Venice Arrhythmias 2015

Atrial fibrillation progression trial (ATTEST)

Andreas Metzner

Hanseatic Heart Center
Asklepios-Klinik St. Georg
Hamburg/Germany

- Disclosures:
  - Consultant: Medtronic, Cardiofocus
  - Travel grants and lecture honoraria from Medtronic, Cardiofocus, Biosense-Webster, Boehringer-Ingelheim

Background

Natural progression of atrial fibrillation over time

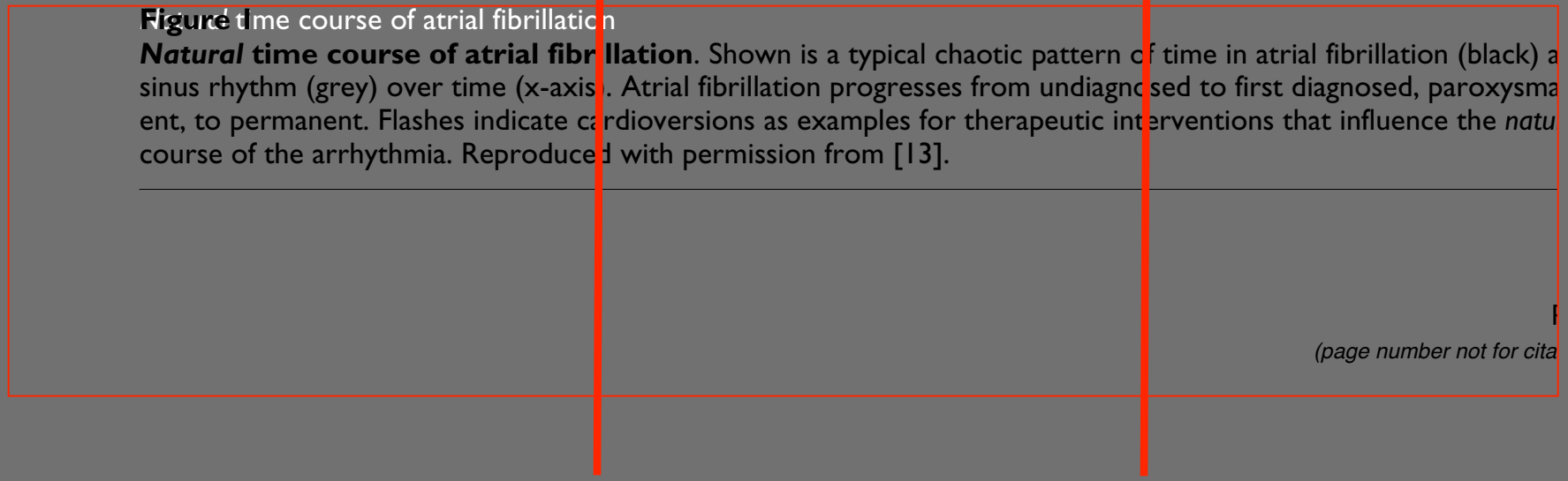


Figure 1
Natural time course of atrial fibrillation
***Natural* time course of atrial fibrillation**. Shown is a typical chaotic pattern of time in atrial fibrillation (black) a sinus rhythm (grey) over time (x-axis). Atrial fibrillation progresses from undiagnosed to first diagnosed, paroxysma ent, to permanent. Flashes indicate cardioversions as examples for therapeutic interventions that influence the *natu* course of the arrhythmia. Reproduced with permission from [13].

ESC: Focused update on treatment of AF 2012

Progression from PAF to chronic AF

	Patients n	Follow-up (y)	PAF —> CAF	
			n Pts	%
Kerr 2005	757	1 (5)	65/757 (187/757)	8.6 (24.7)
Ruigómez 2005	418	2	70/418	17
Abe 1997	122	2	14/122	11
Sakamoto 2013	137	1	30/137	22
Kato 2004	171	14	132/171	77.2
De Vos 2010	1219	1	178/1219	15

Kerr et al. AM Heart J 2005;149:489-96.; Rodruigez et al. BMC Cardiovasc Disord. 2005; Abe Y et al. Circulation 1998;98:1045-6.; Sakimoto T et al. Nihon Rinsho. 2013;7:15-20.; Kato T et al. Circ J 2004;68:568-72.; J Am Coll Cardiol. 2010;55(8):725-31

HATCH Score – Progression from PAF to chronic AF

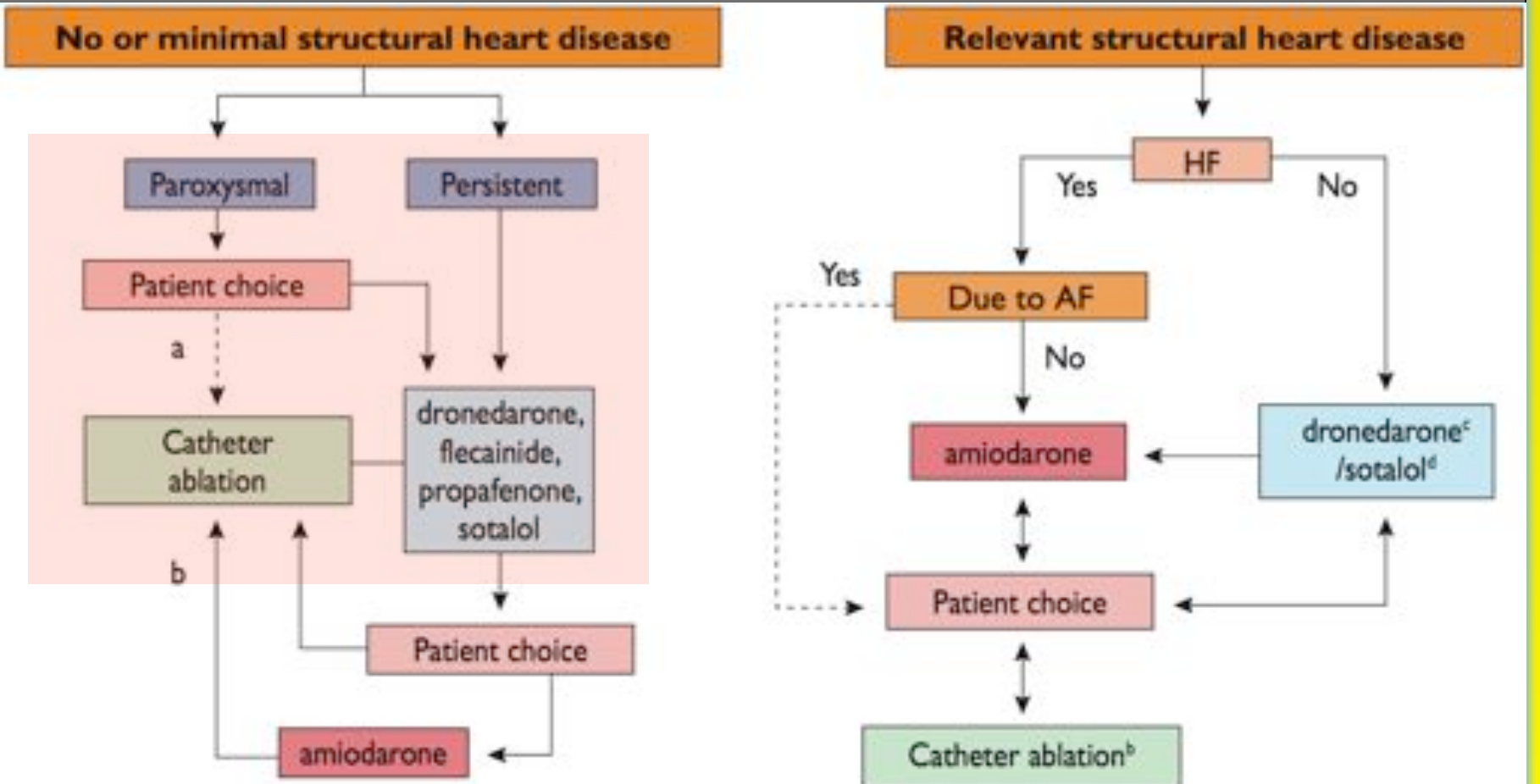
History of stroke or TIA	2.02	1.24–3.31	0.
Age >75 yrs	1.57	1.07–2.30	0.

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

more sustained forms of AF are likely to develop
future. Previous studies showed that the presenc
lying heart disease is associated with poor c
rhythm control therapy (10). However, these p
more likely to have AF progression. In the sam
data suggest that the potential preventive effec
rhythmic drugs on AF progression was outperfor
promoting effect of underlying heart disease a
represented by the HATCH parameters. Th
seems very important to identify patients that a

de Vos et al. JACC 2010; 55: 725-31

Background



AF = atrial fibrillation; HF = heart failure. [a]Usually pulmonary vein isolation is appropriate. [b]More extensive left atrial ablation may be needed. [c]Caution with coronary heart disease. [d]Not recommended with left ventricular hypertrophy. Heart failure due to AF = tachycardiomyopathy.

ESC: Focused update on treatment of AF 2012

Impact of ablation on AF progression

Table 4. Impact of Catheter Ablation on AF Disease Progression: Within-study Comparisons (non-randomized unless noted)

Study	Catheter ablation % progression (n/N)	No catheter ablation % progression (n/N)	Notes
Santinelli 2009 RCT (APAF-2 trial)	1% (1/99)	2% (2/99)	p=NS At 4 years
Dabrowski 2010	0% (0/6)	10% (15/148)	p=NS At 1 year
de Vos 2010	6.5% (4/61)	15% (174/1158)	p=0.065 At 1 year
Pappone 2008	0% (0/11)	53% (24/45)	p=0.029 At 5 years
Bertaglia 2010	10% (10/102)	N/A	3-year followup for patients free from recurrence at 1 year
Ouyang 2010	2.5% (4/161)	N/A	At 5 years
Sawhney 2009	11% (8/71)	N/A	At 5 years

Pappone C et al. Circ A and E 2011;4:808-14.; Pappone C et al. Heart Rhythm 2008;5:1501-7.; Bertaglia et al. Europace 2010;12:181-7.; Ouyang et al. Circulation 2010;122:2368-77.; Sawhney et al. Am J Cardiol.2009;104:366-72.

ATTEST: Study Hypothesis

For subjects undergoing **early RF ablation** for *recurrent, symptomatic PAF*, it is hypothesized that:

- compared to the Drug Therapy (control) Group,
- the PVI (test) Group will demonstrate

  => superior effectiveness

  as evidenced by

  => a longer time needed to progress to persistent AF/AT during follow-up through 3 years

Study-Design: Primary Endpoint

Time to Persistent/AT AF

With peristent being defined as:

"AF/AT lasting longer than 7 consecutive days or requiring termination by cardioversion after 48 hours"

- *Unnecessary Cardioversion < 7 days should be discouraged, but within ethical bounds.*
- *If the Investigator believes the subject's AF symptoms are sufficiently severe to warrant cardioversion, he/she should proceed, regardless of timing.*
  - *AF symptoms sufficiently severe to warrant cardioversion are angina, shortness of breath and/or systolic blood pressure < 90 mmHg; related to AF*

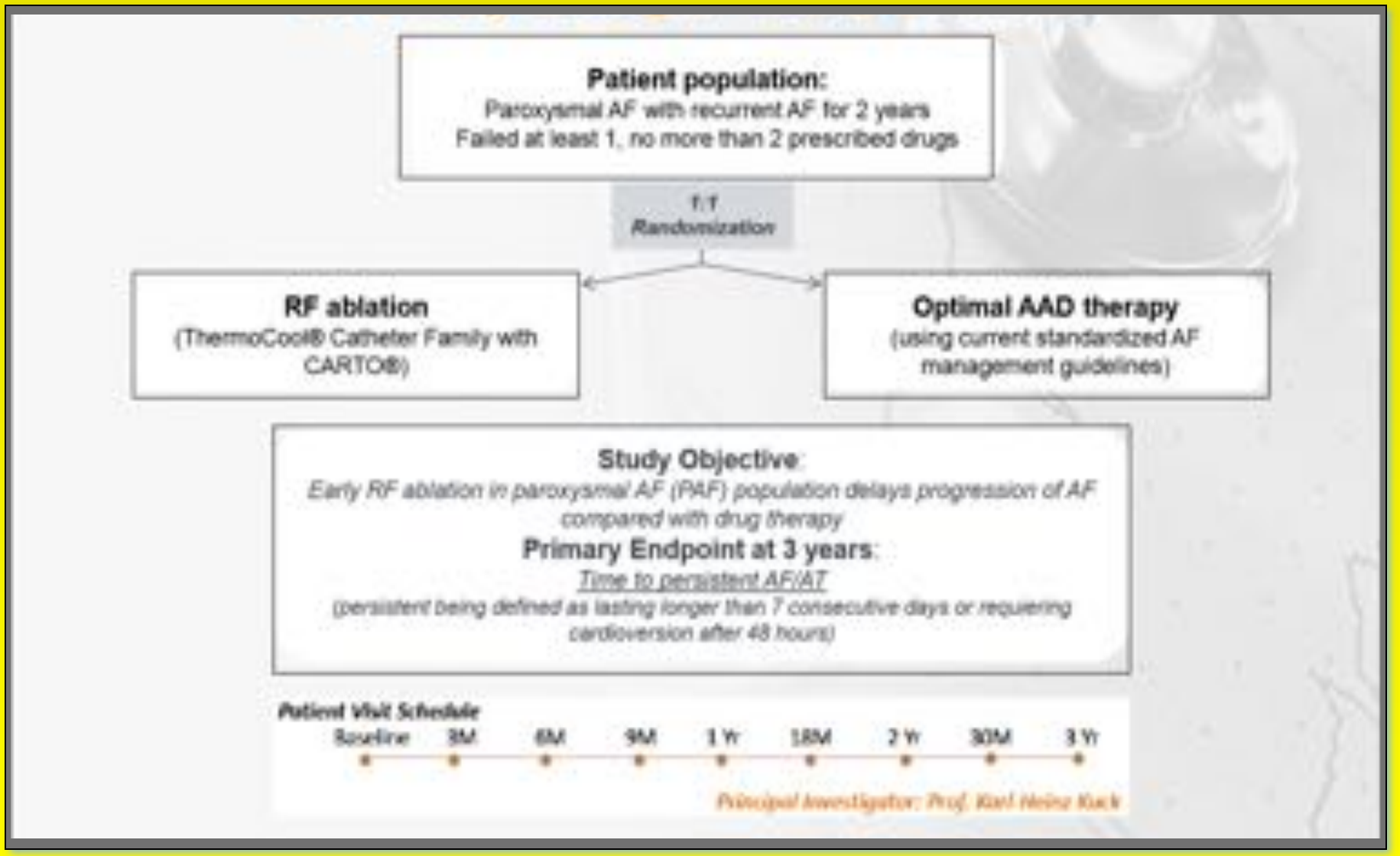
Study-Design: Secondary Endpoints

Effectiveness

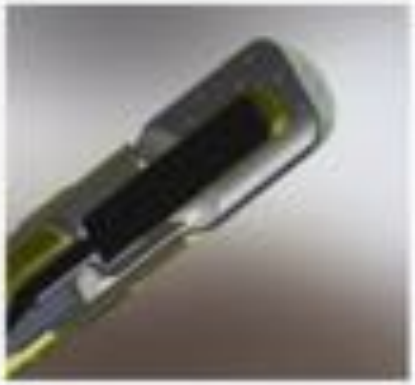
- **Rate and time to persistent AF/AT** at 1 year and 2 years, **rate** of persistent AF/AT by number of ablations at 3 years
- **Number of repeat ablations and new AAD** per subject throughout 3 year FUP
- **Rhythm** (% subjects in SR, % subjects with recurrent AF) throughout 3 years FUP
- **Subject's pre-existing or new onset/worsened condition(s),** that may be associated with AF progression,
  => parameters include: age and gender; LA size; HATCH Score; BP; NYHA Functional Classification of heart disease; diabetes; lipid profile; renal function; dementia
- Subjects will be considered an **effectiveness success** if they do not progress to persistent AF through the 3-year follow-up period

Study-Design: Secondary Endpoints

Study-Design: Study overview



Study-Device/Equipment



Including all catheters from the ThermoCool® Navigation Family of Catheters (eg. RMT, SF, Smarttouch)

CARTO ®3 System
CARTO ® XP System

CARTO ® RMT System

Inclusion Criteria

1.	Patients with recurrent AF for 2 years, with ≥ 2 episodes over the last 6 months
2.	HATCH Score ≥ 1 and ≤ 4
3.	Eligible for catheter ablation AND for anti-arrhythmic or rate control medications, after having failed at least 1, but no more than 2 prescribed drugs (either anti-arrhythmic or rate control drug)
4.	≥ 60 years
5.	LA diameter ≤ 55mm by TTE
6.	LV ejection fraction ≥ 50% when in sinus rhythm or LV ejection fraction ≥ 35% when in AF
7.	Signed Patient Informed Consent Form Able and willing to comply with protocol requirements

Exclusion Criteria

1.	Awaiting cardiac transplantation or other cardiac surgery
2.	Acute illness (ongoing) or active systemic infection or sepsis
3.	Reversible causes of AF e.g. thyroid disorders, acute alcohol intoxication, recent major surgical procedures or trauma, ...
4.	Recent cardiac events incl. MI, PCI, heart failure or valve or bypass surgery in the preceding 3 months
5.	Heart failure decompensation
6.	Previously diagnosed with persistent/permanent AF/AT
7.	Previously required cardioversion >48h after onset AF/AT
8.	Previous stroke - Subject having previous TIA or stroke (cerebrovascular accident) one year prior to patient enrolment and/or no sufficient recovery
9.	Pulmonary embolism or recent atrial embolism/thrombosis
10.	Hypertrophic obstructive cardiomyopathy

Exclusion Criteria cont.

11.	Class IV angina or Class IV CHF (including past or planned heart transplantation)
12.	Mandated anti-arrhythmic drug therapy for disease conditions other than AF
13.	Heritable arrhythmias or increased risk for torsade de pointes with class I or III Drugs
14.	Prior LA catheter ablation with the intention of treating AF; prior surgical interventions for AF such as the MAZE procedure
15.	Prior AV nodal ablation
16.	Contra-indications for the study catheter(s) ref. Instructions For Use
17.	Contraindication to warfarin, other anticoagulation therapy, or all anti-platelet medications
18.	Medical conditions limiting expected survival to < 3 years
19.	Concurrent participation in any other clinical study
20.	Prior history of non-adherence to prescribed drug regimens
21.	Pregnant, lactating or planning to become pregnant during course of trial

Study Schedule

	BL D0	M3 D76-104	M6 D166-210	M9 D240-300	Y1 D330-420	M18 D480-.600	Y2 D630-809	M30 D810-989	Y3 D990-1170	UNS
Clinic Visit	X	X	X		X		X		X	X
Phone follow-up				X		X		X		
Patient Information and Consent	X									
Medical history	X									
HATCH score	X	X	X		X		X		X	X
ECG	X	X	X		X		X		X	X
TTM	X	X	X	X	X	X	X	X	X	X
TEE	X									
TTE	X	X	X		X		X		X	
QoL (EQ-5D, AFEQT)	X	X	X		X		X		X	
Health status	X	X	X		X		X		X	X
Cardiac medication	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X
Cardioversion/re-ablation documented		X	X	X	X	X	X	X	X	X

Time to event monitoring

Patient enrolment

Test group Day 0 = index ablation	Control group Day 0 = Randomization

Start weekly TTM Day 104 (+/-3M FU)

1x/week to capture some asymptomatic episodes

! AF documented → Daily monitoring for 7 consecutive days

Start monthly TTM Day 300 (+/-9M FU)

1x/month to capture some asymptomatic episodes

! AF documented → Daily monitoring for 7 consecutive days

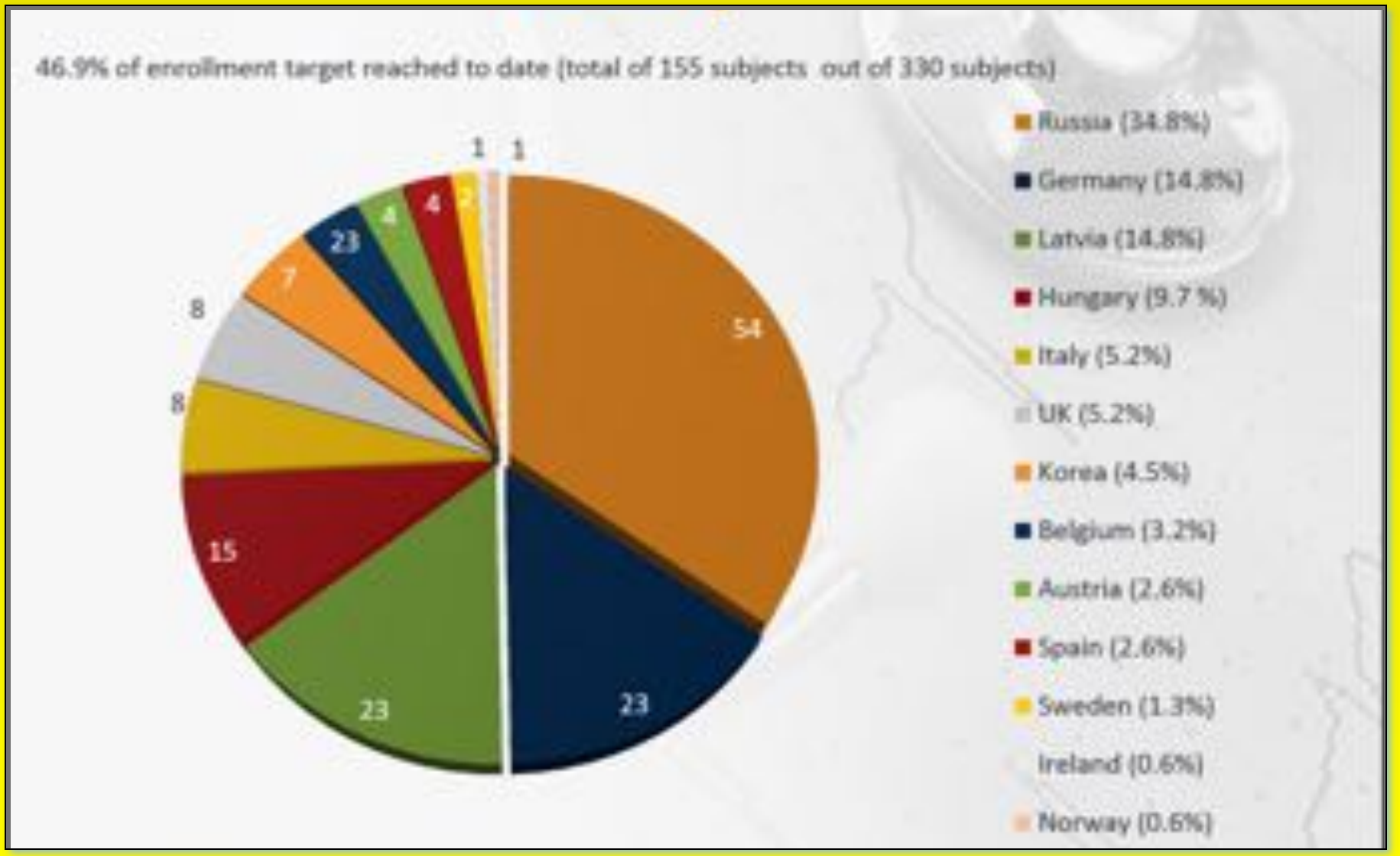
Primary endpoint reached

AF present for 7 consecutive days or requires termination by cardioversion >48h

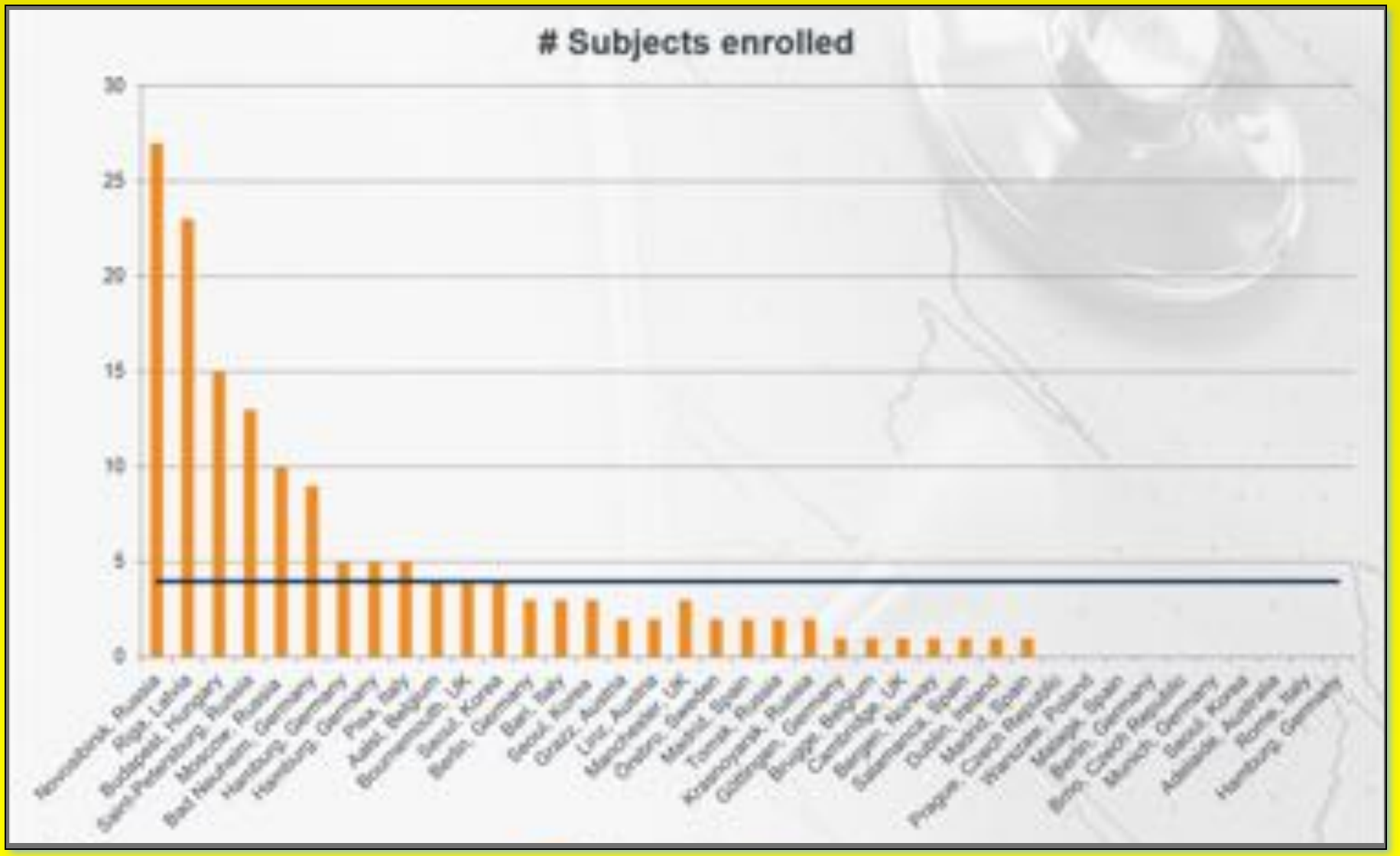
→ Stop TTM monitoring, FUP visit at 3Y, continue safety reporting

Overall Project Status

Overall Project Status – Enrollment by Country



Overall Project Status – Enrollment by Site



Conclusions

- So far only limited data on AF progression is available
- The ATTEST trial aims at assesment of AF progression comparing ablation vs. drug-based treatment in a randomized, prospective, multi-center fashion
- ~50% of patients are enrolled
- → more active centers are required

Thank You!