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CLINICAL RESEARCH

Ability to remotely monitor atrial high-rate episodes using a single-chamber implantable cardioverter-defibrillator with a floating atrial sensing dipole

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Aims

To allow timely initiation of anticoagulation therapy for the prevention of stroke, the European guidelines on atrial fibrillation (AF) recommend remote monitoring (RM) of device-detected atrial high-rate episodes (AHREs) and progression of arrhythmia duration along pre-specified strata (6 min…<1 h, 1 h…<24 h, ≥ 24 h). We used the MATRIX registry data to assess the capability of a single-lead implantable cardioverter-defibrillator (ICD) with atrial sensing dipole (DX ICD system) to follow this recommendation in patients with standard indication for single-chamber ICD.

Methods and results

In 1841 DX ICD patients with daily automatic RM transmissions, electrograms of first device-detected AHREs per patient in each duration stratum were adjudicated, and the corresponding positive predictive values (PPVs) for the detections to be true atrial arrhythmia were calculated. Moreover, the incidence and progression of new-onset AF was assessed in 1451 patients with no AF history. A total of 610 AHREs ≥6 min were adjudicated. The PPV was 95.1% (271 of 285) for episodes 6min…<1 h, 99.6% (253/254) for episodes 1 h…<24 h, 100% (71/71) for episodes ≥24 h, or 97.5% for all episodes (595/610). The incidence of new-onset AF was 8.2% (119/1451), and in 31.1% of them (37/119), new-onset AF progressed to a higher duration stratum. Nearly 80% of new-onset AF patients had high CHA_2DS_2-VASc stroke risk, and 70% were not on anticoagulation therapy. Age was the only significant predictor of new-onset AF.

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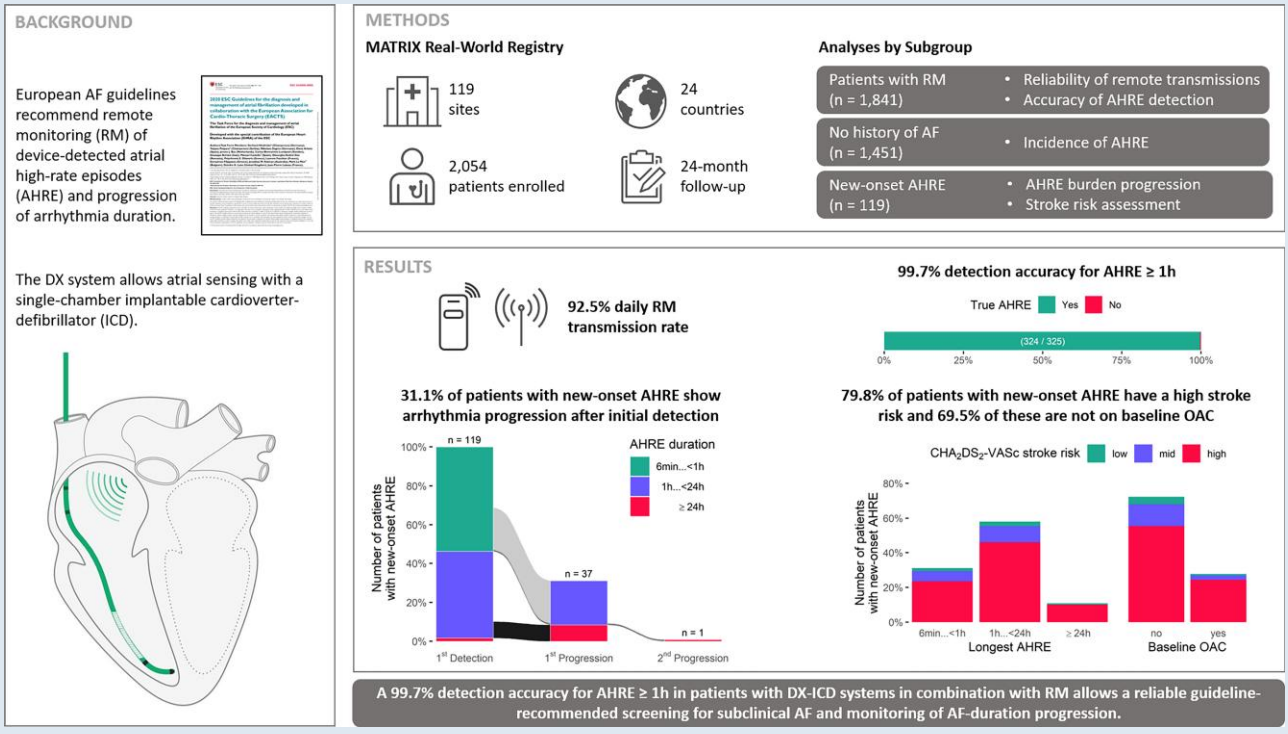
Conclusion A 99.7% detection accuracy for AHRE ≥1 h in patients with DX ICD systems in combination with daily RM allows a reliable guideline-recommended screening for subclinical AF and monitoring of AF-duration progression.

Graphical Abstract



Keywords Single-lead ICD with atrial sensing • DX ICD • Atrial fibrillation • AHRE • Remote monitoring • Risk of stroke

What's new?

- In accordance with the recommendation of European guidelines on atrial fibrillation to monitor remotely device-detected atrial high-rate episodes (AHREs) and progression of AHRE duration along pre-specified strata (6min…<1 h, 1 h…<24 h, ≥ 24 h) in order to allow timely initiation of anticoagulation therapy for stroke prevention, we evaluated the ability of a single-lead implantable cardioverter-defibrillator (ICD) with atrial sensing dipole (the DX ICD system) to serve this purpose in patients with a standard indication for single-chamber ICD.
- In 1841 DX ICD patients with daily automatic remote monitoring transmissions over 2 years, intracardiac electrograms of first device-detected AHREs per patient in each duration stratum (total 610 AHREs) were adjudicated, and the corresponding positive predictive values (PPVs) for the detections to be true atrial arrhythmia were calculated.
- The PPV was 95.1% for episodes 6min…<1 h, 99.6% for episodes 1 h…<24 h, and 100% for episodes ≥24 h. This detection accuracy allows reliable guideline-recommended remote monitoring of subclinical atrial fibrillation.

Introduction

The most common sustained cardiac arrhythmia, atrial fibrillation (AF), is associated with an up to five-fold increase in the risk of stroke, up to 3.5-fold higher all-cause mortality, and congestive heart failure in 20–30% of patients.[1] With an estimated prevalence of 2–4% in adults, AF poses a significant burden on healthcare systems, which is expected to increase due to aging population.[1] The 2020 European Society of Cardiology guidelines for the diagnosis and management of AF (hereafter referred to as the 'European AF guidelines') recommend an integrated AF management by multidisciplinary teams, preferably using the 'ABC pathway' with anticoagulation for stroke prevention as the first step.[1] However, the often asymptomatic nature of AF hampers the diagnosis and treatment of AF.[1,2]

Cardiovascular implantable electronic devices (CIEDs) with an atrial lead allow automated continuous monitoring of the atrial rhythm and storage of the intracardiac electrograms (IEGMs) related to arrhythmia.[1–3] Atrial high-rate episodes (AHREs) detected in a growing number of CIED patients are associated with an increased risk of thromboembolic events in correlation with AHRE burden and the CHA_2DS_2-VASc score.[1,2,4,5] To enable timely initiation of anticoagulation therapy, the European AF guidelines recommend monitoring of AHRE progression with the support of remote CIED monitoring.[1]

Of all implanted CIEDs, one-third are implantable cardioverter-defibrillators (ICDs).[5,6] Implantable cardioverter-defibrillator candidates without antibradycardia indications can receive a single-chamber ICD without an atrial lead to reduce the procedure time and related complications.[7–9] An alternative solution is a DX ICD system capable of atrial signal detection via a floating atrial sensing dipole integrated in the ICD lead and offering atrial IEGM recordings and arrhythmia

discrimination similar to that in dual-chamber ICD devices.[10–13] The aims of the present study were (i) to evaluate the ability of a DX ICD system to remotely monitor AHREs and their duration progression and (ii) to analyse the clinical implications of the AHRE detection and progression findings in the light of existing literature and the European AF guidelines.

Methods

The Management and Detection of Atrial Tachyarrhythmias in Patients Implanted with Biotronik DX Systems (MATRIX) was a prospective, single-arm, multicentre registry study with 2041 patients followed for 2 years. To meet the enrolment criteria, patients had to be at least 18 years old and to have a DX ICD system recently implanted based on a standard single-chamber ICD indication for primary or secondary prevention of sudden cardiac death. Exclusion criteria were life expectancy <2 years, malignant disease, pregnancy, breast-feeding, and participation in another study. All patients gave written informed consent. Relevant national and local ethics committees approved the protocol of the study which was conducted in accordance with the guidelines for good clinical practice and the Declaration of Helsinki (ClinicalTrials.gov Identifier: NCT01774357).

The DX ICD system

All MATRIX patients received Lumax 540 VR-T DX ICD or a successor model (Biotronik SE & Co. KG, Berlin, Germany). The input stage of these devices amplifies the atrial signal up to four-fold.[12] The SMART algorithm was used to discriminate between ventricular and supraventricular tachyarrhythmias.[10,12] Detected arrhythmia episodes, including AF, are stored in the implant memory along with ≈30 s dual-chamber IEGM recordings. The DX ICD device was combined with the Linox^{smart} S DX screw-in lead that incorporates a widely spaced floating atrial sensing dipole (for lead description and dimensions, see Supplementary material online, *Figure S1* in Supplementary material online, *Appendix*).

Equipped with the Biotronik Home Monitoring® technology, hereafter referred to as 'Home Monitoring®',[14] the implanted device transmitted recorded diagnostic and therapy data automatically every night to a receiver located in the patient's home. The receiver relayed the remote data and IEGM recordings via mobile phone links to be posted on a secured webpage for online review by the treating physician.

Study procedures

At enrolment, patient demographic and medical data were collected. The patients were followed up for 24 months according to the centre's routine follow-up scheme, and the Home Monitoring® option was recommended. Adverse events, including thromboembolic events, were reported. Clinical data came from routine procedures with no mandatory steps or assessments required by study protocol. The only exception was rating of atrial signal detection by investigators on a scale from 1 (excellent) to 5 (poor) at enrolment and during in-office follow-ups.

Background and objectives of the present analysis

The European AF guidelines recommend a combination of remote monitoring of AHRE burden (i.e. subclinical AF burden after a confirmation that AHRE represents true atrial tachyarrhythmia) and a regular re-assessment of stroke risk by the CHA_2DS_2-VASc score. Based on this information, administration of oral anticoagulation may be considered in selected patients with high stroke risk if there are no doubts on AF diagnosis at device tracings analysis and if a net clinical benefit can be anticipated.[1] Since AHRE burden is a dynamic category that can progress quickly, already a detection of AHRE episodes lasting for 5–6 min is of interest, while anticoagulation can be considered for episodes ≥1 h when daily burden is high.[1]

The present data analysis of the MATRIX registry has two objectives: (i) to evaluate the ability of a DX ICD system to remotely monitor AHREs and progression of arrhythmia duration (i.e. to implement the guideline-recommended remote monitoring of subclinical AF) and (ii) to analyse the clinical implications of findings on AHRE detection and progression.

In addition, we present the investigators' assessment of atrial signal detection quality at in-office follow-ups and 2-year data on atrial sensing amplitudes (stability and magnitude) obtained through automatic daily Home Monitoring® in this large cohort of patients with DX ICD devices.

The ability of a DX ICD system to remotely monitor atrial high-rate episodes

An independent external electrophysiologist (see Supplementary material online, *Appendix*) evaluated the accuracy of patient-wise (i) first detected AHRE lasting for ≥6 min and (ii) first detected AHRE per three duration strata: 6 min to <1 h, 1 h to <24 h, and ≥24 h. The positive predictive values (PPVs) for AHRE detections to be true atrial arrhythmia were calculated, and the reasons for misclassification were noted. The analysis was performed on patients with Home Monitoring® transmissions.

Incidence of new-onset atrial high-rate episodes and arrhythmia duration progression

The incidence of new-onset AHRE ≥6 min and progression of episode duration along duration strata, ≥ 6min…<1 h, 1 h…<24 h, and ≥24 h, was quantified in the Subgroup 'No AF history', comprising Home Monitoring® patients without AF history. Only episodes showing AF in the intracardiac electrogram were considered. The risk of thromboembolic events was summarized in new-onset AF patients, according to the CHA_2DS_2-VASc score and anticoagulation therapy status.

Clinical risk factors for new-onset AF were evaluated using ten covariates obtained at baseline: age, sex, body mass index, ICD indication (primary vs. secondary prevention), congestive heart failure, ischaemic aetiology, hypertension, diabetes, and mid- and high stroke risks based on the CHA_2DS_2-VASc score. Since some of these covariates are part of the CHA_2DS_2-VASc score, two separate models were calculated to avoid a bias due to collinearity.

Atrial signal detection quality and P-wave amplitudes

The ratings of atrial signal detection quality by investigators are summarized. The 2-year Home Monitoring® data on atrial sensing amplitudes were analysed in the Home Monitoring® patients with no history of long-standing persistent or permanent AF. A technical limitation was that remotely transmitted P-wave amplitudes >8 mV were not available by value but labelled as '>8 mV'. These values are not included in calculations. An overview of data evaluations and the corresponding patient subgroups is provided in *Figure 1*.

Statistical methods

The sample size of 2000 patients was projected based on the expectation that a yearly incidence of stroke in MATRIX cohort would be ≈10 per 1000 people,[15] which should translate into 30–40 strokes in 2000 patients over 2 years assuming a < 15% drop-out rate. This number of strokes and other possible complications was supposed to enable exploratory subgroup analyses after completion of the study.

Continuous data are reported as mean ± standard deviation or median with interquartile range (IQR) and minimum–maximum. Categorical data are reported as absolute and relative frequencies. The PPVs for AHRE detection accuracy and the corresponding confidence intervals (CI) were calculated for the binomial distribution. Independent clinical risk factors for new-onset AF were evaluated by a multivariable Cox proportional hazards model. The analyses were performed using the SAS for Windows (Version 9.4 or higher; SAS Institute Inc., Cary, NC, USA) and R (Version 4.0; R Core Team 2020, https://www.R-project.org/) statistical software.

Results

General analysis population and its characteristics at baseline

Between 14 January 2013 and 31 March 2016, a total of 2054 patients were enrolled at 119 sites in 24 countries (see Supplementary material

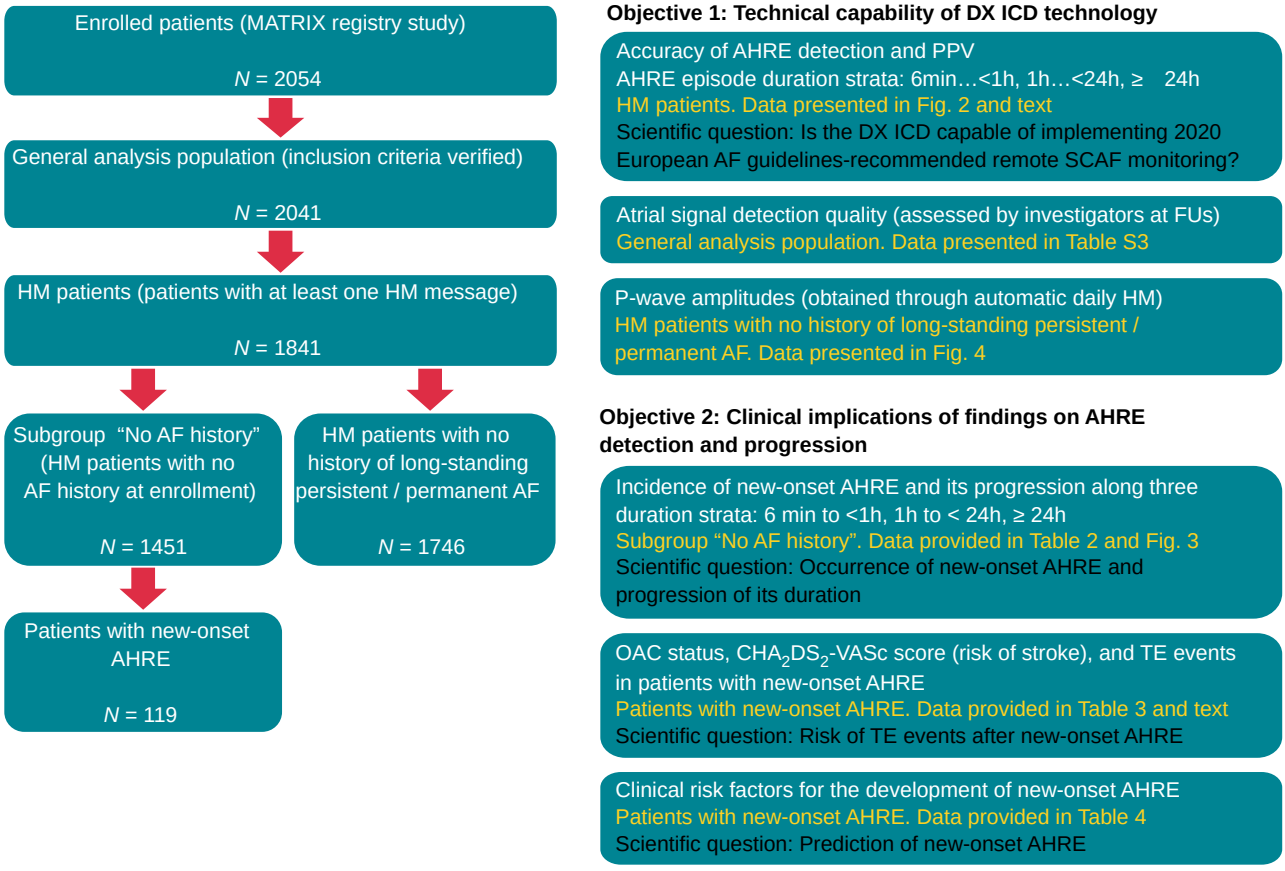


Figure 1 Formation of the subgroups used in different evaluations and the overview of evaluations (Objectives 1 and 2). Abbreviations: AF, atrial fibrillation; AHRE, atrial high-rate episode; CHA_2DS_2-VASc, stroke risk score combining Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke (two points), Vascular disease, Age 65–74 years, and Sex category (female); DX ICD, single-lead implantable cardioverter-defibrillator system capable of atrial sensing via floating dipole; FU, in-office follow-up; HM, Home Monitoring; OAC, oral anticoagulation; PPV, positive predictive value; SCAF, subclinical atrial fibrillation; TE event, thromboembolic event.

online, Appendix *Tables S1A* and *S1B*). Thirteen patients were excluded early due to participation in another study ($n = 6$), malignancy ($n = 4$), and implantation of an inappropriate device ($n = 3$). The remaining 2041 patients represented the general analysis population, hereafter referred to as 'All patients'. Patients were relatively young at enrolment (mean age <60 years) and mostly had only mild or no symptoms of heart failure (*Table 1*). AF was known in 443 patients (21.7%), one third of which had no AF-related symptoms. Previous stroke was reported in 123 (6.0%) and any thromboembolic event in 208 (10.2%) patients. According to the CHA_2DS_2-VASc score, 1650 (80.9%) patients had a high risk of stroke at baseline (i.e. score ≥2 in men and ≥3 in women) and 630 (30.9%) were on oral anticoagulation therapy (*Table 1*).

Patients were enrolled at 15 ± 22 days after DX ICD implantation. Implanted devices are summarized in Supplementary material online, *Table S2* in the Supplementary material online, *Appendix*.

Follow-up data and Home Monitoring®

The mean follow-up period after enrolment was 677 ± 173 days (median 727, IQR 685–759). Regular study termination after 2 years was achieved in 1641 (80.4%) patients. Among 400 patients with premature study termination, 145 died (7.1% of general analysis population), 140 were lost to follow-up (6.9%), 57 had their DX ICD system explanted (2.8%), 43 withdrew consent (2.1%), and 15 dropped out for other reasons (0.7%). The devices were explanted because of heart transplant ($n = 17$), upgrade to cardiac resynchronization therapy defibrillator ($n = 12$) or dual-chamber ICD ($n = 4$), infection ($n = 15$), lead defect or malfunction ($n = 8$), or other reasons ($n = 1$).

At least one Home Monitoring® message was transmitted in 1841 patients (90.2%, referred to as 'Home Monitoring® patients'). The transmission performance, defined as the number of days with Home Monitoring® transmission divided by the number of days during follow-up period in these patients was 85.4% ± 18.2% (median 92.5%, IQR 81.4–97.3%).

Accuracy of atrial high-rate episode detection

In 327 of 1841 Home Monitoring® patients (17.8%), 26 905 AHREs lasting for ≥6 min and with an IEGM for adjudication were detected, or 82 ± 141 AHREs on average per patient. For practical reasons, the adjudication was limited to the first occurring AHRE in each patient. True atrial tachyarrhythmia was found in 313 of 327 cases, corresponding to a PPV of 95.7% (95% CI: 92.9–97.6%). Of the 313 true AHREs, AF was the underlying arrhythmia in 309 (98.7%) cases.

Table 1 Characteristics of patients at enrolment

Parameter	All patients ($n = 2041$)	[a]Subgroup 'No AF history' ($n = 1451$)
Age, years	59.9 ± 13.0	58.1 ± 13.1
Male gender	1652 (81.0)	1163 (80.2)
Body mass index, kg/m^2	27.5 ± 5.2	27.3 ± 5.1
New York Heart Association class		
No heart failure	526 (25.8)	424 (29.3)
I	306 (15.0)	214 (14.8)
II	846 (41.5)	593 (40.9)
III	331 (16.2)	202 (13.9)
IV	28 (1.4)	16 (1.1)
LVEF, % (data availability 86%)	35.3 ± 14.0	35.7 ± 14.4
Congestive heart failure	1442 (70.7)	969 (66.8)
Primary prevention ICD indication[b]	1276 (62.6)	926 (63.8)
Ischaemic heart failure aetiology	1068 (52.4)	767 (52.9)
Hypertension	966 (47.4)	646 (44.5)
Diabetes	546 (26.8)	356 (24.5)
Chronic kidney disease	216 (10.6)	122 (8.4)
COPD	180 (8.8)	107 (7.4)
Sleep apnoea	86 (4.2)	54 (3.7)
Known history of AF	443 (21.7)	0
Paroxysmal	260 (12.8)	0
Persistent (>7 days, up to 1 year)	76 (3.7)	0
Long-standing persistent (>1 y)	107 (5.2)	0
Oral anticoagulation	630 (30.9)	296 (20.4)
History of stroke	123 (6.0)	71 (4.9)
History of any TE[c]	208 (10.2)	130 (9.0)
CHA_2DS_2-VASc score		
0	91 (4.5)	80 (5.5)
1	237 (11.6)	187 (12.9)
2	376 (18.4)	294 (20.3)
3	483 (23.7)	344 (23.7)
4	409 (20.1)	280 (19.3)
5	259 (12.7)	159 (11.0)
6	115 (5.6)	70 (4.8)
7	55 (2.7)	33 (2.3)
8	13 (0.6)	4 (0.3)
9	1 (0)	0
CHA_2DS_2-VASc stroke risk		
Low (0 male, 1 female)	127 (6.2)	112 (7.7)
Mid (1 male, 2 female)	262 (12.8)	209 (14.4)
High (≥2 male, ≥ 3 female)	1650 (80.9)	1130 (77.9)

Data are shown as mean ± standard deviation or *n* (%, of available data). Data availability is 98–100% unless otherwise stated.
AF, atrial fibrillation; CHA_2DS_2-VASc, stroke risk score combining Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke (two points), Vascular disease, Age 65–74 years, and Sex category (female); COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; TE, thromboembolic event.
[a]Excluding patients who did not have any Home Monitoring message transmitted.
[b]In the remaining patients, secondary prevention ICD indication.
[c]Stroke, transient ischaemic attack, or peripheral arterial embolism.

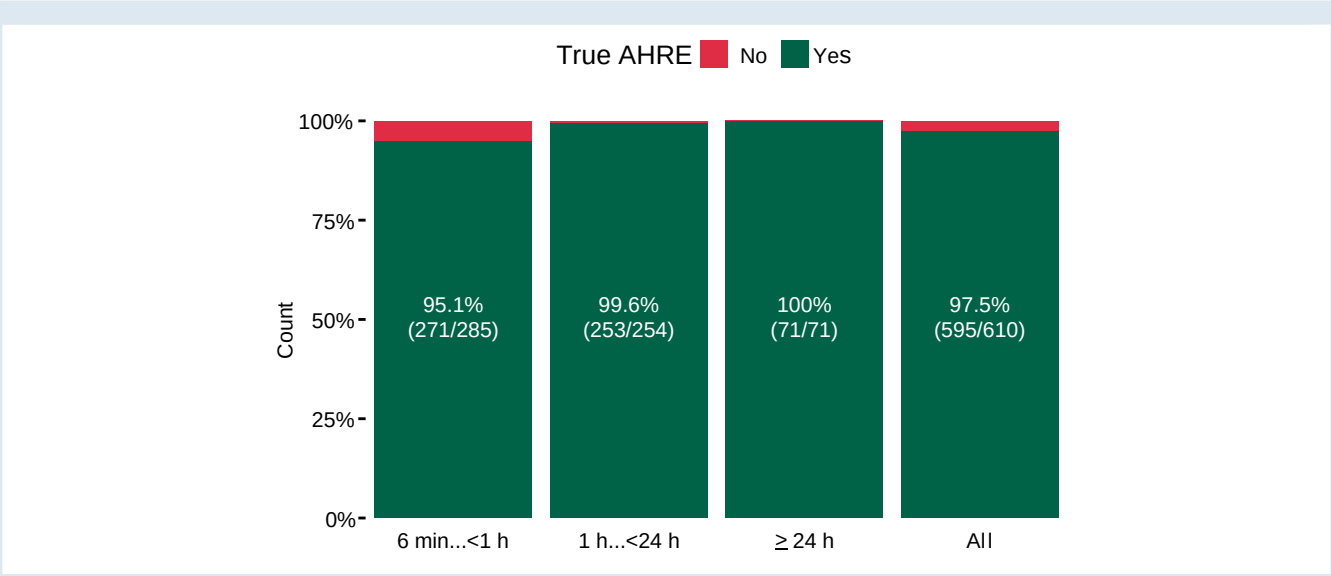


Figure 2 Adjudication outcome for the first atrial high-rate episode (AHRE) in each duration stratum in 327 patients with AHREs ≥6 min. The percentage of true positive detections increased from 95.1% for AHREs <1 h to 100% for AHREs ≥24 h. The reason for 15 false-positive detections were atrial sensing artefacts ($n = 13$) and R-wave oversensing ($n = 2$).

Table 2 Progression of episode duration in new-onset atrial high-rate episode patients

	New-onset AHRE (AF) duration[a]			
	6min…<1 h ($n = 64$)	**1 h…<24 h ($n = 53$)**	**≥24 h ($n = 2$)**	**Total ($n = 119$)**
No progression	37 (57.8)	43 (81.1)	2 (100)	82 (68.9)
Progression				
1 h…<24 h	26 (40.6)	—	—	26 (21.8)
≥ 24 h	1 (1.6)	10 (18.9)	—	11 (9.3)
Total	27 (42.2)	10 (18.9)	0	37 (31.1)

Data are shown as *n* (%). AF, atrial fibrillation; AHRE, atrial high-rate episode.
[a]In all cases, new-onset AHRE episode was AF.

The broader assessment according to AHRE duration strata, with 610 contributing episodes in 327 patients as some patients had episodes in two or three strata, showed a rate of true positive detections ranging from 95.1% for AHRE duration 6min…<1 h, 99.6% for AHRE duration 1h…<24 h to 100% for AHRE duration ≥24 h (*Figure 2*). The PPV for pooled AHRE durations was 97.5% (95% CI: 96.0–98.6%).

Incidence of new-onset atrial high-rate episode and progression of atrial high-rate episode duration

After exclusion of 390 Home Monitoring® patients with a history of AF at baseline, the Subgroup 'No AF history' had 1451 candidates for a new-onset AF detection through Home Monitoring®. The new-onset AHRE (≥6 min) occurred in 119 patients (8.2%); in all cases, intracardiac electrogram showed AF. The first AF episode lasted for <1 h in 64 (53.8%) patients, between 1 and 24 h in 53 (44.5%) patients, and ≥24 h in 2 (1.7%) patients (*Table 2*). In 31.1% of new-onset AF cases, episode duration progressed to a stratum of longer duration (*Table 2*, *Figure 3*).

By the end of follow-up, 13 of 119 new-onset AF patients had episode(s) ≥ 24 h (0.9% of the Subgroup 'No AF history'), 69 had longest episode(s) 1 h…<24 h (4.8%), and 37 had longest episode(s) 6min…<1 h (2.5%).

The Subgroup 'No AF history' had very similar baseline characteristics to all patients (*Table 1*), except for the lower use of oral anticoagulants (20.4% vs. 30.9%) and a slightly lower prevalence of congestive heart failure (66.8% vs. 70.7%).

Anticoagulation status, CHA_2DS_2-VASc score, and thromboembolic events in new-onset atrial fibrillation patients

Of the 119 patients with new-onset AF, 86 (72.3%) were not on anticoagulation therapy at baseline, including 66 patients with a high risk of stroke, 15 with mid risk, and 5 with low risk. Among 33 (27.7%) anticoagulated patients, 29 had a high risk (*Table 3*).

A thromboembolic event eventually occurred in 4 (3.4%) of 119 new-onset AF patients, including transient ischaemic attack at 88 days after the last AHRE and peripheral arterial embolism at 22, 83, and 191 days after the last AHRE. All four patients were at high risk of stroke, with a CHA_2DS_2-VASc score of 4, 4, 5, and 7, respectively. Only the patient with the score 5 was on oral anticoagulation at baseline and had an underlying cause of thromboembolism other than AF.

Clinical risk factors for new-onset atrial fibrillation

The analysis of clinical risk factors identified only age as an independent predictor of new-onset AF, with a hazard ratio of 1.02 per year (i.e. 1.20 per 10 years; $P = 0.017$). No other covariate had a statistically significant predictive power. There was a tendency for male sex ($P = 0.10$), secondary prevention ICD indication ($P = 0.15$), congestive heart failure ($P = 0.20$), and both high ($P = 0.15$) and mid ($P = 0.19$)

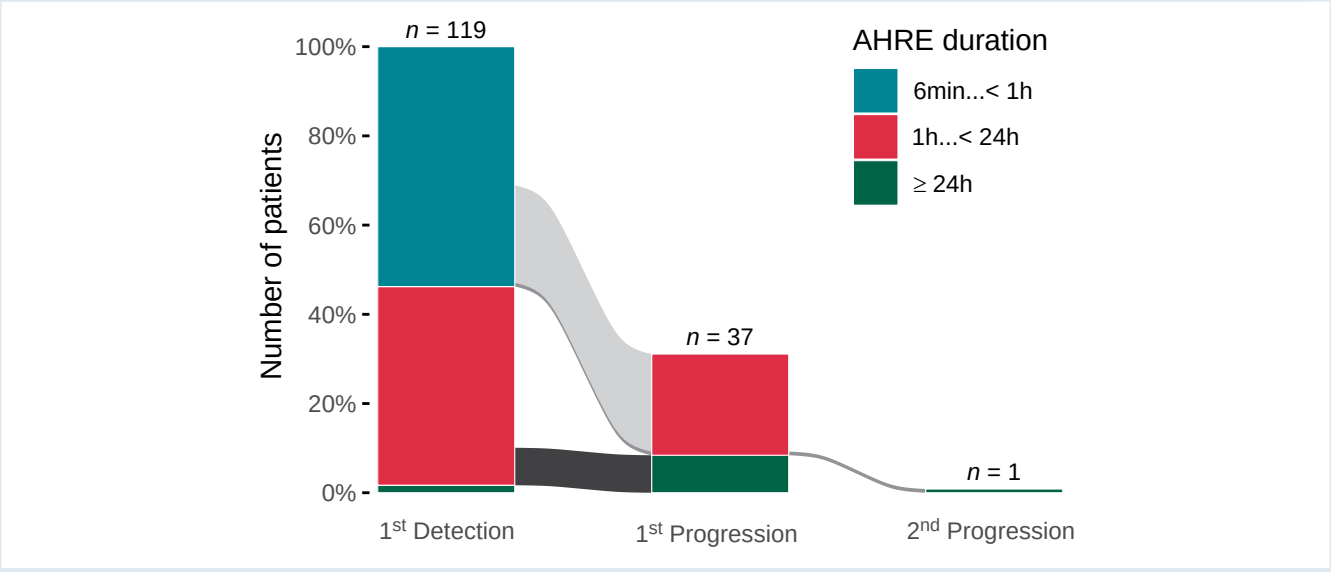


Figure 3 Sankey flow chart showing progression of atrial high-rate episode (AHRE) duration along three strata in 119 patients with new-onset atrial fibrillation (AF) confirmed by intracardiac electrogram.

Table 3 Anticoagulation status and CHA_2DS_2-VASc stroke risk in new-onset AF patients

CHA_2DS_2-VASc stroke risk	OAC: No	OAC: Yes	All
High (CHA_2DS_2-VASc score ≥2 male, ≥ 3 female)	66 (55.5)	29 (24.4)	95 (79.8)
Mid (CHA_2DS_2-VASc score 1 male, 2 female)	15 (12.6)	3 (2.5)	18 (15.1)
Low (CHA_2DS_2-VASc score 0 male, 1 female)	5 (4.2)	1 (0.8)	6 (5.0)
All	86 (72.3)	33 (27.7)	119 (100)

Data are shown as *n* (% of 119 new-onset AF patients).
AF, atrial fibrillation; CHA_2DS_2-VASc score, a stroke risk score combining Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke (two points), Vascular disease, Age 65–74 years, and Sex category (female); OAC, oral anticoagulation.

Table 4 Clinical risk factors for new-onset AF (multivariable cox regression analysis)

Baseline variable	Hazard ratio (95% CI)	*P* value
All covariates except for CHA_2DS_2-VASc stroke risk		
Age (1-year increment)	1.02 (1.00–1.04)	**0.017**
Male gender	1.55 (0.92–2.61)	0.10
Body mass index (1 kg/m^2 increment)	1.00 (0.97–1.04)	0.82
Secondary prevention ICD indication	1.33 (0.90–1.97)	0.15
Congestive heart failure	1.33 (0.86–2.06)	0.20
Ischaemic aetiology	0.85 (0.57–1.25)	0.40
Hypertension	1.14 (0.77–1.68)	0.51
Diabetes	0.71 (0.44–1.13)	0.15
Covariates that are not integral part of CHA_2DS_2-VASc stroke risk plus mid and high stroke risks		
Body mass index (1 kg/m^2 increment)	1.00 (0.96–1.04)	0.99
Secondary prevention ICD indication	1.31 (0.90–1.90)	0.16
Ischaemic aetiology	0.97 (0.64–1.46)	0.87
Mid CHA_2DS_2-VASc stroke risk[a]	1.85 (0.73–4.70)	0.19
High CHA_2DS_2-VASc stroke risk[a]	1.93 (0.79–4.68)	0.15

AF, atrial fibrillation; CHA_2DS_2-VASc, stroke risk score combining Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke (two points), Vascular disease, Age 65–74 years, and Sex category (female); CI, confidence interval; ICD, implantable cardioverter-defibrillator.
[a]For the definition, see *Table 1*.

CHA_2DS_2-VASc stroke risks to be associated with the development of new-onset AF (*Table 4*).

Atrial signal detection quality and P-wave amplitudes

The investigators rated atrial signal detection quality as excellent in 65.0%, good in 26.3%, adequate in 5.0%, and unsatisfactory or poor in 3.7% of patients during the follow-up period of 2 years (see Supplementary material online, *Appendix Table S3*).

Home Monitoring® data in the 1746 Home Monitoring® patients without history of long-standing persistent or permanent AF showed a stable mean (4.4 ± 2.0 mV) and median (4.6 mV, IQR 2.8–6.2 mV) value of the patient-wise median right atrial sensing amplitudes during 2 years of follow-up. In 95.6% of all transmitted measurements, the right atrial sensing amplitude was ≥1.0 mV. As seen in *Figure 4*, distribution of patient-wise overall median sensing amplitudes was broad, while the time course of patient-wise monthly median values was stable.

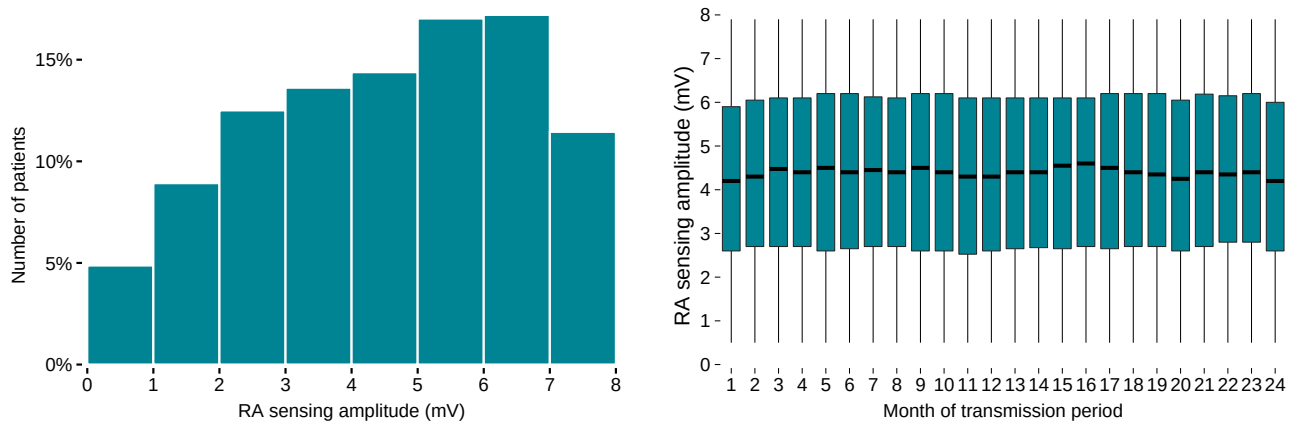


Figure 4 Right atrial (RA) sensing amplitudes in 1746 patients with Home Monitoring® messages and no history of long-standing persistent or permanent atrial fibrillation at enrolment. Left-side panel: distribution of patient-wise median values. Right-side panel: median (interquartile range, minimum–maximum) amplitudes per patient and month.

Discussion

Technical capability of DX ICD systems

The MATRIX study is the largest clinical investigation of DX ICD systems to date, with 2041 patients followed for 2 years by automatic, daily remote monitoring. The single-chamber ICD with atrial sensing capabilities correctly classified 97.5% of all adjudicated device-detected AHREs ≥6 min. The PPV for AHRE detection increased with episode duration, from 95.1% for episodes <1 h to 99.7% for ≥1 h. A reliable detection of episodes ≥1 h is especially important in monitoring AHRE duration progression and in oral anticoagulation decision making.[1]

To our knowledge, this is the first study of DX ICD patients evaluating the accuracy of AHRE detection for episode durations relevant for AF management. In previous studies, the rate of incorrect AHRE detections ranged from 13% to 48% for unselected episode durations, most of which were short.[12,13,16,17] Very short AHRE episodes (≤10–20 s/day) are considered clinically irrelevant for AF management, as they are not significantly associated with longer episodes or with an increased risk of stroke or systemic embolism.[1] Two recent smaller studies showed a 2.45 to 3.85 greater likelihood of detecting AHREs or subclinical AF with a DX ICD system than with a conventional single-chamber ICD,[17–19] whereas no difference was found between DX ICD and dual-chamber ICD.[17]

A PPV of 99.7% for AHREs ≥1 h in combination with a 92.5% median Home Monitoring® transmission performance (days with Home Monitoring® messages) in patients with active Home Monitoring®, shown in the present high-volume DX ICD study in an unselected, real-life clinical setting, allows a reliable guideline-recommended remote monitoring of subclinical AF in the vast majority of patients.

Clinical implications and literature discussion

During the study, 8.2% of patients with no AF history presented with AF episodes ≥6 min. Most of these patients also had episodes ≥1 h (5.7% of the Subgroup 'No AF history') or ≥24 h (0.9%). The use of oral anticoagulants at baseline in new-onset AF patients was uncommon (27.7%) and was only marginally greater in a subset with high risk of stroke (30.5%). New-onset AF patients not being on anticoagulation (4–6% of the Subgroup 'No AF history') would potentially benefit from a guideline-conform AF monitoring strategy targeting timely prescription of anticoagulants.

According to the European AF guidelines, AHRE episodes (i.e. subclinical AF after proof that AHRE represents true atrial tachyarrhythmia) lasting for a minimum of 5–6 min are associated with an increased risk of clinical AF (AF documented by surface electrocardiogram), ischaemic stroke, major adverse cardiovascular events, and cardiovascular death.[1] Subclinical AF burden is not static but changes daily and should be reassessed regularly.[1] The guidelines recommend consideration of oral anticoagulation in selected patients with longer durations of subclinical AF, such as ≥24 h with high monthly burden or ≥1 h with high daily burden, and with an estimated high individual risk of stroke, while accounting for the anticipated net clinical benefit and informed patient's preferences.[1]

In our study, a thromboembolic event, mostly peripheral arterial embolism, occurred in 3.4% of new-onset AF patients, all of whom had a high risk of stroke (CHA_2DS_2-VASc scores 4–7). By comparison, Kaplan RM *et al.* retrospectively evaluated the stroke and systemic embolism rate in 21 768 non-coagulated CIED patients as a function of CHA_2DS_2-VASc score and maximum daily AF duration in the previous 6 months, stratified as <6 min ('no AF'), 6–23.5 min, and >23.5 min per day.[5] Both CHA_2DS_2-VASc score and AF duration were significantly associated with the annualized risk of stroke and systemic embolism. This risk was low for a CHA_2DS_2-VASc score of 0–1 regardless of device-detected AF duration, but it crossed an actionable threshold (>1%/year) in patients with a CHA_2DS_2-VASc score of 2 and >23.5 h AF (1.5% yearly risk) or those with a CHA_2DS_2-VASc score of 3–4 and ≥6 min AF (up to 1.8% yearly risk). In patients with a CHA_2DS_2-VASc score ≥5, the stroke and systemic embolism rate ranged from 1.8%/year (without AF) to 2.2%/year (with AF).[5]

The temporal distance of 22–191 days between the last AHRE and thromboembolic event in our study corroborates previous observations that mostly no direct temporal link exists between atrial arrhythmias and thromboembolism.[1,3] Although 20–30% of all strokes are considered to be due to AF, the temporal dissociation from acute stroke suggests that AHRE/subclinical AF may represent a marker rather than a risk factor for stroke.[1,3] Moreover, in a recent retrospective study, the vast majority of 891 CIED patients with ischaemic stroke, who had their heart rhythm continuously monitored during 120 pre-stroke days, actually presented with no or very little AF, and only ≈6% had significant AF duration (pre-defined as ≥5.5 h) in this period.[6] In patients with

significant AF duration, the stroke risk was increased mostly in Days 1 to 5 following an AF episode, when the odds ratio reached 5.0, to diminish rapidly thereafter.[6] The authors concluded that their results are consistent with the traditional view that AF is directly and transiently associated with ischaemic stroke and that time-delimited anticoagulation may be used in patients with infrequent multi-hour AF episodes and rigorous continuous rhythm monitoring.[6]

In another recent study, the authors suggest that not all AF seems to be worth screening for and not all screen-detected AF merits anticoagulation.[20] Namely, after randomization of 6004 individuals to implantable loop recorder or usual care, the diagnosis of AF increased 3.2-fold, and the consequent anticoagulation prescription increased 2.7-fold in the implant group, which did not translate in a significant reduction of stroke or systemic arterial embolism after a median follow-up period of 64.5 months.[20]

Increasing age is a prominent AF risk factor, and the only significant predictor of new-onset AF in our study.[1] Also, a clear tendency for male sex, congestive heart failure, and mid- to high CHA_2DS_2-VASc stroke risks (integrating age and heart failure) to be associated with new-onset AF is in line with previous knowledge.[1] In contrast, secondary prevention ICD indication, which had similar association with new-onset AF in our study as male sex and heart failure, was not addressed in the European AF guidelines as a risk factor for AF.[1]

Atrial fibrillation poses significant burden to patients and healthcare systems with an estimated prevalence of 2–4% in adults, which is expected to double in the coming decades, reflecting extended life expectancy in the general population and an intensifying search for undiagnosed AF.[1] In parallel, a steadily growing number of patients implanted with devices capable of remote AF monitoring enhances the global relevance of this technology for early diagnosis and management of AF.

Atrial signal detection quality and P-wave amplitudes

Conventional atrial sensing performance evaluated during 2 years of follow-up at 119 investigational sites was adequate to excellent in 96.3% patients, with an overall mean (amplified) atrial sensing amplitude of 4.4 mV. By comparison, in previous DX ICD studies, atrial sensing performance was satisfactory in ≈95–99% of patients, and an average atrial signal amplitude measured in office during up to 2 years of follow-up ranged from 3.5 to 7.3 mV between studies (no study used remote daily measurements to demonstrate long-term stability).[10–13,17,18]

Study limitations

The potential under-detection of AF episodes and the accuracy of device-reported daily AF burden over 2 years of follow-up were not determinable with current technological means. The number of new-onset AF patients with subsequent thromboembolic events was too low to investigate the influence of AF progression on the event rate.

Conclusions

A 99.7% detection accuracy for AHRE lasting for ≥1 h, and 97.5% accuracy for AF ≥6 min, in combination with a 92.5% Home Monitoring® transmission performance allows a reliable guideline-recommended remote monitoring of subclinical AF in the vast majority of patients treated with a single-chamber ICD with atrial sensing capabilities (DX ICD). About 70% of DX ICD patients with device-detected new-onset AF are not on anticoagulation therapy and mostly have a mid- (15%) to high (80%) CHA_2DS_2-VASc stroke risk. These patients can benefit from a guideline-conform monitoring strategy to timely initiate anticoagulation for stroke prevention.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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