European Heart Journal 2012;33:2719-2747 -
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2012 focussed update of the ESC Guidelines for the Management of Atrial Fibrillation

An update of the 2010 ESC Guidelines for the Management of Atrial Fibrillation

Developed with the special contribution of the European Heart Rhythm Association (EHRA)

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Management of Atrial Fibrillation

Focus of 2012 Update

- Anticoagulation risk stratification
- Use of novel oral anticoagulants (NOACs)
- Left atrial appendage occlusion/excision
- Pharmacological cardioversion (vernakalant)
- Oral antiarrhythmic therapy (dronedarone, and short term therapy)
- Left atrial catheter ablation

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Opportunistic Screening

Recommendations for screening AF		
Recommendations	**Class[a]**	**Level[b]**
Opportunistic screening for AF in patients ≥65 years of age using pulse-taking followed by an ECG is recommended to allow timely detection of AF.	I	B

[a]Class of recommendation. [b]Level of evidence.
AF = atrial fibrillation; LoE = level of evidence.

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Score de risco tromboembólico na FA

Table 8 CHA_2DS_2VASc score and stroke rate

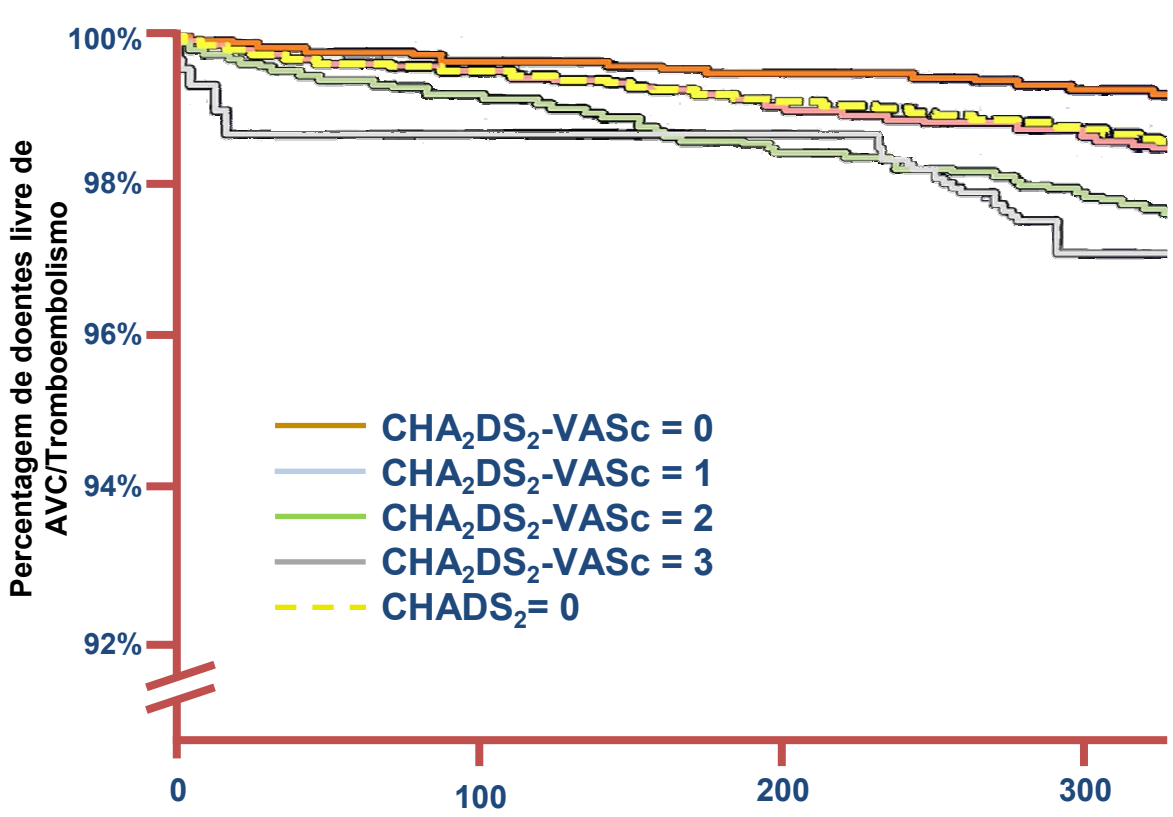
(a) Risk factors for stroke and thrombo-embolism in non-valvular AF	
'Major' risk factors	**'Clinically relevant non-major' risk factors**
Previous stroke, TIA, or systemic embolism Age ≥75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤40%) Hypertension - Diabetes mellitus Female sex - Age 65–74 years Vascular disease[a]

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)	
Risk factor	**Score**
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score		
CHA_2DS_2-VASc score	**Patients (n=7329)**	**Adjusted stroke rate (%/year)[b]**
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest* 2010;**137**:263–272.

CHA_2DS_2-VASc na redefinição da estratificação do risco de AVC em doentes com valores de $CHADS_2$ entre 0 e 1



	1 year follow-up		
	Person-years	Events	Stroke rate (95%CI)
$CHADS_2$ score 0–1	40,272	1,405	3.49 (3.31–3.68)
CHA_2DS_2-VASc = 0	6,919	58	0.84 (0.65–1.08)
CHA_2DS_2-VASc = 1	8,880	159	1.79 (1.53–2.09)
CHA_2DS_2-VASc = 2	11,863	435	3.67 (3.34–4.03)
CHA_2DS_2-VASc = 3	11,473	660	5.75 (5.33–6.21)
CHA_2DS_2-VASc = 4	1,137	93	8.18 (6.68–10.02)
$CHADS_2$ score = 0	17,327	275	1.59 (1.41–1.79)
CHA_2DS_2-VASc = 0	6,919	58	0.84 (0.65–1.08)
CHA_2DS_2-VASc = 1	6,811	119	1.75 (1.46–2.09)
CHA_2DS_2-VASc = 2	3,347	90	2.69 (2.19–3.31)
CHA_2DS_2-VASc = 3	250	8	3.20 (1.60–6.40)
$CHADS_2$ score = 1	22,945	1,130	4.92 (4.65–5.22)
CHA_2DS_2-VASc = 1	2,069	40	1.93 (1.42–2.64)
CHA_2DS_2-VASc = 2	8,516	345	4.05 (3.65–4.50)
CHA_2DS_2-VASc = 3	11,223	652	5.81 (5.38–6.27)
CHA_2DS_2-VASc = 4	1,137	93	8.18 (6.68–10.02)

Mesmo em doentes categorizados com "baixo risco" utilizando um valor de $CHADS_2$=0, o valor de CHA_2DS_2-VASc aumentou de forma significativa o valor preditivo apenas de $CHADS_2$ e um valor de CHA_2DS_2-VASc=0 poderia identificar os doentes de verdadeiro baixo risco

Olesen et al Thromb Haemost. 2012 107(6):1172-9

Anticoagulation - General

Recommendations for prevention of thromboembolism in non-valvular AF - general		
Recommendations	**Class**	**Level**
Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those patients (both male and female) who are at low risk (aged <65 years and lone AF), or with contraindications.	I	A
The choice of antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the net clinical benefit for a given patient.	I	A
The CHA_2DS_2-VASc score is recommended as a means of assessing stroke risk in non-valvular AF.	I	A
Female patients who are aged <65 and have lone AF (but still have a CHA_2DS_2-VASc score of 1 by virtue of their gender) are low risk and no antithrombotic therapy should be considered.	IIa	B

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	Dabigatran (RE-LY)[70,71]			Rivaroxaban (ROCKET-AF)[3]		Apixaban (ARISTOTLE)[4]	
Drug characteristics							
Mechanism	Oral direct thrombin inhibitor			Oral direct factor Xa inhibitor		Oral direct factor Xa inhibitor	
Bioavailability, %	6			60–80		50	
Time to peak levels, h	3			3		3	
Half-life, h	12–17			5–13		9–14	
Excretion	80% renal			2/3 liver, 1/3 renal		25% renal, 75% faecal	
Dose	150 mg b.i.d.			20 mg o.d.		5 mg b.i.d.	
Dose in renal impairment	110 mg b.i.d.			15 mg o.d. (if CrCl 30-49 mL/min)		2.5 mg b.i.d.	
Study characteristics							
Study design	Randomized, open-label			Randomized, double-blind		Randomized, double-blind	
Number of patients	18 111			14 264		18 201	
Follow-up period, years	2			1.9		1.8	
Randomized groups	Dose-adjusted warfarin vs. blinded doses of dabigatran (150 mg b.i.d., 110 mg b.i.d.)			Dose-adjusted warfarin vs. rivaroxaban 20 mg o.d.		Dose-adjusted warfarin vs. apixaban 5 mg b.i.d.	
Baseline patient characteristics							
Age, years	71.5 ± 8.7 (mean ± SD)			73 (65–78) [median (interquartile range)]		70 (63–76) [median (interquartile range)]	
Male sex, %	63.6			61.3		64.5	
$CHADS_2$ (mean)	2.1			3.5		2.1	
Outcomes (% per year)							
	Warfarin	Dabigatran 150	Dabigatran 110	Warfarin	Rivaroxaban	Warfarin	Apixaban
	(*n* = 6022)	(*n* = 6076)	(*n* = 6015)	(*n* = 7133)	(*n* = 7131)	(*n* = 9081)	(*n* = 9120)
		(RR, 95% CI; *P* value)	(RR, 95% CI; *P* value)		(HR, 95% CI; *P* value)		(HR, 95% CI; *P* value)
Stroke/systemic embolism	1.69	1.11 (0.66, 0.53–0.82; *P* for superiority <0.001)	1.53 (0.91, 0.74–1.11; *P* for non-inferiority <0.001)	2.4	2.1 (0.88, 0.75–1.03; *P* for non-inferiority <0.001, *P* for superiority = 0.12) (ITT)	1.6	1.27 (0.79, 0.66–0.95; *P* <0.001 for non-inferiority, *P* = 0.01 for superiority)
Ischaemic stroke	1.2	0.92 (0.76, 0.60–0.98; *P* = 0.03)	1.34 (1.11, 0.89–1.40; *P* = 0.35)	1.42	1.34 (0.94; 0.75–1.17; *P* = 0.581)	1.05	0.97 (0.92, 0.74–1.13; *P* = 0.42)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; *P* <0.001)	0.12 (0.31, 0.17–0.56; *P* <0.001)	0.44	0.26 (0.59; 0.37–0.93; *P* =0.024)	0.47	0.24 (0.51, 0.35–0.75; *P* <0.001)
Major bleeding	3.36	3.11 (0.93, 0.81–1.07; *P* = 0.31)	2.71 (0.80, 0.69–0.93; *P* = 0.003)	3.4	3.6 (*P* = 0.58)	3.09	2.13 (0.69, 0.60–0.80; *P* <0.001)
Intracranial bleeding	0.74	0.30 (0.40, 0.27–0.60; *P* <0.001)	0.23 (0.31, 0.20–0.47; *P* <0.001)	0.7	0.5 (0.67; 0.47–0.93; *P* = 0.02)	0.80	0.33 (0.42, 0.30–0.58; *P* <0.001)
Extracranial bleeding	2.67	2.84 (1.07, 0.92–1.25; *P* = 0.38)	2.51 (0.94, 0.80–1.10; *P* = 0.45)	–	–	–	–

Novos ACO:
Eficácia e segurança

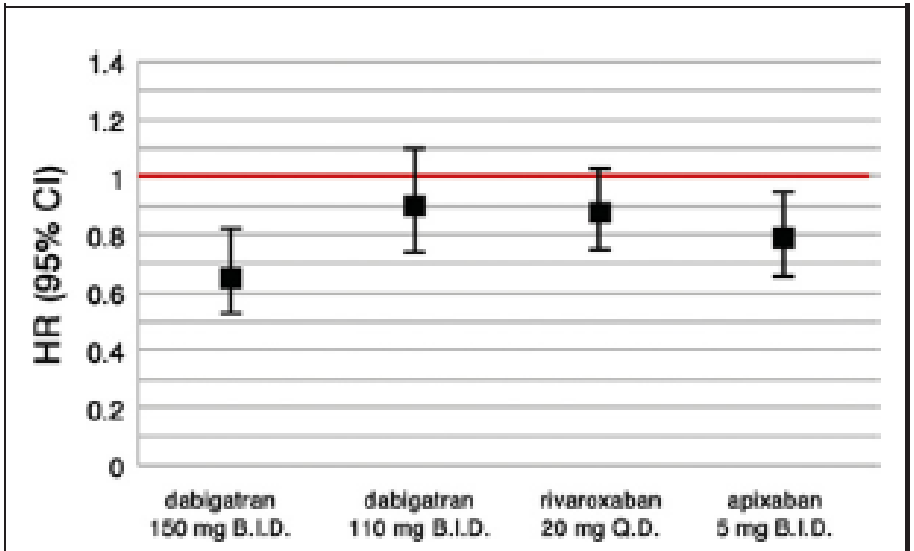

Figure 2 Comparable Primary Efficacy Endpoints of Stroke or Systemic Embolism

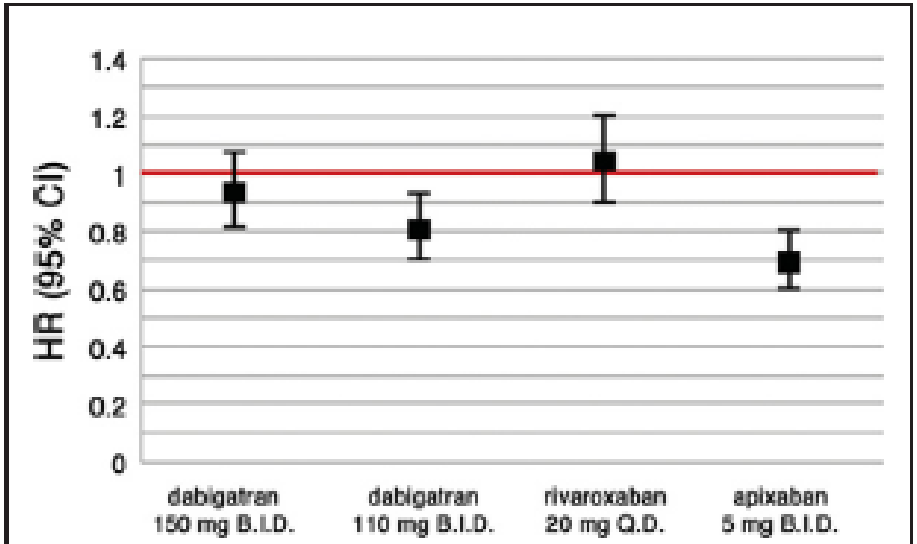

Figure 3 Comparable Primary Safety Endpoints of Major Bleeding

Anticoagulation – General (Cont..)

Recommendations	Class	Level
In patients with a CHA_2DS_2-VASc score of 0 (i.e., aged <65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy is recommended.	I	B
In patients with a CHA_2DS_2-VASc score ≥2, OAC therapy with: • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban)[d] …. is recommended, unless contraindicated.	I	A
In patients with a CHA_2DS_2-VASc score of 1, OAC therapy with: • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban)[d] …. should be considered, based upon an assessment of the risk of bleeding complications and patient preferences.	IIa	A

[d] = pending EMA/FDA approval – prescribing information is awaited

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Anticoagulation - General

Recommendations for prevention of thromboembolism in non-valvular AF - general		
Recommendations	**Class**	**Level**
When patients refuse the use of any OAC (whether VKAs or NOACs), antiplatelet therapy should be considered, using combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or – less effectively – aspirin 75–325 mg daily.	**IIa**	**B**

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Anticoagulation - NOACs

Recommendations for prevention of thromboembolism in non-valvular AF - NOACs		
Recommendations	**Class**	**Level**
When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban)[d] … is recommended.	I	B
Where OAC is recommended, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban)[d] … should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit.	IIa	A

[d]Apixaban (pending approval EMA and FDA approval): prescribing information is awaited.

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Recommendations	Class	Level
Where dabigatran is prescribed, a dose of 150 mg b.i.d. should be considered for most patients in preference to 110 mg b.i.d., with the latter dose recommended in: • elderly patients, age ≥ 80 • concomitant use of interacting drugs (e.g. verapamil) • high bleeding risk (HAS-BLED score ≥3) • moderate renal impairment (CrCl 30–49 mL/min).	IIa	B
Where rivaroxaban is being considered, a dose of 20 mg o.d. should be considered for most patients in preference to 15 mg o.d., with the latter dose recommended in: • high bleeding risk (HAS-BLED score ≥3) • moderate renal impairment (CrCl 30–49 mL/min).	IIa	C
Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year.	IIa	B
NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min).	III	A

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Bleeding risk (significant >3)

Table 10 Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

[a]'Hypertension' is defined as systolic blood pressure >160 mmHg. 'Abnormal kidney function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 μmol/L. 'Abnormal liver function' is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal, etc.). 'Bleeding' refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc. 'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (e.g. <60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc.
INR = international normalized ratio. Adapted from Pisters *et al.*[60]

Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess one-year risk of major bleeding in atrial fibrillation patients: The Euro Heart Survey. *Chest* 2010; March 18 [Epub ahead of print].

Anticoagulation - Bleeding

Recommendations for prevention of thromboembolism in non-valvular AF - bleeding		
Recommendations	**Class**	**Level**
Assessment of the risk of bleeding is recommended when prescribing antithrombotic therapy (whether with VKA, NOAC, aspirin/clopidogrel, or aspirin).	I	A
The HAS-BLED score should be considered as a calculation to assess bleeding risk, whereby a score ≥3 indicates 'high risk' and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or antiplatelet therapy (LoE = A). Correctable risk factors for bleeding [e.g. uncontrolled blood pressure, labile INRs if the patient was on a VKA, concomitant drugs (aspirin, NSAIDs, etc.), alcohol, etc.] should be addressed (LoE = B). Use of the HAS-BLED score should be used to identify modifiable bleeding risks that need to be addressed, but should not be used on its own to exclude patients from OAC therapy (LoE = B).	IIa	A B
The risk of major bleeding with antiplatelet therapy (with aspirin–clopidogrel combination therapy and – especially in the elderly – also with aspirin monotherapy) should be considered as being similar to OAC.	IIa	B

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Anticoagulation – Peri-cardioversion

Recommendations for prevention of thromboembolism in non-valvular AF – peri-cardioversion		
Recommendations	**Class**	**Level**
For patients with AF of ≥48 h duration, or when the duration of AF is unknown, OAC therapy (e.g. VKA with INR 2-3 or dabigatran) is recommended for ≥3 weeks prior to and for ≥4 weeks after cardioversion, regardless of the method (electrical or oral/i.v. pharmacological).	I	B
In patients with risk factors for stroke or AF recurrence, OAC therapy, whether with dose-adjusted VKA (INR 2-3) or a NOAC, should be continued lifelong irrespective of the apparent maintenance of sinus rhythm following cardioversion.	I	B

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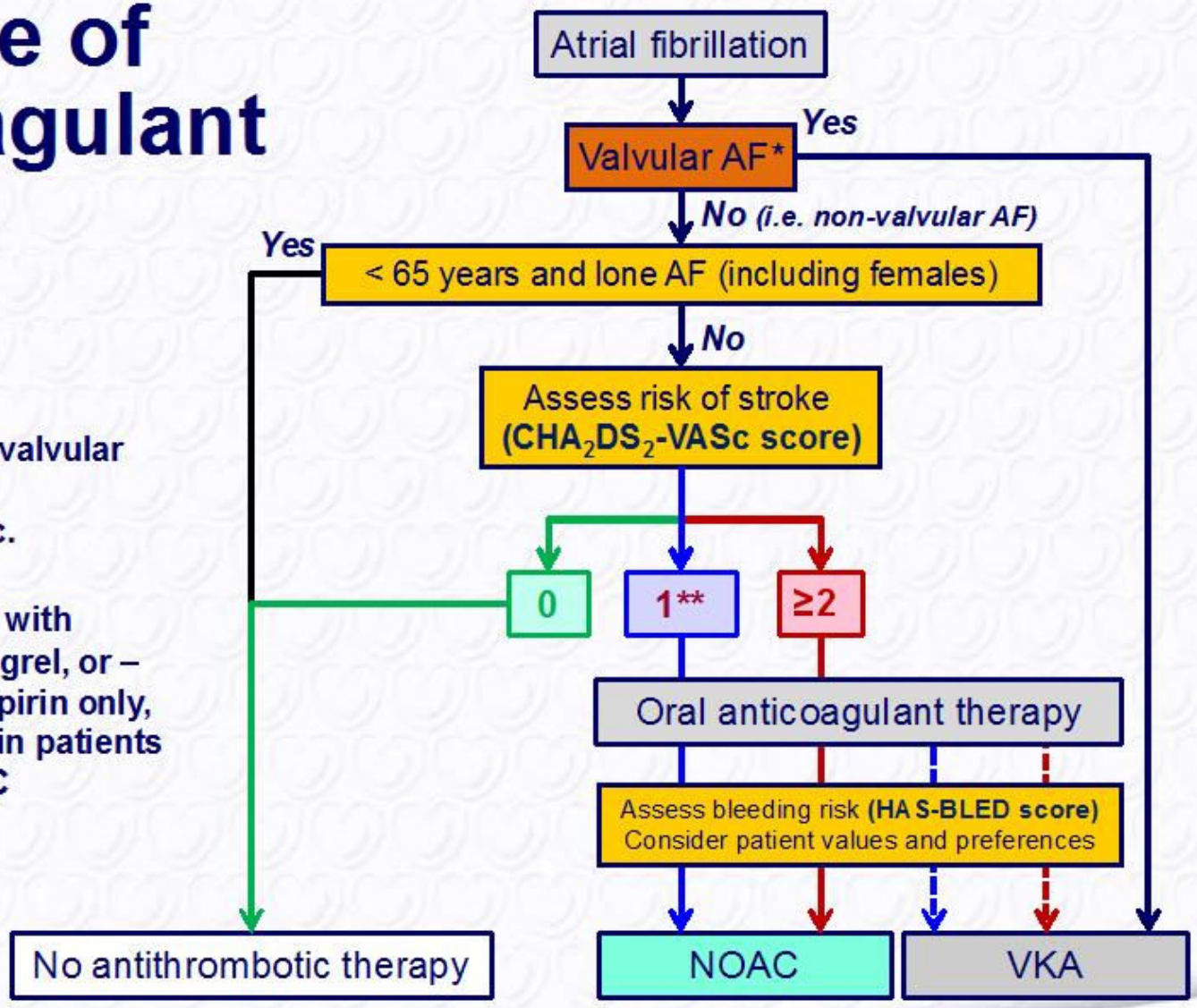
Choice of Anti-coagulant



- Includes rheumatic valvular AF, hypertrophic cardiomyopathy, etc.

** Antiplatelet therapy with aspirin plus clopidogrel, or – less effectively – aspirin only, may be considered in patients who refuse any OAC

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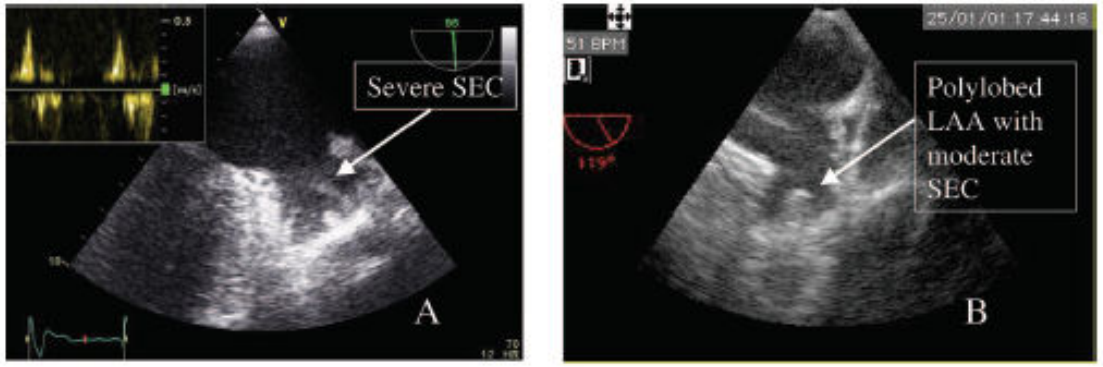
Left Atrial Appendage occlusion



Example of a polylobed LAA with severe SEC and the corresponding pulsed Doppler of LAA flows.

PROTECT AF (Watchman trial)
- 707 pts
- Non-inferiority to VKA on primary efficacy event rate (stroke, cardiovascular death, systemic embolism)
- Higher rate of adverse effects in intervention group

Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;**374**:534–542.

LAA Closure/Occlusion/Excision

Recommendations for LAA closure/occlusion/excision		
Recommendations	**Class**	**Level**
Interventional, percutaneous LAA closure may be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulation.	IIb	B
Surgical excision of the LAA may be considered in patients undergoing open heart surgery.	IIb	C

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Heart Rhythm Disorders

CME

A Randomized Active-Controlled Study Comparing the Efficacy and Safety of Vernakalant to Amiodarone in Recent-Onset Atrial Fibrillation

A. John Camm, MD,* Alessandro Capucci, MD,† Stefan H. Hohnloser, MD,‡ Christian Torp-Pedersen, MD,§ Isabelle C. Van Gelder, MD,‖¶ Brian Mangal, MSc,# Gregory Beatch, PhD,# on behalf of the AVRO Investigators

London, United Kingdom; Ancona, Italy; Frankfurt, Germany; Hellerup, Denmark; Groningen and Utrecht, the Netherlands; and Vancouver, British Columbia, Canada

A Randomized Active-Controlled Study Comparing the Efficacy and Safety of Vernakalant to Amiodarone in Recent-Onset Atrial Fibrillation

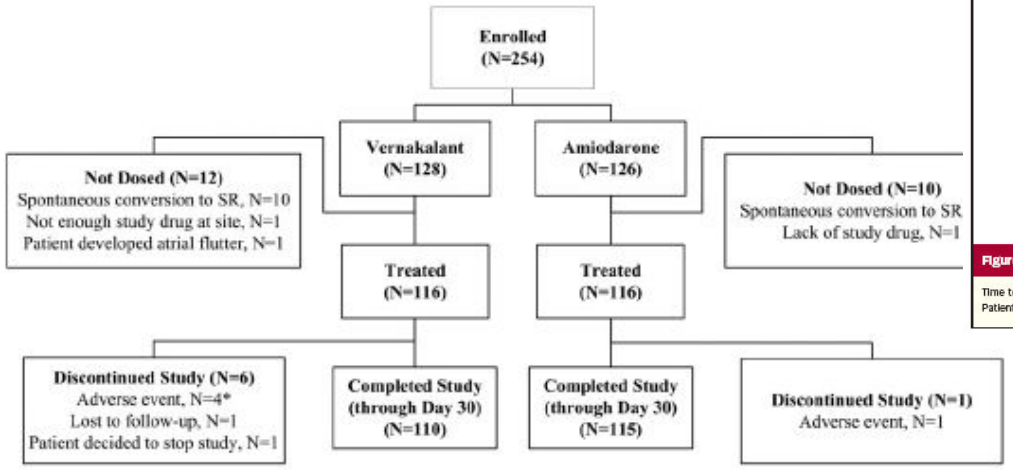
Objectives This randomized double-blind study compared the efficacy and safety of intravenous vernakalant and amiodarone for the acute conversion of recent-onset atrial fibrillation (AF).

Background Intravenous vernakalant has effectively converted recent-onset AF and was well tolerated in placebo-controlled studies.

Methods A total of 254 adult patients with AF (3 to 48 h duration) eligible for cardioversion were enrolled in the study. Patients received either a 10-min infusion of vernakalant (3 mg/kg) followed by a 15-min observation period and a second 10-min infusion (2 mg/kg) if still in AF, plus a sham amiodarone infusion, or a 60-min infusion of amiodarone (5 mg/kg) followed by a maintenance infusion (50 mg) over an additional 60 min, plus a sham vernakalant infusion.

Results Conversion from AF to sinus rhythm within the first 90 min (primary end point) was achieved in 60 of 116 (51.7%) vernakalant patients compared with 6 of 116 (5.2%) amiodarone patients ($p < 0.0001$). Vernakalant resulted in rapid conversion (median time of 11 min in responders) and was associated with a higher rate of symptom relief compared with amiodarone (53.4% of vernakalant patients reported no AF symptoms at 90 min compared with 32.8% of amiodarone patients; $p = 0.0012$). Serious adverse events or events leading to discontinuation of study drug were uncommon. There were no cases of torsades de pointes, ventricular fibrillation, or polymorphic or sustained ventricular tachycardia.

Conclusions Vernakalant demonstrated efficacy superior to amiodarone for acute conversion of recent-onset AF. Both vernakalant and amiodarone were safe and well tolerated in this study. (A Phase III Superiority Study of Vernakalant vs Amiodarone in Subjects With Recent Onset Atrial Fibrillation [AVRO]; NCT00668759) (J Am Coll Cardiol 2011;57:313–21) © 2011 by the American College of Cardiology Foundation



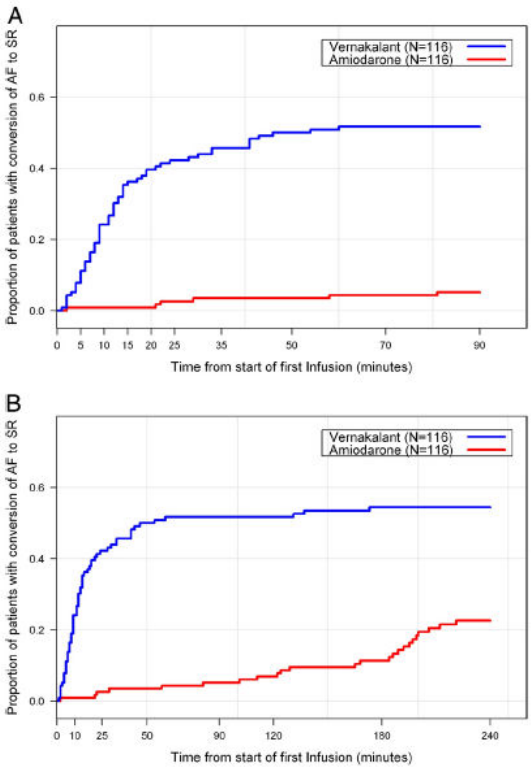


Figure 2 Time to Treatment-Induced Conversion

Time to treatment-induced conversion from atrial fibrillation (AF) to sinus rhythm (SR) within (A) 90 and (B) 240 min post-dose. Patients who had electrical cardioversion attempted were censored at the time of electrical cardioversion.

Pharmacological Cardioversion

Recommendations for pharmacological cardioversion of recent-onset AF		
Recommendations	**Class**	**Level**
When pharmacological cardioversion is preferred and there is no or minimal structural heart disease, intravenous flecainide, propafenone, ibutilide, or vernakalant are recommended.	I	A
In patients with AF ≤7 days and moderate structural heart disease [but without hypotension <100 mm Hg, NYHA class III or IV heart failure, recent [<30 days] ACS, or severe aortic stenosis] ntravenous vernakalant may be considered. Vernakalant should be used with caution in patients with NYHA class I–II heart failure.	IIb	B
Intravenous vernakalant may be considered for cardioversion of postoperative AF ≤3 days in patients after cardiac surgery.	IIb	B

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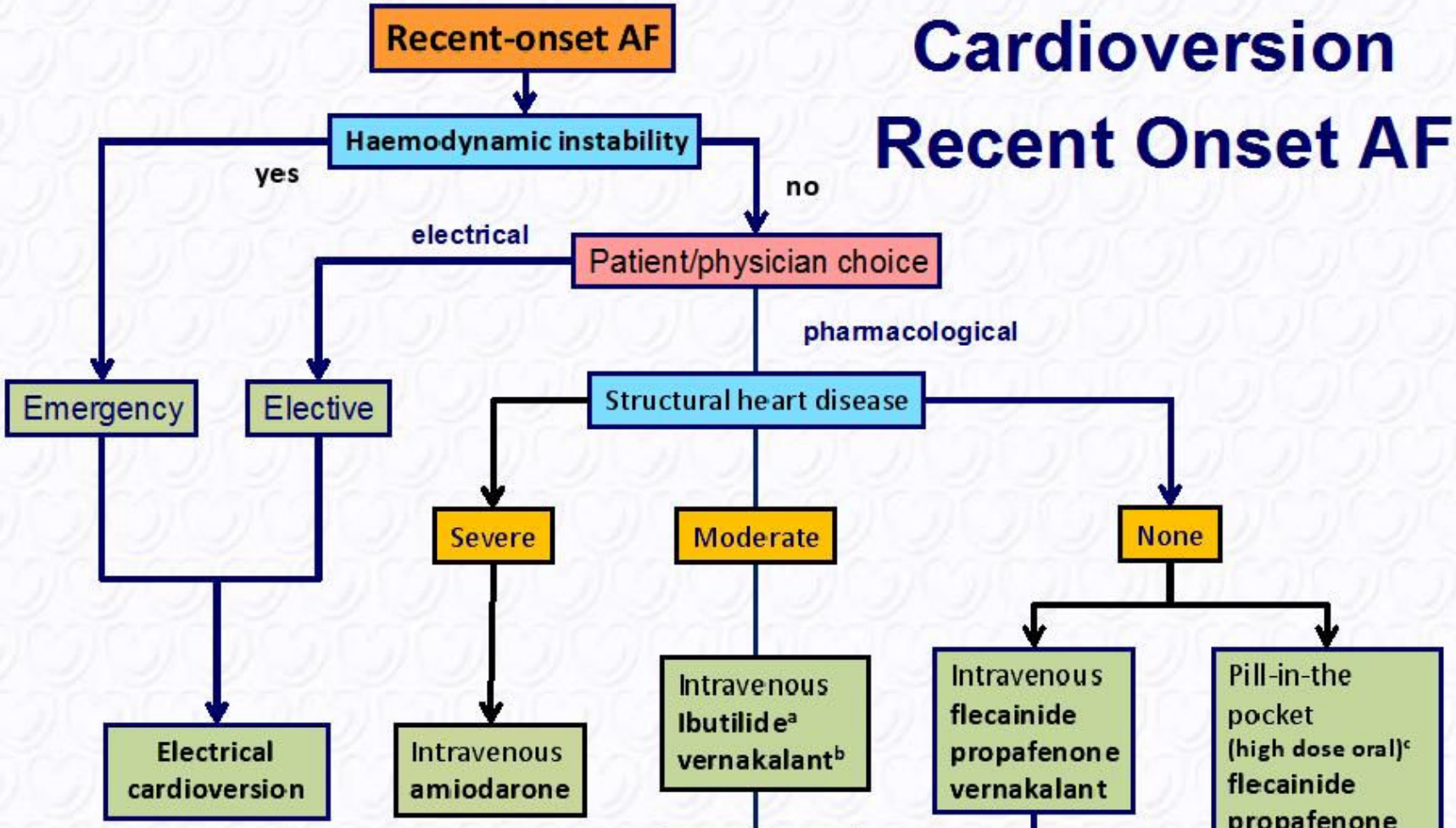
Cardioversion Recent Onset AF



[a]Ibutilide should not be given when significant left ventricular hypertrophy (≥1.4 cm) is present.
[b]Vernakalant should not be given in moderate or severe heart failure, aortic stenosis, acute coronary syndrome or hypotension. Caution in mild heart failure.
[c]'Pill-in-the-pocket' technique – preliminary assessment in a medically safe environment and then used by the patient in the ambulatory setting.

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European Heart Journal 2012;33:2719-2747 - doi:10.1093/eurheartj/ehs253

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

ATHENA - Results

- Mean F/u: 21 months
- Descontinuation: dronedarone 30,2%; placebo 30,8%
- Dronedarone greater incidence: bradycardia, QT prolongation, nausea, diarhea, rash, creatinine rise
- Primary end-point : dronedarone 31,9%; placebo 39,4% (relative risk dronedarone 0,76, p<0.001)
- Secondary end-point:
  - Total mortality: dronedarone 5%; placebo 6% (relative risk 0,84, p=0.18)
  - CV mortality: dronedarone 2,7%; placebo 3,9 % (relative risk 0,71, p=0.03), due to arrhythmic mortality

N Engl J Med 2009;360:668-78.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Estudo ATHENA

Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation

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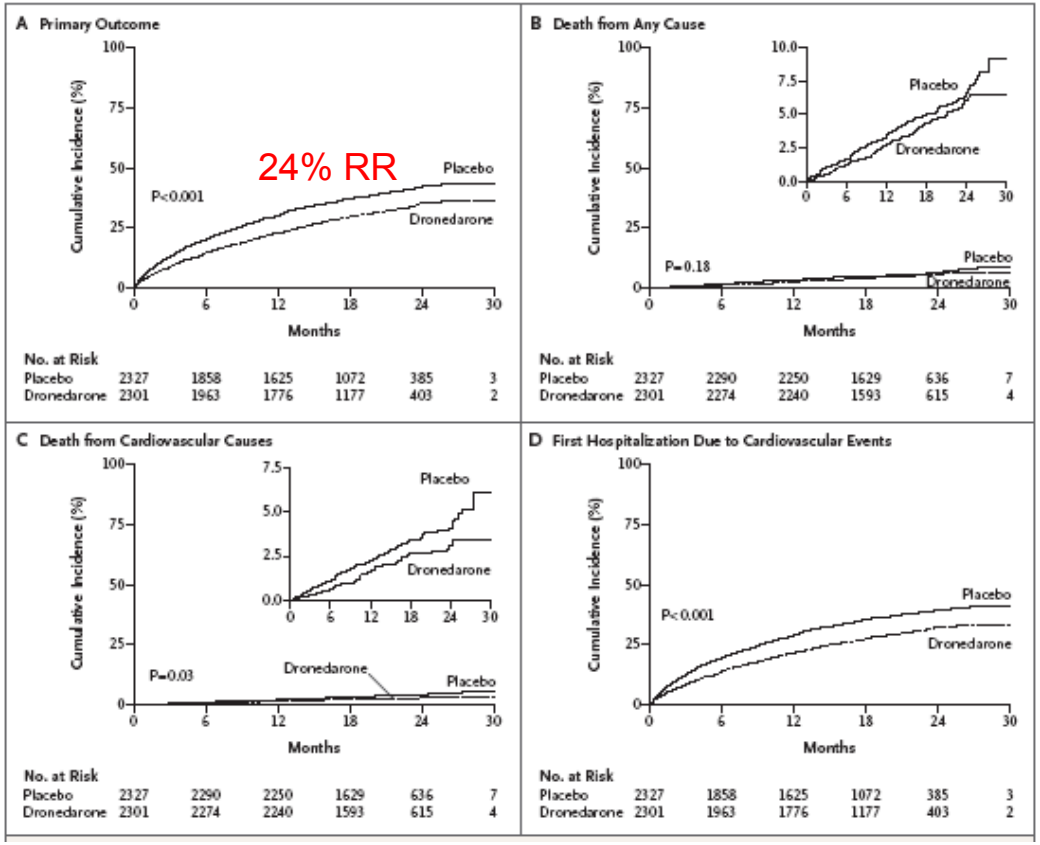

- Dronedarona reduz a incidência de hospitalização em doentes com fibrilhação auricular por redução de eventos cardiovasculares ou morte

N Engl J Med 2009;360:668-78.

Estudo Pallas:
Dronedarona na FA permanente

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

Table 3. Adverse Events and Abnormalities on Laboratory Testing.*

Event	Dronedarone (N=1614)	Placebo (N=1609)	P Value
	number (percent)		
Any adverse event	797 (49.4)	600 (37.3)	<0.001
Any serious adverse event	113 (7.0)	77 (4.8)	0.008
Any adverse event leading to treatment discontinuation	212 (13.1)	80 (5.0)	<0.001
Any reported liver-function abnormality	61 (3.8)	28 (1.7)	<0.001
Asthenic conditions (asthenia, fatigue)	89 (5.5)	46 (2.9)	<0.001
Breathing abnormalities (dyspnea)	75 (4.6)	36 (2.2)	<0.001
Diarrhea	101 (6.3)	38 (2.4)	<0.001
Electrocardiographic investigations (QT prolonged)	33 (2.0)	16 (1.0)	0.02
Edema (peripheral edema)	60 (3.7)	29 (1.8)	<0.001
Gastrointestinal or abdominal pain	33 (2.0)	15 (0.9)	0.009
Increased creatinine level	49 (3.0)	11 (0.7)	<0.001
Lower respiratory tract or lung infection	40 (2.5)	42 (2.6)	0.81
Nausea or vomiting	76 (4.7)	28 (1.7)	<0.001
Neurologic signs or symptoms (dizziness)	76 (4.7)	39 (2.4)	<0.001
Rate and rhythm disorders (bradycardia)	67 (4.2)	19 (1.2)	<0.001
Renal failure or impairment	35 (2.2)	12 (0.7)	<0.001
Upper respiratory tract infection	34 (2.1)	35 (2.2)	0.89
Alanine aminotransferase and bilirubin†			
Alanine aminotransferase >3× ULN	23 (1.5)	9 (0.6)	0.013
Alanine aminotransferase >3× ULN and bilirubin >2× ULN	1 (<0.1)‡	0	NA

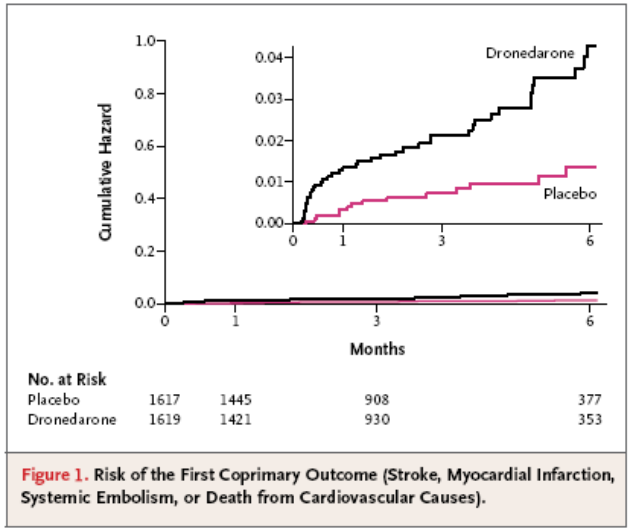

Figure 1. Risk of the First Coprimary Outcome (Stroke, Myocardial Infarction, Systemic Embolism, or Death from Cardiovascular Causes).

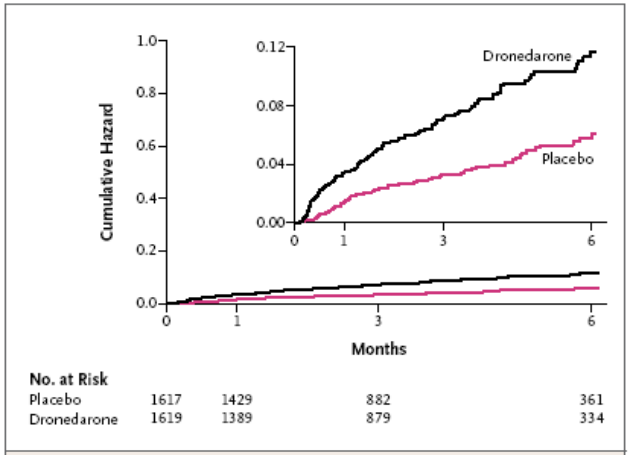

Figure 2. Risk of the Second Coprimary Outcome (Unplanned Hospitalization for Cardiovascular Causes or Death).

Estudo Pallas:
Dronedarona na FA permanente

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		
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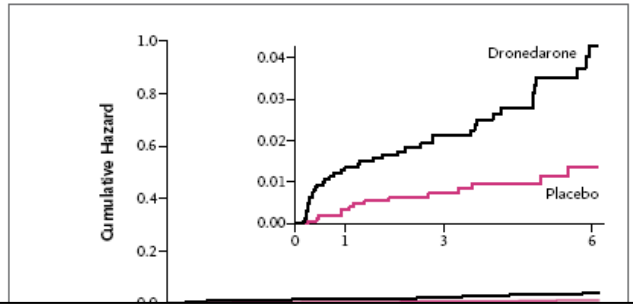

CONCLUSIONS

Dronedarone increased rates of heart failure, stroke, and death from cardiovascular causes in patients with permanent atrial fibrillation who were at risk for major vascular events. Our data show that this drug should not be used in such patients. (Funded by Sanofi-Aventis; PALLAS ClinicalTrials.gov number, NCT01151137.)

Event	Dronedarone (N=1614)	Placebo (N=1609)	P Value
	number (percent)		
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Any adverse event leading to treatment discontinuation	212 (13.1)	80 (5.0)	<0.001
Any reported liver-function abnormality	61 (3.8)	28 (1.7)	<0.001
Asthenic conditions (asthenia, fatigue)	89 (5.5)	46 (2.9)	<0.001
Breathing abnormalities (dyspnea)	75 (4.6)	36 (2.2)	<0.001
Diarrhea	101 (6.3)	38 (2.4)	<0.001
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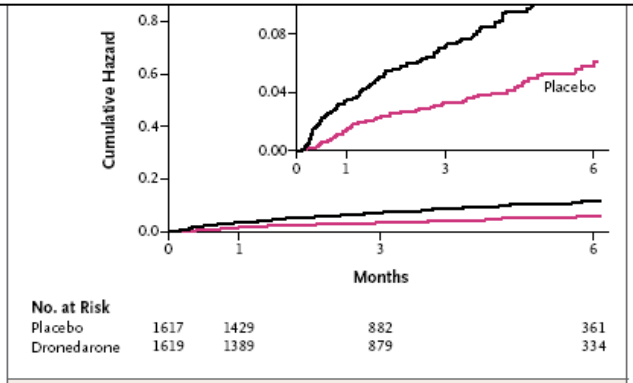

Figure 2. Risk of the Second Coprimary Outcome (Unplanned Hospitalization for Cardiovascular Causes or Death).

Oral Antiarrhythmic Drugs

Recommendations for oral antiarrhythmic agents		
Recommendations	**Class**	**Level**
Dronedarone is recommended in patients with recurrent AF as a moderately effective antiarrhythmic agent for the maintenance of sinus rhythm.	I	A
Short-term (4 weeks) antiarrhythmic therapy after cardioversion may be considered in selected patients e.g., those at risk for therapy associated complications.	IIb	B
Dronedarone is not recommended in patients with permanent AF.	III	B

European Heart Journal 2012;33:2719-2747 - doi:10.1093/eurheartj/ehs253

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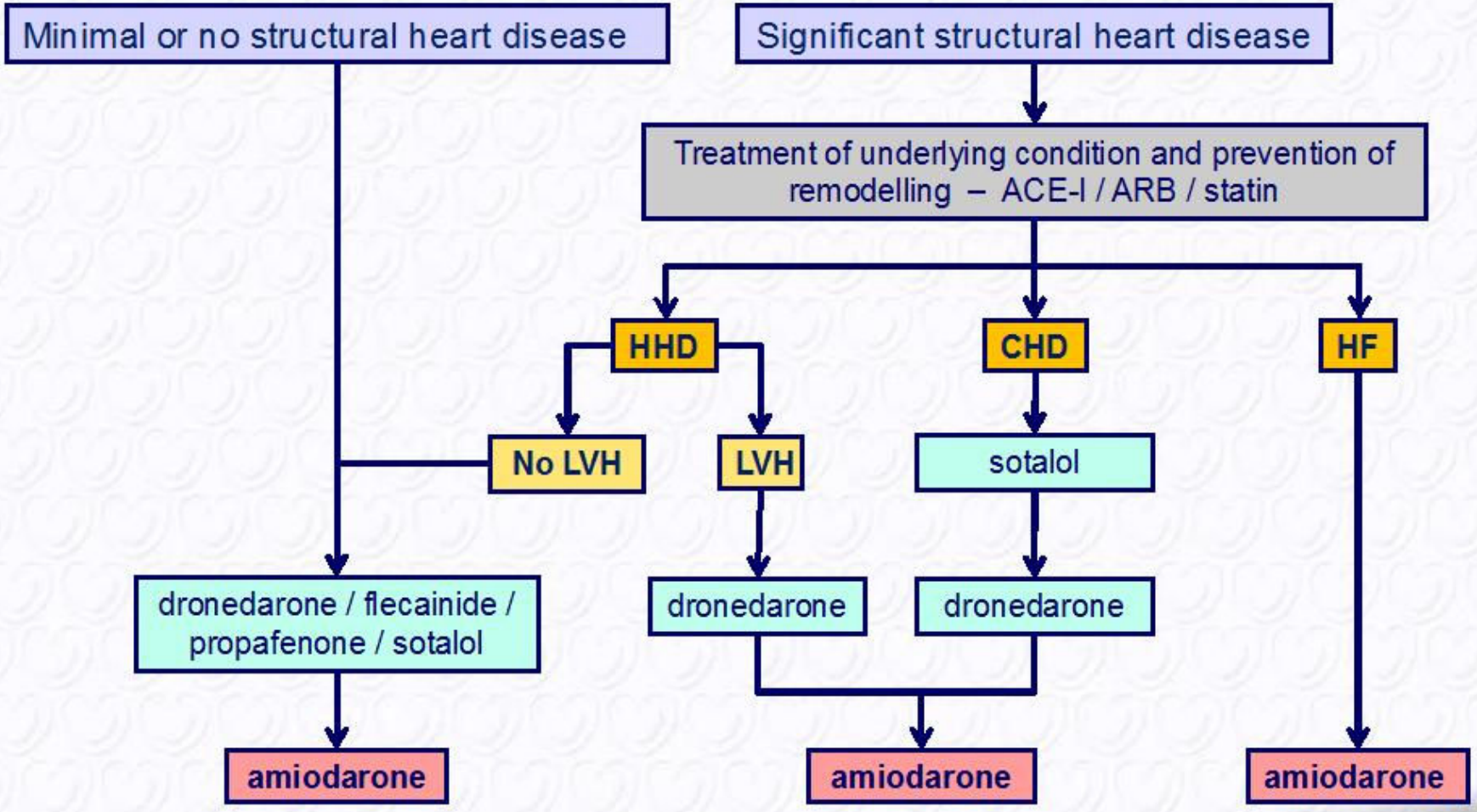
Choice of Oral Antiarrhythmic Drug



ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; HHD = hypertensive heart disease; CHD = coronary heart disease. HF = heart failure; LVH = left ventricular hypertrophy, NYHA = New York Heart Association.

www.escardio.org/guidelines

European Heart Journal 2012;33:2719-2747 - doi:10.1093/eurheartj/ehs253

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Ablação FA:Meta-análise

Approach to the Catheter Ablation Technique of Paroxysmal and Persistent Atrial Fibrillation: A Meta-Analysis of the Randomized Controlled Trials

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JOHN L. SAPP, M.D.,* and GEORGE WELLS, PH.D.‡

From the *Queen Elizabeth II Health Sciences Centre, Halifax, Canada; †Royal Jubilee Hospital, Victoria, Canada; and ‡University of Ottawa Heart Institute, Ottawa, Canada

Review of the Catheter Ablation Technique in AF. *Background:* Several randomized controlled trials (RCTs) have been published to investigate the optimal techniques for atrial fibrillation (AF) ablation. Many of these are small in number and include both paroxysmal and persistent AF; however, the techniques for each of these types of AF may differ.

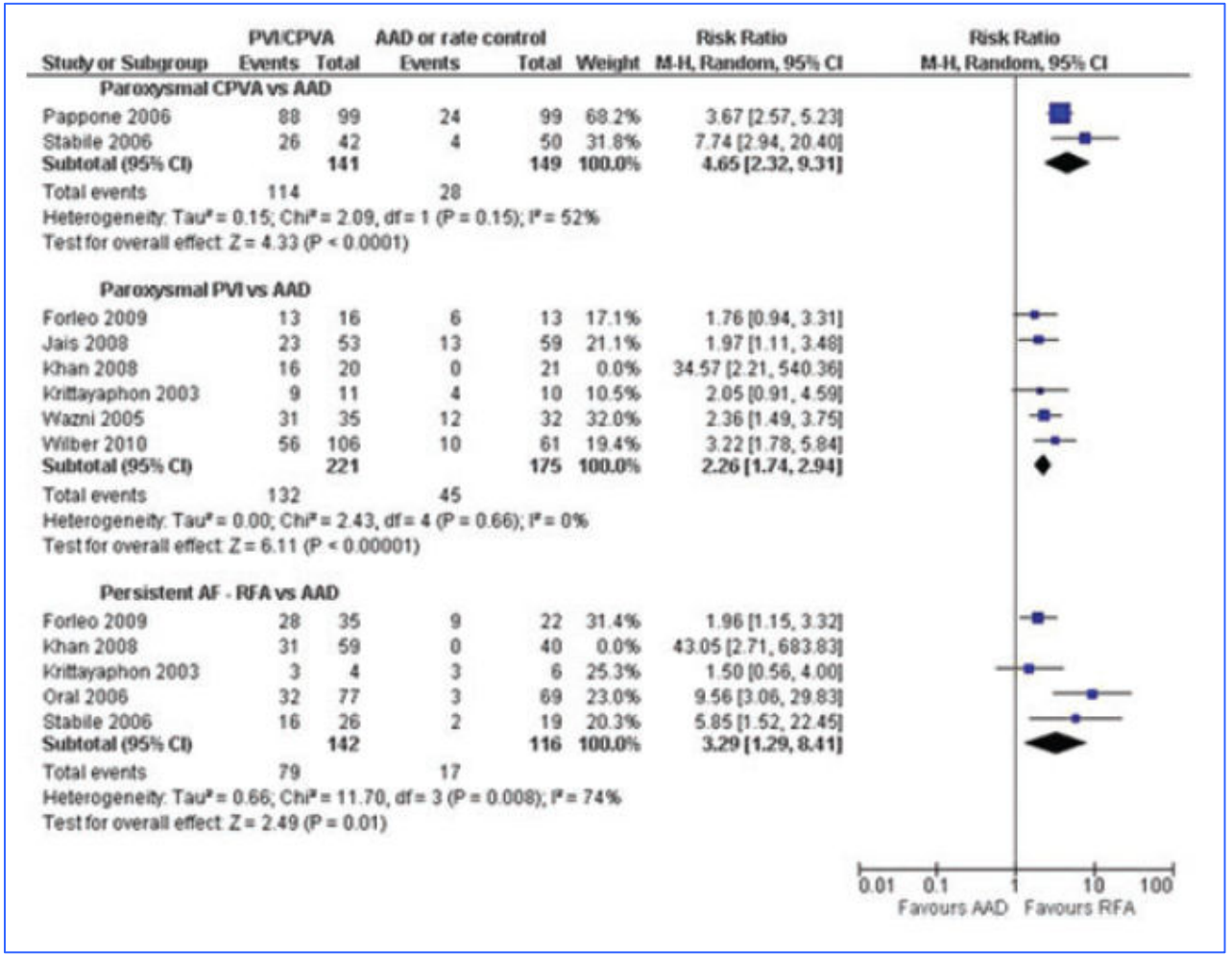
Method and Results: We searched MEDLINE, EMBASE, and the Cochrane Controlled Trials Register for RCTs evaluating AF ablation for either paroxysmal or persistent AF. The primary endpoint was freedom from AF after a single procedure. A total of 35 unique randomized controlled trials were found to fulfill the criteria. A significant degree of heterogeneity was present given the differing sample sizes, populations studied, and outcomes. Radiofrequency ablation (RFA) was found to be favorable in prevention of AF over antiarrhythmic drugs (AADs) in either paroxysmal (5 studies, RR 2.26; 95% CI 1.74, 2.94) or persistent AF (5 studies, RR 3.20; 95% CI 1.29, 8.41). When comparing specific techniques, wide-area PVI appeared to offer the most benefit for both paroxysmal (6 studies, RR 0.78; 95% CI 0.63, 0.97) and persistent AF (3 studies, RR 0.64; 95% CI 0.43, 0.94). CTI-ablation provided only benefit for persistent AF when combined with antral PVI (4 studies, RR 0.55; 95% CI 0.34, 0.87).

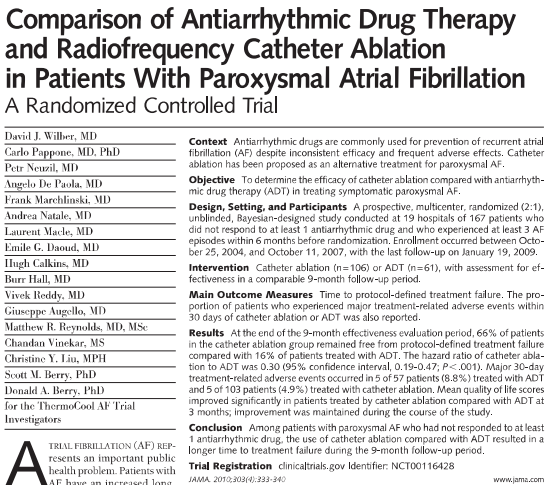
Conclusions: Despite significant methodological limitations, it appears that additional ablations beyond PVI are necessary for persistent AF but not proven for paroxysmal AF. The optimal technique for persistent AF, however, deserves a further study, in the setting of a large, randomized controlled trial. *(J Cardiovasc Electrophysiol, Vol. 22, pp. 729-738, July 2011)*

TABLE 2
Complications

Complication	Risk (%) n = 4128
Cardiac tamponade	0.19
Atrioesophageal fistula	0.0
Stroke/TIA	0.27
Death	0.07
PV stenosis	0.46
Pulmonary edema	0.15
Other*	0.34
Total	1.47

*Vascular complications, hemo/pneumothorax.





Comparison of Antiarrhythmic Drug Therapy and Radiofrequency Catheter Ablation in Patients With Paroxysmal Atrial Fibrillation

A Randomized Controlled Trial

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Carlo Pappone, MD, PhD
Petr Neuzil, MD
Angelo De Paola, MD
Frank Marchlinski, MD
Andrea Natale, MD
Laurent Macle, MD
Emile G. Daoud, MD
Hugh Calkins, MD
Burr Hall, MD
Vivek Reddy, MD
Giuseppe Augello, MD
Matthew R. Reynolds, MD, MSc
Chandan Vinekar, MS
Christine Y. Liu, MPH
Scott M. Berry, PhD
Donald A. Berry, PhD
for the ThermoCool AF Trial Investigators

Context Antiarrhythmic drugs are commonly used for prevention of recurrent atrial fibrillation (AF) despite inconsistent efficacy and frequent adverse effects. Catheter ablation has been proposed as an alternative treatment for paroxysmal AF.

Objective To determine the efficacy of catheter ablation compared with antiarrhythmic drug therapy (ADT) in treating symptomatic paroxysmal AF.

Design, Setting, and Participants A prospective, multicenter, randomized (2:1), unblinded, Bayesian-designed study conducted at 19 hospitals of 167 patients who did not respond to at least 1 antiarrhythmic drug and who experienced at least 3 AF episodes within 6 months before randomization. Enrollment occurred between October 25, 2004, and October 11, 2007, with the last follow-up on January 19, 2009.

Intervention Catheter ablation (n=106) or ADT (n=61), with assessment for effectiveness in a comparable 9-month follow-up period.

Main Outcome Measures Time to protocol-defined treatment failure. The proportion of patients who experienced major treatment-related adverse events within 30 days of catheter ablation or ADT was also reported.

Results At the end of the 9-month effectiveness evaluation period, 66% of patients in the catheter ablation group remained free from protocol-defined treatment failure compared with 16% of patients treated with ADT. The hazard ratio of catheter ablation to ADT was 0.30 (95% confidence interval, 0.19-0.47; $P<.001$). Major 30-day treatment-related adverse events occurred in 5 of 57 patients (8.8%) treated with ADT and 5 of 103 patients (4.9%) treated with catheter ablation. Mean quality of life scores improved significantly in patients treated by catheter ablation compared with ADT at 3 months; improvement was maintained during the course of the study.

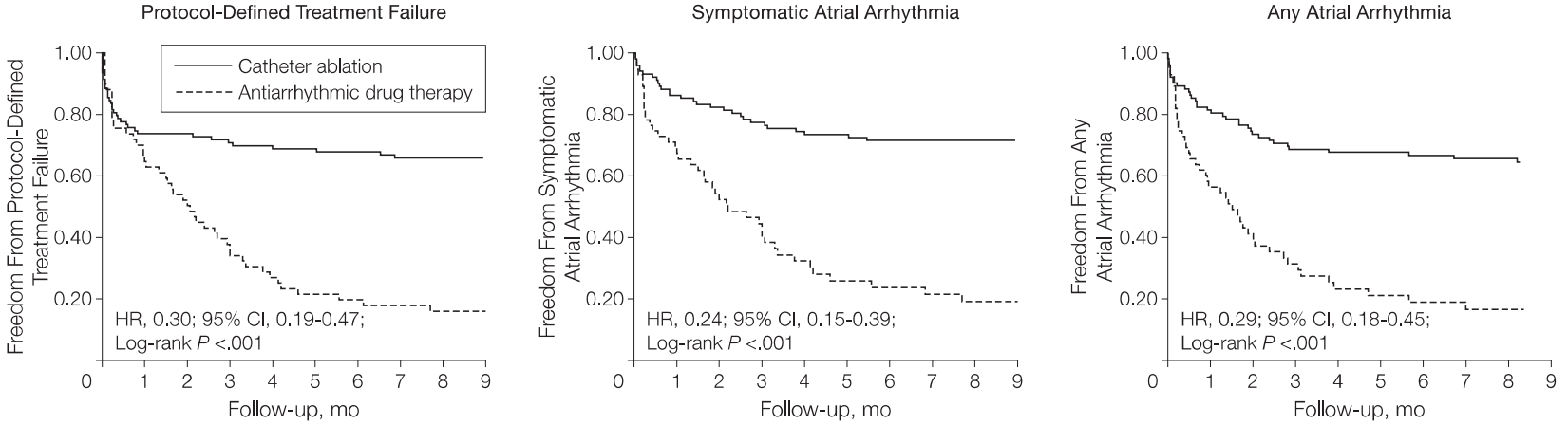
Conclusion Among patients with paroxysmal AF who had not responded to at least 1 antiarrhythmic drug, the use of catheter ablation compared with ADT resulted in a longer time to treatment failure during the 9-month follow-up period.

Trial Registration clinicaltrials.gov Identifier: NCT00116428

JAMA. 2010;303(4):333-340 www.jama.com

ATRIAL FIBRILLATION (AF) REPresents an important public health problem. Patients with AF have an increased long

Figure 2. Kaplan-Meier Curves of Time to Protocol-Defined Treatment Failure, Recurrence of Symptomatic Atrial Arrhythmia, and Recurrence of Any Atrial Arrhythmia by Treatment Group



No. at risk

Catheter ablation	106	75	75	72	70	70	69	67	65	51
Antiarrhythmic drug therapy	61	36	28	20	15	12	11	10	7	3

Catheter ablation	106	88	84	79	75	75	73	73	71	57
Antiarrhythmic drug therapy	61	37	27	21	15	12	11	10	7	4

Catheter ablation	106	84	78	72	70	70	69	68	65	52
Antiarrhythmic drug therapy	61	33	22	17	13	11	10	9	6	4

HR indicates hazard ratio; CI, confidence interval.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 25, 2012 VOL. 367 NO. 17

MANTRA-AF Study

Radiofrequency Ablation as Initial Therapy in Paroxysmal Atrial Fibrillation

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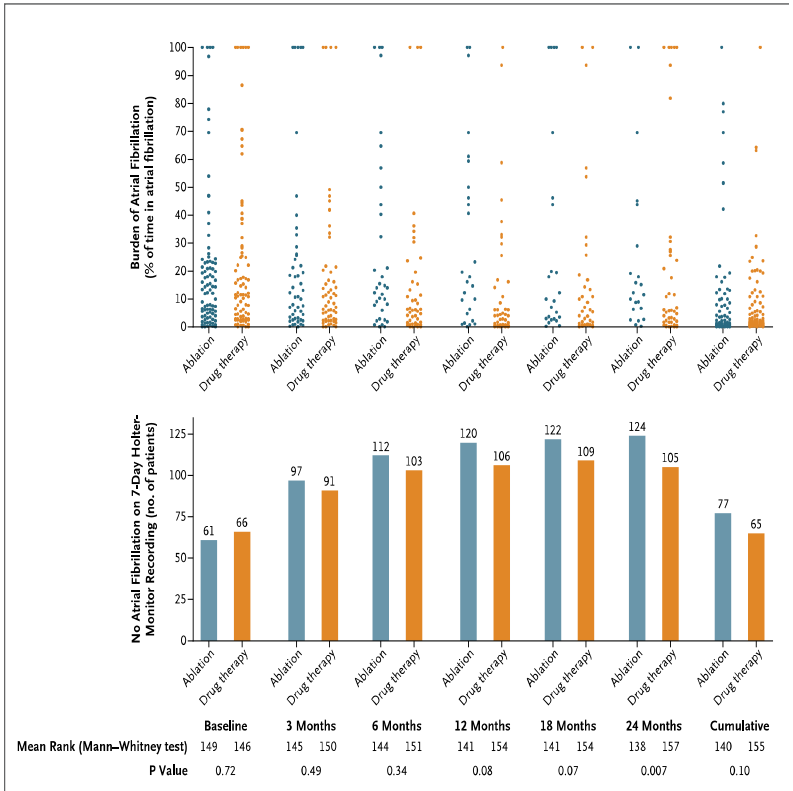

Figure 1. Burden of Atrial Fibrillation and Proportion of Patients Who Were Free of Atrial Fibrillation during the 2-Year Study Period, According to Treatment Group.

Shown are the burden of atrial fibrillation (upper graph) and the number of patients without atrial fibrillation (lower graph) in 7-day Holter-monitor recordings at baseline, at each follow-up visit, and cumulatively during follow-up. The mean rank (Mann–Whitney test) and P values for group comparisons of the burden of atrial fibrillation are shown at the bottom of the figure.

Table 3. Serious Adverse Events.*

Event	Ablation	Drug Therapy
	no. of events	
Death	3†	4‡
Cancer	6	4
Atrial flutter with an atrioventricular conduction ratio of 1:1	0	2
Atrial flutter or atrial tachycardia	3	3
Perimyocarditis	1	0
Stroke	1	0
TIA	1	1
Tamponade	3	0
Pericardial effusion without the need for pericardial puncture	0	1
Suspected perforation at transseptal puncture, no pericardial effusion	1	0
Pulmonary-vein stenosis	1	0
Hospitalization for heart failure	0	2
Hematoma related to anticoagulation	1	0
Bradycardia with the need for a cardiac pacemaker	0	1
Ventricular tachycardia and implantation of an ICD	1	0
Retroperitoneal bleeding, coiling of small artery	1	0
Chest discomfort	1	0
Discomfort probably due to medication§	0	2
Rupture of the rotator cuff	0	1
Knee osteoarthritis requiring arthroscopy	1	0
Gallbladder surgery	0	1
Total	25	22

Left Atrial Ablation

Recommendations for left atrial ablation		
Recommendations	**Class**	**Level**
Catheter ablation of symptomatic paroxysmal AF is recommended in patients who have symptomatic recurrences of AF on antiarrhythmic drug therapy (amiodarone, dronedarone, flecainide, propafenone, sotalol) and who prefer further rhythm control therapy, when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced centre.	I	A
Catheter ablation of AF should be considered as first-line therapy in selected patients with symptomatic, paroxysmal AF as an alternative to antiarrhythmic drug therapy, considering patient choice, benefit, and risk.	IIa	B

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Left Atrial Ablation

Recommendations	Class	Level
Catheter ablation of AF should target isolation of the pulmonary veins.	IIa	A
When catheter ablation of AF is planned, continuation of oral anticoagulation with a VKA should be considered during the procedure, maintaining an INR close to 2.0.	IIa	B
When AF recurs within the first 6 weeks after catheter ablation, a watch-and-wait rhythm control therapy should be considered.	IIa	B

European Heart Journal 2012;33:2719-2747 -
doi:10.1093/eurheartj/ehs253

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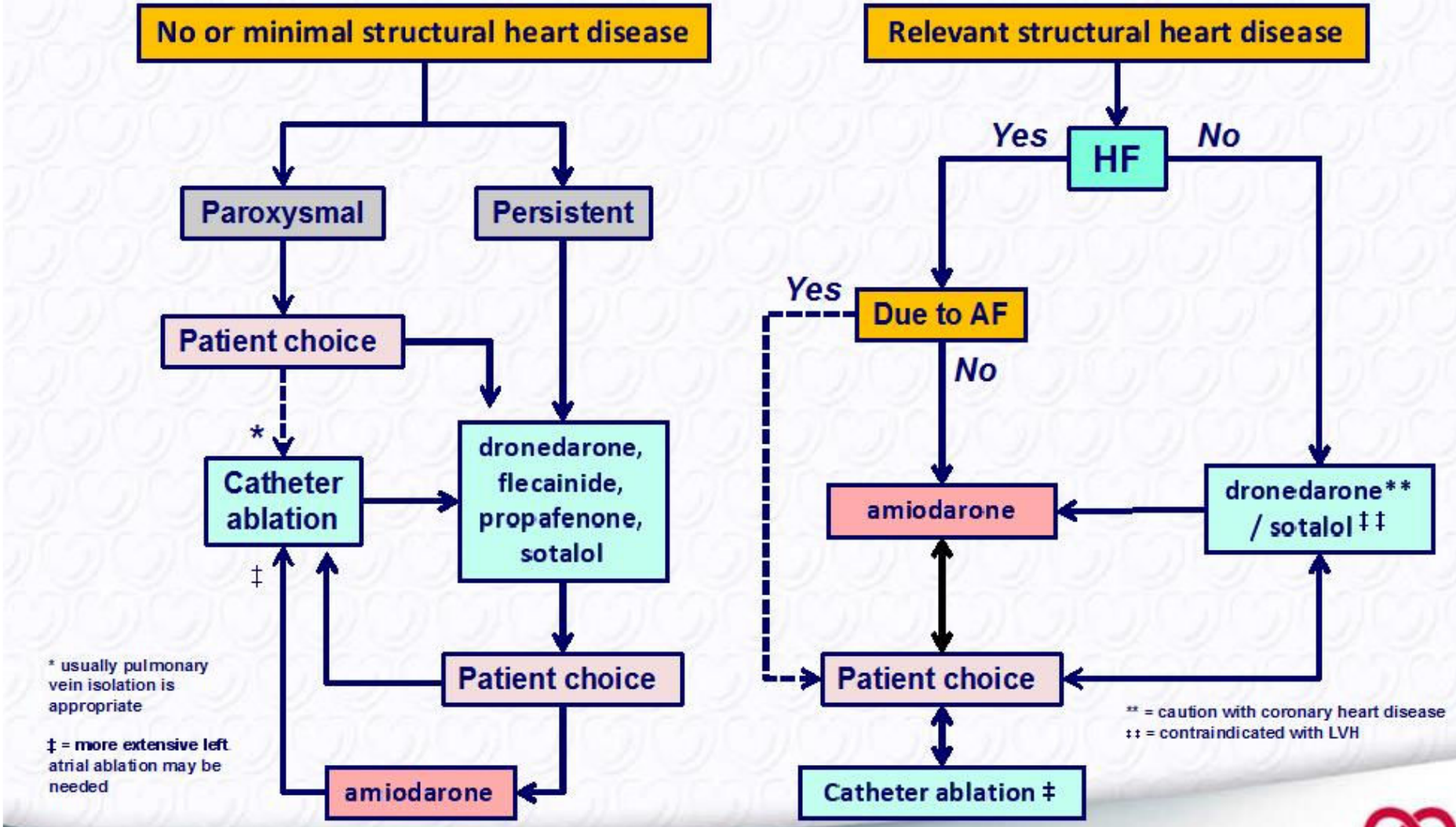
Left Atrial Ablation (and AAD)



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European Heart Journal 2012;33:2719-2747 -
doi:10.1093/eurheartj/ehs253

2012 focused update of the ESC Guidelines for the Management of Atrial Fibrillation

An update of the 2010 ESC Guidelines for the Management of Atrial Fibrillation

Developed with the special contribution of the European Heart Rhythm Association

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Classes of Recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

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Levels of Evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.

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