

HOT TOPICS IN CARDIAC PACING

Modalità avanzata di stimolazione come prevenzione della fibrillazione atriale: risultati dello studio B3

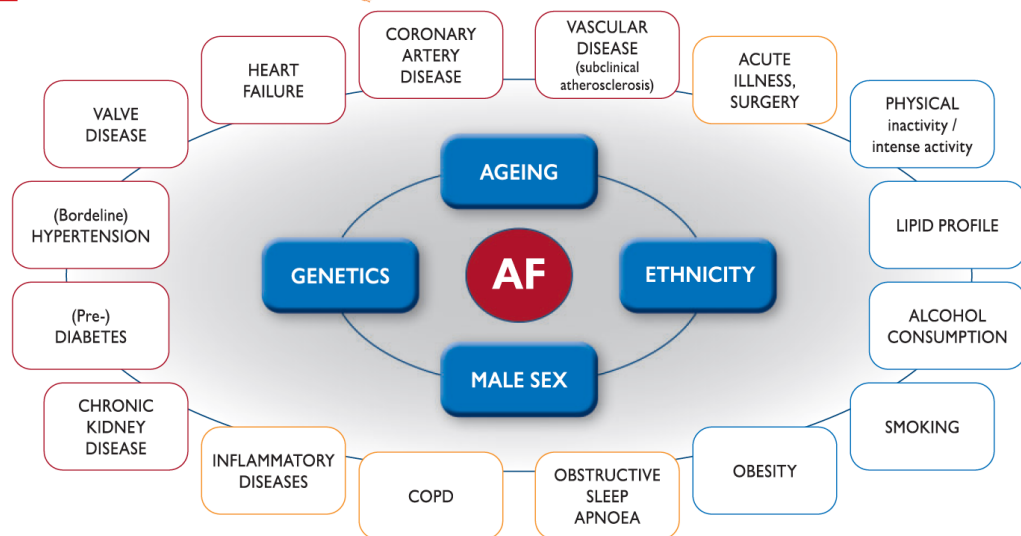
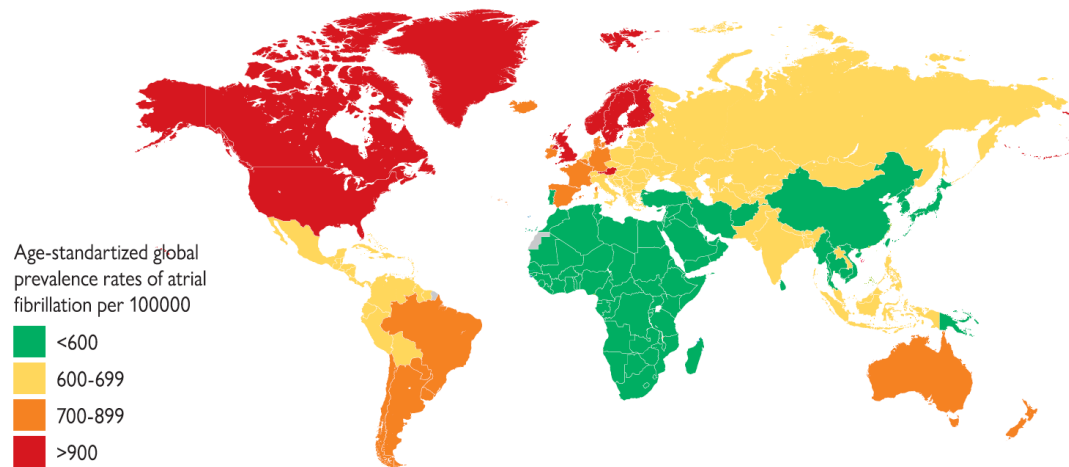
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GLOBAL PREVALENCE OF AF

(globally, 43.6 million individuals had prevalent AF/AFL in 2016)



LIFETIME RISK for AF

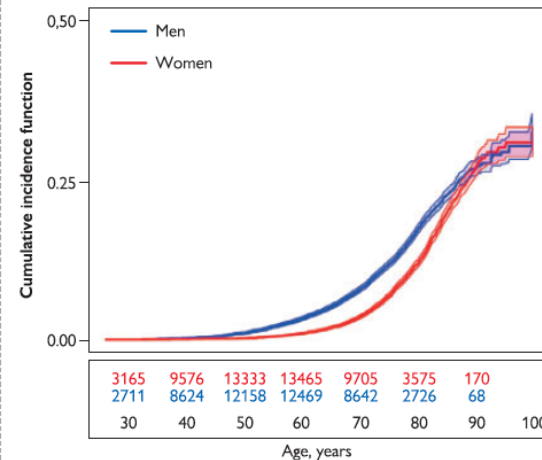
1 in 3 individuals



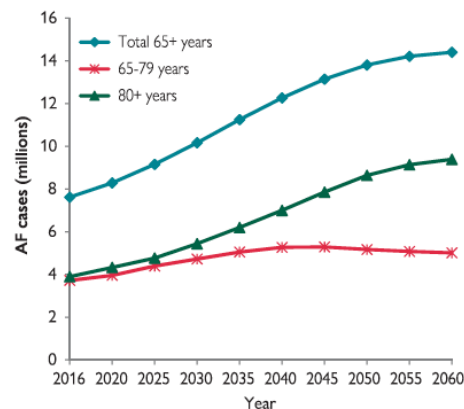
of European ancestry
at index age of 55 years
37.0% (34.3% to 39.6%)

AF is more common in males

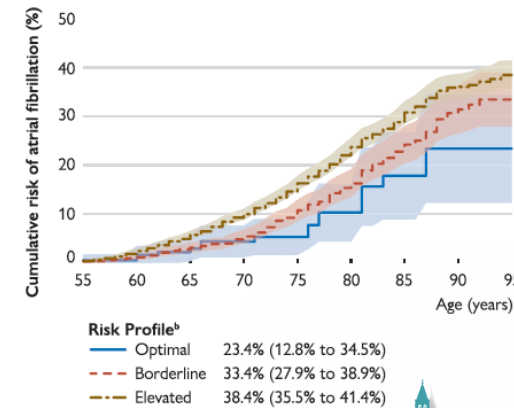
Cumulative incidence curves and 95% CIs
for AF in women and men with death as a competing risk



Projected increase in AF prevalence among elderly in EU 2016-2060



Lifetime risk of AF increases with increasing risk factor burden^a



Afib in Pacemaker patients

- A significant source of information

Major clinical trials in pacemaker patients in the last 15 years.

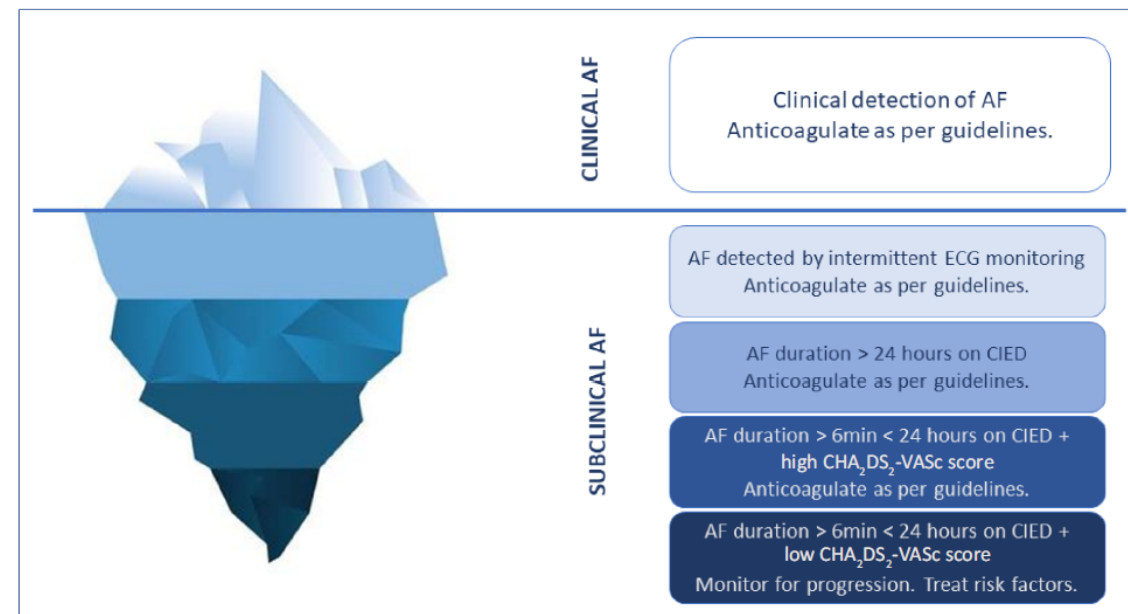
Trial	Main publication	Year of publication	RCT	Number of patients	Mean follow-up duration	Endpoints related to atrial arrhythmias
SAVE PACE	N Engl J Med	2007	Yes	1,065	1.7 years	Persistent clinical AF (12-lead ECG documentation)
TRENDS	Circ Arrhythmia Electrophysiol	2009	No	2,486	1.4 years	AHRE burden without episode adjudication
DANPACE	European Heart Journal	2011	Yes	1,415	5.4 years	Clinical AF (12-lead ECG documentation)
ASSERT	N Engl J Med	2012	Yes	2,280	2.5 years	Subclinical atrial tachyarrhythmias with central adjudication but without classification by arrhythmia type
B3	EP Europace	2024	Yes	1,210	2.6 years	AHRE with central adjudication and classification of the arrhythmia type



The rationale of the B3 trial

Preventing device-detected subclinical Atrial Fibrillation (AF)

- Device-detected subclinical (AF) - or true-positive atrial high-rate episodes (**AHREs**) – correlate with an increased risk of
 - clinical/permanent AF,
 - stroke,
 - heart failure hospitalizations,
 - all-cause deaths in patients with structural heart disease
- It is considered the **underwater part of the AF iceberg**.
- The 2024 update of the ESC guidelines¹ also recommend AHRE monitoring for progression to clinical AF, but recent trials (ARTESiA and NOAH AFNET 6) have left many questions unanswered regarding initiation of oral anticoagulation (OAC) for stroke prevention only basing on subclinical AF.
- Therefore, **prevention of subclinical AF is a key factor**.
- In patients with an indication for dual-chamber rate-responsive pacing for sinus node dysfunctions (SND), identifying optimal pacing strategy to prevent subclinical AF and its consequences is warranted.
- The objective of the B3 randomized clinical trial (RCT) was to assess whether the **Closed Loop Stimulation (CLS)** is superior to standard DDDR pacing in preventing the onset of subclinical AF.



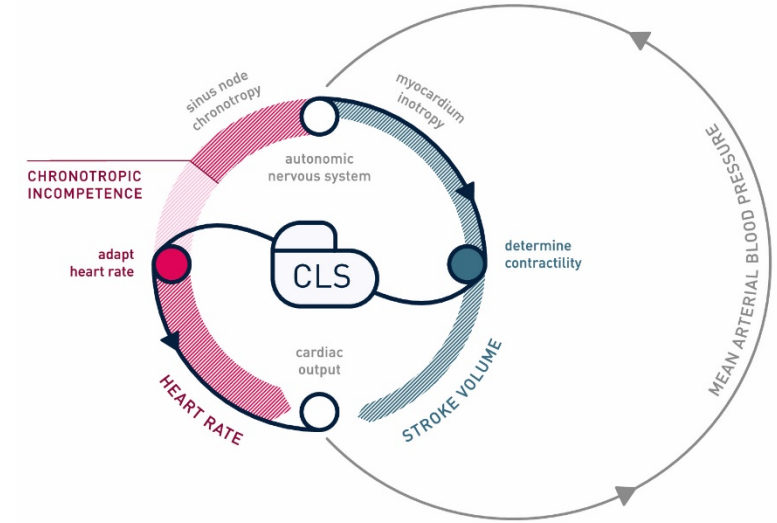
1) European Heart Journal (2024) 45, 3314–3414.



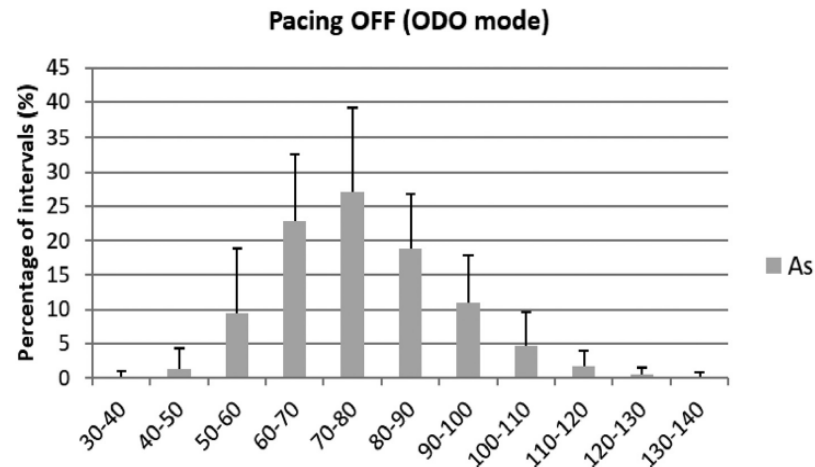
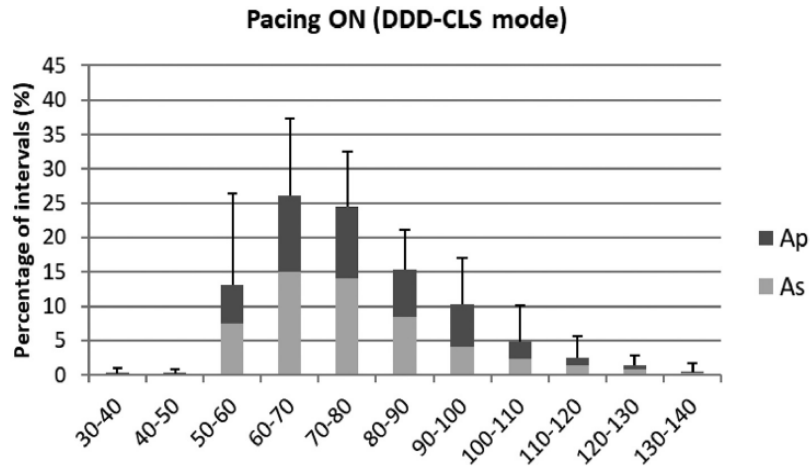
Closed Loop Stimulation

How is the loop closed?

- Well-known closed-loop rate adaptive system based on continuous monitoring of contraction speed and contractility.
- A detected increase in contractility is translated into a corresponding increase in pacing rate.
- The heart rate increase affects autonomic mechanisms of cardiac output regulation, including contractility.
- Therefore, the output of the CLS system (heart rate) affects its input (contraction speed and contractility), closing the loop



p=0.98



- CLS has been shown to mimic heart rate profile of a healthy sinus node in the BIOSync trial¹

¹Russo V, et al. Heart rate distribution in paced and non-paced patients with severe recurrent reflex syncope and tilt-induced asystole: Findings from the BIOSync CLS study. Int J



Previous results of CLS in patients with AF history

Three small, retrospective studies previously reported reduced AF burden with CLS

Study	Design / Groups	Population	Results
BURDEN I ¹ , EHJ 2003	Randomized / DDDR, DDD+, or CLS	149 patients with brady-tachy syndrome	CLS was associated with a lower AF burden compared to the other pacing algorithms.
BURDEN II ² , PACE 2008	Randomized with crossover / DDDR, DDD+, or CLS	451 patients with brady-tachy syndrome and documented AF	Atrial overdrive showed the worst performance in terms of AF burden reduction and should not be preferred to heart rate modulation approaches that still have to be considered as a first-choice pacing mode in BTS.
Ikeda et al. ³ , JCE 2020	Retrospective / CLS or non-CLS	146 patients with SND and AF history	CLS was associated with lower AF burden after pacemaker implantation in patients with sinus node dysfunction and AF history.

¹Puglisi A et al. Impact of Closed-Loop Stimulation, overdrive pacing, DDDR pacing mode on atrial tachyarrhythmia burden in Brady-Tachy Syndrome. A randomized study. Eur Heart J. 2003 Nov;24(21):1952-61.

²Puglisi A, et al. Overdrive versus conventional or closed-loop rate modulation pacing in the prevention of atrial tachyarrhythmias in Brady-Tachy syndrome: on behalf of the Burden II Study Group. Pacing Clin Electrophysiol. 2008 Nov;31(11):1443-55.

³Ikeda S, et al. Closed-loop stimulation as a physiological rate-modulated pacing approach based on intracardiac impedance to lower the atrial tachyarrhythmia burden in patients with atrial fibrillation. J Cardiovasc Electrophysiol. 2020 May;31(5):1187-1194.





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Europace (2024) **26**, euae175
<https://doi.org/10.1093/europace/euae175>

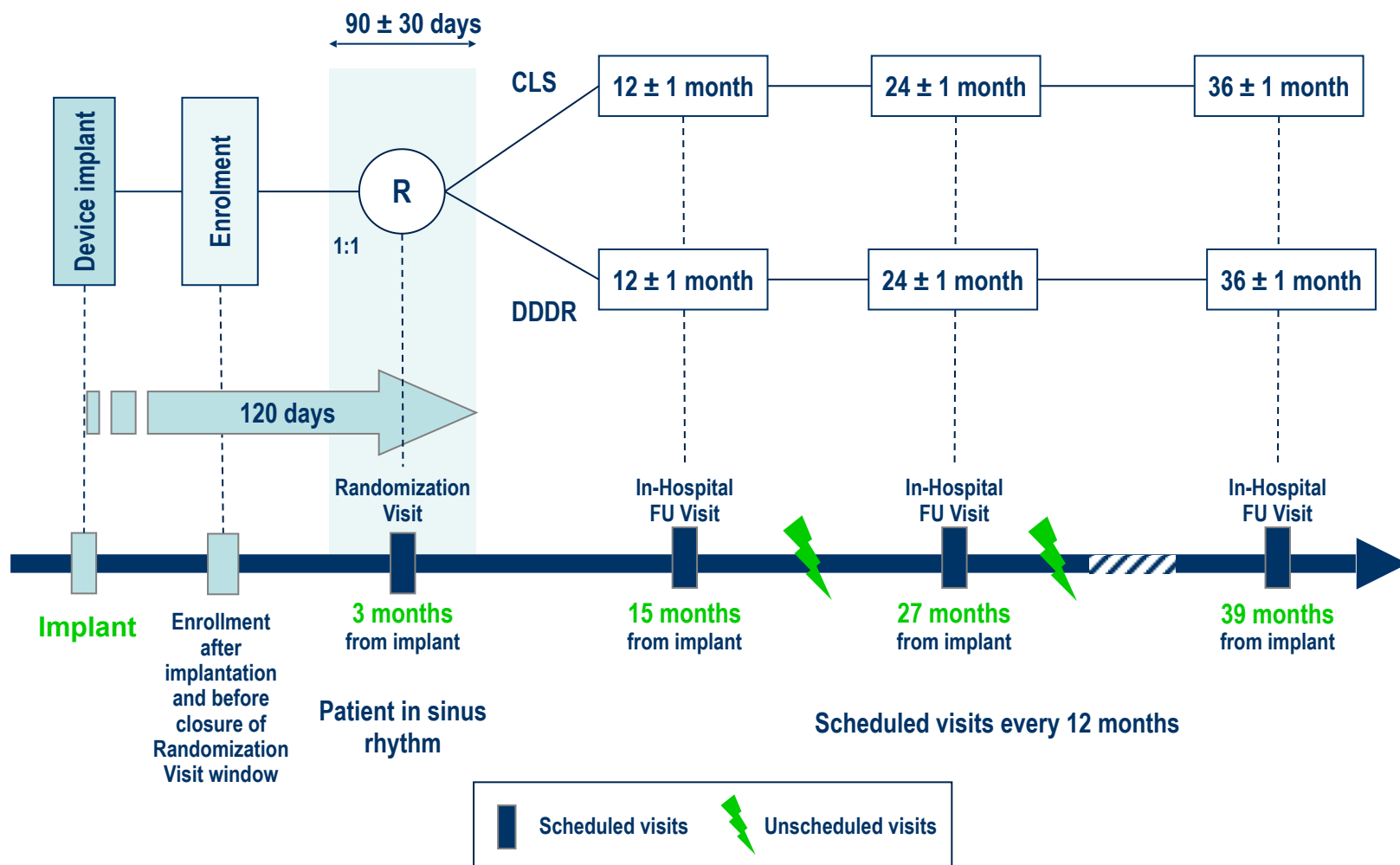
CLINICAL RESEARCH

Closed loop stimulation reduces the incidence of atrial high-rate episodes compared with conventional rate-adaptive pacing in patients with sinus node dysfunctions

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B3 design Flowchart



B3 design

Inclusion and exclusion criteria

Inclusion Criteria

- Patients with Class I or II recommendations for permanent pacing due to SND, with or without AV block according to the current guidelines
- Patients for whom rate-responsive dual-chamber pacing is indicated or preferred
- Patients with an optimized and stable antiarrhythmic medical therapy at the time of enrollment

Exclusion Criteria

- Permanent AF
- NYHA Class IV Heart Failure
- Stage V kidney dysfunction
- Any indication to Cardiac Resynchronization Therapy (CRT)
- Life expectancy < 1 years
- Atrial fibrillation ablation (left pulmonary veins) or other cardiac surgery < 3 m
- Minors
- Pregnant or breast-feeding patients
- Participation in another interventional trial



B3 design

Definitions, objective, and endpoints

Definition of true-positive AHRE: any detected episode with ≥ 190 bpm atrial rate and ≥ 6 -minute duration, assessed by blind adjudication of available EGM recordings stored in the device memory.

Primary objective: international, randomized, single-blind trial to test superiority of CLS over standard DDDR, in terms of the incidence (time to first episode) of AHRE ≥ 6 minutes or stroke in SND patients with indication for dual-chamber rate responsive pacing (with or without atrioventricular block and including pacemakers or implantable defibrillators).

Combined primary endpoint

First occurrence of either

AHRE ≥ 6 minutes, or

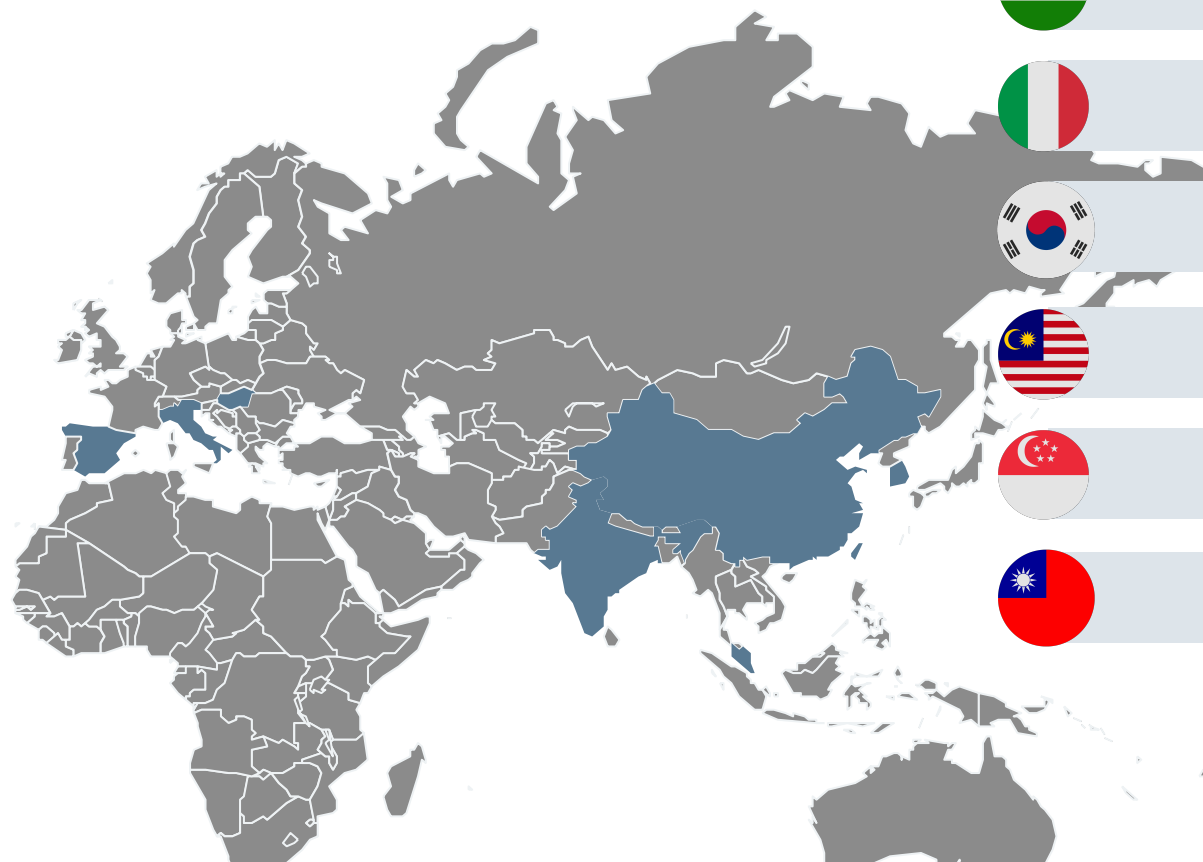
Stroke or Transient Ischemic Attack (TIA).

Secondary endpoints: Analyses of different AHRE duration cutoff; worsening Heart Failure (wHF) hospitalization; cardiovascular and all-cause death; stroke/TIA.



Study Results

- Participating sites: 53 within 9 territories
- Enrolled patients: 1,390
- Enrolment period: 2015-2019
- 2020-2021: COVID-19 pandemic
- Group sequential design



China



Spain



Hungary



India



Italy



Korea



Malaysia



Singapore



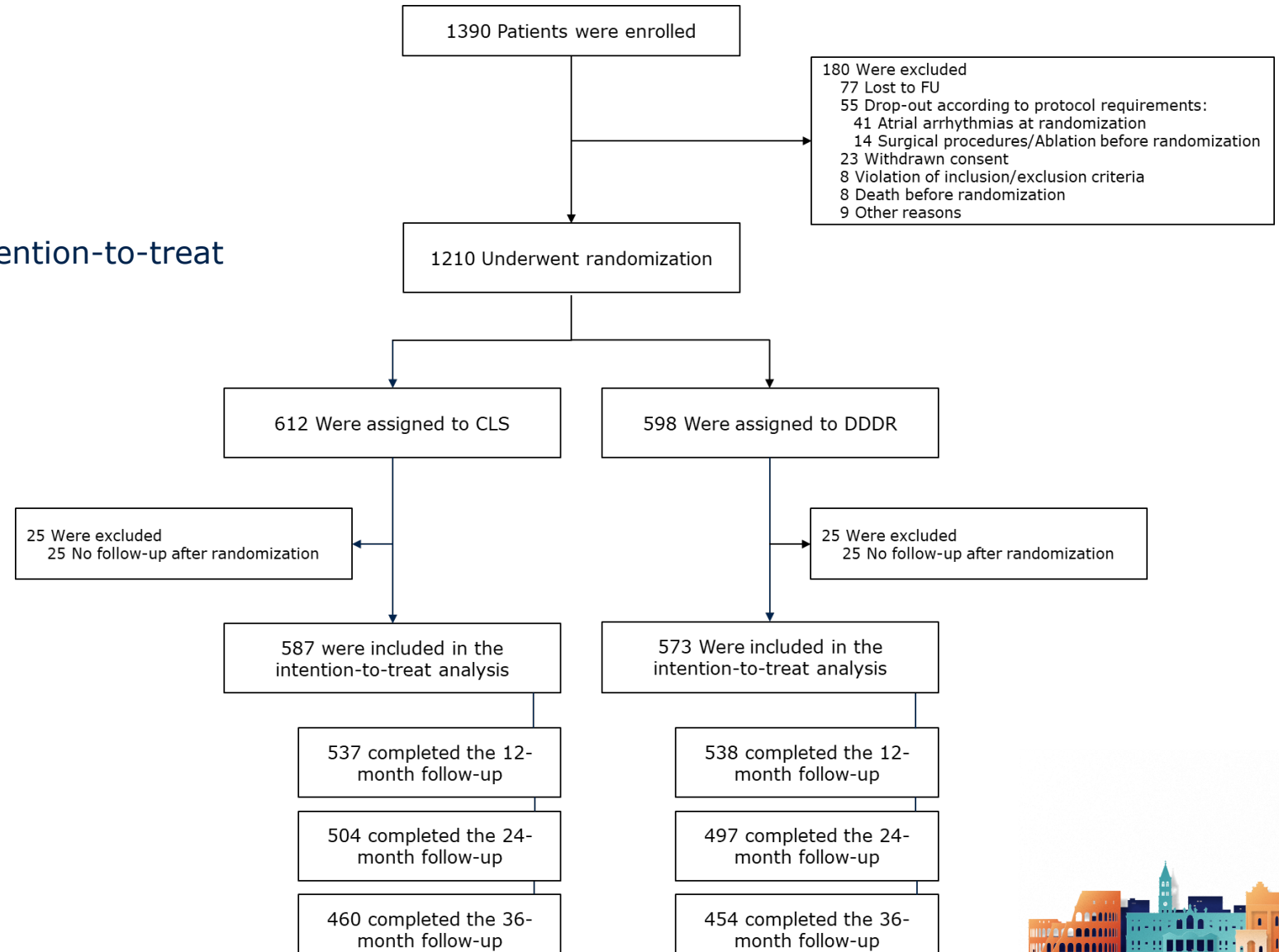
Taiwan

- Statistical analysis independently validated by the Unit of Biostatistics, University of Padua, Italy.



Study Results

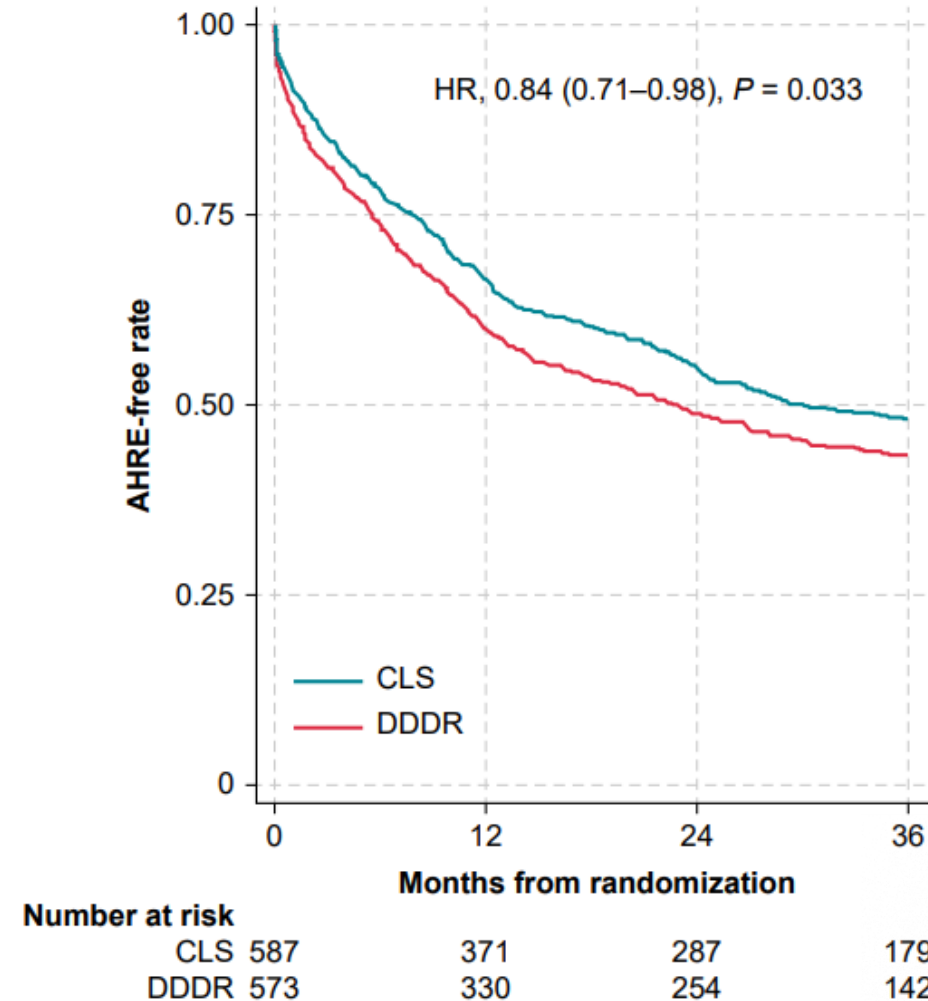
- 1,210 patients randomly assigned to
 - CLS (n = 612) or
 - DDDR mode (n = 598)
- 1,160 patients contributed to the intention-to-treat analysis
- 89% completed the 12-month FUP
- 83% completed the 24-month FUP
- 76% completed the 36-month FUP



Study Results

AHRE incidence

- Incidence of AHRE ≥ 6 min in CLS versus DDDR on the intention-to-treat basis:
- Intention-to-treat
 - HR, 0.84; 95% CI, 0.71–0.98; $p=0.033$.
- Per-protocol
 - HR, 0.82; 95% CI, 0.69–0.97; $p=0.021$.



Study Results

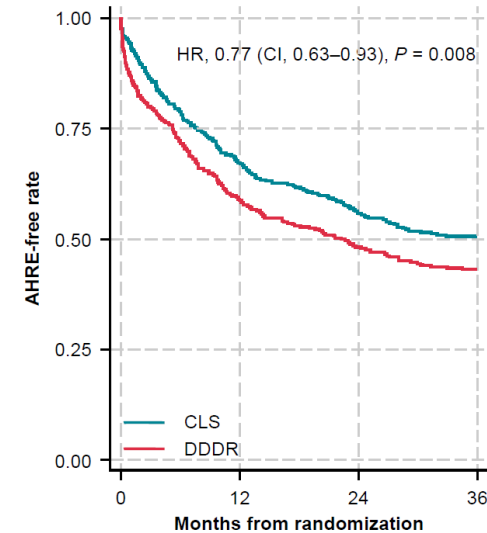
Subgroup analysis of AHRE incidence

- In a post-hoc analysis of AHRE incidence by subgroups, the incremental effect of CLS was greatest in patients without AV block and less than 20% right ventricle pacing burden or without history of AF.

Subgroup	CLS	DDDR	HR (95% CI)	P	P for interaction
Sex					0.66
Male	144/299	170/310	0.79 (0.63–1.00)	0.05	
Female	153/287	149/263	0.85 (0.67–1.08)	0.18	
Age					0.39
<76 years	130/281	132/272	0.94 (0.73–1.21)	0.63	
≥76 years	167/305	187/301	0.81 (0.65–1.00)	0.06	
Resting heart rate					0.44
<70 bpm	107/213	108/197	0.76 (0.57–1.02)	0.06	
≥70 bpm	51/98	56/99	1.08 (0.70–1.66)	0.74	
Atrioventricular block					0.15
No	202/417	231/409	0.77 (0.63–0.93)	0.008	
Yes	95/170	88/164	1.04 (0.76–1.42)	0.72	
Ventricular pacing%					0.41
<20%	190/401	222/402	0.78 (0.64–0.95)	0.014	
≥20%	104/180	92/161	0.82 (0.61–1.11)	0.21	
History of atrial fibrillation					0.036
No	135/385	156/353	0.73 (0.57–0.92)	0.009	
Yes	162/202	160/215	1.04 (0.82–1.31)	0.76	
CHA2DS2-VASc score					0.82
<3	81/179	94/186	0.81 (0.59–1.12)	0.20	
≥3	216/408	224/385	0.84 (0.69–1.02)	0.07	
Diabetes mellitus					0.32
No	246/464	249/444	0.87 (0.73–1.05)	0.14	
Yes	51/123	69/127	0.72 (0.48–1.08)	0.12	
Congestive heart failure					0.98
No	243/486	250/458	0.85 (0.71–1.02)	0.08	
Yes	54/101	68/113	0.86 (0.57–1.28)	0.45	
All patients	297/587	319/573	0.84 (0.71–0.99)	0.033	

0.5 1 1.5
← CLS better DDDR better →

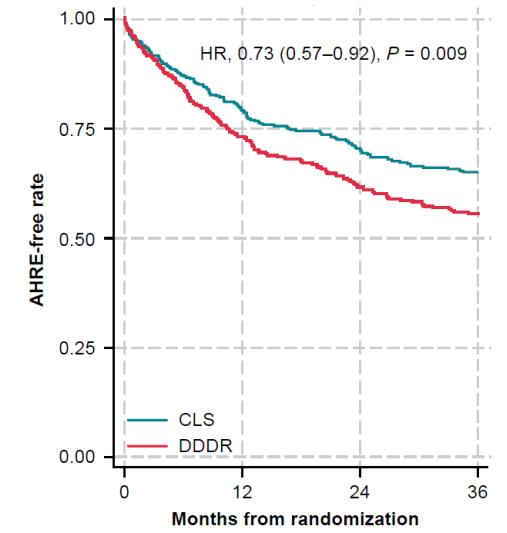
no AV block



Number at risk	0	12	24	36
CLS	417	267	206	127
DDDR	409	232	181	104

Number needed-to-treat: 13.9

no AF history



Number at risk	0	12	24	36
CLS	385	293	244	160
DDDR	353	247	201	111

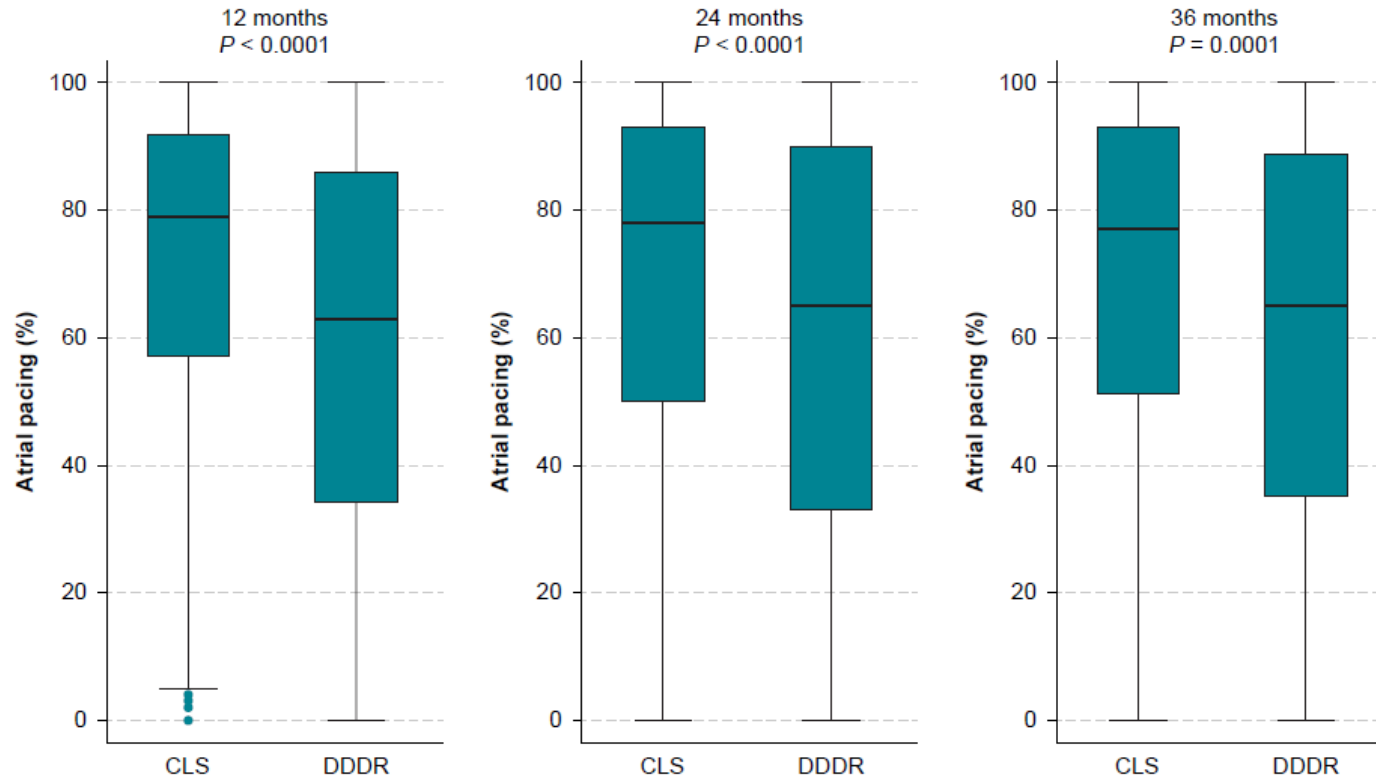
Number needed-to-treat: 10.6



Study Results

Pacing percentages

- The median RV pacing percentage was 4% at 1 year, 5% at 2 years and 6% at 3 years of follow-up, with no significant differences between the study groups.
- The median percentage of atrial pacing was consistently higher in the CLS arm (77–79%) than in the DDDR arm (63–65%) during the 3-year follow-up period ($P < 0.001$).



The clinical relevance of AHRE in sick sinus dysfunction

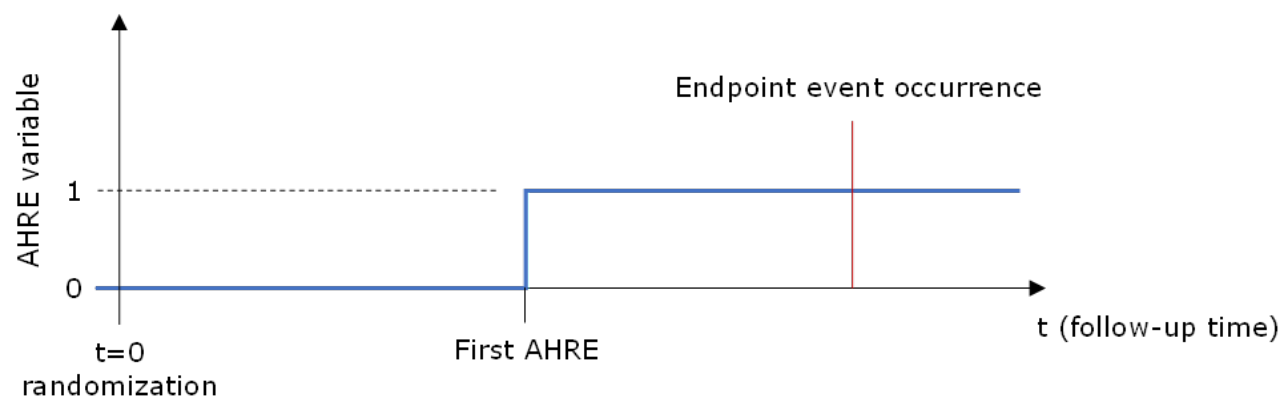
Background and objective

- The degree of correlation of device-detected AHREs with the risk of major cardiovascular events is assumed to increase with episode duration.
- However, an AHRE duration cutoff has not been identified yet (≥ 6 minutes; ≥ 6 hours; ≥ 24 hours)
- Our aim was to assess the relationship between AHRE duration and the risk of worsening heart failure hospitalization (WHFH), cardiovascular (CV) death, stroke, transient ischaemic attack (TIA), and permanent AF, using the B3 dataset

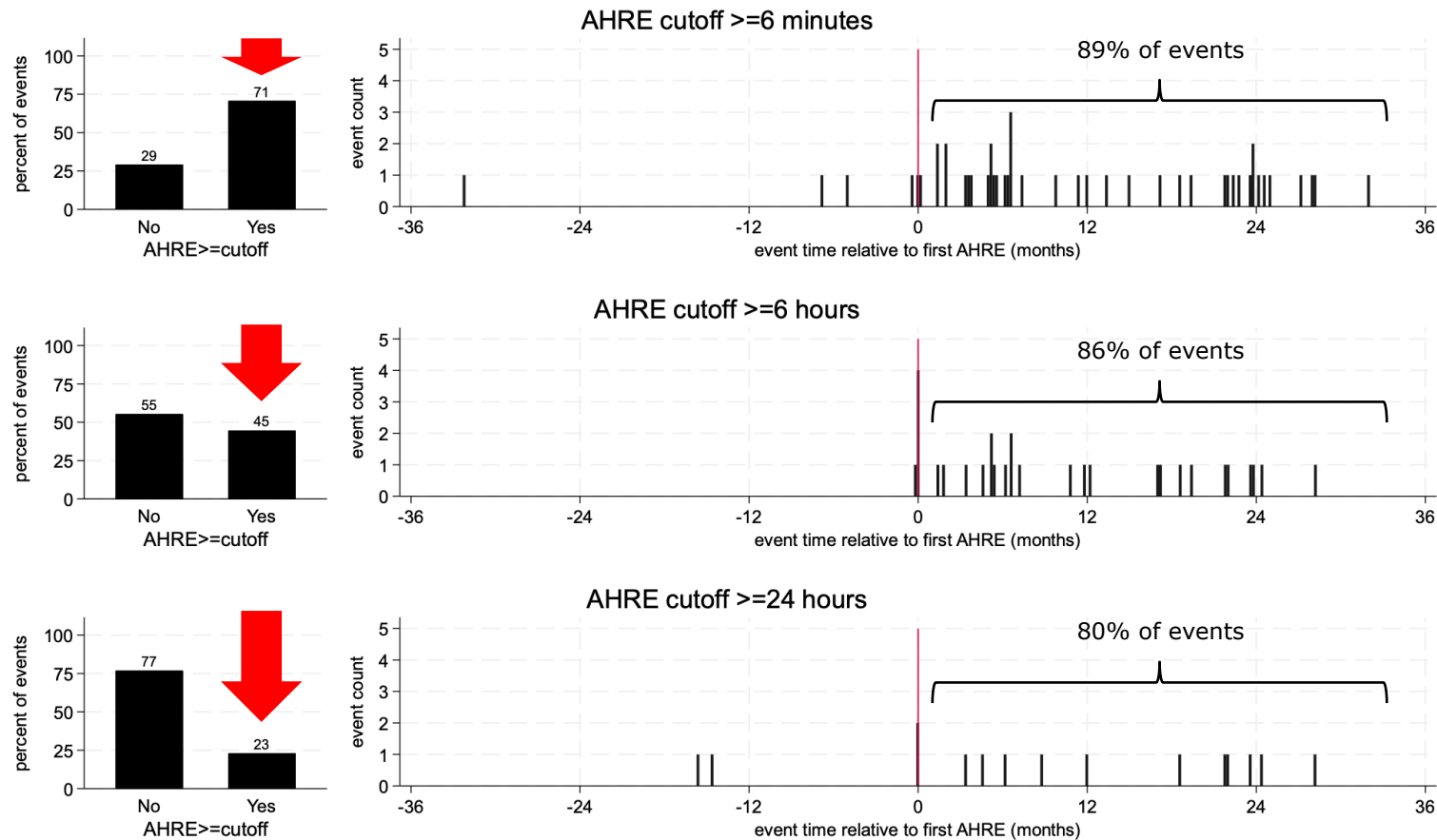


Methods

- Primary outcome: combined endpoint including CV death, WHFH, and haemorrhagic or ischaemic stroke or TIA
- Secondary endpoints were individual components of the combined endpoint (CV death, WHFH, stroke/TIA) and progression to permanent AF.
- Analysis hypothesis: AHREs are markers of patient status change only if episode duration exceeded the pre-specified cut-off of ≥ 6 minutes, ≥ 6 hours, or ≥ 24 hours.
- Does the risk of endpoint events increase significantly AHRE onset according to the duration cut-offs?



- The percentage of events occurring in patients with AHREs $\geq$ duration cut-off decreased with increasing duration cut-off



Clear tendency of the events to occur after the first AHRE regardless of AHRE duration cut-off: 89%, 86%, and 80% of events



Results: combined endpoint

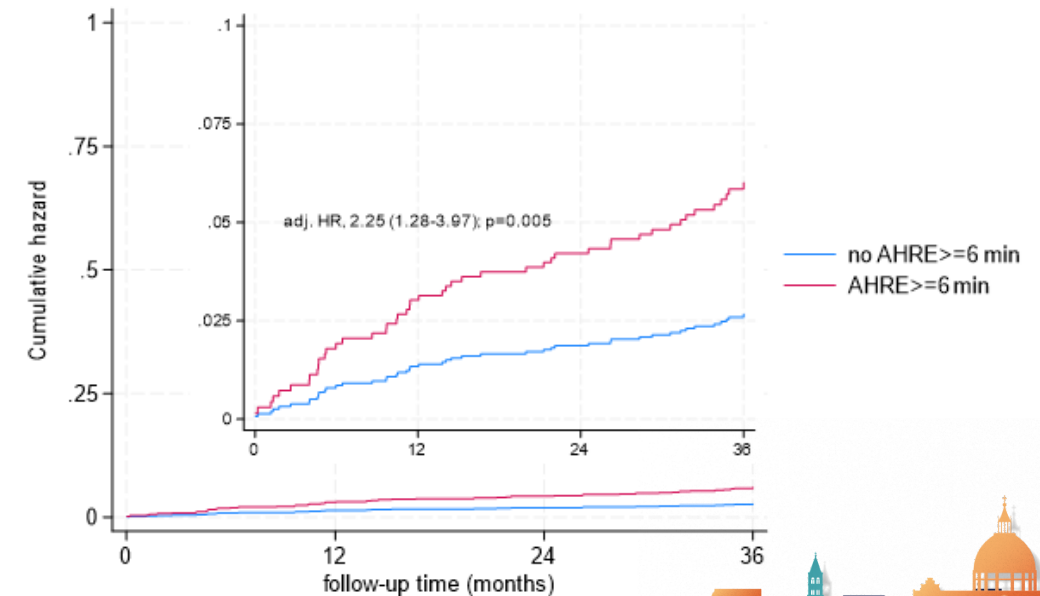
- In a competing risk time-varying survival analysis, there was an increased risk after AHRE onset starting from the 6 minutes duration cutoff.
- The CHA₂DS₂-VASc-adjusted HRs were 2.25 (AHRE ≥6 minutes, p=0.005), 2.54 (AHRE ≥6 h, p=0.002), and 2.05 (AHRE ≥24 h, p=0.052) versus patients without AHREs.

AHRE duration cut-off	Unadjusted HR (95% CI)	P-value	Adjusted* HR (95% CI)	P-value
≥6 minutes	2.46 (1.39–4.35)	0.002	2.25 (1.28–3.97)	0.005
≥6 h	2.68 (1.51–4.76)	0.001	2.54 (1.42–4.52)	0.002
≥24 h	2.33 (1.13–4.77)	0.021	2.05 (0.99–4.21)	0.052

In all regression models, non-CV death (n=69, including unknown death causes) was a competing event.

°AHRE was used as a time-varying covariate switching from 0 to 1 at the onset of the first AHRE longer than the pre-specified cut-off value.

*Using CHA₂DS₂-VASc score as adjusting covariate.



Results: secondary endpoints

- The difference between patients with AHREs and patients without AHREs was statistically significant for WHFH (annual rate, 2.0% in patients with AHREs vs. 0.3% in those without AHREs; adjusted HR, 4.15; $p < 0.001$) and for arrhythmia progression to permanent AF (annual rate, 2.8% with AHREs vs. 0.0% without AHREs; adjusted HR, 64; $p < 0.001$).
- The risks of CV death (overall annual rate, 0.3%) and stroke/TIA (annual rate, 0.5%) did not differ significantly between patients with and without AHREs

Endpoint (dependent variable)	Unadjusted HR (95% CI)	P-value	Adjusted* HR (95% CI)	P-value
CV death	0.84 (0.24–2.95)	0.79	0.76 (0.22–2.66)	0.67
WHFH	4.53 (2.13–9.64)	<0.001	4.15 (1.93–8.92)	<0.001
Stroke or TIA	1.81 (0.59–5.6)	0.30	1.79 (0.57–5.59)	0.32
Permanent AF	64 (11–386)	<0.001	64 (11–383)	<0.001

In all regression models, non-CV death (n=69, including unknown death causes) was a competing event.

*AHRE was used as a time-varying covariate switching from 0 to 1 at the onset of the first AHRE longer than the pre-specified cut-off value.

*Using CHA₂DS₂-VASc score as adjusting covariate.



Study Results

Key findings

- Dual-chamber CLS mode was associated with a 16% lower risk of the composite endpoint of first subclinical AF, stroke, or TIA, as compared to the DDDR mode.
- This difference was mostly driven by fewer AHREs lasting between 6 hours and 7 days in the CLS arm.
- Patients without AV block (i.e., with low ventricular pacing) and patients without history of AF had the greatest incremental benefit from CLS.
- The incidence of stroke/TIA was low and did not differ significantly between the two pacing strategies.
- In a post-hoc analysis of the randomized clinical trial B3, we observed a double risk of the combined event of CV mortality, WHFH, and stroke/TIA after the onset of AHREs, regardless of episode duration.
- The risk increase was driven by an increased annual rate of WHFHs after AHRE onset. Permanent AF was strongly predicted by AHREs.
- These results underscore the importance of AHRE monitoring beyond prevention of thromboembolic risk. AHRE onset should prompt evaluation of patient's conditions and modification of risk factors.

