Cardiology and Vascular Medicine
ESC Update Programme in Cardiology
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Atrial Fibrillation

ESC Guidelines: Paroxysmal Atrial Fibrillation

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Declaration of Interest

Advisor / Speaker / Investigator:

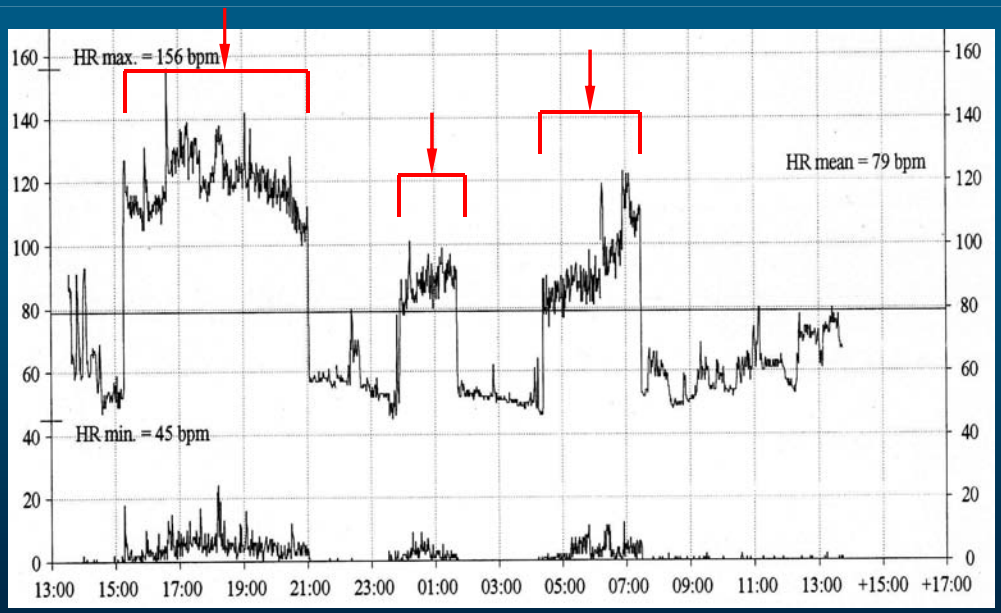
Bristol Myers Squibb, Pfizer, Daiichi, Servier, Sanofi, Boehringer Ingleheim, Takeda, Bayer Pharma AG, MSD, Astellas, Menarini, Solvay Pharma, Mitsubishi Pharma, Richmond Pharmacology

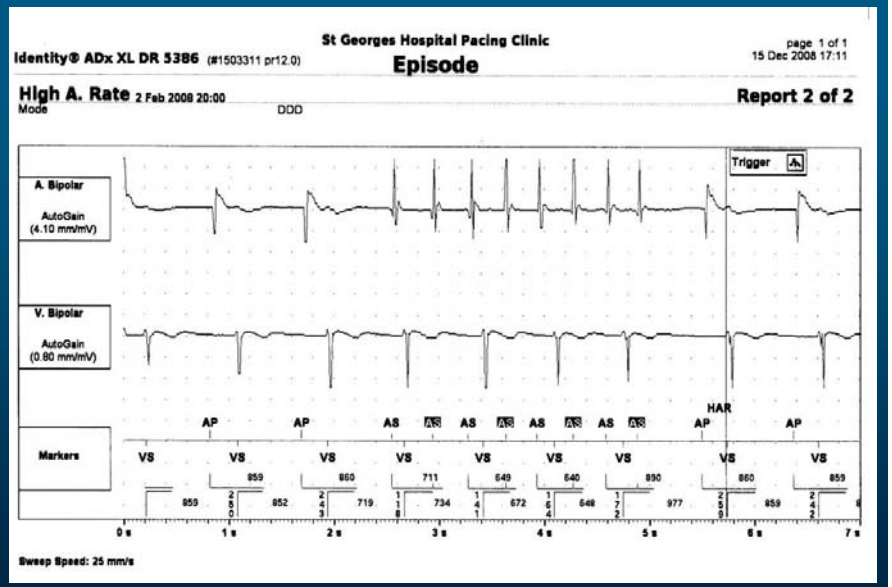
“Paradoxes” of Paroxysmal Atrial Fibrillation

- Definitions
- Detection / “measurement”
- Anticoagulation - AHREs
- Progression
- Early intervention
- Ablation as first choice

“Paradox” of Paroxysmal Atrial Fibrillation: Definitions

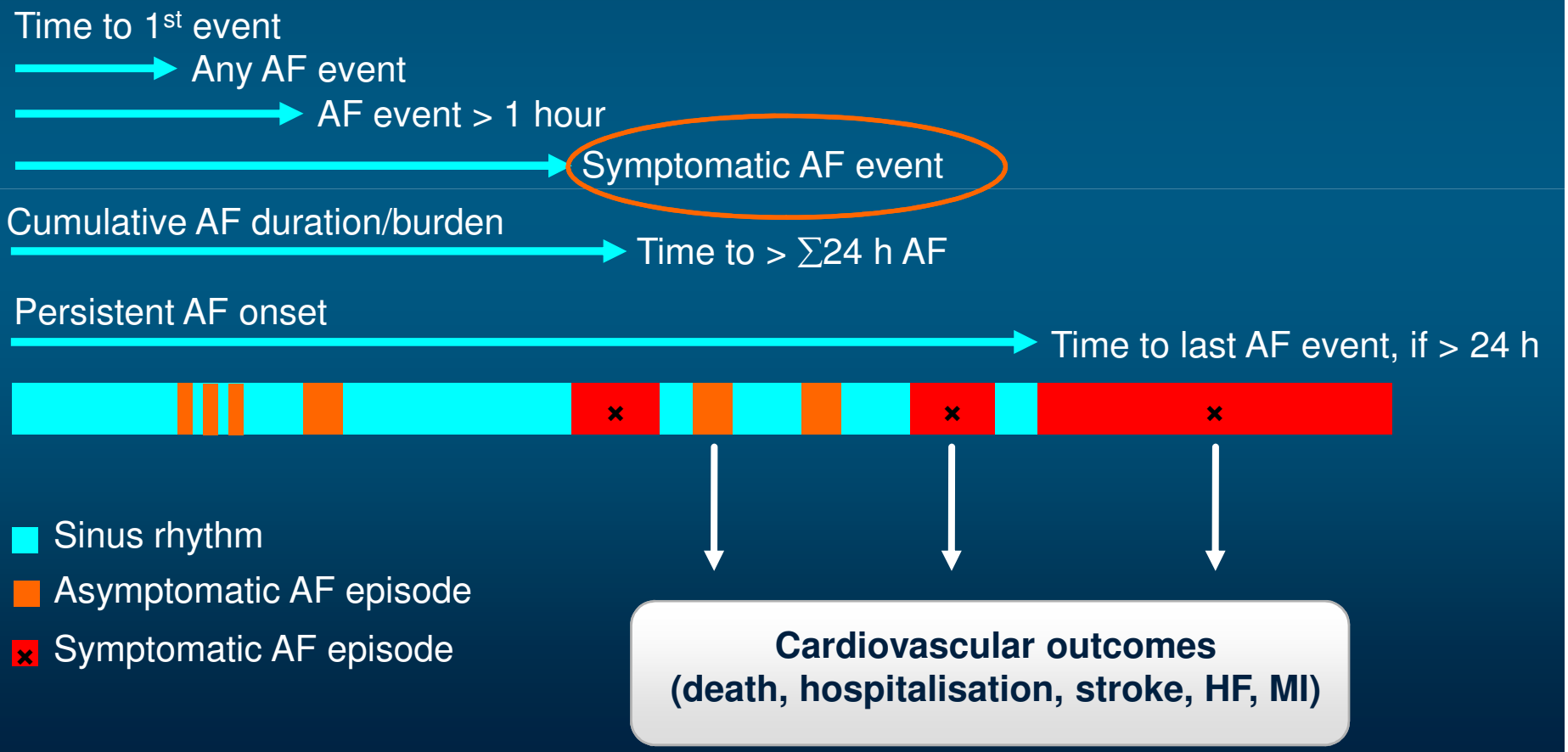
- ESC definition: Paroxysmal AF is self-terminating, usually within 48 h, although AF paroxysms may continue for up to 7 days…
- Definitions in clinical trials: from 30 sec – 1 min to 7 days





"Paradox" of Paroxysmal Atrial Fibrillation: How to Measure PAF

The intensity and duration of monitoring should be determined by the clinical need to establish the diagnosis



How to Measure PAF: AF Burden Concept

Study	No of pts	Drug	Design	Definition of AF burden	AF monitoring	Duration of the study
J-RHYTHM II, 2011	318	Candesartan vs amlodipine	OL, no placebo	Number of days with AF per month (difference between baseline and the final month)	Daily TTM	12 months
ANTIPAF (NCT 00098137), reported 2010	425	Olmesartan	DB, PC	% days with AF (number of days with AF / total days	Daily TTM	12 months
ARYx, 2009	6	Budiodarone (ATI-2042)	OL, dose-escalating, no placebo	% time in AF (time in AF divided by the total time in each study period)	EGM data	12 weeks
PASCAL (NCT 00389792), reported 2009	72	Budiodarone	DB, PC, dose-escalating	% time in AF (change from baseline over 12 weeks of treatment compared with placebo)	EGM data	20 weeks
HESTIA (NCT 01135017), ongoing	430	Dronedarone	DB, PC, parallel group	% of time in AF	EGM data	12 months
NCT 01356914), planned	20	BMS-914392	DB, PC, 4-way crossover	Not specified	EGM data	12 weeks

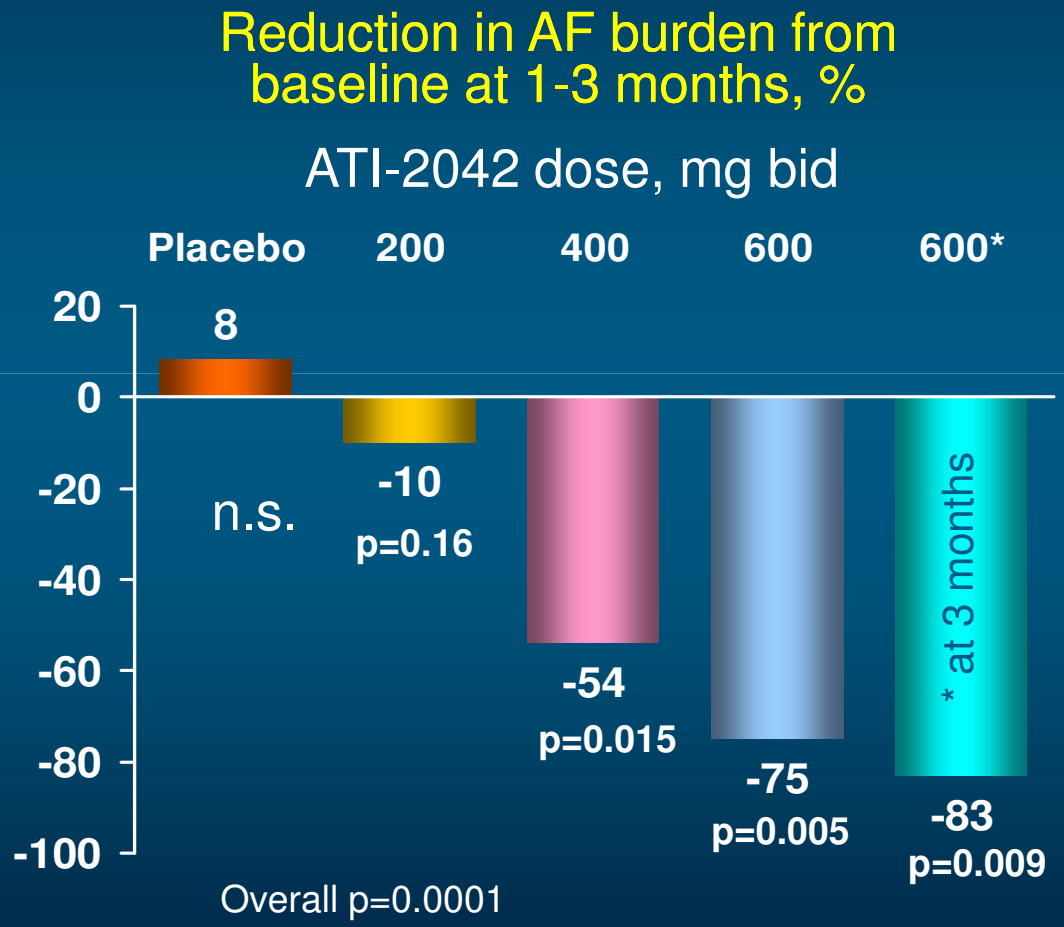
Savelieva I, et al. Europace 2011

PAF Assessed as AF Burden:
PASCAL Study

(P)aroxysmal (A)trial fibrillation (S)tudy with (C)ontinuous (A)trial fibrillation (L)ogging

Phase IIb PASCAL

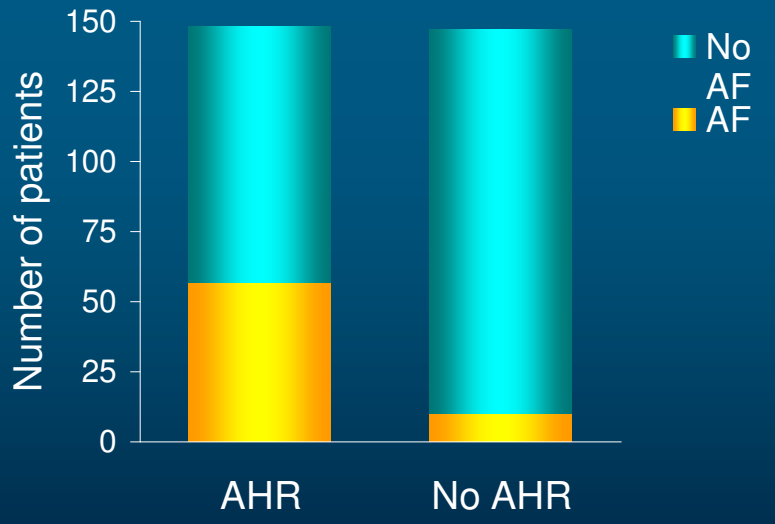
n = 72
PAF and DDD PM
Dose ranging:
200, 400, 600 mg bid
Parallel Groups
Duration: 4 weeks baseline
12 weeks DB therapy

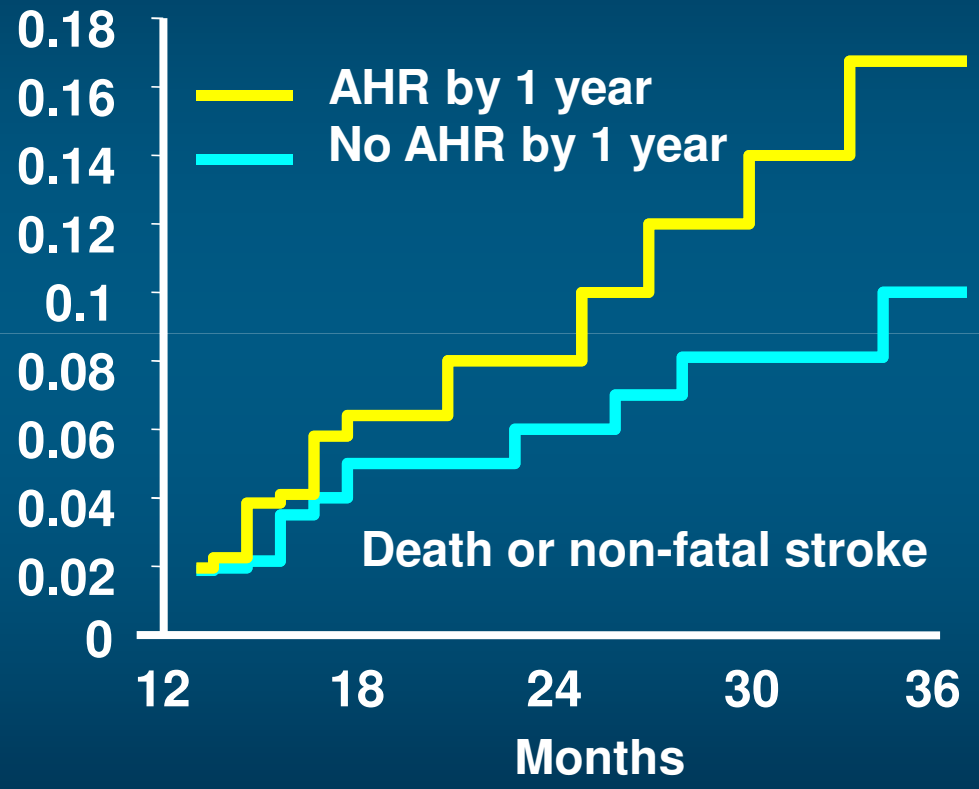


http://ClinicalTrials.gov

AHRE and Risk of Stroke or Death: *Post hoc* Analysis from the MOST Study

- **Ancillary MOST Study**
- **312 patients**
- **Event logged if AR > 220 bpm for 10 beats**



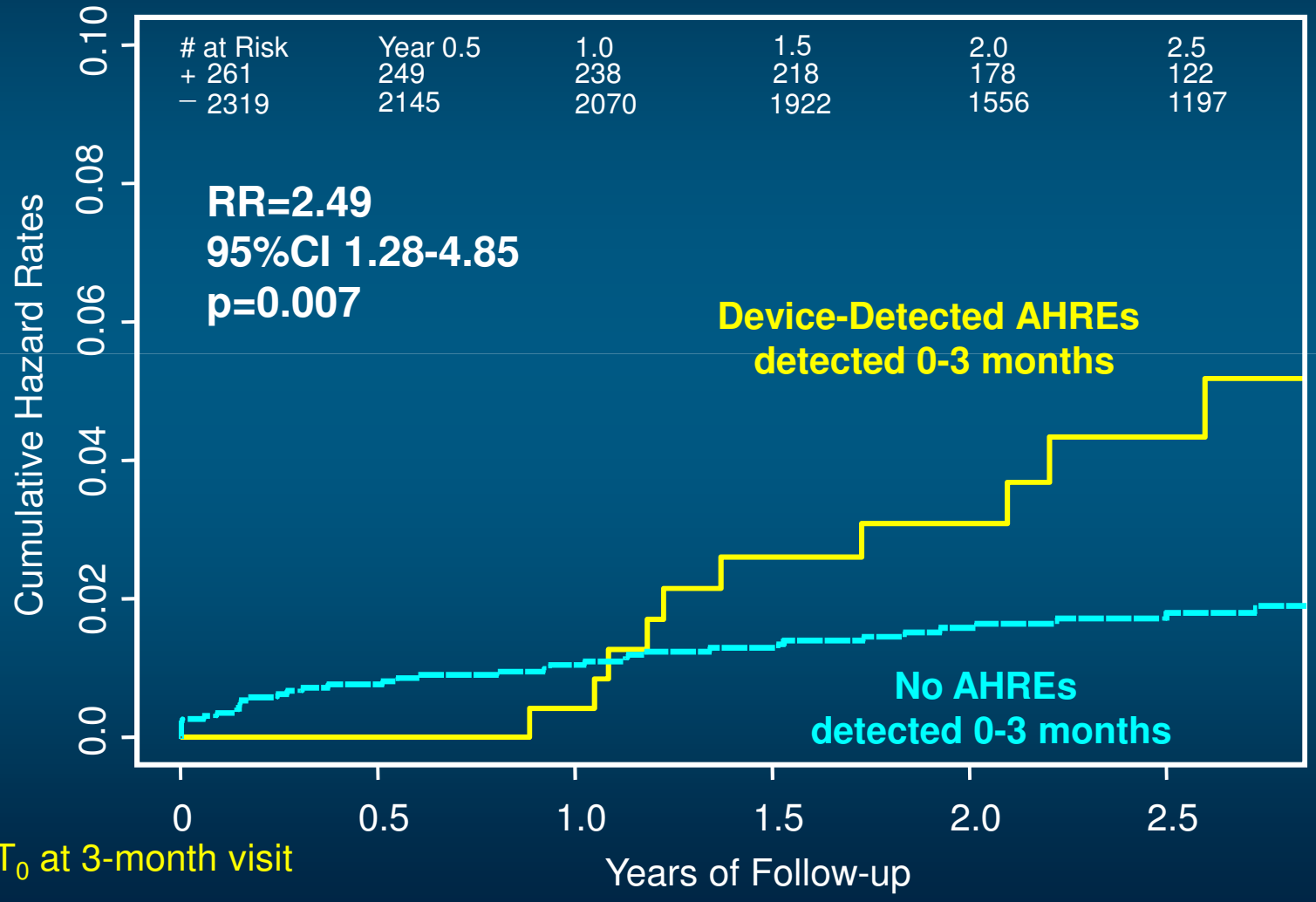


AHR predicts
Total mortality 2.48 [1.25-4.91], p = 0.0091
Death or non-fatal stroke 2.79 [1.51-5.15], p = 0.0011
AF 5.93 [2.88-12.2], p = 0.0001

Glotzer TV, et al. Circulation 2003;1614-9

ASSERT Study:

Ischemic Stroke or Systemic Embolism

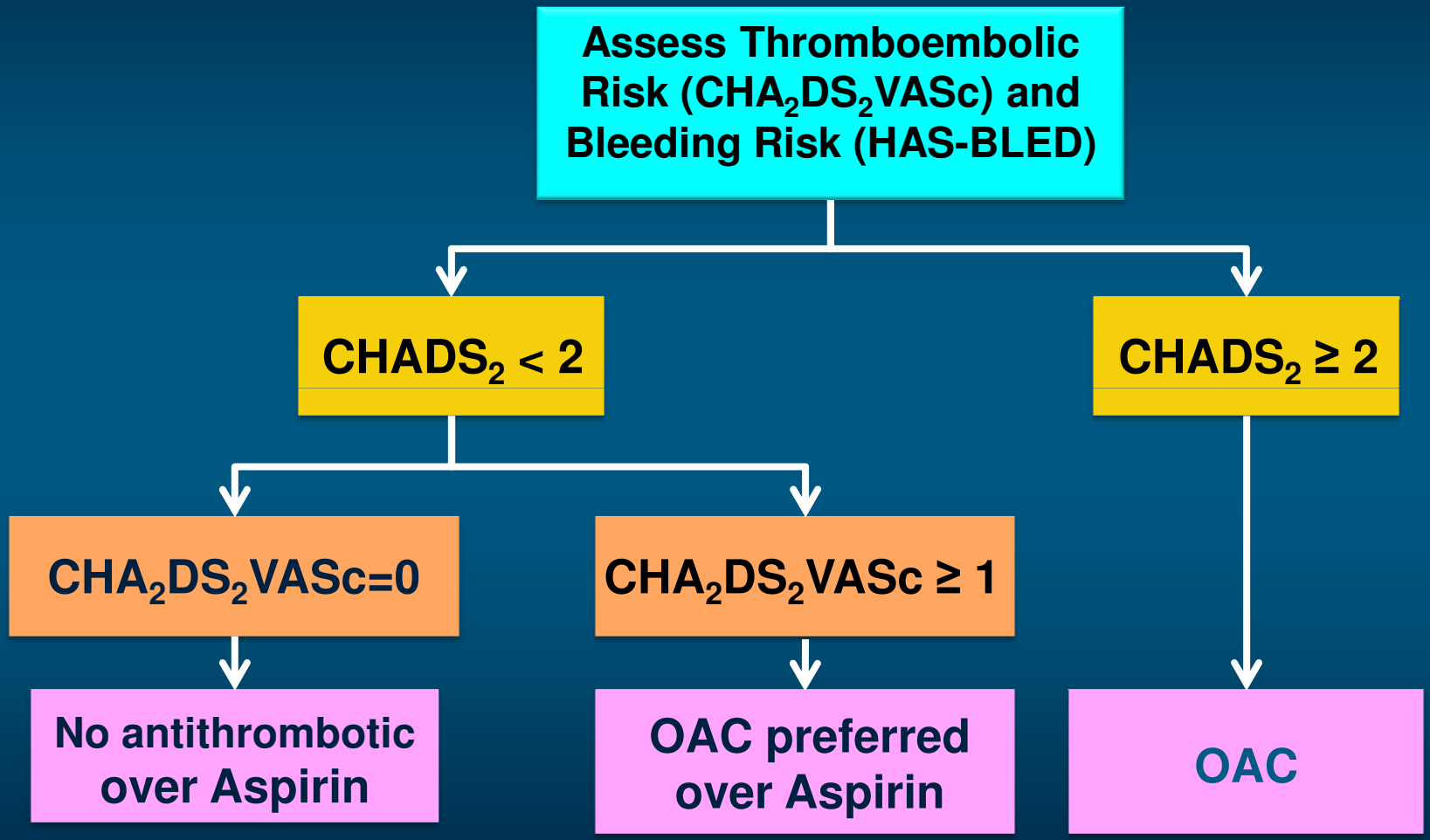


Healey J, et al. N Engl J Med 2012;366:120-9

Monitoring of AF by Implantable Devices and Outcome: Clinical Trials and Registries

Study	TRENDS NCT00279981	ASSERT NCT00256152	IMPACT NCT00559988	RATE Registry NCT00837798
Sponsor	Medtronic	**St Jude**	Biotronik	St. Jude
# patients	2486	**2580**	2718	5000
Inclusion criteria	Class I/II indication for DDD PM, ICD or CRT; $CHADS_2$ ≥1 (age ≥65)	**Class I/II indications for pacing; no previous AF; age ≥ 65 with hypertension**	Class I/II ICD or CRT-D indications; $CHADS_2$ ≥1	Conventional indications for PM or ICD
Device and monitoring	Device interrogation every 3 mos; AHRE ≥20 s detected; AF burden in 30-day rolling window	**Identity ADx DR or similar; device interrogation every 6 mos; AHRE > 190 bpm, > 6-min detected**	Lumax HF-T or DR-T with home monitoring for AF > 48 h and active OAC upon detection	Victory, Atlas II, Frontier II, etc., with advanced AT/AF diagnostics
1º endpoint	Ischemic stroke, TIA, SE	**Composite: ischemic stroke and SE**	Composite: stroke, SE, major bleed	AT/AF burden and frequency; patterns of AF onset; CHF; stroke or SE; QoL; therapy; hospitalizations for AF and CHF; inappropriate shocks; mortality
2º endpoints	QoL; costs; VR; AF progression; impact of new onset AF	**ECG-documented AF; composite of MI, vascular death, SE, CHF admission; AF burden; major bleed**	ACM, stroke (any); major bleed; AF burden; QoL; HR	
Follow-up	Mean, 1.4 years Published in full 2010	**Mean 2.8 years Results November 2010**	Completion expected 2014	Completion expected 2014

CHA_2DS_2-VASc-guided Anticoagulation



CHA_2DS_2-VASc to be used for initial risk stratification

CHA_2DS_2-VASc

- Congestive heart failure/ LV dysfucntion 1
- Hypertension 1
- Age ≥ 75 2
- Diabetes mellitus 1
- Stroke/TIA/TE 2
- Vascular disease (CAD, CArD, PAD) 1
- Age 65-74 1
- Sex category (female) 1

Score 0 – 9

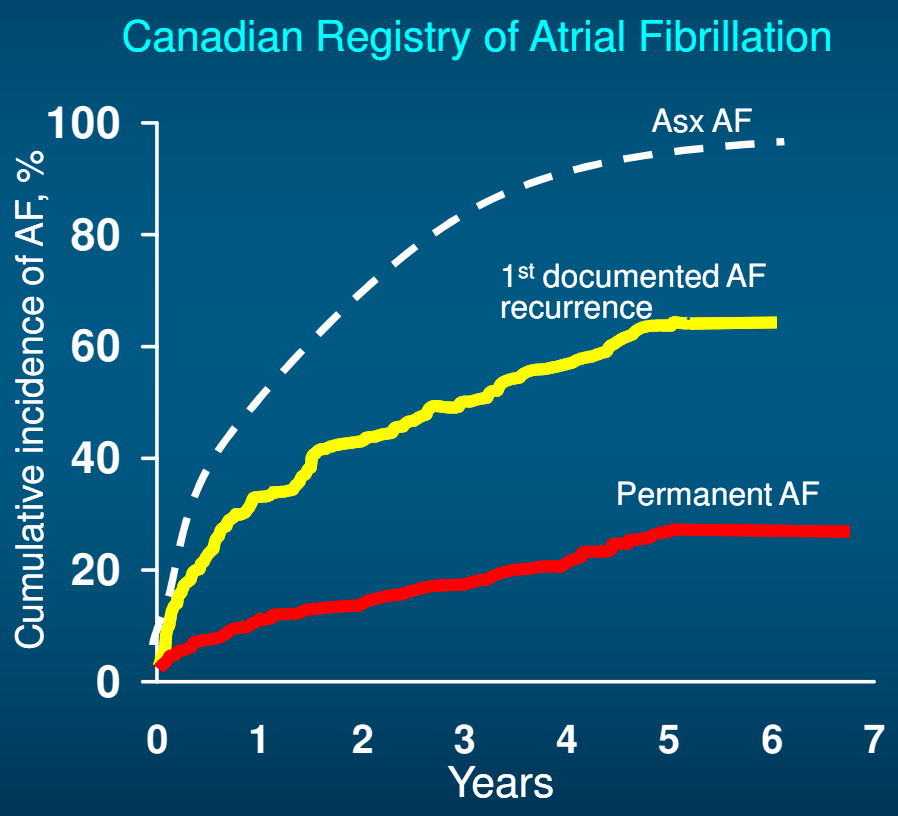
Validated in 1084 NVAF pts not on OAC with known TE status at 1 year in Euro Heart Survey
OR for stroke if:
Female: 2.53 (1.08 – 5.92), p=0.029
Vascular disease: 2.27 (0.94 – 5.46), p=0.063

Score	Annual stroke rate, %
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

Are AHREs Risk Factors or Markers?
Substudies from ASSERT

- AHREs of any duration (ranging from ≥ 6 min to ≥ 24-48 h) had similar risk of stroke
- There was no clear temporal relationship between AHREs and imminent stroke; risk remained increased after the occurrence of AHRE for the duration of follow-up
- Only 6 of 59 strokes were associated with AHRE > 6 min within 1 month of the episode
- Need to be incorporated in CHA_2DS_2VASc?

Natural History and Progression from Paroxysmal to Permanent AF



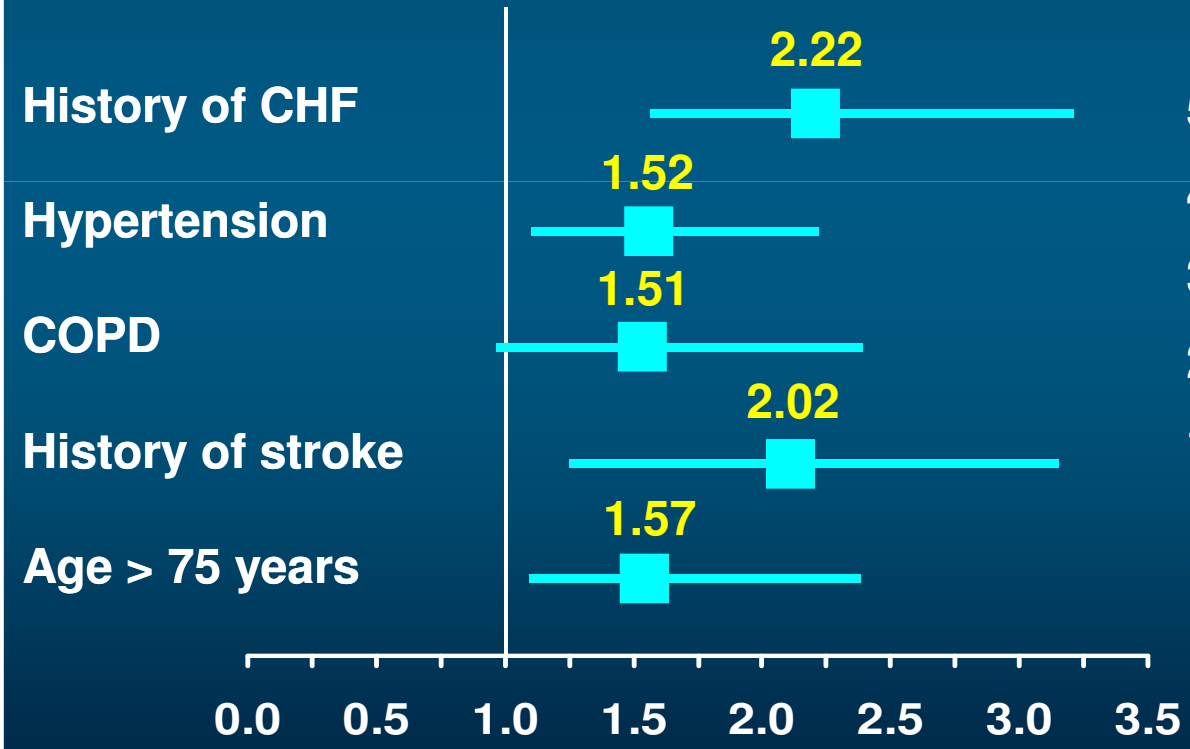
Kerr CR, et al. Am Heart J 2005;149:489-96

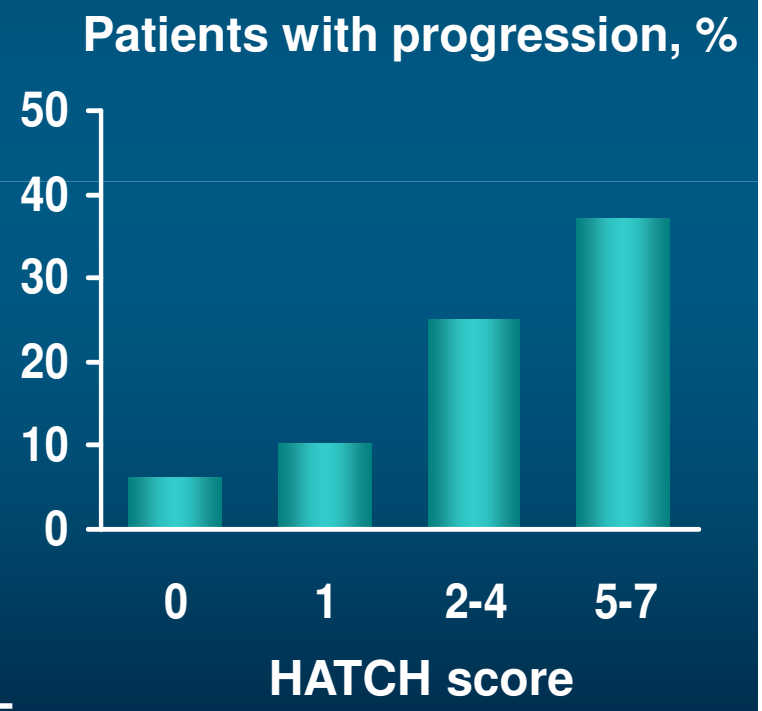
Study	No. of pts	Follow-up, years	Progression to permanent AF
Euro Heart Survey, 2010	1219	1	15%
Tokyo study, 1995	137	1	22%
UK general practice, 2005	525	2.7	17%
CARAF, 2001	899	4.14	19%
Italian study (Pappone), 2008	106	5	28.8%
CARAF, 2005	757	8	25%
Danish study, 1986	426	9	33%
Parkinson, 1930	200	10	25%
Tokyo study, 2004	171	14	77%
Olmsted County (Ione AF), 2007	71	25.2	31%

Progression of AF: HATCH

- Euro Heart Survey on AF
- 1219 patients with PAF
- Follow-up: 1 year
- Progression: 178 (15%)

- Hypertension x 1, Age > 75 yrs x 1, Stroke/TIA x 2, COPD x 1, Heart failure x 2

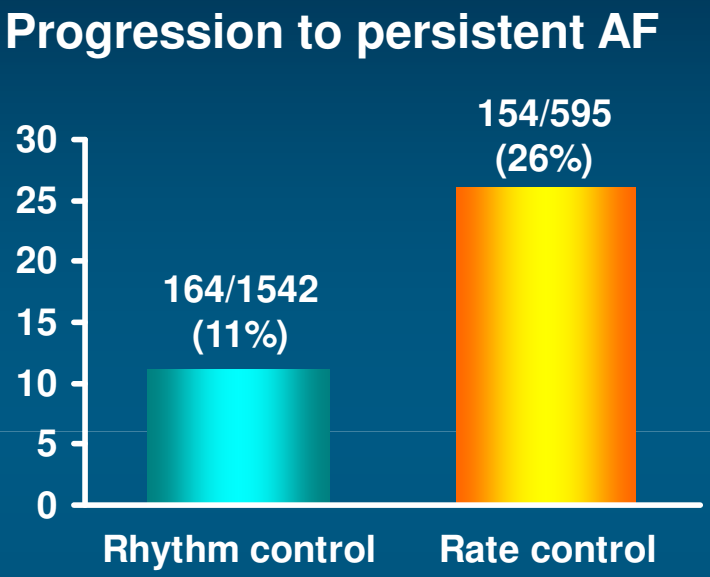




De Vos CB, et al. JACC 2010;55:725-31

Progression of AF: RECORD-AF

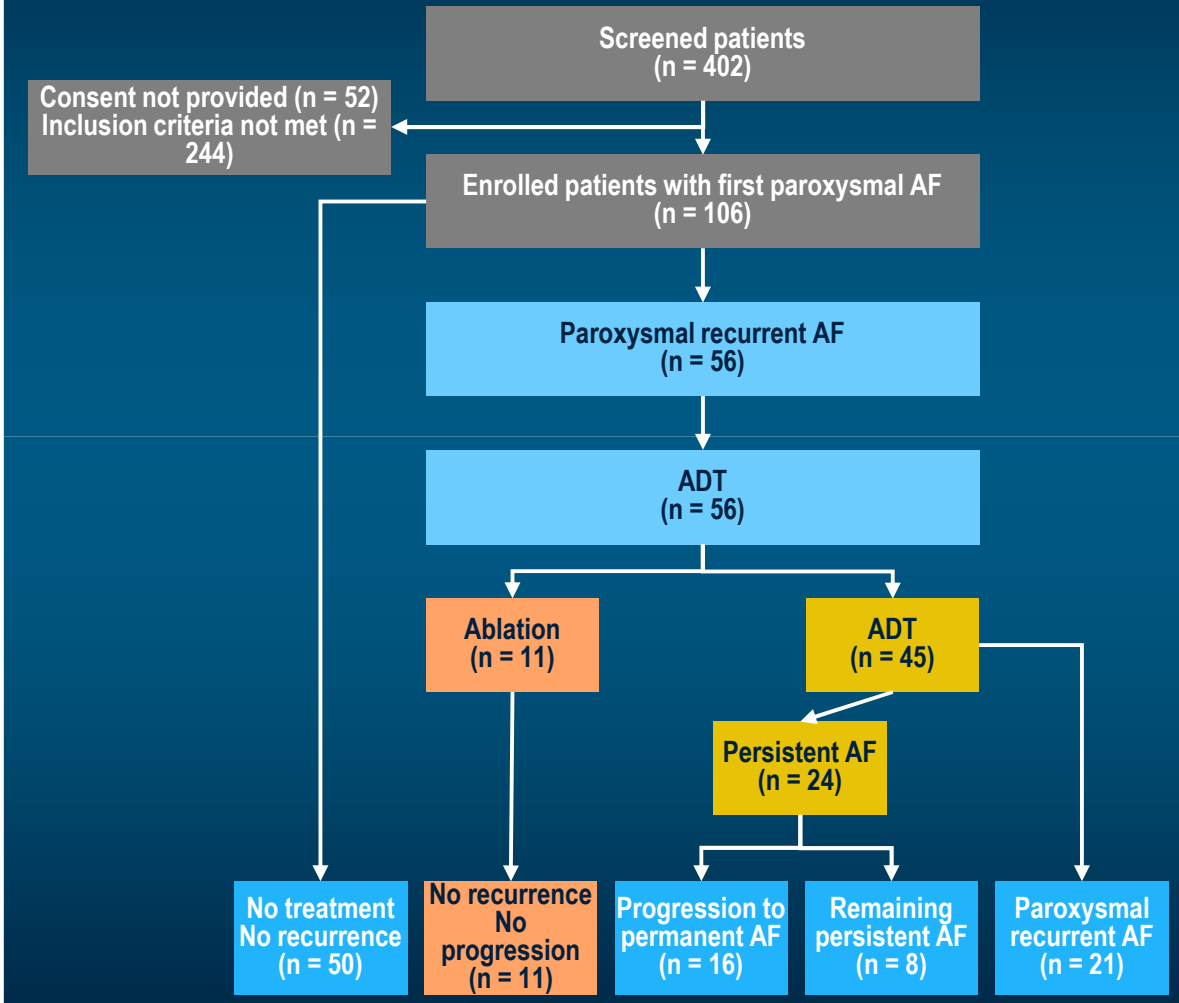
- Enrolled AF within 1 year of diagnosis
- 2,137 patients with PAF
- Follow-up: 1 year
- Progression: 318 (15%)



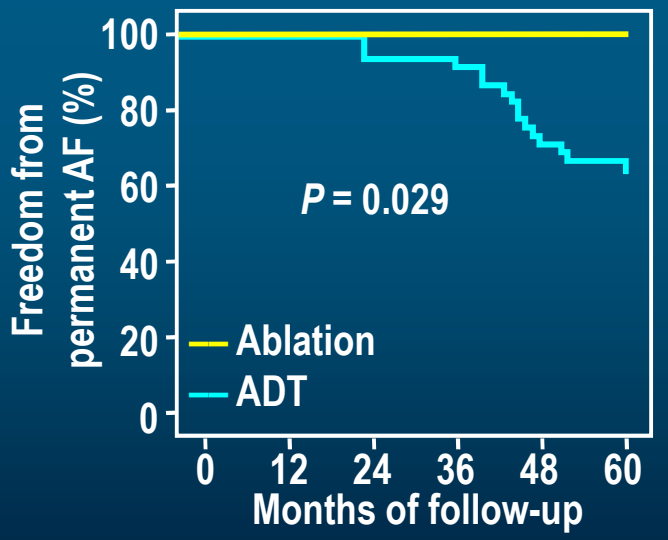
Variable	OR (95% CI)	p
Hypertension	1.5 (1.1 – 2.0)	0.01
CHF	2.2 (1.7 – 9.0)	<0.0001
Rate vs rhythm control	3.2 (2.5 – 4.1)	<0.0001

De Vos CB, et al. Am Heart J 2012;163:887-93

Early Intervention Impacts Progression?

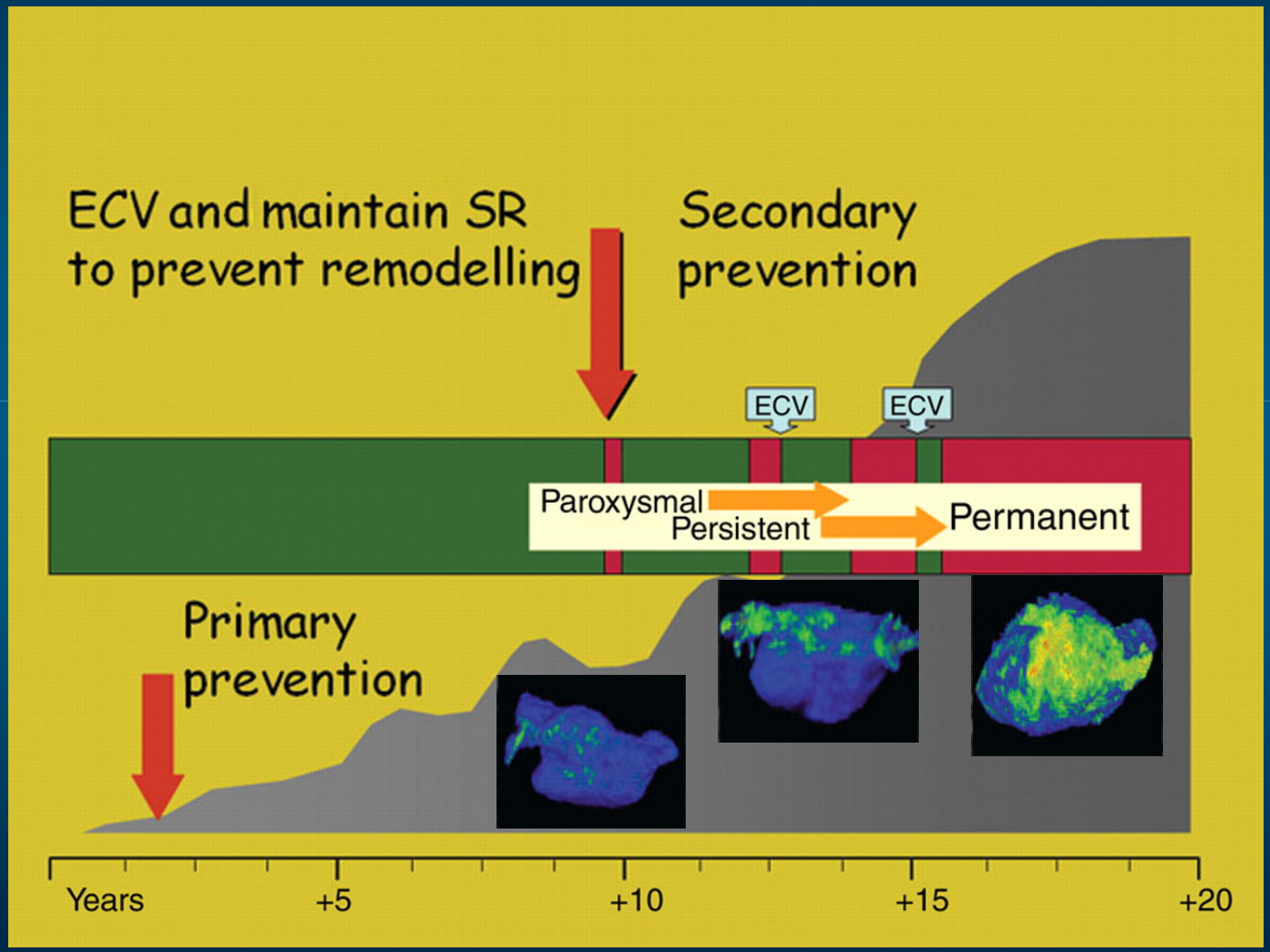


- Age 58 ± 12 years
- LAD dimension < 40 mm: 87% pts
- "Lone" AF: 51% pts
- Comorbidities predicted progression



Pappone C, et al. Heart Rhythm 2008;5:1501-7

Time Course of Atrial Substrate Remodeling: When to Intervene



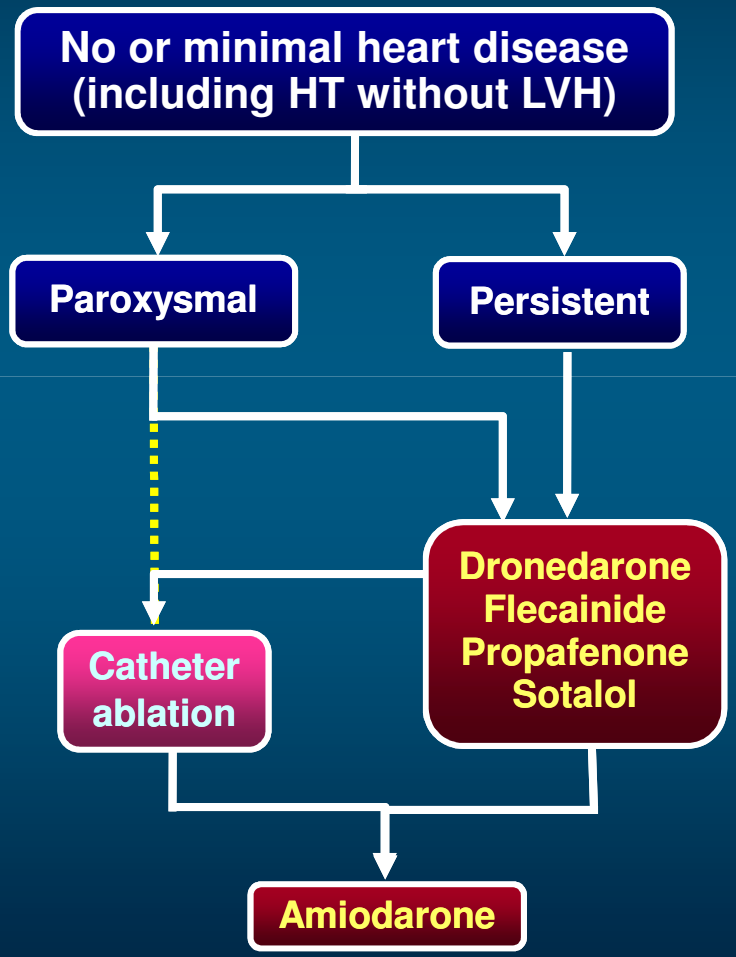
Cosio FG, et al. Europace 2008;10:21-27

RCTs of Ablation vs AADs or No Treatment in AF

Study	Number of patients	Type of AF	Previous use of AAD	Crossed to ablation in the AAD group	AF free at 1 year	
					Ablation	AAD
Krittayaphong, et al. 2003	30	Paroxysmal, persistent	≥1	Not stated	79%	40%
Wazni, et al. 2005, (RAAFT)	70	Mainly paroxysmal	No	49%	87%	37%
Stabile, et al. 2005 (CACAF)	137	Paroxysmal, persistent	≥2	57%	56%	9%
Oral, et al. 2006	146	Persistent	≥1 (mean 2.1±1.2)	77%	74%	4%
Pappone, et al. 2006 (APAF)	198	Paroxysmal	≥2 (mean 2±1)	42%	86%	22%
Jais, et al. 2008, (A4 study)	112	Paroxysmal	≥1	63%	89%	23%
Forleo, et al. 2008	70	Paroxysmal, persistent	≥1	Not stated	80%	43%
Wilber, et al. 2009 (Thermocool)	167	Paroxysmal	≥1 (mean 1.3)	59%	66%	16%
Packer, et al. 2010, (STOP-AF)	245	Paroxysmal	≥1	79%	69.9%	7.3%

Modified from Savelieva I and Camm J. Nat Rev Cardiol 2009;6:332-4

Recommendation for Catheter Ablation: Patients with No Significant Structural Heart Disease



ESC Recommendation	Class	Level
Catheter ablation for paroxysmal AF should be considered in symptomatic patients who have previously failed a trial of antiarrhythmic medication	IIa	A
Ablation of persistent symptomatic AF that is refractory to antiarrhythmic therapy should be considered a treatment option	IIa	B
Catheter ablation of AF may be considered prior to antiarrhythmic drug therapy in patients with paroxysmal symptomatic AF despite adequate rate control and no significant underlying heart disease	IIb	B

Ablation as First-line Therapy: RAAFT II

Radiofrequency ablation versus Antiarrhythmic drugs in Atrial Fibrillation Trial

- N = 127, mean age 55 years, 87.5% PAF
- Mean # episodes: 48 in the ablation group vs 33 in the AAD group
- AADs: flecainide and propafenone
- TTM every 2 weeks and during symptoms
- 1º endpoint: symptomatic or asymptomatic recurrence at 2 years
- Cross-over: 10.6% vs 47.5%; re-ablation: 15.2%

Endpoint	Ablation N = 66 (%)	AAD N = 61 (%)	HR (95% CI)	p
All AF, flutter, AT	55	72	0.56 (0.35 – 0.90)	0.02
Symptomatic AF, flutter, AT	47	59	0.56 (0.33 – 0.95)	0.03
Symptomatic AF	41	58	0.52 (0.30 – 0.89)	0.01
Clinical recurrence	24	31	0.86 (0.42 – 1.72)	0.66

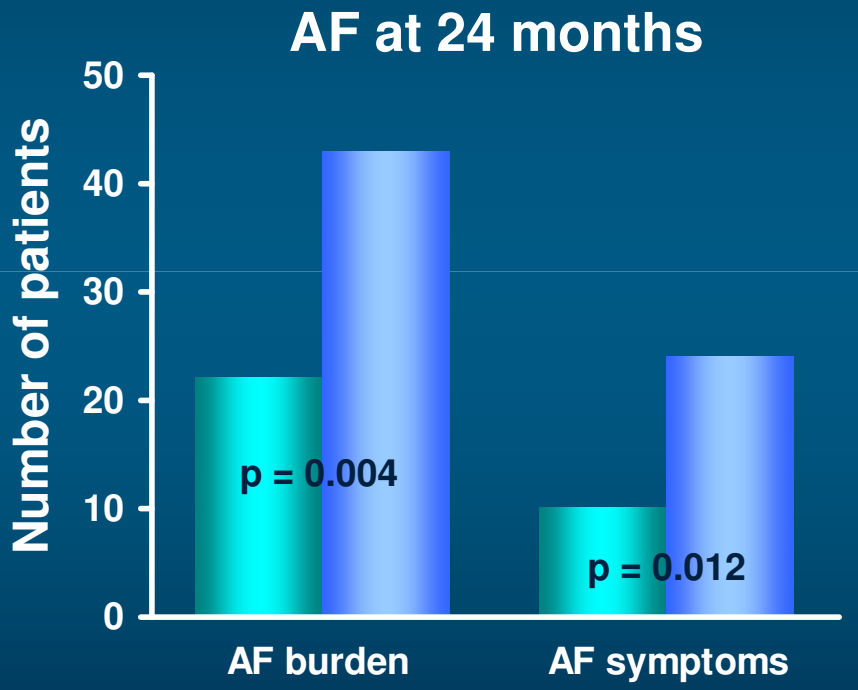
Morillo C, et al. LBR, HRS 2012

Complications: 7.7% versus 19.7%

Ablation as First-line Therapy: MANTRA-PAF

Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation

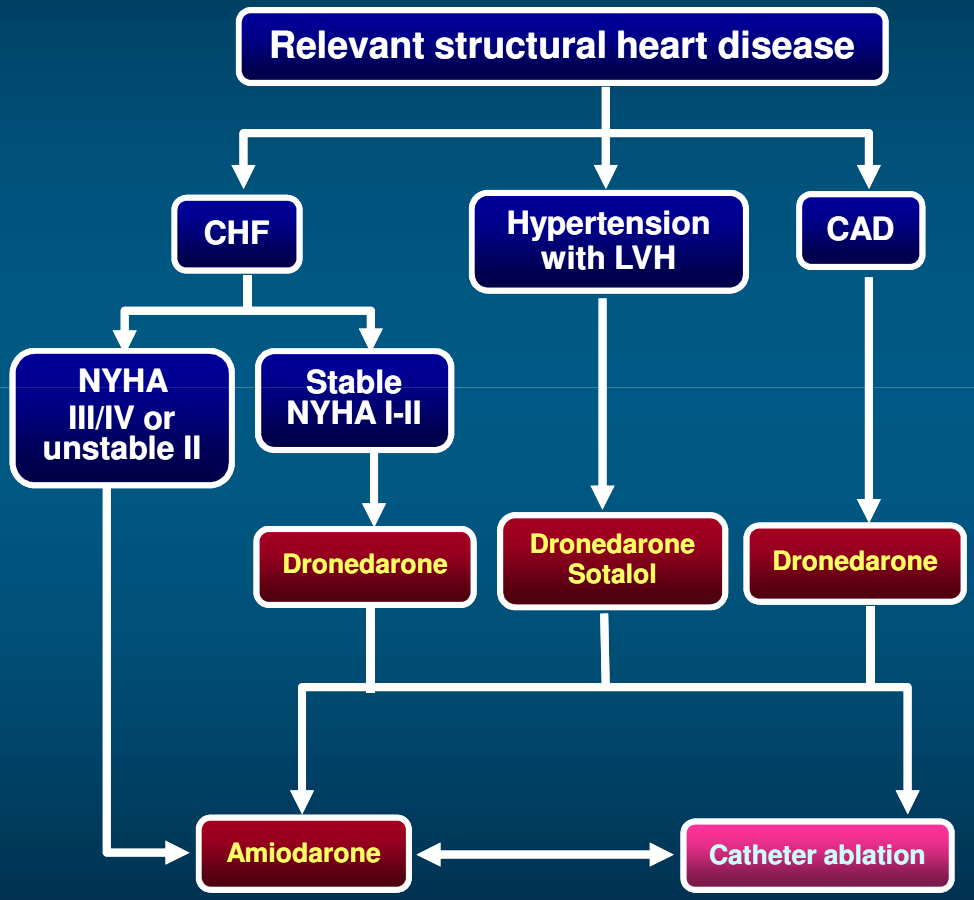
- N = 294 with PAF
- Follow-up: 2 years (n = 194)
- 7-day Holter at 3, 6, 12, 18, 24 months
- 1º endpoint: cumulative AF burden over 35 days and in follow-up
- 2º endpoints: any AF and symptomatic AF at 24 months, burden of symptomatic AF at each follow-up interval, flutter, QoL, SAEs



No difference in primary endpoint
Improvement in QoL

Cosedis Nielsen J, et al. NEJM 2012 [In press]

Recommendation for Catheter Ablation: Patients with Structural Heart Disease



ESC Recommendation	Class	Level
Catheter ablation of AF in patients with heart failure may be considered when antiarrhythmic medication, including amiodarone, fails to control symptoms	IIb	B
Catheter ablation of AF may be considered in patients with symptomatic long-standing persistent AF refractory to antiarrhythmic drugs	IIb	C

On-going Trials of Catheter Ablation

Acronym	Study Title	N	Endpoint
SARA	Study of Ablation versus anti-aRrhythmic drugs in persistent Atrial fibrillation	208	Freedom from AF > 24 hrs
AATAC	Ablation vs Amiodarone for Treatment of Atrial fibrillation in patients with CHF and an ICD	120	AF > 15sec
CASTLE-AF	Catheter Ablation versus Standard conventional Treatment in patients with LEft ventricular dysfunction and Atrial Fibrillation	400	All-cause mortality and HF hospitalisations
CABANA	Catheter ABlation versus ANtiarrhythmic drug therapy for Atrial fibrillation	3000	All-cause mortality
EAST	Early Atrial fibrillation Stroke Prevention Trial	3000	All-cause mortality + CV hospitalisations

Recommendations for Secondary Prevention of AF with Upstream Therapy

ESC Recommendation	Class	Level
Pretreatment with ARBs or ACEIs may be considered in patients with recurrent AF undergoing electrical cardioversion ***and*** receiving antiarrhythmic drug therapy	IIb	B
ARBs or ACEIs may be useful for prevention of recurrent paroxysmal AF or in patients with persistent AF in the absence of significant structural heart disease if these agents are indicated for other reasons (e.g. hypertension)	IIb	B

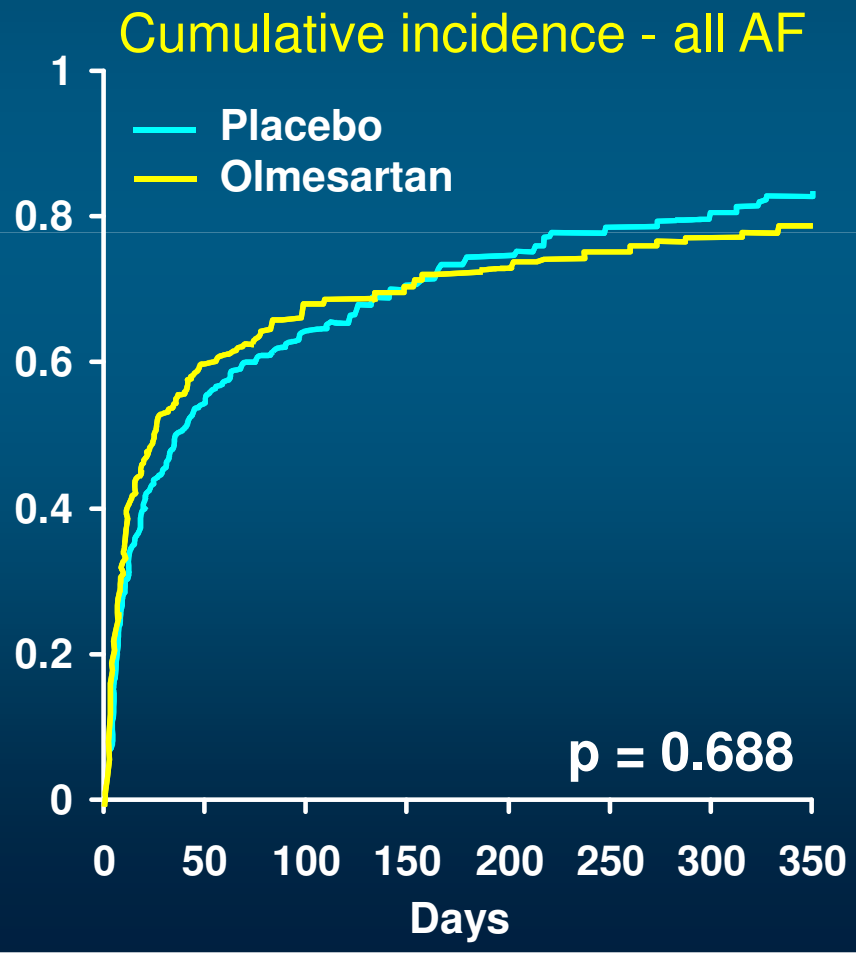
ANTIPAF: Angiotensin II ANTagonist In Paroxysmal Atrial Fibrillation

Primary endpoint:
Percentage of days with documented episodes of PAF (number of days with PAF divided by number of days with TTM recording) during 1-year follow-up

- 425 patients with documented PAF and SR (≤ 6 months)n
- Placebo vs Olmesartan 40 mg
- Age ~ 61 years, men ~ 60%, HTN ~ 50%, LAE ~ 35%

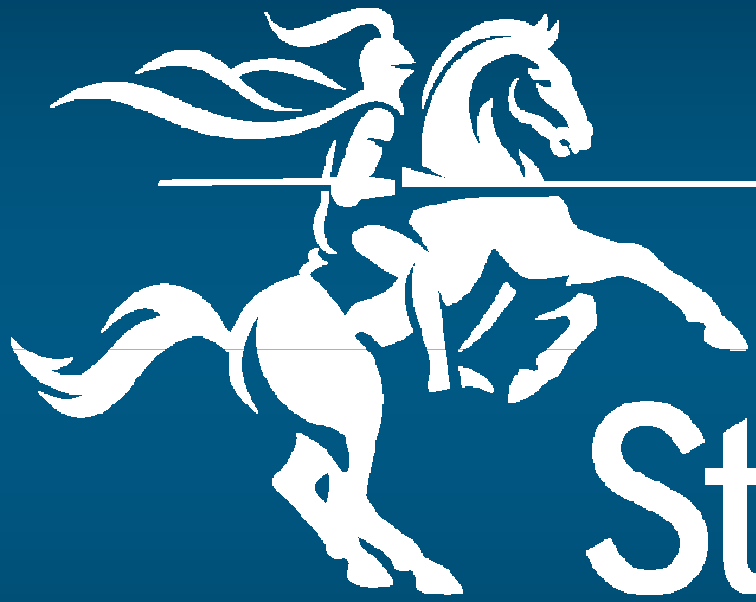
No difference in AF burden, cumulative incidence of all AF (symptomatic and asymptomatic), or progression to persistent AF

Goette A, et al. Circ Arrh Electrophysiol 2012



Intervene Early to Prevent PAF

- PAF is a progressive disease due to remodeling associated with ageing, underlying heart disease, and AF itself
- Insufficient, unstructured and delayed therapy of AF is a likely contributor to the limited efficacy of rhythm control therapy
- Ablation is a viable first-line therapy for PAF in (still) selected patients
- Whether early and comprehensive rhythm control therapy including ablation is beneficial is currently being tested



Thank you!

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