«Αντιθέσεις στην Κολπική Μαρμαρυγή»

Η κατάλυση πρώτης γραμμής θεραπεία στην παροξυσμική κολπική μαρμαρυγή: Υπέρ

Παναγιώτης Ιωαννίδης

Διευθυντής Τμήματος Αρρυθμιών & Επεμβατικής Ηλεκτροφυσιολογίας Βιοκλινικής Αθηνών

2ο Αρρυθμιολογικό Συνέδριο

Αθήνα, 1-10-2016

Randomized Trials Ablation vs AADs

Study	PAF/PsAF	Procedures (n)	Patients (n)	AF freedom Ablation	AF freedom AADs
Krittayaphong et al. [1]	100% PsAF		30	79%	40%
Wazni et al. [2]	96%PAF/4%PsAF	1	70	85%	21%
Pappone et al. [3]	100%PAF	1	198	85% without AAD	35%
Oral et al. [4]	100%PAF	32% Redo	146	74% without AAD	58% (77% cross-over to ablation)
Stabile et al. [5]	67%PAF/33%PsAF	1	137	66%	8,7%
Jais et al. [6]	100%PAF	1,8	112	89% without AAD	23%
Forleo et al. [7]	41%PAF/59%PsAF	1	70	80% without AAD	43%
Wilber et al. [8]	100% PAF	12.6% Redo within 80 d	167	66%	16%

[1] Krittayaphong et al. J Med Assoc Thai 2003;86(S1):S8-16

[2] Wazni et al. JAMA 2005;293:2634-40

[3] Pappone et al. JACC 2006;48:2340-7

[4] Oral et al. NEJM 2006;354:934-41

[5] Stabile et al. Eur Heart J 2006;27:216-21

[6] Jais et al. Circulation 2008;118:2498-2505

[7] Forleo et al. J Cardiovasc Electrophysiol 2009;20:22-28

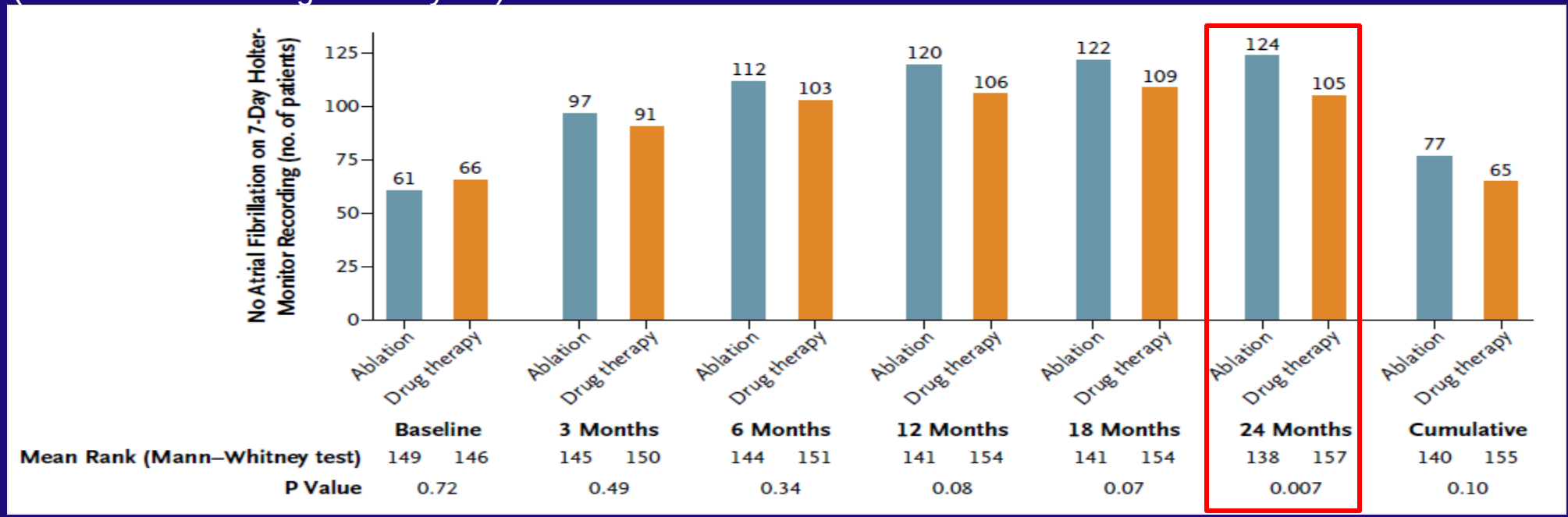
[8] Wilber et al. JAMA. 2010;303:333-340

MANTRA-PAF Trial:
Radiofrequency Ablation as Initial Therapy in Paroxysmal AF

- 294 patients with paroxysmal atrial fibrillation and **no history of antiarrhythmic drug use**
- Randomization to either radiofrequency catheter ablation (146 patients /1.6±0.7 procedures/pt) or therapy with class IC or III antiarrhythmic agents (148 patients).
- Follow-up with 7-day Holter recordings after 3, 6, 12, 18 and 24 months
- Intention-to-treat analysis (36% cross-over from AAD therapy to Ablation (most of them during the 1st year)

Table 2 Recommended anti-arrhythmic drugs and corresponding initial doses used in the study

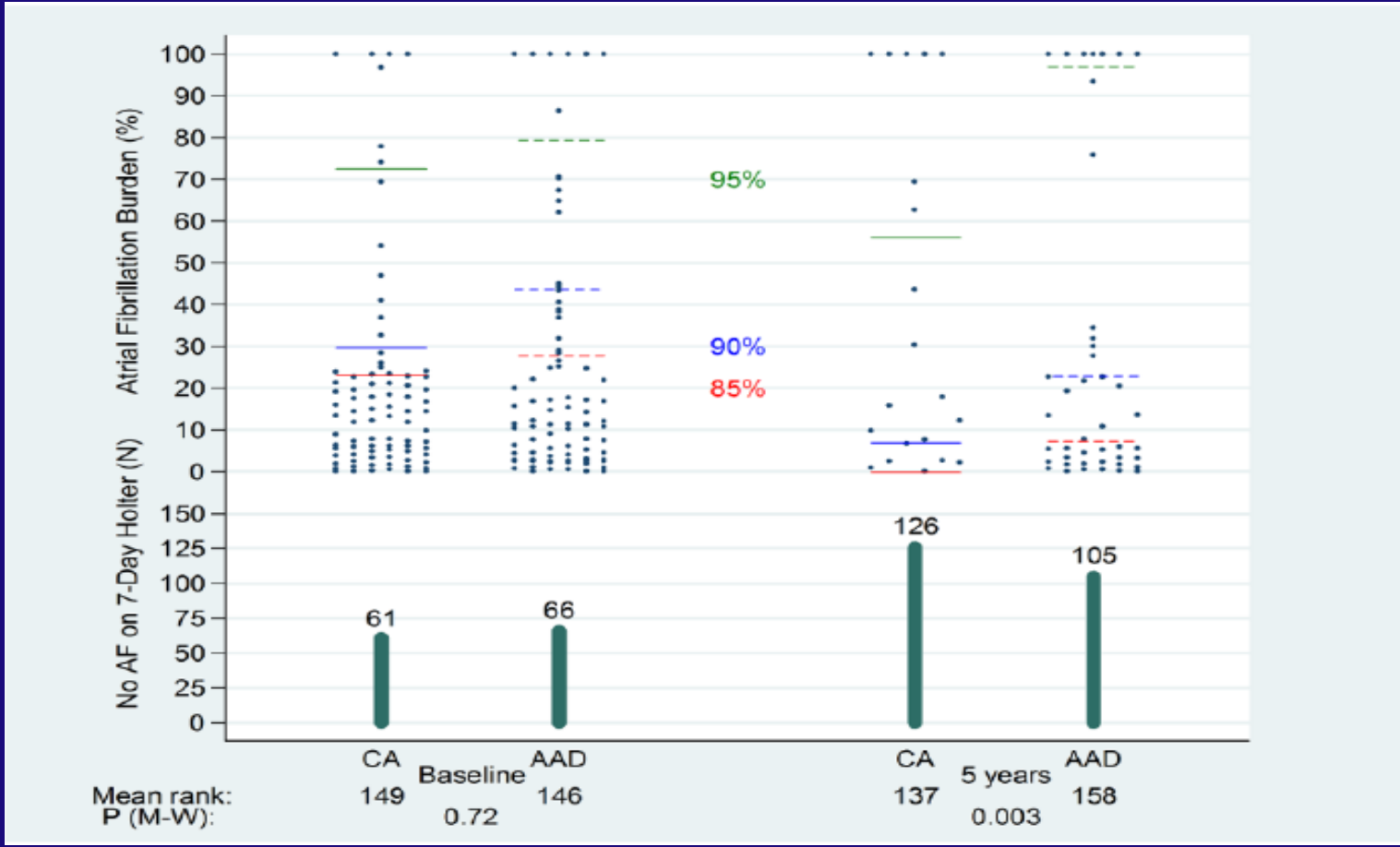
	1st choice		2nd choice	3rd choice
	Flecainide	Propafenone	Amiodarone	Sotalol
Dose	100 mg twice a day	300 mg twice a day	200 mg once a day	80 mg twice a day



Nielsen et al. N Engl J Med 2012;367:1587-95

Five-year follow-up in MANTRA-PAF

Long-term efficacy of catheter ablation as first-line therapy for paroxysmal atrial fibrillation: 5-year outcome in a randomised clinical trial



Nielsen et al. Heart 2016 Aug 26

Radiofrequency Ablation vs Antiarrhythmic Drugs as First-Line Treatment of Paroxysmal Atrial Fibrillation (RAAFT-2)
A Randomized Trial

Carlos A. Morillo, MD, FRCPC; Atul Verma, MD, FRCPC; Stuart J. Connolly, MD, FRCPC; Karl H. Kuck, MD, FHRS; Girish M. Nair, MBBS, FRCPC; Jean Champagne, MD, FRCPC; Laurence D. Sterns, MD, FRCPC; Heather Beresh, MSc; Jeffrey S. Healey, MD, MSc, FRCPC; Andrea Natale, MD; for the RAAFT-2 Investigators

IMPORTANCE Atrial fibrillation (AF) is the most common rhythm disorder seen in clinical practice. Antiarrhythmic drugs are effective for reduction of recurrence in patients with symptomatic paroxysmal AF. Radiofrequency ablation is an accepted therapy in patients for whom antiarrhythmic drugs have failed; however, its role as a first-line therapy needs further investigation.

OBJECTIVE To compare radiofrequency ablation with antiarrhythmic drugs (standard therapy) in treating patients with paroxysmal AF as a first-line therapy.

DESIGN, SETTING, AND PATIENTS A randomized clinical trial involving 127 treatment-naive patients with paroxysmal AF were randomized at 16 centers in Europe and North America to received either antiarrhythmic therapy or ablation. The first patient was enrolled July 27, 2006; the last patient, January 29, 2010. The last follow-up was February 16, 2012.

INTERVENTIONS Sixty-one patients in the antiarrhythmic drug group and 66 in the radiofrequency ablation group were followed up for 24 months.

MAIN OUTCOMES AND MEASURES The time to the first documented atrial tachyarrhythmia of more than 30 seconds (symptomatic or asymptomatic AF, atrial flutter, or atrial tachycardia), detected by either scheduled or unscheduled electrocardiogram, Holter, transtelephonic monitor, or rhythm strip, was the primary outcome. Secondary outcomes included symptomatic recurrences of atrial tachyarrhythmias and quality of life measures assessed by the EQ-5D tool.

RESULTS Forty-four patients (72.1%) in the antiarrhythmic group and in 36 patients (54.5%) in the ablation group experienced the primary efficacy outcome (hazard ratio [HR], 0.56 [95% CI, 0.35-0.90]; P = .02). For the secondary outcomes, 59% in the drug group and 47% in the ablation group experienced the first recurrence of symptomatic AF, atrial flutter, atrial tachycardia (HR, 0.56 [95% CI, 0.33-0.95]; P = .03). No deaths or strokes were reported in either group; 4 cases of cardiac tamponade were reported in the ablation group. In the standard treatment group, 26 patients (43%) underwent ablation after 1-year. Quality of life was moderately impaired at baseline in both groups and improved at the 1 year follow-up. However, improvement was not significantly different among groups.

CONCLUSIONS AND RELEVANCE Among patients with paroxysmal AF without previous antiarrhythmic drug treatment, radiofrequency ablation compared with antiarrhythmic drugs resulted in a lower rate of recurrent atrial tachyarrhythmias at 2 years. However, recurrence was frequent in both groups.

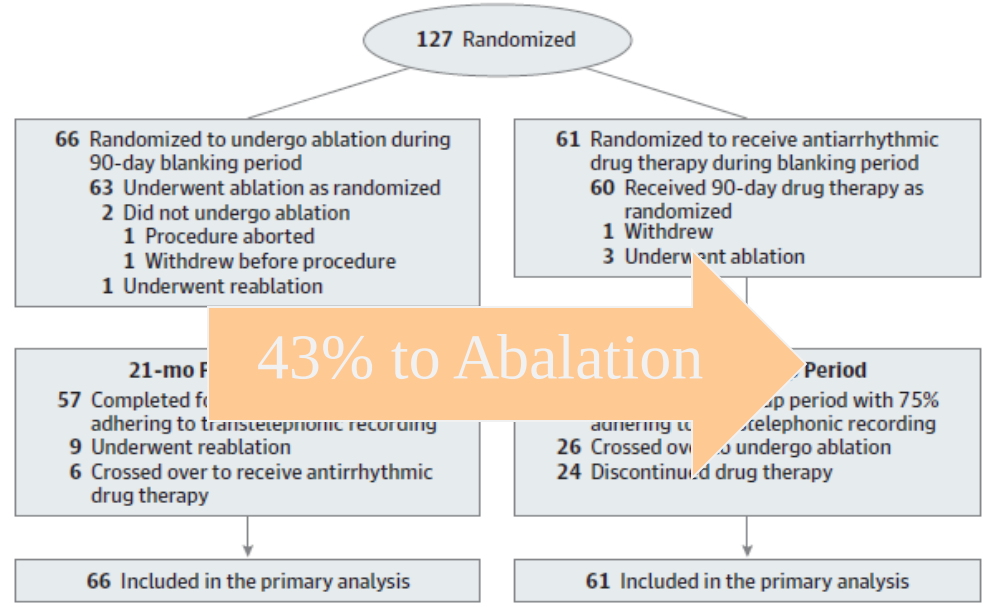
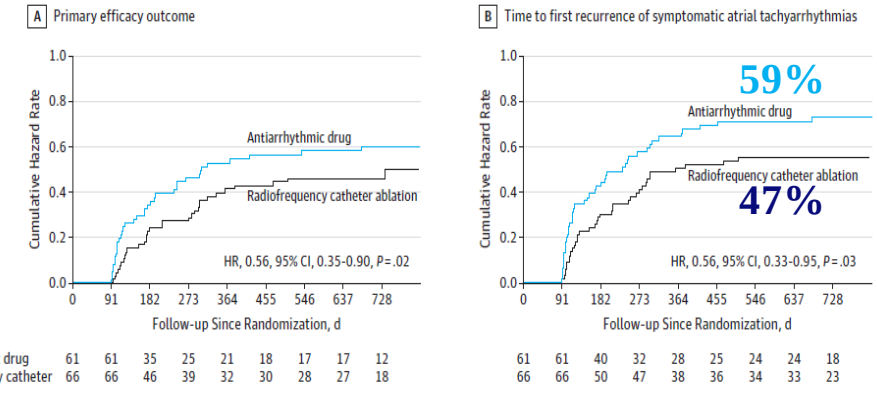


Figure 2. Kaplan-Meier Curves of Time to First Recurrence of Any Atrial Tachyarrhythmias (A) and Time to First Recurrence of Symptomatic Atrial Tachyarrhythmias (B)



Tachyarrhythmias include atrial fibrillation, tachycardia, and flutter. HR indicates hazard ratio.

Morillo et al. JAMA. 2014;311(7):692-699

Trials comparing Rate Control vs Rhythm control in AF

Trial Name	Primary Endpoint	Pts. Reaching Primary Endpoint [n/N (%)] Rate	Rhythm	*P* value	Total Deaths n (rate/rhythm)	CV Deaths	Non-CV Deaths	Stroke
AFFIRM[1,2]	All-cause mortality	310/2027 (25.9)	356/2033 (26.7)	.08	666 (310/356)	130/129	113/169	28/28
RACE[3]	Composite: CV death, CHF, severe bleeding, pacemaker implantation, thromboembolic events, severe adverse events from AADs	44/256 (17.2)	60/266 (22.6)	.11	36	18/18	N/A	N/A
PIAF[4]	Symptom improvement	76/125 (60.8)	70/127 (55.1)	.317	4	1/1	N/A	N/A
STAF[5]	Composite: overall mortality, cerebrovascular complications, CPR, embolic events	10/100 (10.0)	9/100 (9.0)	.99	12 (8/4)	8/3	0/1	1/5
AF-CHF[6]	Death from CV causes	175 (25.0)	182 (27.0)	.53	445 (228/217)	175/182	53/35	11/9

Wyse et al. NEJM 2002;347:1825-33
Stelnberg et al. Circulation 2004;109:1973-80
Van Gelder et al. NEJM 2002;347:1834-40
Hohnloser et al. Lancet 2000;356:1789-94
Carlsson et al. JACC 2003;41:1690-6
Roy et al. NEJM 2008;358:2667–77

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AF-CHF[6]	Death from CV causes	175 (25.0)	182 (27.0)	.53	445 (228/217)	175/182	53/35	11/9

65% experienced more than one episode of AF

65% had dilated LA

previously undergone cardioversion with relapse of AF

persistent AF

persistent AF

median duration of AF was 103–118 days prior to entry

persistent AF

two-thirds of patients had persistent AF, 46% had AF for >6 months

Wyse et al. NEJM 2002;347:1825-33
Stelnberg et al. Circulation 2004;109:1973-80
Van Gelder et al. NEJM 2002;347:1834-40

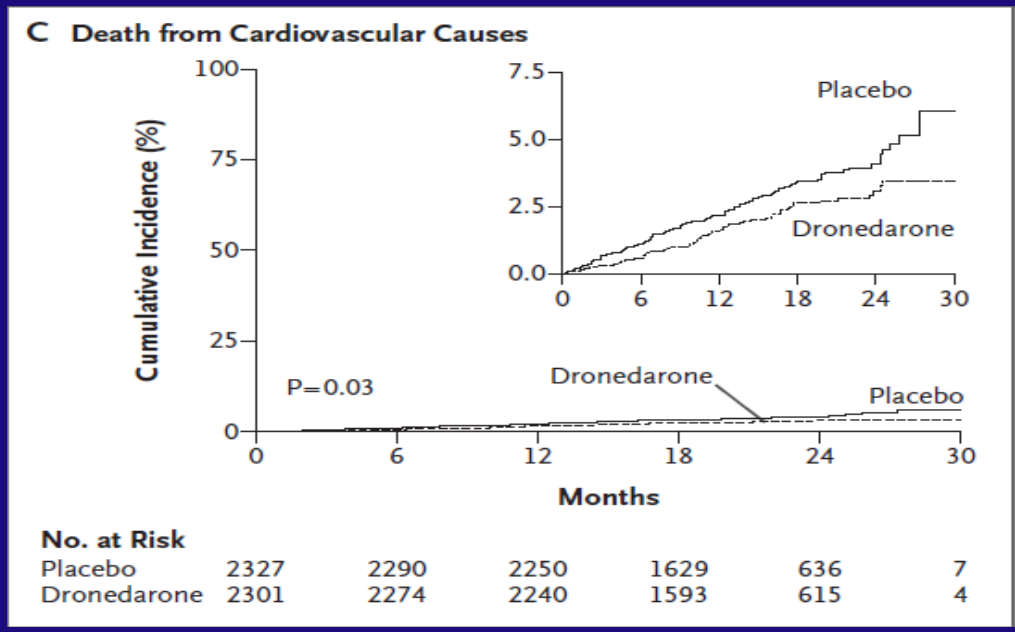
Hohnloser et al. Lancet 2000;356:1789-94
Carlsson et al. JACC 2003;41:1690-6
Roy et al. NEJM 2008;358:2667–77

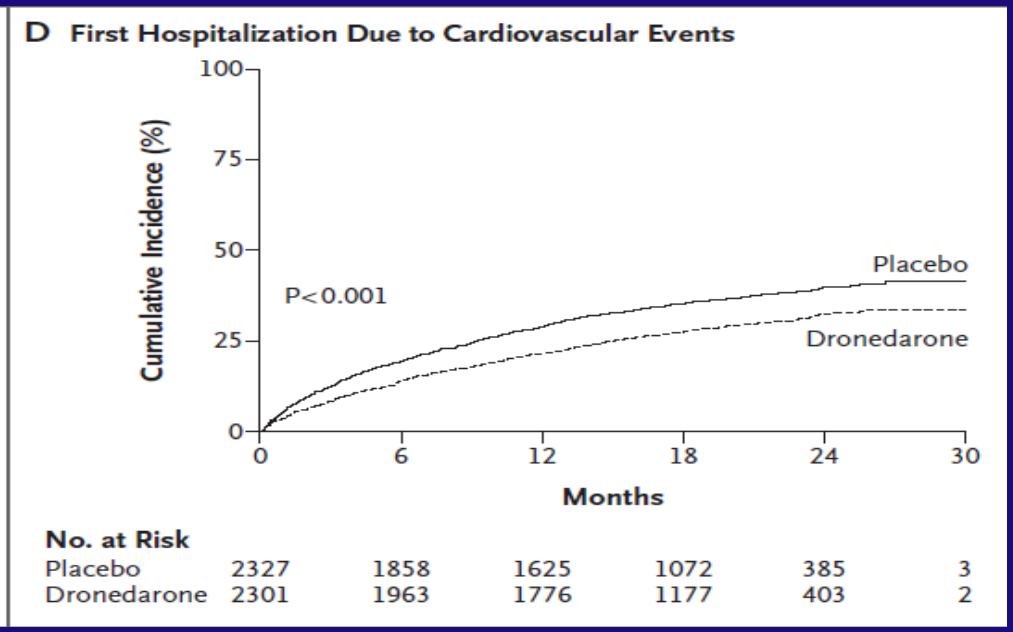
ATHENA Trial

Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation

Stefan H. Hohnloser, M.D., Harry J.G.M. Crijns, M.D., Martin van Eickels, M.D., Christophe Gaudin, M.D., Richard L. Page, M.D., Christian Torp-Pedersen, M.D., and Stuart J. Connolly, M.D., for the ATHENA Investigators*

- **4628 patients with recurrent (paroxysmal or persistent) atrial fibrillation and at least one of the following requirements: age >/=70 years, arterial hypertension, diabetes mellitus; previous stroke, TIA, or systemic embolism; left atrial diameter >/= 50 mm, LVEF</=40%.**





Hohnloser et al NEJM 2009;360:668-78

ATHENA Trial (post hoc analysis): Dronedarone reduces the risk of stroke

- Dronedarone reduced the risk of stroke from 1.8% per year to 1.2% per year
- The effect was similar whether or not patients receiving oral anticoagulant therapy,
- Significantly greater effect in patients with higher CHADS2 scores.

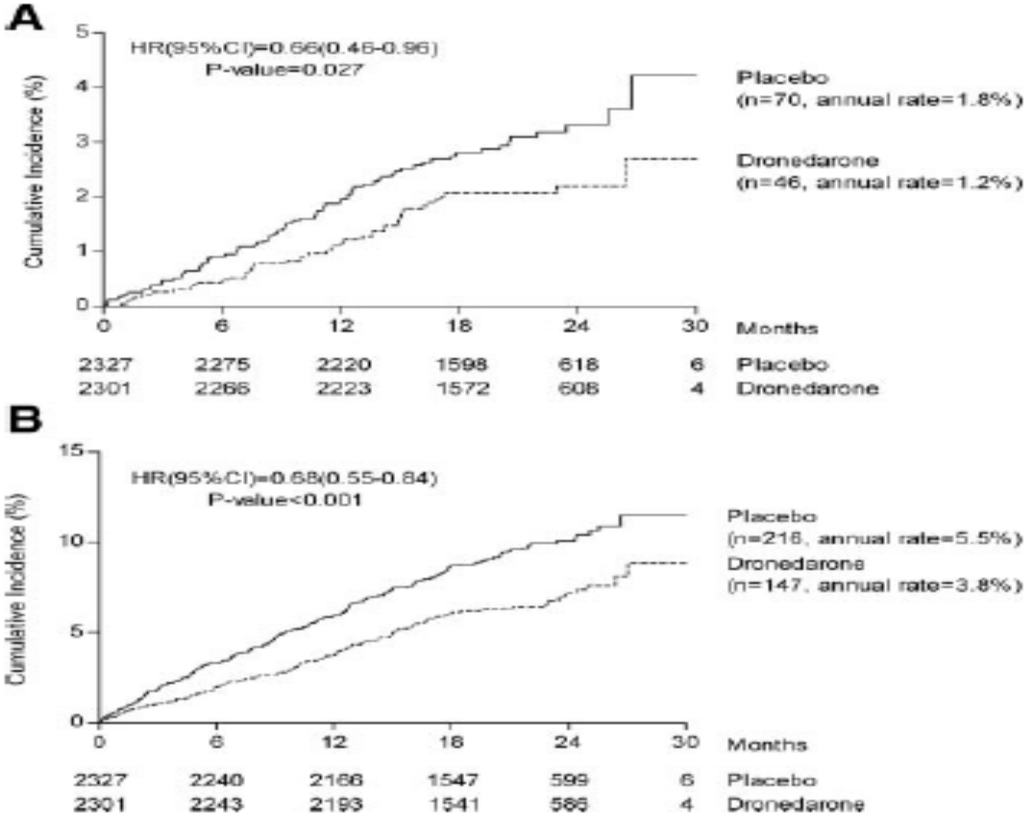


Figure 2. Cumulative risk of stroke (A) and composite outcome of stroke, acute coronary syndrome, or cardiovascular death (B). HR indicates hazard ratio.

Connolly et al. Circulation 2009;120:1174-1180

Pharmacological treatment: Not always the safest choice

- The PALLAS study: Dronedarone vs placebo in permanent (>6m) AF

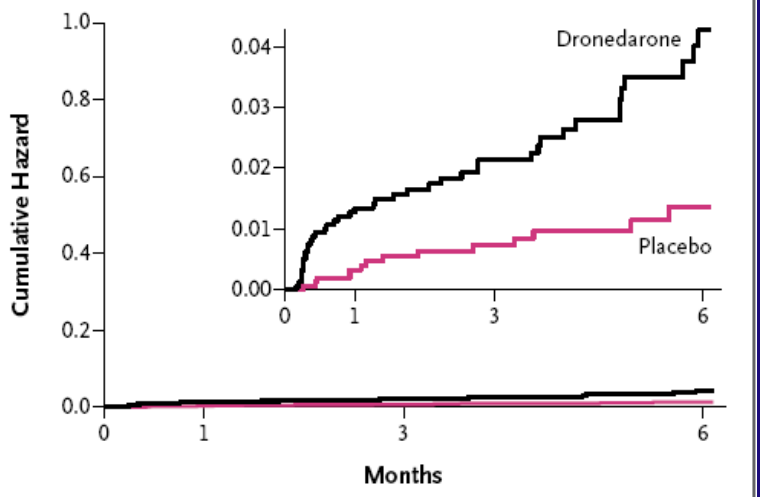


Figure 1. Risk of the First Coprimary Outcome (Stroke, Myocardial Infarction, Systemic Embolism, or Death from Cardiovascular Causes).

Table 2. Study Outcomes.*

Outcome	Dronedarone		Placebo		Hazard Ratio (95% CI)†	P Value
	No. of Events	Rate/100 Patient-Yr	No. of Events	Rate/100 Patient-Yr		
First coprimary outcome	43	8.2	19	3.6	2.29 (1.34–3.94)	0.002
Second coprimary outcome	127	25.3	67	12.9	1.95 (1.45–2.62)	<0.001
Death						
From any cause	25	4.7	13	2.4	1.94 (0.99–3.79)	0.049
From cardiovascular causes	21	4.0	10	1.9	2.11 (1.00–4.49)	0.046
From arrhythmia	13	2.5	4	0.8	3.26 (1.06–10.0)	0.03
Stroke						
Any‡	23	4.4	10	1.9	2.32 (1.11–4.88)	0.02
Ischemic	18	3.4	9	1.7	2.01 (0.90–4.48)	0.08
Systemic embolism	1	0.2	0	0.0	NA	NA
Myocardial infarction or unstable angina	15	2.9	8	1.5	1.89 (0.80–4.45)	0.14
Myocardial infarction	3	0.6	2	0.4	1.54 (0.26–9.21)	0.63
Unplanned hospitalization for cardiovascular causes	113	22.5	59	11.4	1.97 (1.44–2.70)	<0.001
Hospitalization for heart failure	43	8.3	24	4.6	1.81 (1.10–2.99)	0.02
Heart-failure episode or hospitalization§	115	23.2	55	10.7	2.16 (1.57–2.98)	<0.001

Death rate excess: 2,3 %

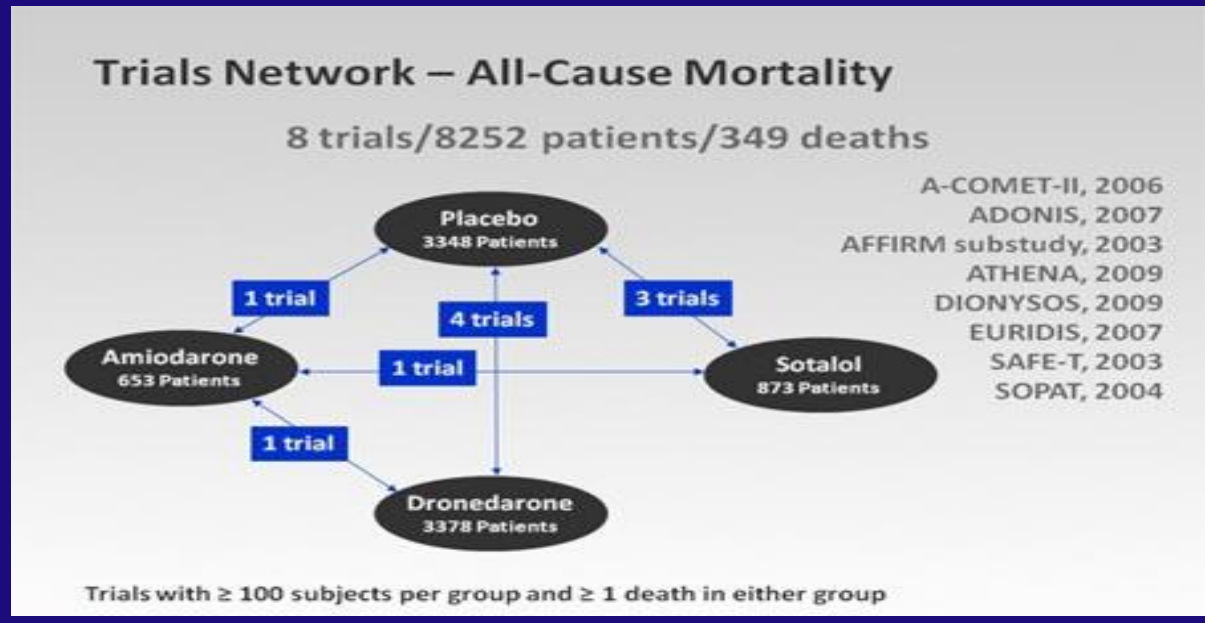
Stroke rate excess: 2,5 %

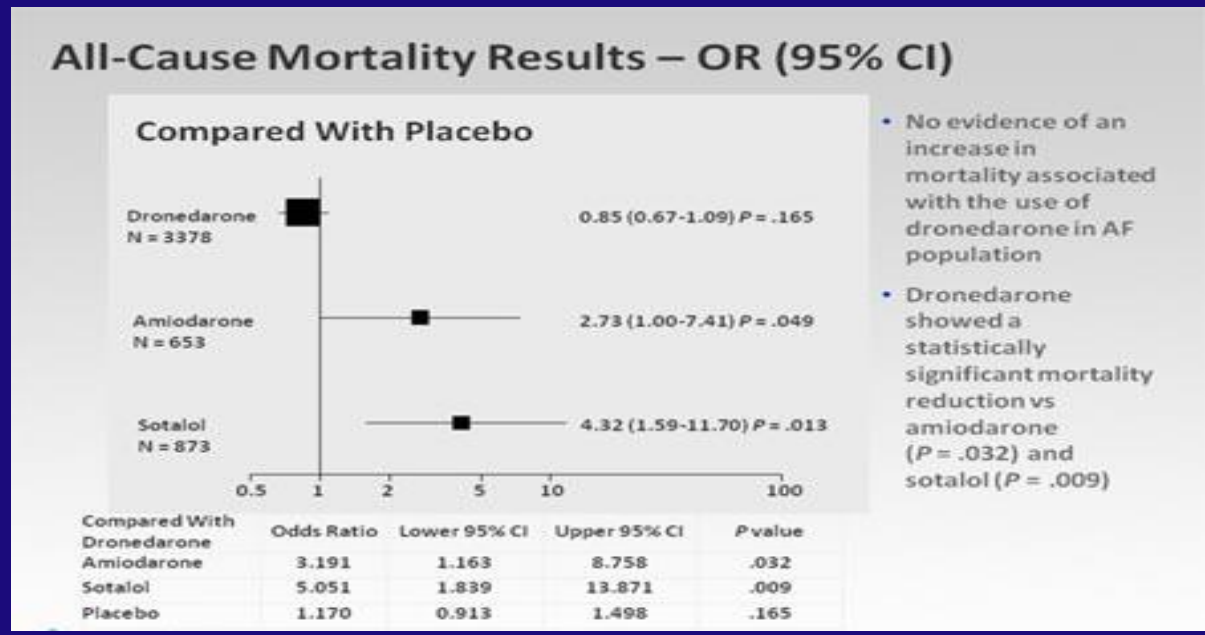
Connolly et al. N Engl J Med. 2011;365:2268-76

AAD for the management of AF: Not always safest choice

AFFIRM substudy[20] 2003
Aliot (Flecainide AF French Study Group)[21] 1996
Bellandi (2001)[36]
Benditt *et al*.[57] 1999
Boos *et al*.[37] 2008
Brodsky *et al*.[65] 1994
Carunchio *et al*.[38] 1995
Channer *et al*.[39] 2004
Chimienti *et al*. (FAPIS)[40] 1996
Cobbe[53] 1995
Connolly and Hoffert[22] 1989
Davy *et al*. (ERATO)[23] 2008
DIONYSOS[18] 2009
Dogan *et al*.[24] 2004
Fetsch *et al*. (PAFAC)[25] 2004
Galperin *et al*. (GEFACA)[41] 2001
Hohnloser *et al*. (ATHENA)[9] 2009
Kochiadakis *et al*.[42] 1998
Kochiadakis *et al*.[43] 2000
Kochiadakis *et al*.[44] 2004

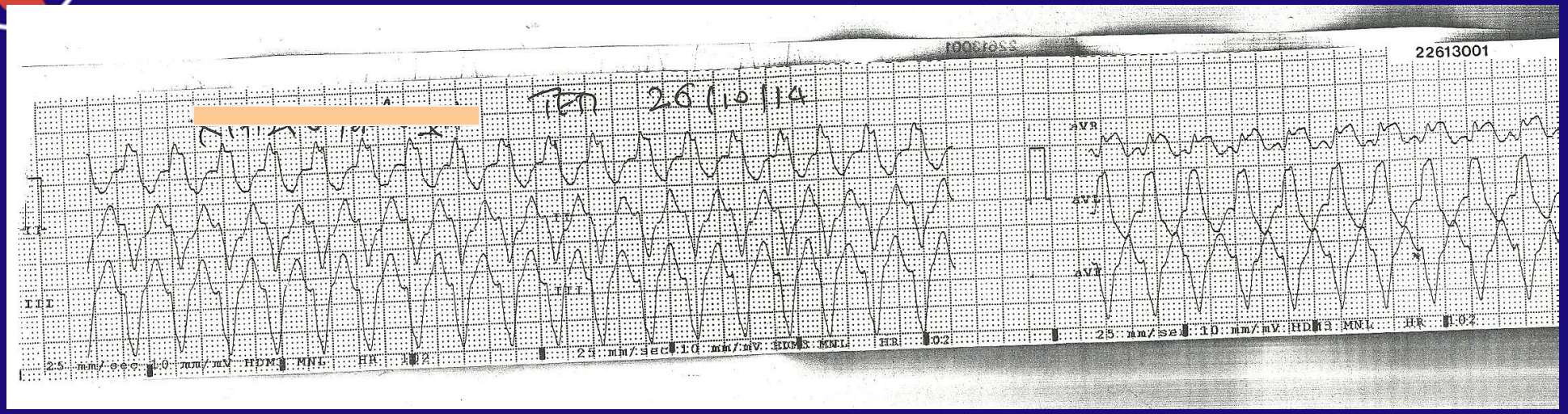
Kochiadakis *et al*.[45] 2004
Lau *et al*.[54] 1992
Lee *et al*. 1997[46]
Lombardi *et al*. (A-COMET-II)[26] 2006
Manios *et al*.[55] 2003
Massacci *et al*.[47] 1992
Meinertz *et al*. (ERAFT)[27] 2002
Pietersen and Hellemann
(Danish-Norwegian Flecainide Multicenter Study Group)[28] 1991
Patten *et al*. (SOPAT)[29] 2004
Pritchett *et al*.[48] 1991
Pritchett *et al*. (RAFT)[49] 2003
Reimold *et al*.[30] 1993
Roy *et al*. (The Canadian Trial of Atrial Fibrillation)[50] 2000
Singh *et al*. (SAFE-T)[31] 2003
Singh *et al*.[51] 1991
Singh *et al*. (EURIDIS ADONIS)[32] 2007
Stroobandt *et al*.[33] 1997
Touboul *et al*. (DAFNE)[34] 2003
de Simone *et al*. (VEPARAF)[56] 2003
Van Gelder *et al*.[52] 1989
Vijayalakshmi *et al*.[35] 2006

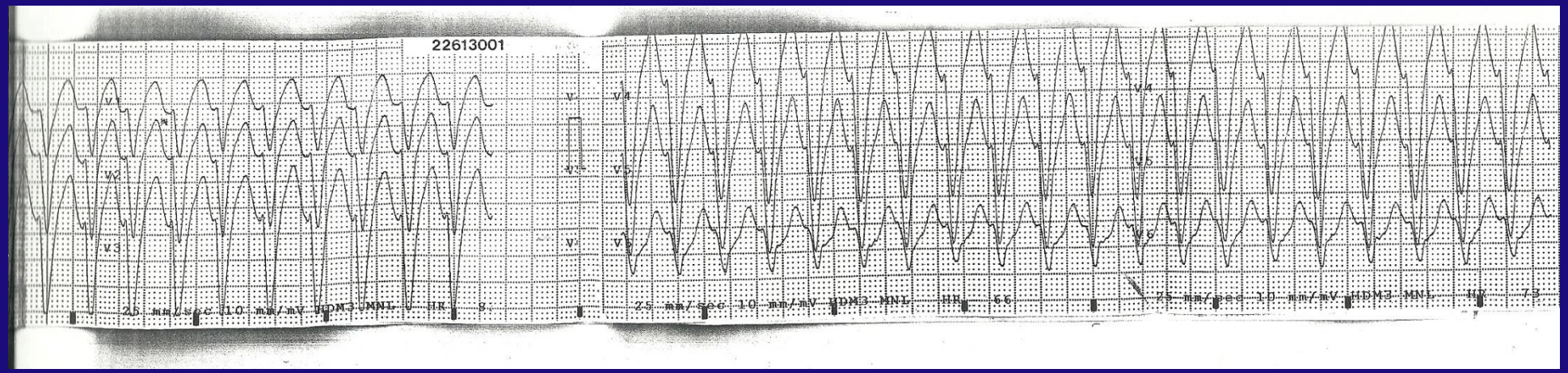




Compared With Dronedarone	Odds Ratio	Lower 95% CI	Upper 95% CI	P value
Amiodarone	3.191	1.163	8.758	.032
Sotalol	5.051	1.839	13.871	.009
Placebo	1.170	0.913	1.498	.165

Freemantle et al, Europace 2011;13:329-345





Ρυθμική ταχυκαρδία ευρέων συμπλεγμάτων με συχνότητα 175σ/λ.
Η μορφολογία ήταν με LBBB με αριστερό άξονα (-60^{o}),

Complications of Catheter Ablation of Atrial Fibrillation

A Systematic Review

Aakriti Gupta; Tharani Perera; Anand Ganesan, MBBS, PhD; Thomas Sullivan, BMa&CompS; Dennis H. Lau, MBBS, PhD; Kurt C. Roberts-Thomson, MBBS, PhD; Anthony G. Brooks, PhD; Prashanthan Sanders, MBBS, PhD

Background—Atrial fibrillation ablation is an established therapy; however, limited data are available on associated complications. This systematic review determines the incidence and potential predictors of acute complications.

Methods and Results—Electronic searches were conducted in MEDLINE and EMBASE for English scientific literature up to the 18th June 2012. A total of 2065 references were retrieved and evaluated for relevance. Reference lists of retrieved studies and review articles were examined to ensure all relevant studies were included. Data were extracted from 192 studies, total of 83 236 patients. The incidence of periprocedural complications for catheter ablation of atrial fibrillation was 2.9% (95% confidence interval, 2.6–3.2). There was a significant decrease in the acute complication rate in 2007 to 2012 compared with 2000 to 2006 (2.6% versus 4.0%; P=0.003). The complication rates reported were higher in prospective studies compared with those that retrospectively described complications (3.5% versus 2.7%; P=0.03). There were no significant associations among procedure duration, ablation time or ablation strategy, and acute complication rate.

Conclusions—Catheter ablation of atrial fibrillation has a low incidence of periprocedural complications. The acute complication rate has decreased significantly in recent years. This may reflect improved catheter technology and experience. The use of different strategies across centers worldwide seems to be safe with no established relationship between procedural variables and complication rate. (*Circ Arrhythm Electrophysiol.* 2013;6:1082-1088.)

Table 2. Major Complications

	No. of Studies	% Pooled Complication Rate (95% CI)	I^2 Statistic
Acute complication rate	183	2.9 (2.60–3.22)	83.8
Type of complication			
Death	58	0.06 (0.03–0.09)	0.0
Atrioesophageal fistula	67	0.08 (0.05–0.11)	0.0
Pulmonary vein stenosis*	118	0.5 (0.34–0.60)	79.6
Vascular complications†	117	1.4 (1.02–1.79)	94.1
Arteriovenous fistula	45	0.40 (0.28–0.55)	45.5
Femoral pseudoaneurysm	49	0.5 (0.34–0.60)	41.2
Stroke/TIA‡	155	0.6 (0.50—0.67)	46.8
Stroke	111	0.4 (0.30–0.44)	34.3
TIA	94	0.4 (0.28–0.47)	37.9
Tamponade	131	1.0 (0.83–1.14)	68.5
Pericardial effusion	67	0.7 (0.56–0.88)	55.0
Phrenic nerve injury	48	0.4 (0.22–0.54)	70.2
Diaphragmatic paralysis	21	0.3 (0.15–0.43)	0.0
DVT/PE	33	0.15 (0.09–0.21)	0.0
Pneumothorax	22	0.2 (0.08–0.29)	0.0
Hemothorax	25	0.2 (0.10–0.28)	0.0
Sepsis, abscesses, or endocarditis	20	0.1 (0.06–0.24)	0.0
Valve damage	26	0.2 (0.08–0.25)	0.0

CI indicates confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; and TIA, transient ischemic attack.

*Pulmonary vein stenosis defined as >50% stenosis and requiring intervention.

†Vascular complications included bleeding, hematoma, arteriovenous fistula, and femoral pseudoaneurysm.

Gupta et al. Circ Arrhythm Electrophysiol. 2013;61082-88

Who is the operator, that is the question: a multicentre study of catheter ablation of atrial fibrillation

Akinori Sairaku[1]*, Yukihiko Yoshida[2], Yukiko Nakano[1], Mayuho Maeda[2], Haruo Hirayama[2], Haruki Hashimoto[1,3], and Yasuki Kihara[1]

- High-volume operator ≥50 cases/year
- Low-volume operator <50 cases/year

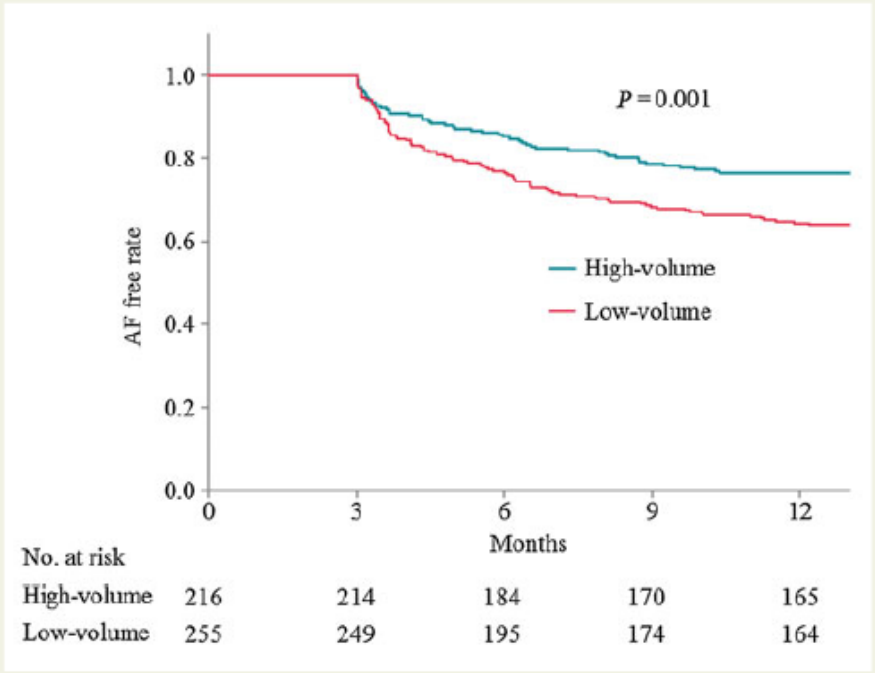


Figure 2 Kaplan–Meier analysis of the time to the recurrence of atrial fibrillation. AF, atrial fibrillation.

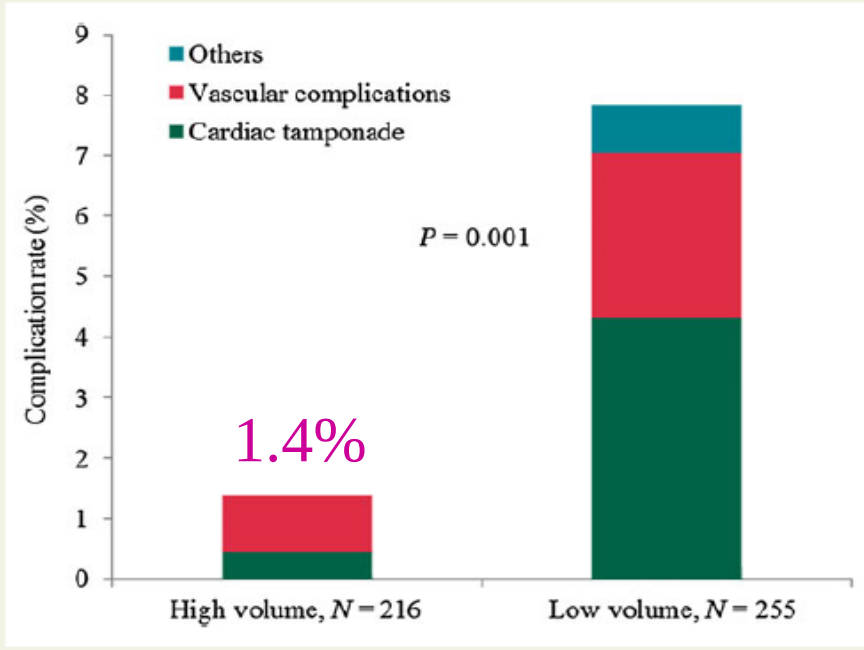
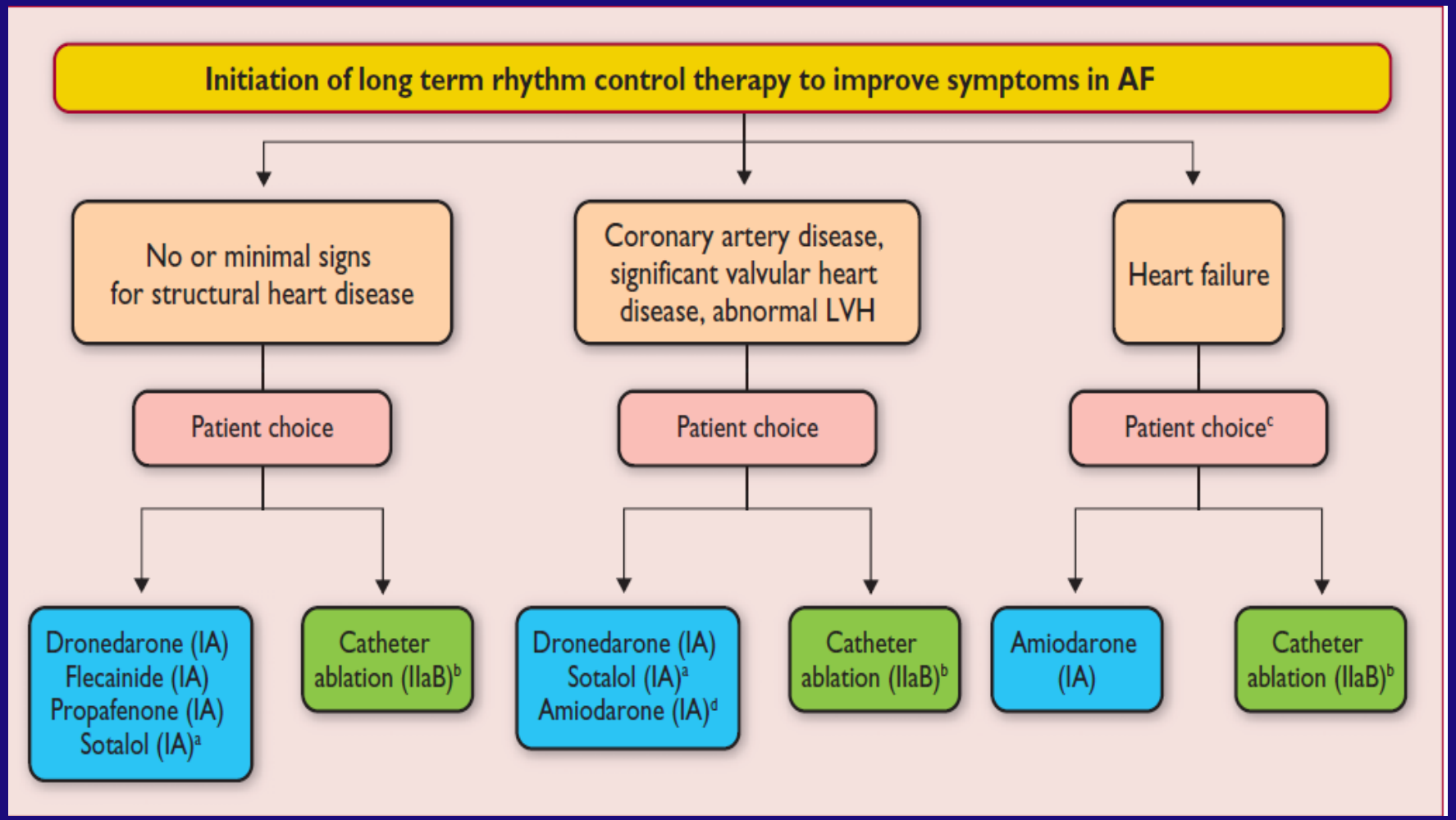


Figure 4 Complication rate. Others include one case of an intracranial haemorrhage and one case of acute renal failure requiring temporary haemodialysis.

Sairaku et al. Europace 2016;18:1352-1356

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS



2016 ESC Guidelines for the management of AF European Heart Journal 2016; Aug 27

Συμπεράσματα

- Πρώιμη επιλογή της κατάλυσης στη θεραπευτική στρατηγική ρυθμού:
  - Καλύτερο αποτέλεσμα στον έλεγχο των συμπτωματικών υποτροπών
  - Η αποτελεσματική παρέμβαση διατήρησης ρυθμού σε πρώιμα σιάδια μπορεί να σχετίζεται με ευνοϊκή πρόγνωση σε κλινικές παραμέτρους
  - Υψηλότερα ποσοστά επιτυχίας της κατάλυσης σε πρώιμα στάδια ΚΜ
- Η φαρμακευτική δοκιμή δεν είναι πάντα η ασφαλέστερη λύση
- Η κατάλυση σε έμπειρα κέντρα είναι μια ασφαλής επιλογή
- Η κατάλυση μπορεί να προσφέρεται ως 1^{ης} επιλογής θεραπεία σε έντονα συμπτωματικούς ασθενείς που αποδέχονται τον επεμβατικό κίνδυνο


Ευχαριστώ για την προσοχή σας!

Summary of incidence of major complications related to AF ablation

	Cappato et. al, 2005 (*n* = 8,745) LA abl (n=7,154)	Cappato et. al, 2010 (*n* = 16,309)	Dagres et. al, 2009 (*n* = 1,000)	Baman et. al, 2011 (*n* = 1,642)	Shah et. al., 2012 (*n* = 4,156)	Gupta et. al, 2013* (*n* = 83,236)
Thromboembolic events (%)	0.94	0.9	0.4	0.2	0.3	0.6
Cardiac tamponade (%)	1.22	1.3	1.3	1.2	2.5	1.0
Vascular complications (%)	0.96	1.5	1.3	2.4	2.6	1.4
Pulmonary vein stenosis (%)	1.6	0.3	0.1	--	--	0.5
Atrioesophageal fistula (%)	--	0.04	0.3	--	--	0.08
Phrenic nerve palsy (%)	0.11	--	--	--	--	0.4
Procedure-related death (%)	0.05	0.15	0.2	--	0.02	0.06
Overall complication rate (%)	**5.9**	**4.5**	**3.9**	**3.5**	**5.1**	**2.9**