutes, 6 hours and 24 hours respectively. The PPV also varies similarly in relation to the increase in the frequency of events.

The AHRE, as shown by several studies, are asymptomatic in 90% of cases: this is due to the fact that the atrial arrhythmia is not accompanied by an irregular contraction of the ventricle. 9.52 Similarly, SCAF by definition is also asymptomatic. Through Holter monitoring for 5 days, it was highlighted that episodes of atrial fibrillation (in particular paroxysmal AF) are up to 12 times more frequent than clinically manifest episodes (34) In fact, in patients with pacemakers with AF known the episodes 38-81% of all AF episodes are symptomatic (35,36). Symptoms, if present, are variable. In the forms of permanent AF the most frequent symptoms are: fatigue, asthenia and dyspnoea; in the forms of paroxysmal AF the most frequent symptom are palpitations, less frequent dizziness, syncope, chest pain, sleep disturbances and psychological disturbances (37-39)

1.2.2 AHRE and outcome

Regarding the prognostic role of AHREs there are still many uncertainties and many research still left several doubts.

The most important relationship studied was between AHREs and risk of cerebrovascular events (TIA and ischemic stroke). Unlike atrial fibrillation, AHREs have been shown to be associated with the development of these events but it is not clear if they are a causal factor.

The MOST (20) ancillary study was the first study to report that patients with Sinus Node Disease (SND) who have even one episode of AHRE lasting at least 5 minutes have a doubled risk of suffering a stroke or death. . This study recruited 312 patients, who were followed up with a median follow-up of 27 months. 51.3% developed at least one AHRE, and of these 20.6% experienced one of the main outcomes of the study (non-fatal stroke or death). 80% of strokes affected those who had experienced at least one AHRE. A multivariate analysis also showed that the presence of AHREs is an independent predictor of total mortality (HR = 2.48), death or non-fatal stroke (HR = 2.79), atrial fibrillation (HR = 5.93). In this way, for the first time, the correlation between AHRE lasting more than 5 minutes and the increase in negative outcomes was demonstrated. Subsequent studies

have confirmed these first results, reporting a risk of stroke and thromboembolic events more than doubled compared to that of subjects without AHRE: OR equal to 2.50 with AHRE> 6 minutes in ASSERT, OR of 1.89 in SOS AF59, OR equal to 2.20 in the TRENDS study (22,40)

The analysis of the studies confirmed a risk of stroke and thromboembolic events equal to 2.4 in subjects with AHRE compared to those who do not have them (41)

However, it should be considered that, although the aforementioned studies have demonstrated the increased risk for thromboembolic events, the absolute risk of patients with AHRE remains lower (approximately 1.7% per year) than in subjects with clinically manifest AF. The daily burden and the duration of the single episodes to be able to define the prognosis, the latter being important factors involved.

An analysis of the ASSERT carried out by Van Gerder et al. (42) managed to highlight the correlation between the duration of SCAF episodes and the risk of negative outcomes. SCAF episodes of different duration (> 6-24h and> 24h) were evaluated, and their incidence was recorded. This study showed that patients with SCAF episodes> 24h have a substantial increase in the risk of ischemic

stroke or systemic embolism (absolute risk equal to 3.1% per year, comparable to the risk of clinical AF).

In this contest an important concept is the definition of the AHRE burden that can change in different studies. Indeed some studies have taken into consideration the duration of the longest episode (42,43) others have evaluated the total time of the AHRE per day and the burden was considered the longest time of the AHRE in a day ("daily AHRE burden"). Finally, other studies have considered the total accumulated time of AHRE in one year (44). The correlation between duration of the recorded AHREs and risk of developing thromboembolic events was highlighted (45).

The TRENDS study was one of the most important prospective and observational studies in this regard. 2480 patients with pacemakers or ICDs were enrolled. In this study the importance of AHRE was demonstrated and also the role and significance of burden of episodes: a burden> 5.5 h in a 30-day window was associated with a doubled risk of thromboembolic events.12

The results of subsequent studies were variable, so a meta-analysis (16) showed that a burden of more than 6 minutes leads to a significant increase in the risk of stroke. However, a clear linear relationship between the increase in burden and the increased risk of

stroke has not been identified, and at the moment the burden of AHRE necessary for thromboembolic manifestations is not known.

Moreover several studies (18,22,46,47) have tried to define the temporal relationship between AHRE and the onset of thromboembolic phenomena.

It was initially thought that AHREs could trigger thrombogenesis mechanisms due to the irregular electrical activity of the atrium, resulting in systemic embolization that determines the development of cerebrovascular events above all. In reality, this possibility seems to have been completely denied. In fact, in the studies carried out, only a low percentage of subjects had had an episode of SCAF in the 30 days prior to a stroke: 50% in TRENDS, 35% in ASSERT and only 29% in IMPACT AF. According to this data AHREs seem to be a marker of the disease and not a trigger.

In the first studies carried out it was seen how the risk of stroke is increased in patients with SCAF and AHRE, but still lower (48) than in subjects with clinically manifest atrial fibrillation. This risk is similar to risk of AF patients from more recent studies (49). This could be due to lower AF burden (50) in the most recent studies, lower CHADS2 score of the population studied (18,61), and to oral anticoagulant therapy practiced in patients, even if with SCAF.

Furthermore, the thromboembolic risk of SCAF patients has been stratified according to their CHADS2 score: for example in the ASSERT the risk is quadrupled in case of CHADS2 score> 2.3 As the score increases, the risk of developing thromboembolic events also increases.

Furthermore AHREs have been shown to predict other negative outcomes. AHREs have been associated with both an increased risk of death and a composite outcome of death and non-fatal stroke.

This association was initially showed by ancillary study of the MOST. Another study showed that AHREs are predictors of a combined end-point of stroke and cardiovascular death (18). However, the association with the increased risk of death is not detected in the case of short episodes of atrial tachyarrhythmia (15-20 seconds) (52)

Regarding heart failure AHRE and SCAF are related to higher incidence of hospitalization and cardiovascular death but pathogenic mechanisms are not already clear.

Patients with a predisposition to heart failure may not tolerate the elevated ventricular rate during SCAF episodes and eventually decompensation may develop after prolonged episodes of AHRE (53).

Another factor that can contribute to the development of decompensation is the lack of atrial contribution to cardiac output in

already predisposed patients (54). Other pathogenic mechanisms that could be involved are myocardial inflammation and fibrosis, which predispose to diastolic dysfunction, atrial stiffness and FA. (55,56) Finally, abnormal calcium transport, activation of the renin-angiotensin-aldosterone system, and modulation of natriuretic peptides during SCAF episodes can predispose to the development of heart failure.

The work of Wong et al. (57) showed that hospitalization rate for heart failure was equal to 8.9% per year. The risk of hospitalization for heart failure is therefore associated with the progression of SCAF, with HR = 4.10 (95% Cl: 1.64 up to 12.8; p = 0.004).

Management of AHRE includes anticoagulation and antiarrhythmic drugs.

A useful approach to distinguish which patients require treatment is to stratify them in relation to their risk of developing thromboembolic events. Currently there are no specific indications on AHREs, so the risk is calculated using the current tools available, such as the CHA2DS2-VASC score (to calculate the risk of stroke) and the HAS-BLED score for risk of bleeding, before to initiate therapy with oral anticoagulants (58,59).

The CHA2DS2-VASC score allows patients to be divided according to their clinical characteristics into subjects at low risk (score equal to 0 in males and 1 in females), at intermediate risk (score≥1) and high risk (score≥2). Once the risk class has been established, a decision can be made whether or not to initiate therapy with oral anticoagulants.

A high HAS-BLED score does not involve the suspension of anticoagulant therapy, but we need to identify that patient with a high risk of bleeding so that we can follow him with more regular follow-ups, evaluating the change in the score over time and treating any risk factors for reversible bleeding (60).

In any case, it should be noted that the currently available scores have a modest predictive value as regards the attribution of risk.

1.3 REMOTE MONITORING OF PATIENTS WITH CIEDs

Monitoring after implant of patients with cardiac implantable electronic devices (CIED) is an important part of HF follow up.

The responsibility of the follow-up is challenged by the increasing number and technical complexity of CIEDs coupled to the increasing clinical complexity of recipient patients, and available resources. Current practice is based on 6-month in-office visits, with an increased frequency in Elective Replacement Interval (ERI) device or in case of advisories. However, maintaining post implant monitoring schedules has proven difficult. A review of recent U.S. Medicare beneficiaries revealed that almost a quarter of patients were not seen in the year after implant. A major limitation of this conventional follow-up model, which relies on patient presentation, is that no monitoring takes place between office visits. And this became worse during pandemic emergencies, with the consequence of important events missing, especially if asymptomatic, such as system integrity or onset of AHRE and atrial fibrillation.

Home monitoring is a technology that, in subjects suffering from atrial fibrillation, has given excellent results, as demonstrated by several randomized trials (61,62). Home monitoring is a long-distance

telemetry system, installed in the CIED, which automatically sends the data collected by the device to a Service Center. In this way, the medical team is warned in real time and automatically when particular events are recorded. In this way, patient management will be more immediate with a consequent improvement in the patient's prognosis. In addition, unnecessary visits are reduced, with a better distribution of health resources.

Atrial fibrillation is the most frequent cause of alerts sent by the home monitoring device (60% of cases 50). This technology has been shown to be more effective than standard follow-up, detecting atrial fibrillation earlier than a few months, from 1 to 5 months (63). The Lumos-T Reduces Routine Office Device Follow-Up Study (TRUST) trial was the first large randomized trial to test RM for extended clinical management of patients post-CIED implant: patients were scheduled for in person evaluation at 3 months post implant, and then yearly with interim management dependent on RM. Results demonstrated that RM safely reduced the number of in-hospital visits (combined scheduled and unscheduled) by nearly 50%per year, safely (Fig. 2). This result has since been reproduced by different studies with differing proprietary systems (64). The overall reduction in face-to-face visits in RM was obtained without any increase in incidence of

death, strokes, and events requiring surgical interventions, despite the lack of any regular in-clinic appointment for 1 year or more. Thus, committing patients to a remote management plan only during extended periods is a safe management strategy.

Fore these reasons RM of implantable cardiac devices is becoming the new standard of care for patients with such devices. Faced with an increasing number of patients and an increased technical complexity of the devices, in fact, RM allows to optimize the organization of work and to improve both the surveillance of the devices and the clinical management of the patient himself, making it possible to reduce number of outpatient visits and less time spent on follow-up, with the final result of an optimization of the medical work and a reduction in social assistance costs.

In recent years, in consideration of the fact that several clinical studies have shown that no device programming or modification of drug therapy is necessary by the physician in 80% of traditional outpatient checks performed in hospitals, the main PM manufacturers and ICD have developed specific monitoring systems capable of guaranteeing control of the device without the need for hospital access. In general, the device connects via the Internet or via telephone and transmits the data to a centralized website which can be accessed, in a secure

manner, by the clinical staff who are treating the patient. This allows for a continuous flow of information regarding the status of the device and various clinical variables. Through the use of RM, unnecessary visits were limited and healthcare personnel were able to focus on the most compromised patients. In this sense, RM allows the early identification of malfunctions of the implanted system and any clinical events such as arrhythmias, reducing urgent visits to the emergency room and hospitalizations for inappropriate shocks. An early reaction to such events can in fact improve the clinical management and prognosis of these; as well as greater adherence to the follow-up program than the traditional system in this pandemic period.

It is a technology that has been shown to be safe especially in low-risk patients. With regard to AHRE, the usefulness that home monitoring may have in subjects with AHRE is still uncertain; studies are in fact underway to determine this aspect.

1.3.1 Evolution of remote monitoring in patients with CIEDs

In recent years, thanks also to the considerable development of telecommunication technologies, various RM systems (home monitoring) have been introduced into clinical practice, through which patients can transmit, via trans telephone to the reference cardiology

centre, the technical and clinical data that can be deduced from the interrogation of the implanted device, without traditional outpatient control. The methods of use of the various home monitoring systems are quite similar, with some differences. The first experiences in the field of trans telephonic monitoring in patients with ICDs date back to the early 1990s. Anderson et al. studied a group of 47 ICD carriers who were provided with the Medtronic Teletrace data transmission system. This system, equipped with a head to be positioned near ICD, was connected to the home telephone and was able to query the implanted device, including reading the technical parameters, the therapies set and the treatments delivered. The data was sent over the telephone line to a collection centre, where the signals were decoded by a special reception system and then printed. In this study, there were 30% failures in data transmission, mainly due to malfunction of the transmission and reception system. However, from a clinical point of view, the home monitoring system proved to be reliable, with a 100% concordance between the trans telephonic interrogation of the device and that carried out in the clinic.

Starting from the early 2000s, thanks to the introduction of the Biotronik HM system, the possibility of automatic daily monitoring was launched, without any interaction by the patient, wherever he is

geographically in the world, being the transmissions based on the GSM network (Global System for Mobile Communication); sends, through a service center, complete daily reports, which can be viewed on the dedicated website, with secure access. In the event of an alarm event concerning various parameters, an alert message is sent to the center with all the parameters, the identification of the reason for the same and the related endocavitary electrocardiogram (IEGM) of 45 seconds, as well as on the web, also via FAX and SMS. It has the possibility to send a message, via the website, to the CardioMessenger (object which is a combination of receiver and mobile phone) on which a light signal is turned on, to indicate to the patient the need to contact the center that monitor. The HM system is used by Biotronik, with small functional differences, both on the PMs and on the ICDs of its own production. The monitoring and transmission system can be activated or deactivated and can be paired with any CardioMessenger device. For transmission, it uses only a frequency band specifically dedicated to implantable devices (MICS, Medical Implantable Communication Service, 402-405MHz), thus eliminating possible interference with other devices. This frequency is also used by CareLink®.

Regarding the Medtronic CareLink system, in case the device is implanted is non-wireless, the patient must position the transmitter head level with the defibrillator and press the interrogation start key. The system is therefore capable of automatically carrying out a complete interrogation of the device and transmitting the parameters through the telephone line to the data collection center. On the other hand, in the case of a wireless device, the reference center sets the dates for the programmed control of the device through a dedicated web page. On these dates, the transmission system automatically interrogates the device and transmits the data to the collection center without any intervention by the patient. The device is also able to initiate an interrogation and an unscheduled data transmission, in case of exceeding some alarm parameters preset by the reference center, such as reaching the elective replacement indicator, alterations of the lead impedance or defibrillation impedance, ventricular or supraventricular arrhythmias, etc. Other monitoring systems used with wireless devices, on the other hand, automatically carry out a daily interrogation of the device, the data of which are sent to a collection center and then communicated to the reference hospital only in case of anomalies of the device or arrhythmic events. The CL system applied on CRT-D devices, monitors with an exclusive built-in sensor, called

OptiVol®, the accumulation of liquid, as an index of worsening of the state of hemodynamic compensation, detected through changes in transthoracic impedance.

Boston Scientific's Latitude® Patient Management System, not yet available in Europe, supports nearly all US-made ICD and CRT-D devices. These, depending on the model, require the use of a transmitter called "communicator", equipped with a telemetry head, or, for more recent models, a wireless communicator. Both systems use a fixed telephone line for long range transmission. The model that uses the communicator telemetry head requires its affixing to the implanted device, while the wireless model receives information from supported devices automatically, without interaction. If the implanted device detects a relevant event, the patient is warned by the flashing of the action button, located on the transmitter device, to activate a communication. The "events" are divided into red or urgent alarms, for conditions that could deprive the patient of the therapeutic function of the device and in yellow for configurable clinical situations. The system is equipped with an exclusive ability to connect to a dedicated scale and sphygmomanometer, in order to monitor the data that can be obtained, which, together with the answer to specific questions, can provide information on any changes in clinical conditions.

The HouseCall Plus system with its MerlinNet evolution supports most of St. Jude Medical's ICD and CRT-D products. The system is active in the USA with the type that involves the use of a programming head that the patient must apply to transmit data relating to symptomatic events. For asymptomatic events, the patient is notified of receiving a warning in the form of device vibration. The periodic checks, which are scheduled, could be activated either by the patient or by a warning from the center. A wireless transmission / reception device, called Merlin @ home RF, has also been created using the MICS frequency band for short range transmissions, while, similarly to the previous 2 systems, it requires a fixed telephone line to send data to long range. The queries for the checks with the latter will be activated, without interaction by the patient, on scheduled dates, while the monitoring will be daily with the possibility of sending alert messages to the data collection center, in the event that predefined programmable events should occur. Similar to the CareLink system, the possibility of using wireless transmission, even at long range, appears to be planned in the near future.

The Sorin Group (now Microport) system, initially applied to the RF ICDs, send the data wirelessly and automatically to a “console” at the patient's home and then automatically by telephone line to a central

server, accessible online. The data are stored on the server and organized in accordance with the standards currently in use; will be processed by the AIDA + expert system (Automatic Interpretation for Diagnosis Assistance). The information may be sent on the scheduled check-up date, when an alarm is triggered by the device or directly by the patient, in the event of symptoms or by the doctor, from the hospital, if necessary. It is possible to view all diagnostic data and related to stored arrhythmias or therapy, with corresponding IEGMs. The system is able to count on an algorithm for the prevention of heart failure called PhD ™ (Predict Heart Failure Development), through the presence of multisensors. To date transmission of data from the implanted device to the home monitor can occur in three different ways: 1) routine or pre-scheduled transmissions arranged by the device follow-up clinic (e.g., daily, monthly, every 3–6 months), 2) alerts sent to the clinic when triggered by medical events, e.g., arrhythmias, ICD shocks, or implanted device malfunctions, and 3) a non-previously scheduled data transmission initiated by the patient; for instance, if they are not feeling well or have experienced an ICD shock and want a review.

1.3.2 Remote monitoring and outcome

An important result of the first trials testing RM was demonstration of early detection ability of clinical events (64).

Despite extension of intervals between face-to-face encounters to yearly, event onset to physician evaluation of combined first AF, ventricular tachycardia (VT) and fibrillation (VF) events in TRUST was preponed to a median interval of 1 day, dramatically less than in conventional care (>1 month) or even remote interrogation based follow-up. Importantly, early detection was maintained for silent, clinically asymptomatic problems. Similar benefits were seen in pacemaker recipients in the COMPAS trial. Moreover "Aside from their therapeutic abilities and arrhythmia detection mechanisms, modern implantable devices also provide diagnostic information potentially useful to monitoring HF decompensation, e.g., rest and night heart rate, heart rate variability, patient daily activity, intrathoracic impedance, or hemodynamic sensors, percentage of right ventricular pacing in single and dual chamber devices, percentage of actual biventricular pacing in CRT devices, and internal electrogram assessment to confirm left ventricular capture. These may change several days to weeks before deterioration of HF and ultimate hospitalization, creating an opportunity for early pre-emptive

intervention when the patient is still asymptomatic, but in which filling pressures increase and sympathetic activation starts. Hemodynamic monitoring may offer incremental benefit. Although indirect assessment using transthoracic impedance alone has shown modest if any effect, integration of this measure with other patient parameters may improve predictive power for deterioration. Direct pulmonary artery hemodynamic monitoring with treatment based on remotely accessed data induced a 37% significant reduction in HF hospitalization (65).

This changes the paradigm of HF management from clinical reaction to decompensation (i.e., development of symptoms, weight increases or pulmonary oedema) to a "pro-active phase" delivered when the patient is asymptomatic, hopefully 2–3 weeks in advance, to prevent heart failure hospitalization and improve patient quality of life." (66)

"Recently, clinical data of IN-TIME (Influence of Home Monitoring on Mortality and Morbidity in Heart Failure Patients with Impaired Left Ventricular Function) trial suggested that RM could ensure a survival benefit in ICD patients. In IN-TIME, RM led to an improved heart failure composite score, a finding driven by a sharp decrease in all-cause mortality in the RM group (10 deaths in the RM arm vs. 27 deaths in the in hospital follow-up arm) (67) Although a single

specific mechanism responsible for the mortality benefit was not clear, the authors proposed that the improved outcomes with RM may have occurred via a combination of early ventricular and atrial arrhythmia detection, early recognition of suboptimal biventricular pacing on CRT-D devices, and increased telephone contact with patients (67). No statistical difference between RM and in hospital follow-up was identified for other heart failure indexes including heart failure hospital admission, New York Heart Association functional class, and global self-assessment

These data are supported by many registries, showing that RM may lead to a significant survival advantage over patients not using RM (68-70). The ALTITUDE study, for example, enrolled 69,556 patients implanted with CIEDs, and showed a 50% reduction in mortality (ICD hazard ratio [HR]: 0.56; CRT-D HR: 0.45; $p < 0.0001$) in remote monitored patients, compared with classical followed ones (70). Findings showed by ALTITUDE were recently confirmed by PREDICT RM (Patient Related Determinants of ICD Remote Monitoring Utilization and Outcomes), a subgroup analysis in which 37,742 patients from the ALTITUDE database were studied with matched outcome data from the National Cardiovascular Data Registry. In PREDICT RM, RM was associated with reduced

mortality (ICD HR: 0.60; CRT-D HR: 0.71) (68,69). Similar data also have been presented for 148,976 patients on the Merlin patient care network database (St. Jude Medical, Inc., Sylmar, California), with RM use associated with increased survival (ICD HR: 2.51; CRT-D HR: 2.44; both $p < 0.001$) (69). However, none of the analyses of the large RM databases were randomized. The mortality of the group undergoing RM was compared with patients who chose not to participate in RM or where the service was not available and this may have potentially resulted in selection bias.

Similar mortality reductions with RM use have been seen in 2 other national databases of more than 100,000 ICD patients (68,69).

Impact of RM on this setting of patients is related to all-cause and cardiovascular (CV) mortality, hospitalization, unscheduled clinic visits and moreover to early atrial arrhythmia detection and device shocks, with a consequently reduction of time between early adverse events and clinical decision" (71). These data are in line with Varma et al. (64) that showed a greater survival advantage with more frequent use of remote monitoring.

On the other hand four RCTs, CONNECT (72), EVOLVO [73], MORE-CARE (74) and a study by Al-Khatib et al. (75) using less

frequent transmission with the Medtronic remote monitoring platform found no differences in mortality.

Several factors may influence mortality in remote monitoring users in addition to the frequency of transmissions. Some data suggest that the remote monitoring platform used may be in part responsible for the differences in observed outcomes, others that time of remote monitoring initiation is crucial to change outcome.

“A recent meta-analysis of nine RCTs with 6500 patients did not show an overall significant reduction in all-cause mortality. However, in their discussion, the authors discuss that differences in the methodologies used, remote monitoring transmission rates, timing of initiation and perhaps the platform itself may explain the mixed results (76).

Minimizing unnecessary ICD shocks is another important factor in improving morbidity and quality of life in patients with these devices. This includes features of device programming to reduce oversensing including rejection of far field R waves and avoidance of T-wave oversensing, constant monitoring of thresholds and impendences to detect lead failure or fracture, and appropriate discrimination between supraventricular tachycardia (SVT) and ventricular tachycardia (VT), which includes the appropriate and timely detection of atrial

fibrillation. Indeed, the number of system-related complications per year (including lead complications and generator malfunctions) is not negligible and their prompt identification can improve patients' management.

In the previously mentioned meta-analysis (76), the odds of receiving an inappropriate shock was significantly reduced in remote monitoring users compared with those with in-person follow-up alone [odds ratio (OR) 0.55, P 1⁄4 0.002] Remote monitoring has also been shown to aid in prevention of inappropriate shocks specifically due to lead fractures. In a study of 115 patients with right ventricular lead fractures, 82 with in-person follow-up and 33 with remote monitoring and in-person visits, the rate of first inappropriate shock was similar between patients with conventional follow-up (32.9%) and remote monitoring (30.3%). However, those using remote monitoring had far fewer inappropriate shocks (62 per patient) than those with conventional follow-up (77) “Device and lead advisories represent a major concern for the physician and for the patient as well. Despite rare, device malfunctions can be life-threatening and, on the other hand, replacement of the generator/leads before an overt malfunction may expose the patient to unnecessary risks as well as an organizational burden and costs for hospitals and the health care

system. In this setting, RM offers a double benefit: provides an immediate detection of abnormal device behaviour through a continuous surveillance of several parameters such as lead impedance and sensing and avoids too early device replacements.

Regarding heart failure prevention a posthoc analysis of the IN-TIME trial (67), which randomized heart failure patients to remote monitoring or audible device alerts without remote monitoring using the Biotronik system between 2007 and 2010, showed that 1-year cardiovascular mortality in heart failure patients was lower in patients randomized to the remote monitoring arm (2.7%) than the control arm (6.8%) [Hazard ratio 0.37, 95% confidence interval (95% CI) 0.16 – 0.83; P 1⁄4 0.012]. Other studies have demonstrated improvement in heart failure specific endpoints. The Evolution of Management Strategies of Heart Failure Patients with Implantable Defibrillators (EVOLVO) trial randomized 310 patients with heart failure and an ICD to either remote monitoring alone with audible device alerts off or audible device alerts alone without access to remote monitoring and showed a 21% reduction in emergency department visits and urgent in-office visits for heart failure, arrhythmias or ICD-related events with the use of remote monitoring (4.40 versus 5.74 events per year; P < 0.001) (73).

“More recently, the Remote Monitoring of Heart Failure using Implantable Electronic Devices (REM-HF) study randomized 1650 patients between 2011 and 2014 and showed no differences with the use of remote monitoring in the composite primary end- point of all-cause mortality or hospitalization. Patients in the study group had devices from three of the major manufactures: Boston Scientific, Medtronic and St. Jude Medical, and weekly CIED downloads were used along with a formalized follow-up approach (78). This contrasts with the results of the IN-TIME trial, and the differences may be due to the remote monitoring platform (Biotronik) and trans- mission frequency (daily) used in IN-TIME. Another recent study used 574 ICD and CRT-D (Medtronic, St. Jude Medical and Biotronik) patients enrolled in the Contemporary Modalities in Treatment of Heart Failure (COMMIT-HF) prospective cohort registry between 2009 and 2013. The 1-year mortality was significantly lower in the remote monitoring group (2.1 versus 11.5%, $P < 0.0001$), and this benefit was maintained at 3 years (4.9 versus 22.3%, $P < 0.0001$) (79)

At last it has been clearly established that remote monitoring can significantly improve the detection of asymptomatic or minimally symptomatic atrial fibrillation using pacemakers, defibrillators and implantable loop recorders (ILRs). RM proved successful in the early

identification of AHREs and may reduce the time to potentially meaningful clinical decision such as the institution of an oral anticoagulant therapy, which offers huge and well-established benefits in patients with clinical AF and, presumably, also in selected patients with AHREs.

The ASSERT trial further showed that atrial fibrillation duration greater than 24h was associated with a significantly increased risk of stroke or systemic embolism (19). Remote monitoring may be beneficial in lowering stroke risk by allowing for early initiation of anticoagulation; however, currently, this has not been clearly established. Ricci et al. (80) conducted a Monte Carlo simulation showing that in patients with AHREs daily RM may reduce the stroke risk with respect to standard in-person visits scheduled every 6 to 12 months, but ad hoc studies are needed to demonstrate the possible clinical benefits of RM in this setting. In a subanalysis of the ASSERT trial, AHREs progression to episodes lasting more than 24 h or to clinical AF was independently associated with HF hospitalization (HR 4.58; 95% CI 1.6-12.8). Therefore, a timely identification of AHREs and of their progression to a higher AF burden or to clinical AF has the potential to improve the outcome of HF patients. In a recently published 4-year observational study

patients with CIEDs and an average CHA2DS2VASc Score of 3, it was found that 94% of atrial fibrillation episodes were detected remotely, and 72% of patients were asymptomatic during episodes. Two-thirds of the patients with atrial fibrillation detected during the study period did not have a prior history of the diagnosis, and 85% of the medical interventions for atrial fibrillation were triggered by remote monitoring notifications. The expected stroke event rate was less than half of what would have been predicted by the CHA2DS2VASc score during the study period that suggests a beneficial effect of remote monitoring given that a significant majority of episodes were remotely detected (80). Finally, ICDs have a well-recognized life-saving role, but inappropriate ICD shocks are fearful and common events associated with increased mortality. In the THORN registry (87) (a large RM database of 1882 ICD patients), a 9% prevalence of inappropriate ventricular arrhythmia detection and a 3% prevalence of inappropriate shocks over 13.7 ± 3.4 months of follow-up was reported. In a substudy of the ECOST trial (88), during 27 months follow-up, 5% of patients in the RM group received 1 or more inappropriate shocks versus 10.4% in the control group, suggesting that RM can be effective in the prevention of inappropriate ICD shocks.

Moreover decreased resource utilization is a major benefit of remote monitoring on health systems. In a recent large cohort study comparing 34 259 patients using remote monitoring versus 58307 nonusers who received a CIED implant from all manufacturers between 2008 and 2013, those using remote monitoring were found to have a lower adjusted risk of all cause hospitalization (hazard ratio 0.82; 95% CI 0.80 – 0.84; $P < 0.001$) and shorter mean length of stay during hospitalization by approximately 3 days. Hospitalization cost for remote monitoring users was reduced by $3700 per patient-year or 30% (81)

Remote monitoring has repeatedly been shown to safely reduce overall ambulatory visits. The TRUST trial demonstrated that by replacing quarterly follow-up appointments with remote monitoring and only seeing patients in-person if necessary, a 45% reduction in total in-office visits could be achieved without differences in adverse events (64). This finding was more recently confirmed in the REFORM trial that found no difference in mortality or hospitalization by extending the follow-up interval from 3 to 12 months after the initial post- implant visit with use of remote monitoring (82). The COMPAS trial extended these results to individuals with permanent pacemakers (83).

In addition to several studies showing beneficial effects of remote monitoring on reducing scheduled outpatient visits, remote monitoring has also been shown to be impactful on reducing unscheduled visits. In the EVOLVO study, a multicentre RCT comparing remote monitoring and standard care in patients with Medtronic devices, the primary end-point of emergency room and urgent in-office visits was found to be 35% less frequent in the remote monitoring arm over the 16-month study period (0.59 versus 0.93 events per year, incident rate ratio 0.65; 95% CI, 0.49 – 0.88; P 1⁄4 0.005) (73). Additional benefit exists for remote monitoring over routine care for other outcomes that can impact resource utilization such as the time to clinical decision making, which was shown to be reduced in patients using remote monitoring in the CONNECT trial (22 days in the control arm, 4.6 days in the remote monitoring arm, $P < 0.001$) (72).

Health systems have been shown to reduce costs through reductions in hospitalizations, outpatient visits and testing. In a recent study of patients in Italy, costs over a 12-month period were reduced by 53% through the use of remote monitoring and replacement of quarterly visits with remote monitoring visits (approximately $1200 in the standard care group versus $550 in the remote monitoring group). The cost savings were not simply the result of a reduction in outpatient

encounters but were also driven by savings in hospitalizations (25 versus 8%), emergency room visits (6 versus 0%) and outpatient diagnostic testing (66 versus 47%). Patients also saw direct cost savings with remote monitoring use of approximately 66% (roughly $190 in the standard care group versus $65 in the remote monitoring group) due to reduced out-of-pocket expenses including travel and time spent for follow-up appointments (84-85)" (86).

More recently a multiparametric approach led to development of a multisensor-based algorithm for the early detection of worsening HF monitoring heart rate, heart sounds, thoracic impedance, respiration, and activity.

"The HeartLogic algorithm alerted a median of 34 days before HFEs, providing enough time for corrective action to be taken. This is critically important, as the goal is to identify patients in order to enact treatment to prevent the event. Because of the high impact of HF on health care expenditures and significant impact on quality of life, even relatively modest reductions in hospitalizations could have a significant benefit on overall disease burden. Furthermore, this benefit comes in the context of regularly used devices and does not introduce any added incremental implant or procedure risks." (89)

2. AIMS OF PhD PROJECT

Studies conducted on heart failure, AHRE and remote monitoring have enriched the scientific literature with important data that became useful to a better definition of the problem, a better understanding of prognostic role of these events and a better management of the pathology. However, there are still some aspects that are not fully understood, including the possible management of patients who experience these episodes at a high atrial frequency, when monitored remotely.

Considering that a single-center observational retrospective preliminary study was conducted during the first year of PhD, with the aim of evaluating the actual clinical prognostic impact of AHREs and their characteristics in a population of patients with CIEDs. The recruited patients, all CIED carriers, were followed up with annual checks at the cardiac stimulation unit of the Cardiology Unit of the "Paolo Giaccone" University Hospital of Palermo. The presence of AHRE was correlated with different outcomes, evaluating their clinical-prognostic impact in terms of stroke, mortality, MACE.

Subsequently a prospective case control study was performed in a subgroup of the studied population with the aim to evaluate the

effective advantage of telemedicine in the follow-up of patients with HF in terms of outcome, management and costs; focusing attention on AHREs and identifying which parameters collected at remote monitoring are early predictors of heart failure and worse outcome.

3. PRELIMINARY STUDY

3.1 Materials and Methods

1683 patients with implantable cardiac devices were recruited. These are subjects of both sexes, of which 777 are males and 906 females (46,2% and 53,8% respectively). Subjects aged 26 to 103 were included, with an average age of the sample equal to 72.6 ± 3.7 years (with 95% C.I. from 68.3 to 74.8).

All the subjects recruited are carriers of CIED, implanted at the UOC of Cardiology of the Palermo University Hospital "P. Giaccone" in a period ranging from 1978 to 2018. Patients were followed at the EP lab of the aforementioned hospital, with regular annual checks.

1303 (77,4%) subjects with pacemakers were included, 320 subjects ICD carriers (19%) and 60 (3.59%) who were instead implanted with a CRT. Those who had a single chamber device, with only the ventricular lead, were therefore excluded from the study, since the presence of an atrial lead is essential to be able to research and study AHREs.

The population studied also presents some known comorbidities: 135 subjects (8%) have a history of clinical AF, 99 subjects (5.88%) have congestive heart failure, 471 (28%) are subjects with type 2 diabetes

mellitus, 364 (21,6%) present ischemic heart disease and finally 55 subjects (3.27%) have valvulopathy.

	Results
N° of Patients	**1683**
Age	**72±3 years**
Male	**777 (46,2%)**
EF	**50±6%**
CAD	**364 (21,6%)**
HF	**99 (5,88%)**
Diabetes	**471 (28%)**
PM	**1303 (77,4%)**
ICD	**320 (19%)**
AF	**135 (8%)**
CHA_2DS_2-VASc	**2,9±0,4**
Follow-up	**4±0,3 years**

Table 2. Clinical characteristics of preliminary studied population

3.1.1 Follow up

Data was collected during the routine follow-up performed for each patient over the years. Patients with implantable cardiac devices are in fact followed from the moment the device is implanted. The first

check is carried out 1 month after surgery, the second 6 months, and then annually. The follow-up period therefore began in 1978 and ended in 2020, with a mean duration of 4.03 ± 2.11 years (95% CI 3.37 to 8.74).

During the annual check-up data were collected and recorded both clinical and related to the CIED and the cardiac activity recorded by it.

Regarding clinical information, the following was investigated:

• The presence of new comorbidities that have arisen (ischemic heart disease, worsening of congestive heart disease, type 2 diabetes mellitus, heart valve disease);

• Onset of adverse events (cerebrovascular events, such as stroke or TIA; myocardial infarction; onset of clinical AF; death);

• Drug therapy carried out (in particular, use of anticoagulants, antiarrhythmic, beta blockers);

All clinical data collected were confirmed by viewing reports of previous cardiological visits and / or patients' medical records.

The diagnosis of Atrial Fibrillation was made in reference to the ESC guidelines of 2016.

As regards the CIED and cardiac electrical activity, the following information were recorded:

• Presence and type of spontaneous cardiac activity

• Atrial and / or ventricular pacing rates

• AV interval

• Atrial output

• Events related to cardiac electrical activity (presence of AHRE, type and their duration; mean atrial rate; episodes of AF).

The devices have been set up to detect and register AHREs according to the criteria established by the consensus document EHRA, HRS, APHRS, SOLACE. According to the latter, AHREs include all those episodes of tachyarrhythmia of atrial origin with a rate> 190 bpm.

3.2 Statistical Analysis

The data analysis was carried out with the statistical calculation software MedCalc 19.0.5.

Data are presented as mean ± standard deviation or discrete numbers and percentages.

The chi-squared test was used to correlate qualitative variables. The relationships between continuous variables were investigated using linear regression tests.

The event-free period was estimated by the Kaplan-Meier method.

3.3 Results

22,3% of the subjects recruited presented one of the events investigated .

Specifically, 57 patients of the population developed a cerebrovascular event, 49 had myocardial infarction, 157 had an episode oh HF, and 113 died.

Events	Results
Ictus	**57 (3,4%)**
AMI	**49 (2,9%)**
HF	**157 (9,3%)**
Death	**113 (6,7%)**
Total	**376 (22,3%)**

Table 3. Adverse events during follow up

A cerebrovascular event was defined as an acute event on an ischemic basis that affected the anatomical structures of the Central Nervous System. They were taken into account for the purposes of our study both transient ischemic attacks (TIA, Transient Ischemic Attack) and actual ischemic strokes, which instead present reliquaries to imaging and / or from a neurological point of view.

With "onset of clinical AF" we mean a new onset of atrial fibrillation that is manifested clinically with symptoms felt by the patient.

Cases of asymptomatic AF discovered accidentally during annual checks of the device were considered AHRE.

In addition to the frequency of events, the average time distance between the implantation of the device and the onset of the event was investigated. The average was expressed in years and was calculated to be equal to:

- 7.42 ± 7.67 years (95% CI 5.05 to 9.77) in the case of cerebrovascular events

-6.75 ± 6.93 years (95% CI 4.95 to 8.54) in the case of MI

-3.44 ± 3.71 years (95% CI 0.59 to 6.29) in the case of onset of clinical AF

- 5.07 ± 5.51 (95% CI 3.56 to 6.57) in the event of death

As for the therapy practiced by patients, it was found that 45.10% took beta-blockers, 25.82% took anticoagulants and finally 8.17% took antiarrhythmic.

Drugs	Numbers	Percentage
Beta-blockers	**757**	**45,10%**
Bisoprololo	466	61,59%
Atenolol	60	7,97%
Metoprolol	77	10,14%
Sotalol	38	5,07%
Nebivolol	27	3,62%
Propanolol	1	1,3%
Carvedilol	77	10,14%
Anticoagulant	**434**	**25,82%**
Coumadin	110	25,32%
Sintrom	11	2,53%
Apixaban	99	22,78%
Rivaroxaban	82	18,99%
Edoxaban	82	18,99%
Dabigatran	44	10,13%
Antiarrhythmic	**137**	**8,17%**
Amiodarone	71	52%
Flecainide	44	32%
Propafenone	22	16,00%

Table 4. Drugs assumption in studied population

With regard to the characteristics of the devices and the electrical activity of the heart, it is found that the percentage of mean atrial pacing was 66 ± 5 (95% CI 58 to 75), while the mean ventricular is 64 ± 3 (95% CI from 55 to 70).

The recruited patients were also divided into three groups:

1. Patients with permanent AF

2. Patients with no history of clinical AF, but with AHRE detected by CIED

3. Patients with no diagnosis of both AF and AHRE

Dividing the recruited subjects into these groups allowed us to study and investigate the role of AHRE in patient prognosis in a more specific way. For this purpose, the incidence of the main outcomes studied was calculated in each of the three groups and, through specific tests, the possible statistical correlation between the latter and the presence of AHRE and / or AF was evaluated.

The risk of developing each of the investigated events was calculated for each of the three groups. Furthermore, survival curves have been developed starting from the period of CIED implantation, to calculate if and how the presence of AHRE, AF or the absence of both can vary the prognosis of the patients, in relation to the investigated outcomes (death, cerebrovascular events, AMI, onset of clinical AF).

3.3.1 Patients with AHRE

This group is made up of 343 subjects (20,38% of the total), who during the follow-up was found to have one or more episodes of AHRE through their implantable device. These subjects have no history of clinical AF.

Specifically, the identified AHREs show a main FA-like pattern in the 65,1% of cases and an atrial tachycardia-like pattern in 34,9%.

	Results
N° AHRE	1343
Patients	343
Mean Atrial Rate	235+12 bpm
Mean Duration	4+2 min
AT Morphology	470 (35%)
AF Morphology	873 (65%)
Symptomatic AF	142 (10,5%)
Cross-over to permanent AF	65

Table 5. AHRE characteristics

There were 767 episodes (57.14% of cases) of short-lived AHRE and 576 (41.50% of cases) long lasting. The cut-off to define the duration has been set at 1 minute. It also emerged that the first recorded episode occurred on average 47.77 months after the device was implanted. The average age of this sample was 72 ± 3 (95% CI from 70.2 to 73.5). Although there was no statistically significant correlation with age, our analysis found that the detection of AHRE occurs mostly in subjects aged 70 to 85.

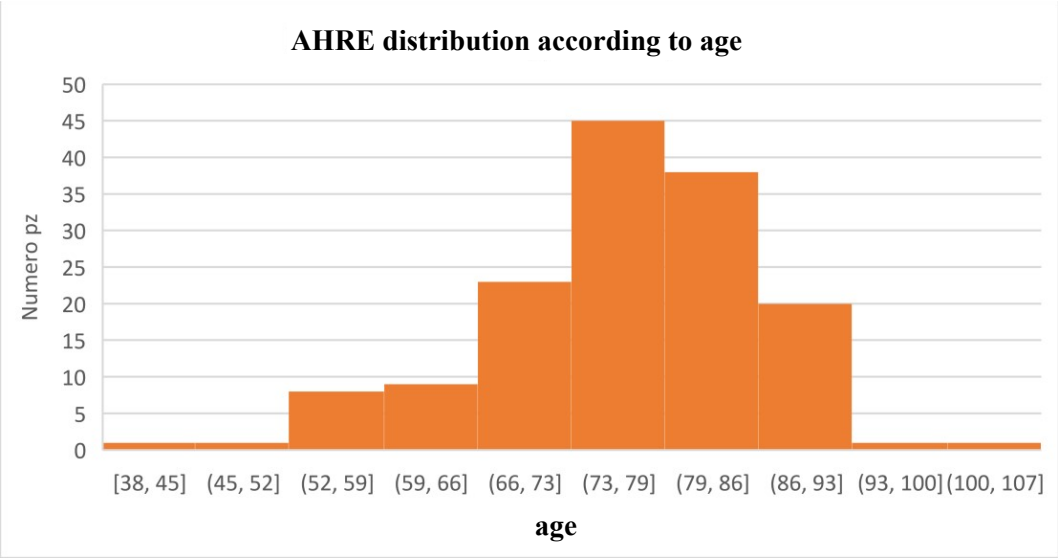

Figure 3. AHRE distribution according to age

There was no statistical correlation between AHREs and the sex of the patients, despite a slight prevalence of this phenomenon in female subjects. 75% of subjects were on therapy with an oral anticoagulant, of which 21.57% with warfarin and 78.43% with a new oral anticoagulant, 47.97% were taking beta-blockers and 10.14 % antiarrhythmic. In this group of subjects the incidence of the investigated outcomes was as follows:

Events	Results
Ictus	**17 (5%)**
AMI	**13 (3,8%)**
HF	**45 (13,2%)**
Death	**30 (8,7%)**
Total	**105 (53%)**

Table 6. Adverse events in patients with AHRE

It was also seen that a cerebrovascular event occurred in our patients with AHRE on average 8.40 ± 9.17 years after implantation of the CIED, an MI after 6.89 ± 6.98 years. Finally, the death occurred on average after 5.88 ± 6.58 years from implantation.

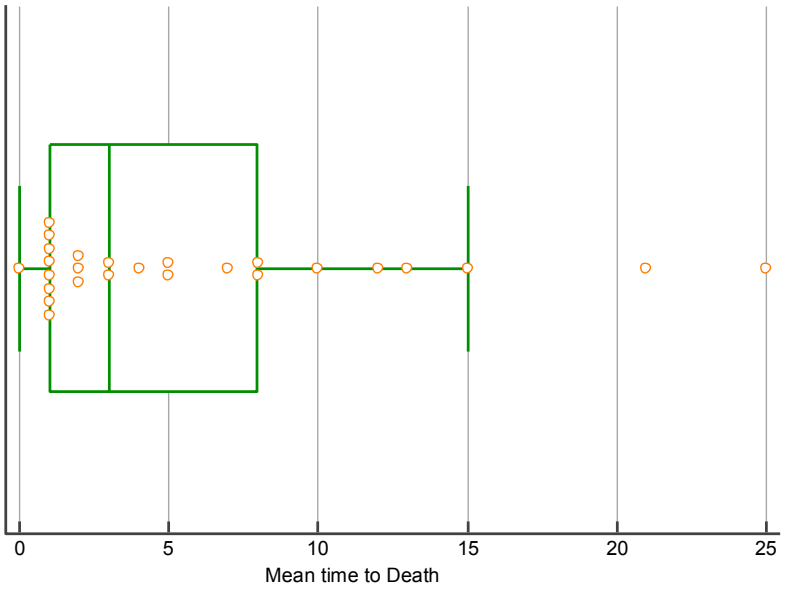

Figure 4. Mean time from CIED implant and death (months).

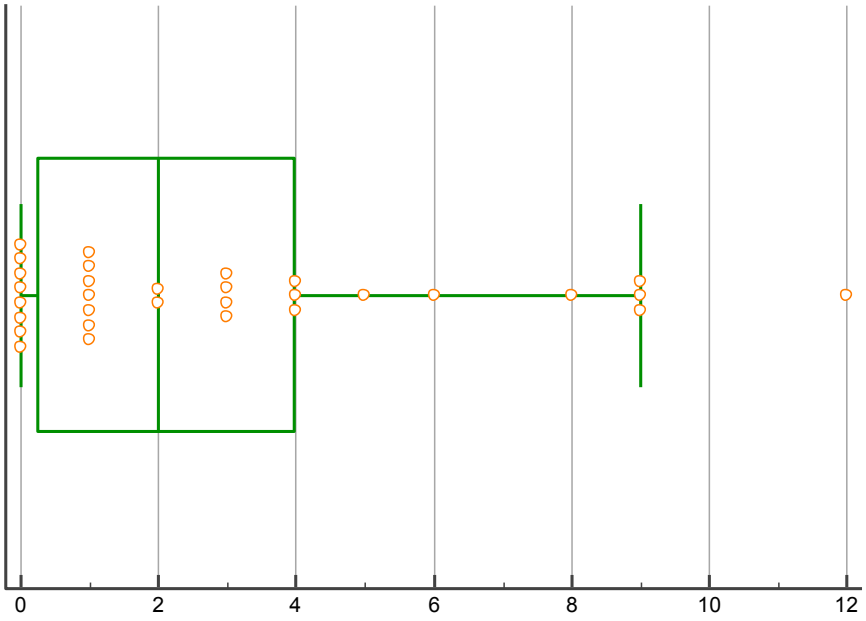

Figure 5. Mean time from CIED implant and heart failure hospitalization (months).

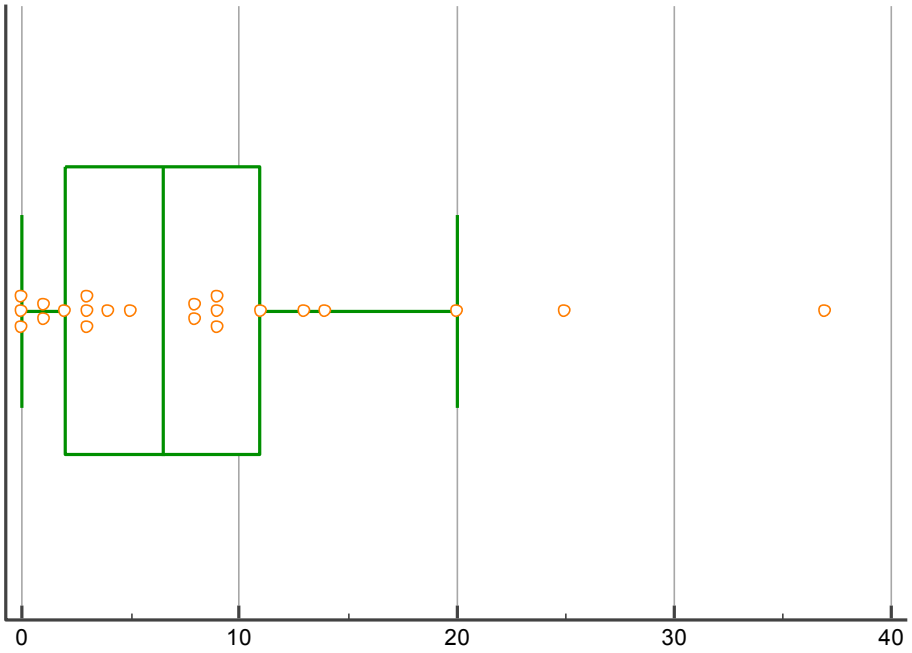

Figure 6. Mean time from CIED implant and cerebrovascular events (months)

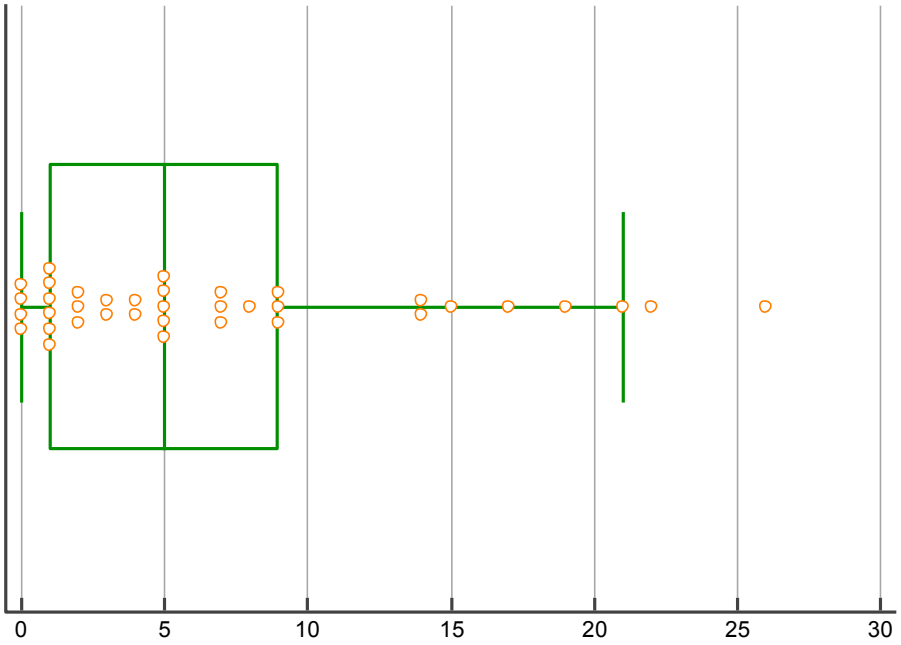

Figure 7. Mean time from CIED implant and myocardial infarction

The presence of AHRE has been compared with the development of cerebrovascular events, AMI, onset of clinical AF, death, presence of heart failure, ischemic heart disease, type 2 diabetes mellitus, valvulopathies and also with the three drug classes investigated by this study.

In addition, any correlations with the atrial and ventricular pacing rates, with the values of the AV interval and also with CIED replacement were evaluated.

In the case of the percentage of atrial pacing and AHRE, a significant correlation was found, with a significance level equal to P 0,02.

In the same way AHREs onset was related to sick sinus syndrome as implant indication (p=0,02) and to CHA2DS2-Vasc score (p<0,001). So a multivariate analysis was performed and results are showed in the table 7.

Variables	OR (CI); p-value
CHA_2DS_2-VASc	2,15 (1,8-5,7); p=0,02
SSS	1,05 (0,99-1,1); p=0,06
% atrial pacing	3,74 (0,85-9,65); p=0,07

Table 7. Predictors of AHRE

3.3.2 Patients with permanent atrial fibrillation

This group is made up of 25% of the subjects who presented a history of permanent AF.

The mean age of the patients is 79 ± 2 (95% CI 76.64 to 80.10), with a higher prevalence of AF in the age group 77 to 86 years and in subjects female. 87% of patients were on oral anticoagulant therapy (22.22% with warfarin and 77.78% with NAO), 95% were on beta-blockers and only 4% were on antiarrhythmic.

Also in this group the incidence of the main outcomes was calculated and statistical correlations were made between the presence of AF and

the development of cerebrovascular events, MI, death, congestive heart failure.

Events	Results
Ictus	**23 (5,5%)**
AMI	**16 (3,8%)**
HF	**61 (14,2%)**
Death	**38 (9%)**
Total	**243 (57,6%)**

Table 8. Adverse events in patients with permanent AF.

In each of these cases, statistically significant data emerged that broadly reflect the current knowledge on AF, known to be the most common chronic arrhythmia, capable of enormously modifying the prognosis of patients.

The survival curves also showed a significant difference in subjects with and without AF relative to the development of cerebrovascular events, with a significance level of $P < 0.0001$.

3.3.3 Patients without AHRE or atrial fibrillation

The latter group is made up of 919 patients (54,6%) who have neither permanent AF nor AHRE. The average age was calculated to be equal to 69 ± 2 (95% CI from 65.59 to 73.39), with a female prevalence

(57%). 5% were taking oral anticoagulants (29.41% warfarin and 70.59% an NAO), 55.85% beta-blockers and 3.47% an antiarrhythmic.

The incidence of the main outcomes is summarized in the Table 9.

Events	Results
Ictus	**17 (1,8%)**
AMI	**20 (2,2%)**
HF	**51 (5,6%)**
Death	**45 (4,9%)**
Total	**133 (14,5%)**

Table 9. Adverse events in patients without AHRE or AF.

The processing of the collected data allowed the comparison between the three groups under study. It emerged that the incidence of cerebrovascular events is reduced in subjects without AHRE and AF, while it increases more and more in the group of subjects with AHRE and in that of subjects with permanent AF, respectively. A similar argument can also be made with regard to death and heart failure.

As regards myocardial infarction, on the other hand, the incidence was statistically similar in the group of subjects with AHRE than in the other two groups.

3.3.4 Kaplan Myers and AHRE characteristics analysis

Finally, survival curves were created according to the Kaplan Meier method, which show whether and how the population survival changes in relation to the presence of AHRE and the development of cerebrovascular events, AMI, onset of clinical AF and death.

In our series, it was found that there is a significant difference between the curves of patients with and without AHRE both for the development of cerebrovascular events (P = 0.005), heart failure (P = 0.01) and death (P = 0.005).

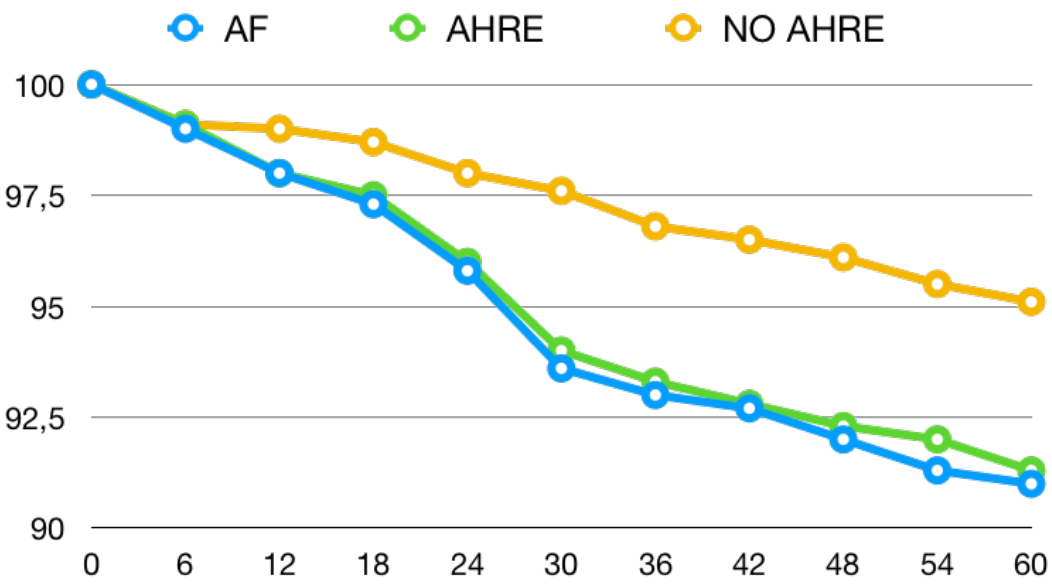

Figure 8. Kaplan-Meier survival curve (months).

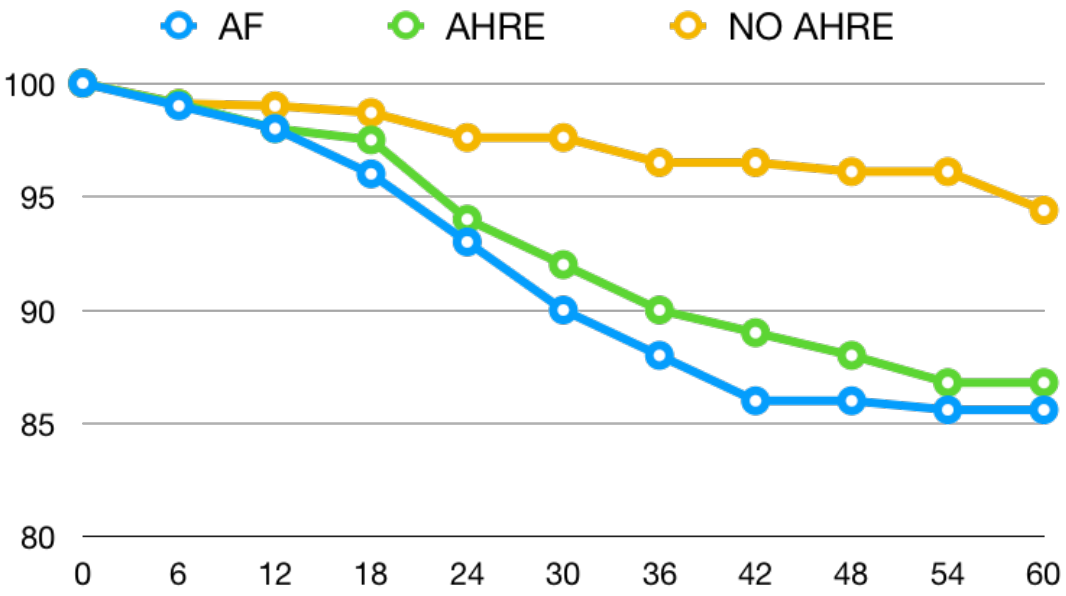

Figure 9. AHREs and HF hospitalizations (months).

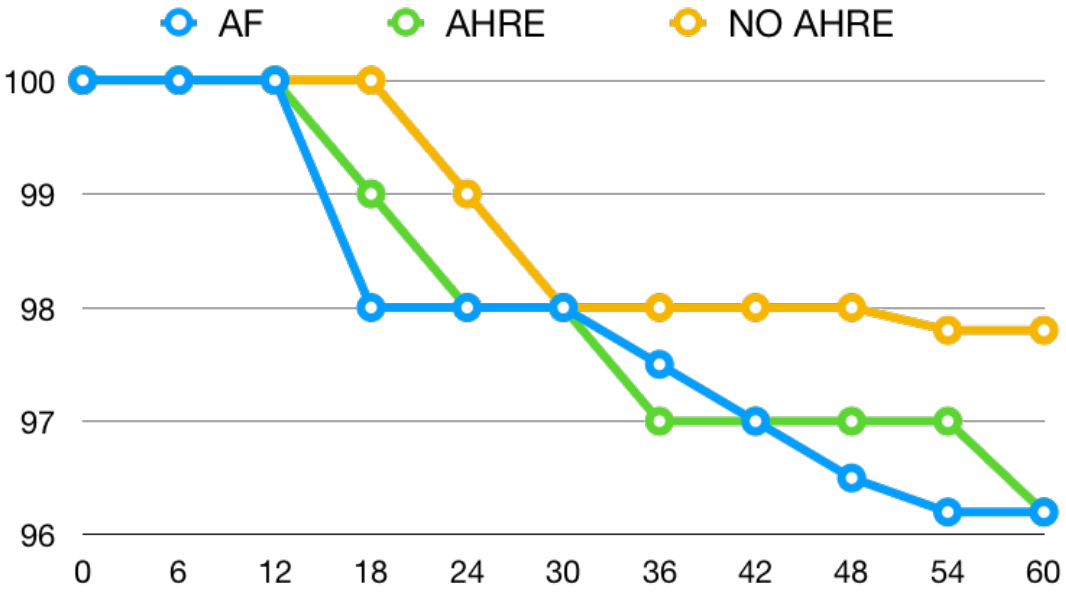

Figure 10. AHREs and acute myocardial infarction (months).

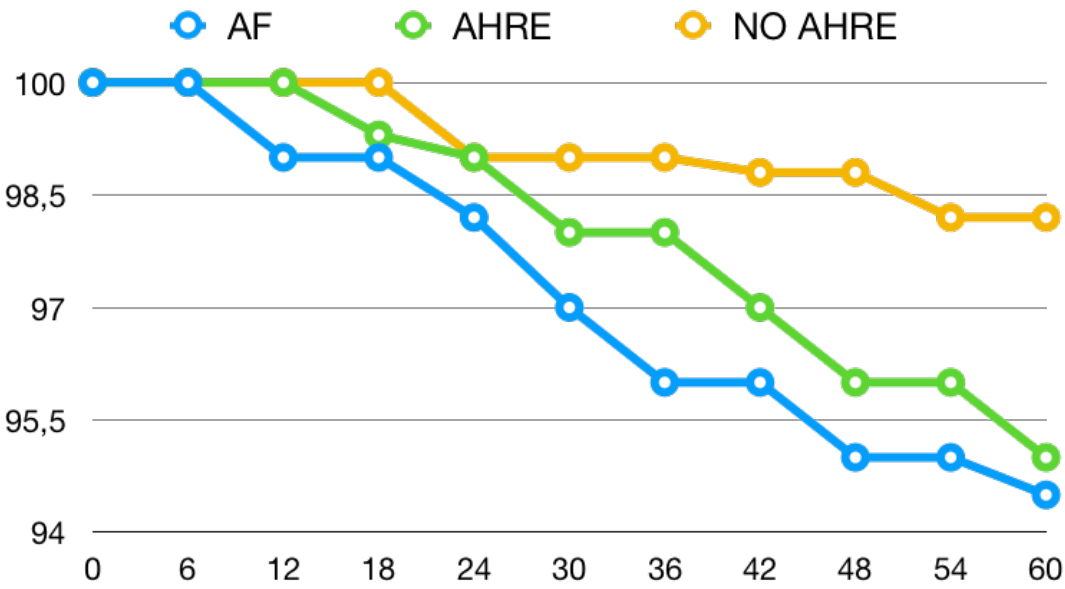

Figure 11. AHREs and cerebrovascular events (months).

Moreover recorded AHRE characteristics were analysed and correlated with outcome of studied population to understand if a better characterization of arrhythmic events could better stratify the population itself.

In these terms AHRE with AF morphology (SCAF) were related with worse outcome than AHRE with AT morphology (p=0,001).

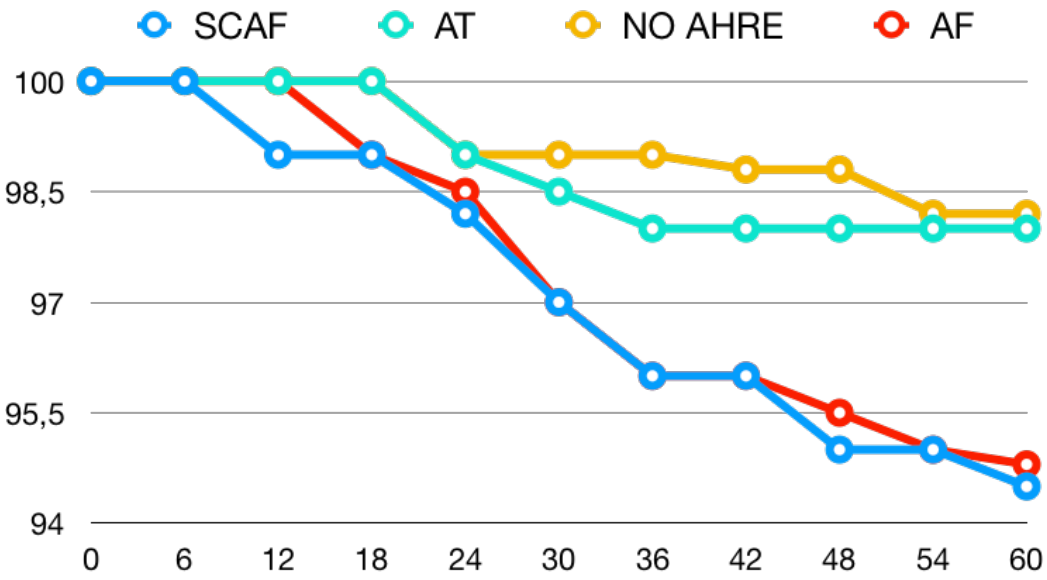

Figure 12. AHRE morphology and outcome (months).

In the same way AHRE with duration more than 1 day expose patients to worse outcome than AHRE between 6h and 24 h and even more than AHRE with duration between 6 minutes and 6 h.

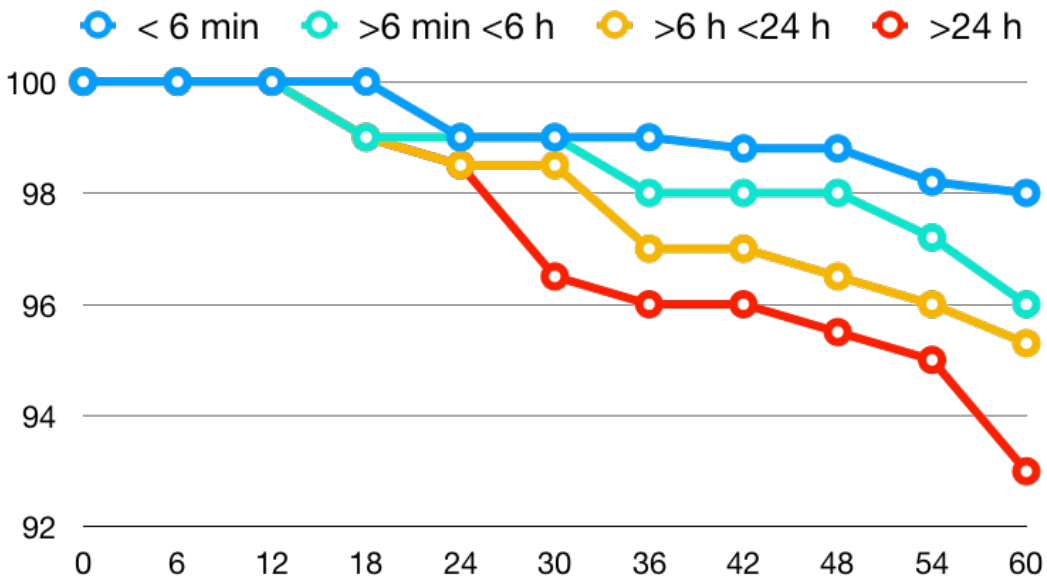

Figure 13. AHRE duration and outcome (months).

No differences were recorded considering asymptomaticity of AHRE or anticoagulant therapy.

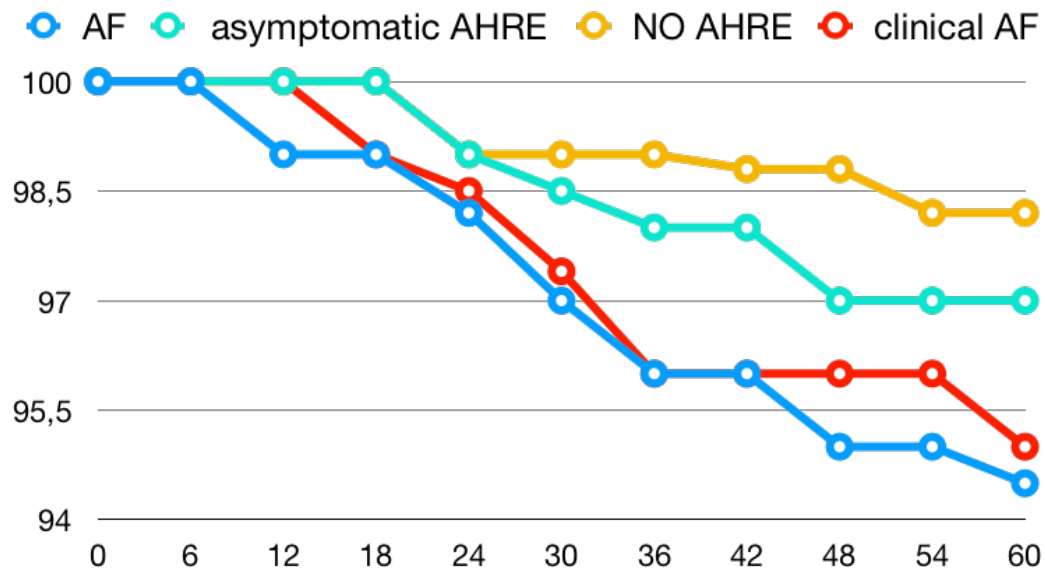

Figure 14. Symptoms of AHRE and outcome (months).

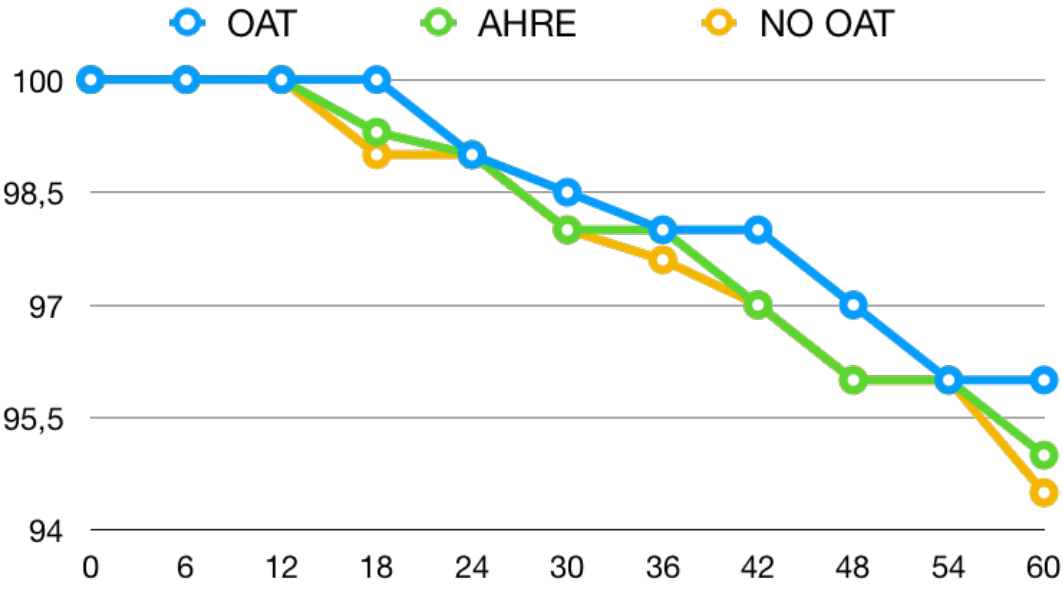

Figure 15. Oral anticoagulant therapy and outcome (months).

3.4 Conclusion of preliminary study

Exposed data showed the important role of AHRE in definition of prognosis of patients with CIEDs.

These data are in line with literature and confirm that AHREs represent an increasingly better known phenomenon that play an important role in AF and HF progression as well in cerebrovascular events incidence. These episodes seem to be a marker of the disease more than the cause of cerebrovascular events, considering that anticoagulation does not seem to impact on the onset of such adverse events.

With regard to the cohort of patients observed by us and the statistical data that emerged, we can affirm that not all the AHRE are the same.

An integrated evaluation of the AHREs in terms of duration, morphology and clinical presentation could better stratify these patients in order to identify subjects that need stricter follow-up or outpatient visits.

At last early identification of AHRE at follow up provides useful information to the clinician for the identification of patients at greater risk of adverse events and therefore should be taken more into consideration.

For all of these reasons remote monitoring could represent an important tool to follow up patients with already known heart failure to change prognosis focusing on AHRE identification and characterization.

4. MATERIALS AND METHODS

One hundred and sixty eight subjects of starting population (1683 patients) was selected for remote monitoring assignment according to CIED manufacture. Inclusion criteria included the presence of a bicameral CIED with possibility of remote monitoring, known heart failure and absence of AHRE and atrial fibrillation history.

Sixty-four remote monitoring systems were assigned to as many patients; one hundred and four subjects was considered as control group and followed with classical outpatients visits.

88 of enrolled patients were males and 80 females (52,4% and 47,6% respectively). Subjects with more than 18 years age were included with a mean age of 72± 3 years (with 95% C.I. from 68.3 to 74.8).

Patients were followed at the EP lab of Villa Sofia Hospital with regular annual checks independently of remote monitoring.

88,1% of studied population was implanted with a ICD and 11,9% had a CRTD.

Clinical characteristics showed a population with a mean EF of 32±6% and an ischemic aetiology in 80,3% of cases. All the patients have an history of Heart failure.

	Results
N° of Patients	**168**
Age	**72±3 years**
Male	**88 (52,4%)**
EF	**32±6%**
CAD	**135 (80,3%)**
Diabetes	**34 (20,2%)**
ICD DDD	**148 (88,1%)**
Virtual CHA_2DS_2-VASc	**3,1±0,4**
Follow-up	**28±5 months**

Table 10. Clinical characteristics of studied population

4.1 Follow up and Statistical analysis

Follow up of studied population was performed as during preliminary study and in the same way statistical analysis. Moreover patients of remote monitoring were followed everyday by remote monitoring system according with manufacture characteristics. When an index event occurs, like an AHRE or a ventricular arrhythmia, patients were contacted by phone to check clinical status.

5. RESULTS

During follow-up 233 AHRE episodes were recorded in 44 patients (97 AHRE in 16 case group patients vs 136 in 28 control group; p=n.s.). Mean atrial rate of these events was 236±25 bpm and only 9% were symptomatic. Duration was very variable with an average of 6±4 minutes. Regarding morphology, this was similar to atrial tachycardia in 39% of cases ad similar to atrial fibrillation in 58,4% of cases. 8 patients cross-over to permanent AF.

	Results
N° AHRE	233
Patients	44
Mean Atrial Rate	236±25 bpm
Mean Duration	6±4 min
AT Morphology	91 (39%)
AF Morphology	136 (58,4%)
Symptomatic AF	21 (9%)
Cross-over to permanent AF	8

Table 11. AHRE characteristics

53 adverse events occurred during follow-up. Composite outcome included cardiovascular death, heart failure and cerebro- or cardiovascular episodes. The outcome occurred in 8 cases during follow-up; 42 patients underwent to hospitalization for heart failure and 3 patient had a transient ischemic attack during observation

period. No myocardial infarctions were recorded and 5 patients had COVID 19.

According to the two arms of studied population heart failure episodes and the composite outcome occurred more frequently in control arm than case one as showed in Table N°12

Events	Remote Monitoring (64)	In Office Follow-up (104)	p value
DEATH (8)	3 (4,6%)	5 (4,8%)	n.s.
HF (42)	10 (15,6%)	32 (30,7%)	0,03
ICTUS/TIA (3)	1 (1,5%)	2 (1,9%)	n.s.
Composite outcome (53)	14 (21,8%)	39 (37,5%)	0,02
COVID 19 (5)	2 (3,1%)	3 (2,8%)	n.s.

Table 12. Adverse events according to study arms

The Kaplan Mayer curves showed that patients with remote monitoring have better outcome than control patients (p value <0.001).

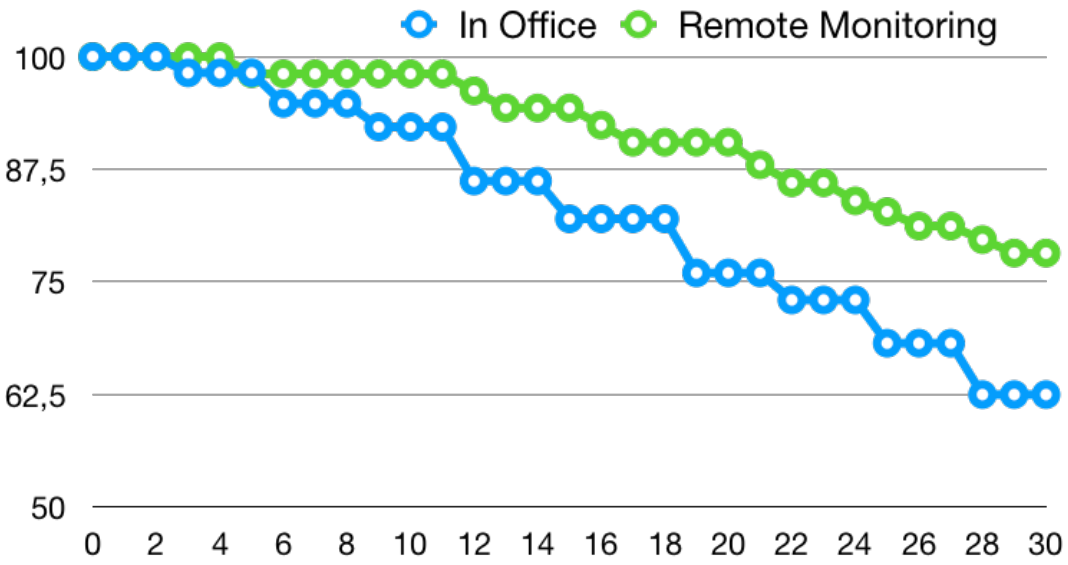

Figure 16. Survival curve according to remote monitoring or in-office follow up (months)

In the same way patients without AHREs showed a better prognosis than patients with AHREs (p value =0.03).

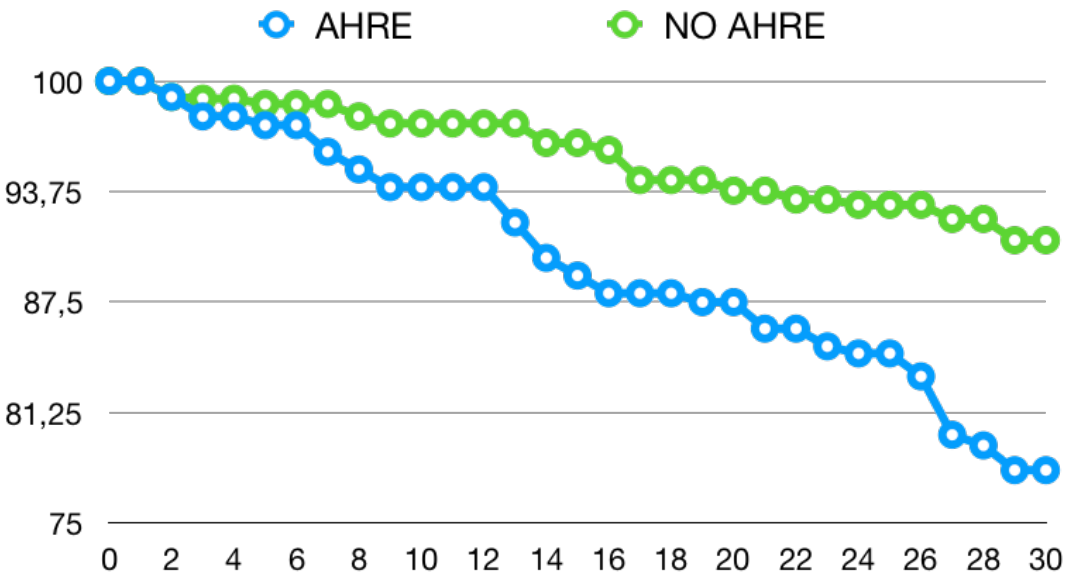

Figure 17. Survival curve according to presence of AHRE (months)

A better stratification of the study population was possible by differentiating the AHRE episodes according to their morphology, duration and others features.

5.1 The DArMoN Score

Starting from data of preliminary study regarding AHRE characteristics that can improve AHRE prognostic impact, a risk score was proposed and tested during the study.

This new predictive score was named **DArMoN** (Duration, Atrial rate, Morphology, Number) and consisting of a 0 to 5 score that included one point for a >6 minutes AHRE **D**uration; one point if **A**trial **r**ate is more than 200 bpm; 2 points if AHRE has an atrial fibrillation **Mo**rphology and 1 point if more than 5 AHREs (**N**umber) are detected 24h

These features were analysed by DArMoN score that showed a mean value of 2,1±0,4.

Distribution of DArMoN score according with two arms is reported in the Table 13.

DArMoN SCORE	Remote Monitoring AHRE (97AHRE in 16 pts)	In Office Monitoring AHRE (136AHRE in 28 pts)	p value
0	22 (22,7%)	26 (19,11%)	ns
1	14 (14,4%)	18 (13,2%)	ns
2	25 (25,7%)	38 (27,9%)	ns
3	20 (20,6%)	29 (21,3%)	ns
4	10 (10,3%)	15 (11%)	ns
5	6 (6,2%)	10 (7,3%)	ns

Table 13. DArMoN score distribution

A multivariate analysis was performed to understand the predictive role of DArMoN score showing that AHREs with higher DArMoN score (OR for 5 point score = 2,7 (1,3-5,7); p=0,04) were more predictive of an index event than AHREs with lower DArMoN score (OR for 1 point score = 1,3 (1,2-1,35); p=0,02) (Table 14).

Moreover time between AHRE and index event was shorter for AHRE with higher DArMoN score than for lower DArMoN score.

DArMoN SCORE (mean 2,1±0,4)	OR (CI); p-value
0	1,2 (0,84-1,38); p=n.s.
1	1,3 (1,2-1,35); p=0,02
2	1,7 (1,3-2,21); p=0,03
3	1,8 (1,6-1,9); p=0,01
4	2,3 (1,32-3,42); p=0,03
5	2,7 (1,3-5,7); p=0,04

Table 14. DArMoN score multivariate analysis.

A ROC curve analysis was performed and a sensitivity of 73,5 and a specificity of 80,8 was recorded for a DArMoN score ≥2.

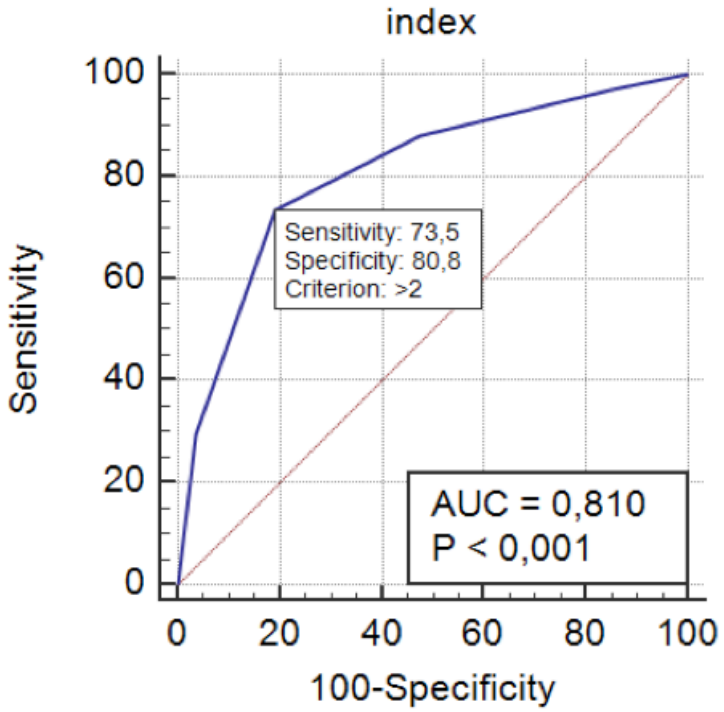

Figure 18. ROC curve analysis for DArMoN score ≥2

6. CONCLUSION

Data of PhD project showed the important role of remote monitoring in patients with heart failure and the prognostic impact of some kind of AHREs on outcome. This entity, until today, was underdiagnosed and undertreated due to asintomaticity and to unclear role in cerebrovascular events' determination. Recent literature data and our study results suggest that AHREs are an important marker of disease but not a pathogenetic cause. Despite this, before introduction of remote monitoring, the clinical impact of AHRE was low, due to possibility of their identification only at one year CIED follow up. Correlation between AHREs and heart failure hospitalization is emerging and, in this setting, role of early identification of this events is decisive to impact on prognosis of this patients. To improve predictive power of AHRE we proposed a new score, named DArMon, demonstrating that not all AHRE are the same in term of clinical impact, and early identification of specific events can change natural history of the disease. Clearly our study have some limitations: first of all, it is a single center experience with a reduced enrolled population; second, a selection bias could be present, considering patients' compliance to remote monitoring according to social and cultural skills. Moreover an important cross-over between two arms

was recorded (7,1%), due to pandemic emergency that accelerate telemedicine approach to follow up. Lastly a fair share of patients lost to follow up should be added to these limitations (17 subjects).

However, confirmed by recent data of the literature and by clinical experience, our data allow us to affirm that remote monitoring represent an important tool for the cardiologist and, to date, it is the gold standard for optimal follow up of patients with high-end devices like ICD or CRT. Remote monitoring can change survival rate alone, but even more when used analysing specific subclinical events like AHREs. An integrative approach to this setting of HF patients should be always considered to better identify patients with higher risk of adverse outcome, combining clinical, laboratory and device-related parameters for stricter and optimized follow up.

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