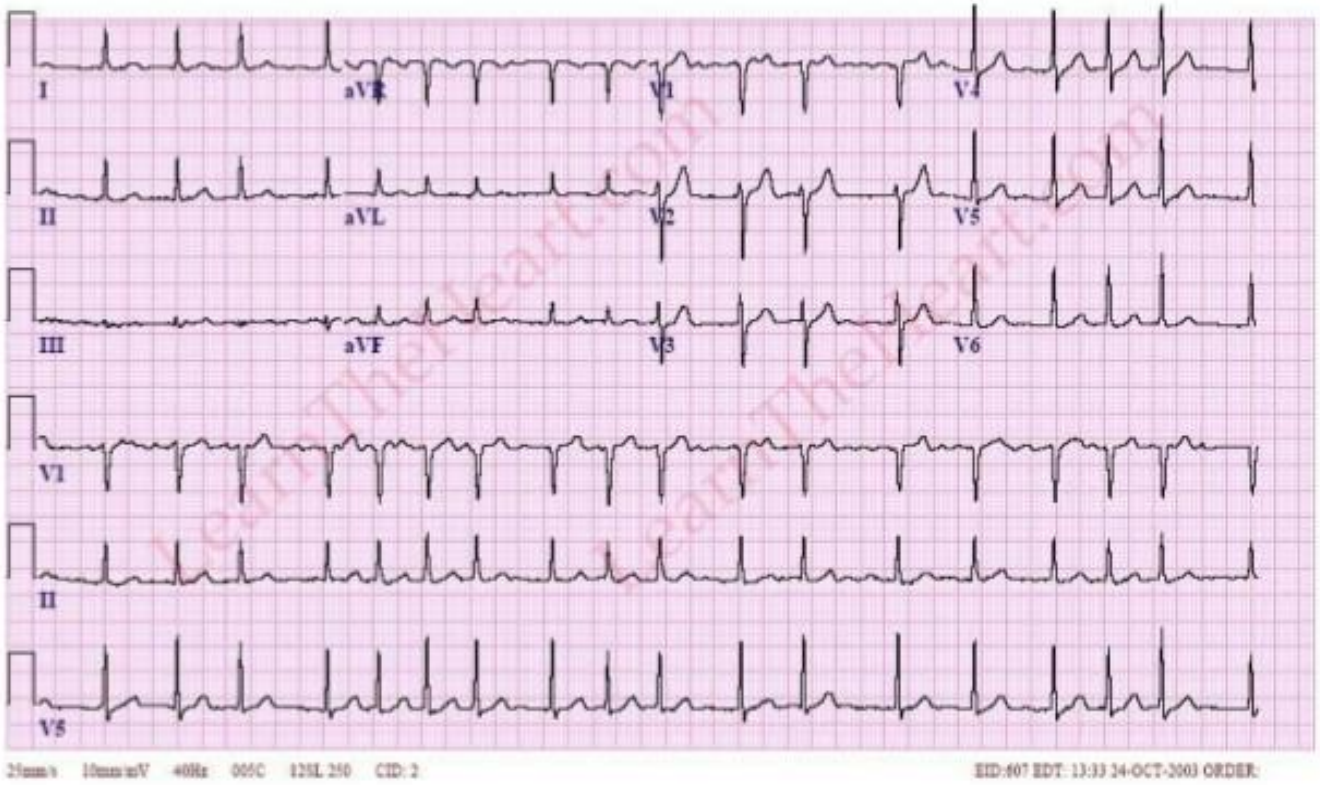
ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ ΦΑΡΜΑΚΕΥΤΙΚΗ ΗΛΕΚΤΡΙΚΗ ΑΝΑΤΑΞΗ

ΣΠΥΡΟΜΗΤΡΟΣ ΓΕΩΡΓΙΟΣ
Καρδιολόγος, Ε/Α , Γ.Ν.Κατερίνης.
F.E.S.C


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
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II
V5
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EID:607 EDT: 13:33 24-OCT-2003 ORDER:

Επισκόπηση Κολπικής Μαρμαρυγής (AF)

- AF είναι η πιο κοινή μορφή αρρυθμίας και η συχνότητα εμφάνισης της αυξάνεται με γρήγορους ρυθμούς[1]
  - AF υπολογίζεται ότι παρουσιάζεται στο 1% to 2% του γενικού πληθυσμού[1]
  - Η συχνότητα εμφάνισης της AF αυξήθηκε 13% στις τελευταίες 2 δεκαετίες[1]
  - Πάνω από 6 εκατομμύρια Ευρωπαίοι έχουν κάποια μορφή AF[1]

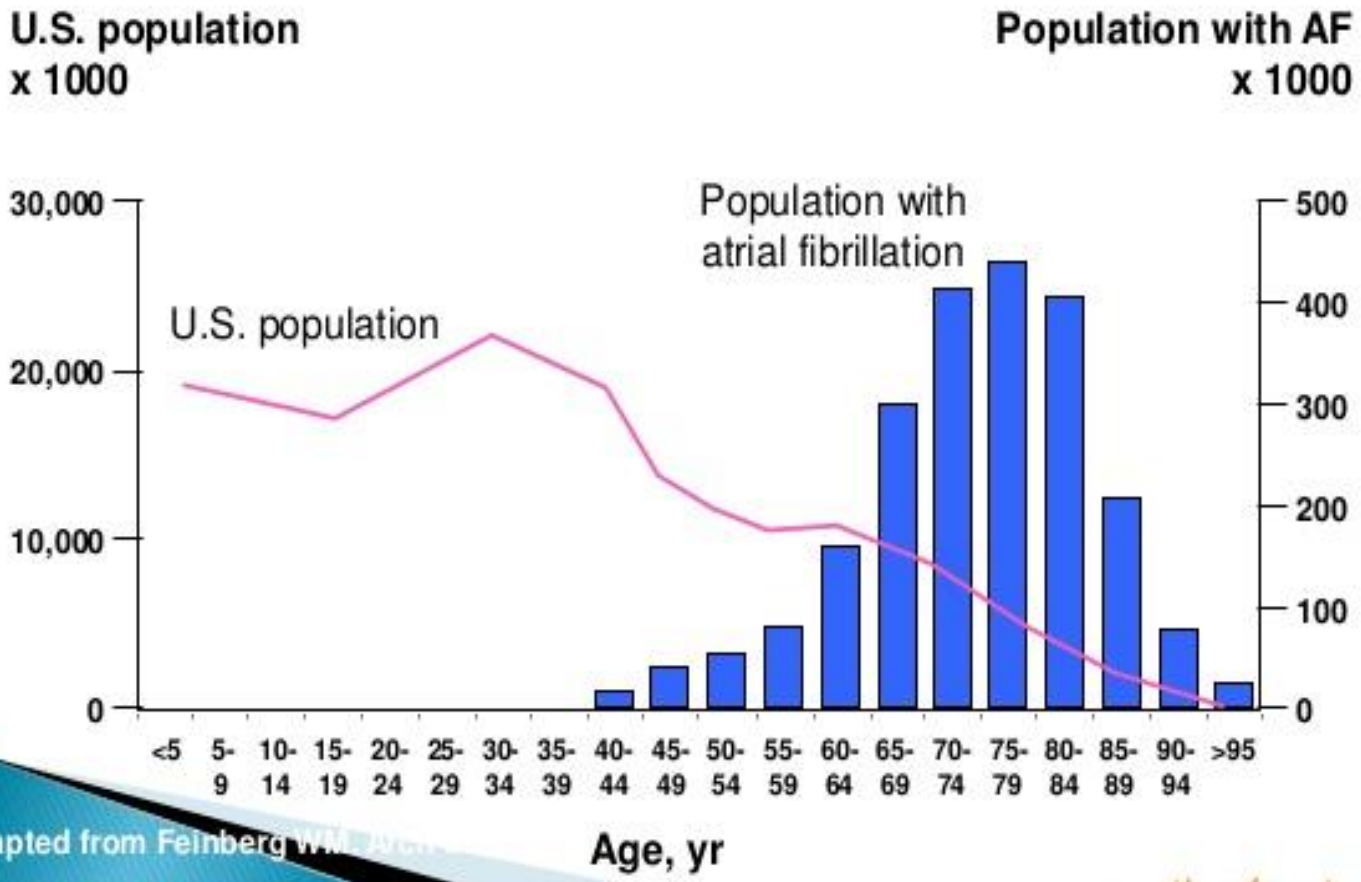
AF = atrial fibrillation.

1. The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31:2369–2429.

Alabama Cardiovascular Group, P.C.

Atrial Fibrillation

Demographics by Age



Adapted from Feinberg WM, Arch...

www.theafcenter.com

Definitions of AF: A Simplified Scheme

Term	Definition
Paroxysmal AF	• AF that terminates spontaneously or with intervention within 7 d of onset. • Episodes may recur with variable frequency.
Persistent AF	• Continuous AF that is sustained >7 d.
Long-standing persistent AF	• Continuous AF >12 mo in duration.
Permanent AF	• The term “permanent AF” is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm. • Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of AF. • Acceptance of AF may change as symptoms, efficacy of therapeutic interventions, and patient and clinician preferences evolve.
Nonvalvular AF	• AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

AF indicates atrial fibrillation.

Classification of AF

Terminology	Clinical features	
Initial event (first detected episode)	Symptomatic Asymptomatic Onset unknown	Rhythm/Rate
Paroxysmal	Spontaneous termination <7 days and most often <48 hours	Rhythm Control
Persistent	Not self-terminating Lasting >7 days or prior cardioversion	Rhythm or Rate control
Permanent ('accepted')	Not terminated Terminated but relapsed No cardioversion attempt	Rate Control

Cardioversion

- Cardioversion is performed as part of a rhythm-control treatment strategy
- There are two types of cardioversion: electrical (ECV) and pharmacological (PCV)
- Cardioversion of AF is associated with increased risk of stroke in the absence of antithrombotic therapy.

Likelihood of Spontaneous Conversion of Atrial Fibrillation to Sinus Rhythm

- 356 pts with AF < 72 h
- Symptoms of < 24 h was only independent predictor of spontaneous conversion (OR: 1.8, p < 0.0001)

AF duration	n	Conversion
< 24 h	292	73%
24 - 72 h	64	45%
Total	356	68%

Danias J Am Coll Cardiol. 1998;31:588-92

Prevention of Thromboembolism

- With AF or atrial flutter for ≥48 h, or unknown duration, anticoagulate with warfarin for at least 3 wk before and 4 wk after cardioversion (Class I)
- With AF or atrial flutter for >48 h or unknown duration, requiring immediate cardioversion, anticoagulate as soon as possible and continue for at least 4 wk (Class I)
- With AF or atrial flutter <48 h and high stroke risk, IV heparin or LMWH, or factor Xa or direct thrombin inhibitor, is recommended before or immediately after cardioversion, followed by long-term anticoagulation (Class I)
- With AF or atrial flutter <48 h and low thromboembolic risk, IV heparin, LMWH, a new oral anticoagulant, or no antithrombotic may be considered for cardioversion (Class IIb)

For patients with AF or atrial flutter of 48 hours' duration or longer or when duration of AF is unknown, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for at least 3 weeks before and 4 weeks after cardioversion.	IIa	C

PRACTICE GUIDELINE

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary

Circulation 2014;130:2071-2104.

Recommendations for anticoagulation pericardioversion

Recommendations	Class[a]	Level[b]	Ref.[c]
For patients with AF of 48 h duration or longer, or when the duration of AF is unknown, OAC therapy (INR 2.0–3.0) is recommended for at least 3 weeks prior to and for 4 weeks after cardioversion, regardless of the method (electrical or oral/i.v. pharmacological).	I	B	63
For patients with AF requiring immediate/emergency cardioversion because of haemodynamic instability, heparin (i.v. UFH bolus followed by infusion, or weight-adjusted therapeutic dose LMWH) is recommended.	I	C	
			63
			54, 63
			63
			54, 63
			42
			42
			63
for 4 weeks or lifelong (if risk factors are present).	IIa	C	
If thrombus remains on repeat TOE, an alternative strategy (e.g. rate control) may be considered.	IIb	C	
For patients with AF duration that is clearly <48 h and no thrombo-embolic risk factors, i.v. heparin or weight-adjusted therapeutic dose LMWH may be considered peri-cardioversion, without the need for post-cardioversion oral anticoagulation.	IIb	C	

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

www.escardio.org/guidelines

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

EUROPEAN SOCIETY OF CARDIOLOGY

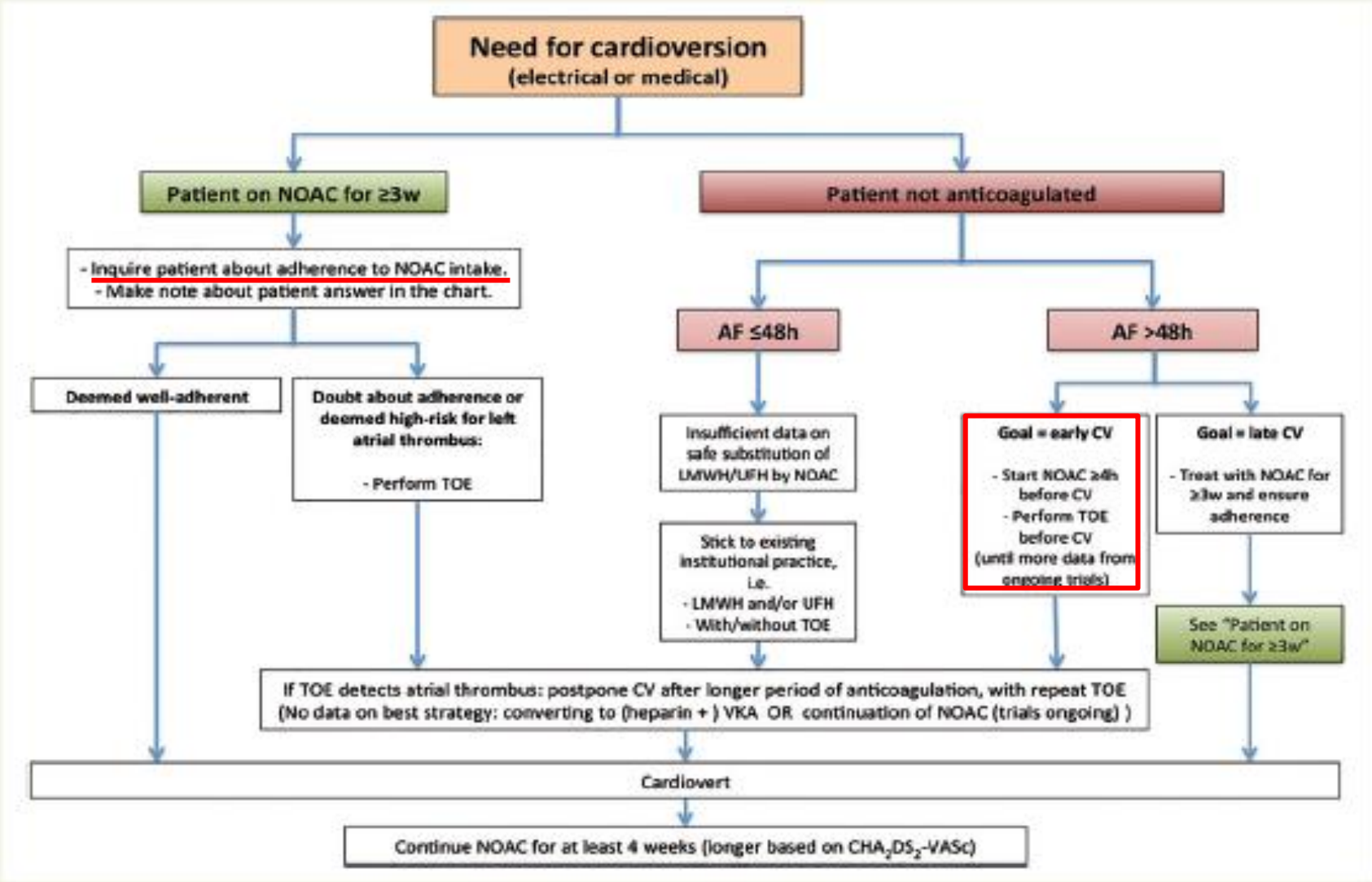
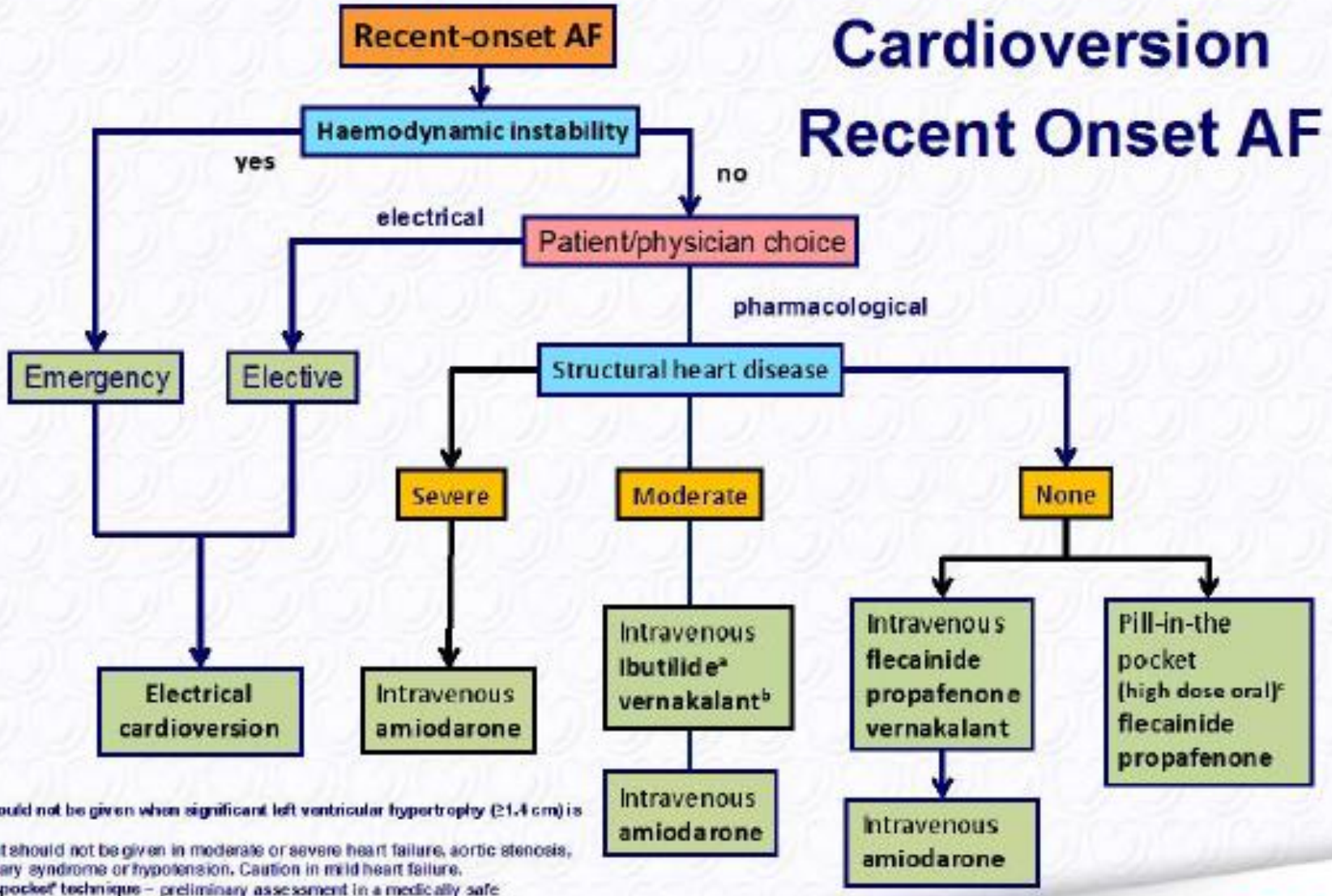


Figure 8 Cardioversion work-flow in AF patients treated with NOAC, depending on the duration of the arrhythmia and prior anticoagulation.

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.

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

www.escardio.org/guidelines

EUROPEAN SOCIETY OF CARDIOLOGY®

Vaughan Williams classification

Class	Drugs
Ia	• Quinidine • Procainamide • Disopyramide
Ib	• Lidocaine • Phenytoin • Mexiletine
Ic	• Flecainide • Propafenone • Moricizine
II	• β-blockers

Class	Drugs
III	• Amiodarone • Sotalol • Ibutilide • Dofetilide
IV	• Verapamil • Diltiazem
V	• Adenosine • Digoxin

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

www.escardio.org/guidelines

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

Pharmacological cardioversion

- Flecainide, dofetilide, propafenone, and IV ibutilide are useful for cardioversion of AF or atrial flutter, provided contraindications to the selected drug are absent (Class I)
- Amiodarone is reasonable for pharmacological cardioversion of AF (Class IIa)
- Propafenone or flecainide ("pill-in-the-pocket") to terminate AF out of hospital is reasonable once observed to be safe in a monitored setting (Class IIa)

PRACTICE GUIDELINE

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary

Circulation 2014;130:2071-2104.

Table 12 Drugs and doses for pharmacological conversion of (recent-onset) AF

Drug	Dose	Follow-up dose	Risks
Amiodarone	5 mg/kg i.v. over 1 h	50 mg/h	Phlebitis, hypotension. Will slow the ventricular rate. Delayed AF conversion to sinus rhythm.
Flecainide	2 mg/kg i.v. over 10 min, or 200–300 mg p.o.	N/A	Not suitable for patients with marked structural heart disease; may prolong QRS duration, and hence the QT interval; and may inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles.
Ibutilide	1 mg i.v. over 10 min	1 mg i.v. over 10 min after waiting for 10 min	Can cause prolongation of the QT interval and torsades de pointes; watch for abnormal T-U waves or QT prolongation. Will slow the ventricular rate.
Propafenone	2 mg/kg i.v. over 10 min, or 450–600 mg p.o.		Not suitable for patients with marked structural heart disease; may prolong QRS duration; will slightly slow the ventricular rate, but may inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles.
Vernakalant	3 mg/kg i.v. over 10 min	Second infusion of 2 mg/kg i.v. over 10 min after 15 min rest	So far only evaluated in clinical trials; recently approved.[68–71]

FLECAINIDE

- Approximately **half of the responding patients** convert within 3 h of the oral dose or within 1 h of the initial infusion time.
- The single loading **oral dose** of flecainide (200-300mg) has a conversion rate of 50–60% at 3 h and 75–85% at 6–8 h.
- **Very effective** antiarrhythmic drug for the pharmacologic conversion of a patient with AF of short (<24 hours) duration, rarely effective for termination of atrial flutter or persistent AF.
- Intravenous flecainide (2 mg/kg over 10 min) acutely reverts recent onset AF in 67 to 92% of patients within six hours and is **more effective** than procainamide, sotalol, propafenone, and amiodarone

ESH 2010

Aliot et al. Europace (2011) 13, 161-173

PROPAFENONE

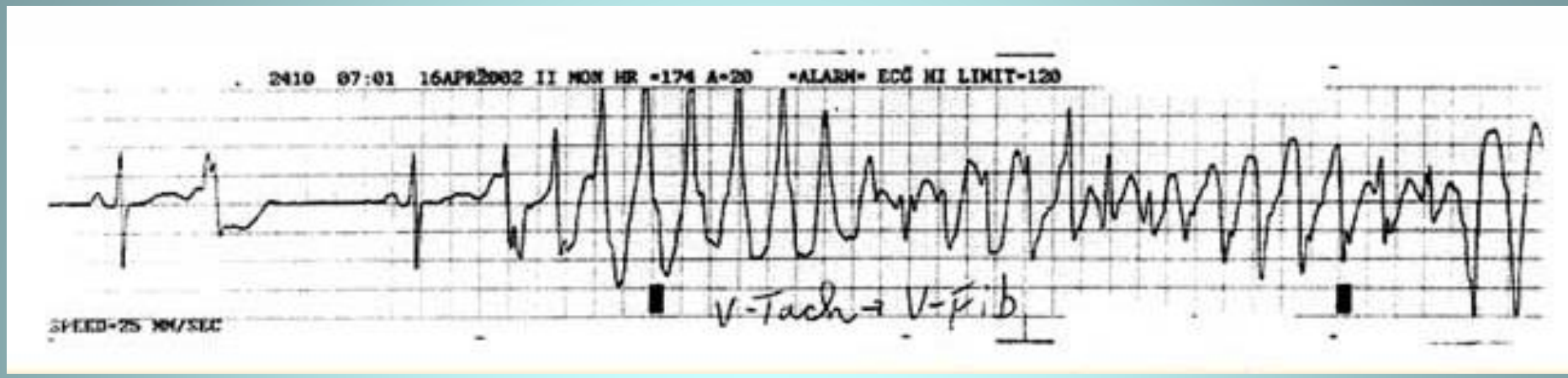
- Significantly more effective in paroxysmal as opposed to persistent AF
- Not suggest using propafenone in patients with structural heart disease, particularly those with *left ventricular systolic dysfunction and those with coronary artery disease*
- Within a few hours, expected convertion rates was *41-91% after i.v*, time 30 min-2h.
- *Oral propafenone* can be given as a large dose of 450 to 600 mg, conversion 2-6h.

ESH 2010

IBOUTILIDE

- Available only as an intravenous preparation (1 mg over 10 minutes and potentially repeated once after 20 minutes)
- Prolong repolarization and the QT interval
- In patients with structural heart disease (but without heart failure).
- The acute AF conversion rate is 28 to 51 %
- Arrhythmia conversion occurred within a mean of *27 to 33* minutes after the start of the infusion
- Do not use ibutilide in combination with other antiarrhythmic medications

ESH 2010

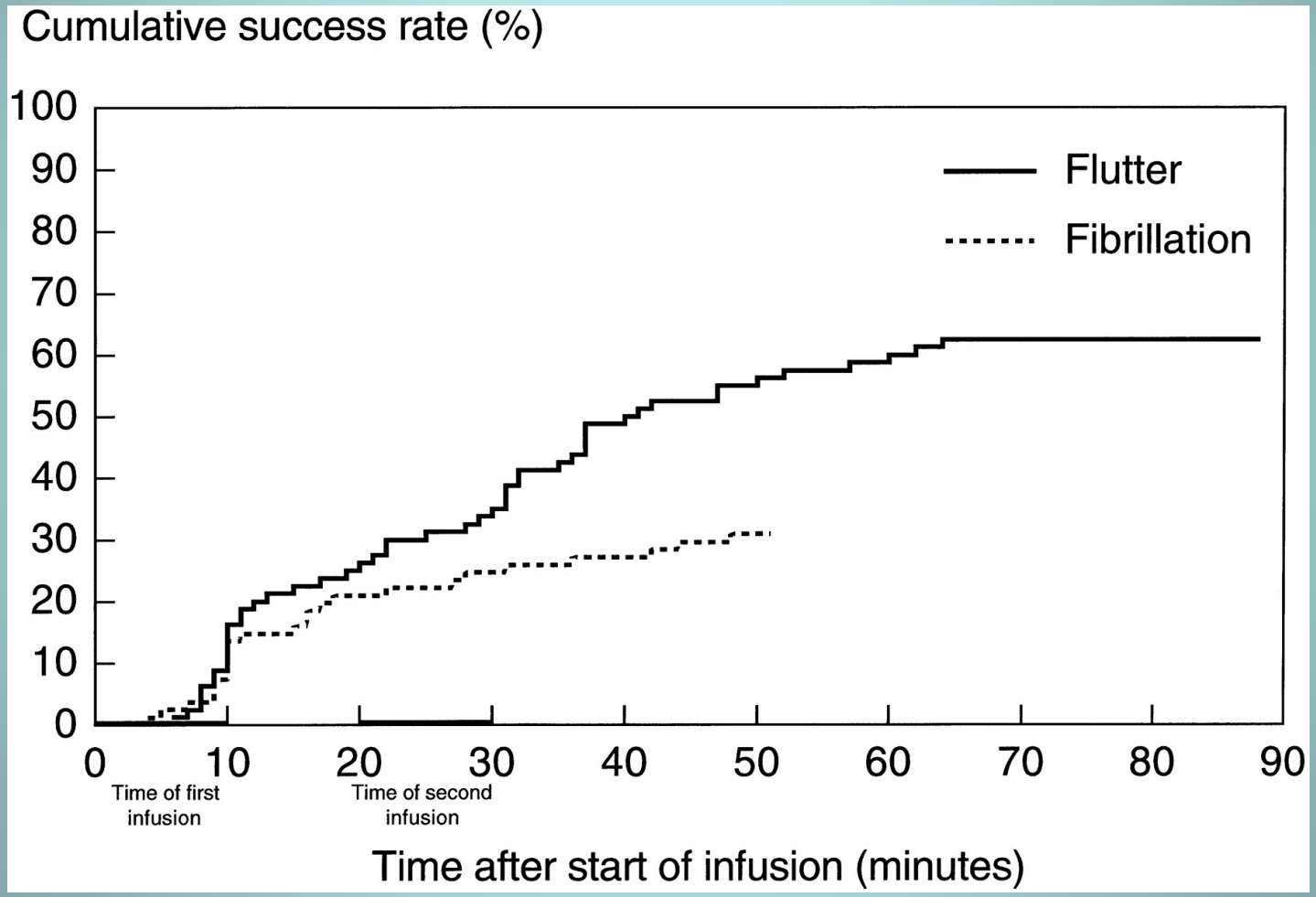


In four large series, the rate of torsade de pointes ranged between 3.6 and 8.3 percent

continuous electrocardiogram monitoring for at least four hours after the infusion or until the QTc interval has returned to baseline

Cardioversion of atrial flutter and fibrillation after ibutilide infusion

(67 y/o, 15 days duration, half with prior episode)



Stambler Circulation. 1996;94:1613-1621

DOFETILIDE

- Primarily been studied for the medical conversion of persistent AF
- Its principle use is to help maintain sinus rhythm, rather than to be used for cardioversion.
- Successfully in patients with structural heart disease
- Rarely used solely for the purpose of cardioversion, prior to anticipated DC cardioversion
- SAFIRE-D study, 500 µg twice daily , incidence of torsade was 1.2 percent

Safire –D study , Circulation,2000

AMIODARONE

- Cardioversion with either intravenous or oral amiodarone ***is not*** particularly effective and occurs several hours later than with flecainide, propafenone, ibutilide, and vernakalant

- Intravenous amiodarone may be more effective in converting AF after it has been given for hours and days
- Oral amiodarone requires long-term loading and is effective in converting about 25% of patients with persistent AF to sinus rhythm after six weeks of loading

- Have value before cardioversion in patients who will receive the drug long term for maintenance and may be considered as adjunctive therapy to increase the likelihood of successful cardioversion in patients who are known to be refractory to electrical cardioversion or in those in whom there is a concern about early relapse

VIETTI,Int.J.Card,1992

Φαρμακολογική Καρδιο-ανάταξη

CARDIOME PHARMA CORP

1. Φάρμακα ***χωρίς*** καμία δράση !

Digoxin	Καμία δράση
Verapamil	Καμία δράση
Sotalol	One study: placebo versus 2 dosages of sotalol: conversion rates 14%, 11%, 13% (ns).
β-blockers	metoprolol, atenolol, carvedilol, bisoprolol, propranolol, timolol and esmolol: no effect/no reports
Ajmaline	Έλλειψη στοιχείων

2. Φάρμακα ***με αποδεδειγμένη*** δράση ?

DAAF trial group: (1997) Eur Heart J, 18, 649-54.
Jordaens L, et al: (1997) Eur Heart J, 18, 643-8.
Bianconi L, et al: (1998) Am J Cardiol, 82, 584-8.
Suttorp MJ, et al: (1989) Am J Cardiol, 63, 693-6.
Platia EV, et al: (1989) Am J Cardiol, 63, 925-9.
Gang RV, et al: (Sotalol Multicenter Study Grp 1995): Am Heart J, 129, 739-48.
Rehnqvist N: (1981) Ann Clin Res, 13 Suppl 30, 68-72.

Flecainide is highly effective in the acute cardioversion of AF

Meta-analysis of acute conversion of AF studies

	Conversion rate	No. of studies
Quinidine	11-86%	(n=6)
Procainamide	63%	(n=1)
Disopyramide	23%	(n=1)
Flecainide	**52-95%**	**(n=8)**
Propafenone	6-91%	(n=15)
Amiodarone	25-92%	(n=6)
Sotalol	8-52%	(n=3)
Ibutilide	10-49%	(n=3)
Control treatment	0-76%	(n=25)

McNamara et al., 2001

Vernakalant – Μηχανισμός Δράσης

- **Αντιαρρυθμικός παράγοντας που δρα εκλεκτικά στους κόλπους για να παρατείνει την κολπική ανερεθιστότητα και να επιβραδύνει την αγωγιμότητα των ώσεων με συχνο-εξαρτώμενο τρόπο**
- Η εκλεκτική δράση στους κόλπους αποδείχτηκε σε προ-κλινικές μελέτες όπου υπήρξε:
  - Αποκλεισμός των συγκεκριμένων I_{Kur} and I_{KAch} ρευμάτων καλίου στους κόλπους
  - Χρόνο και Ηλεκτρο – εξαρτώμενος αποκλεισμός ρευμάτων Νατρίου επικεντρώνει την δράση του φαρμάκου στις υψηλές καρδιακές συχνότητες
- Πολλαπλός αποκλεισμός καναλιών K^+ and Na^+ σε όλες τις φάσεις του δυναμικού δράσης των κόλπων
- Αποκλεισμός των όψιμων ρευμάτων νατρίου I_{Na}
- Κατά την κολπική μαρμαρυγή, ο αποκλεισμός των διαύλων νατρίου που εξαρτάται από τη συχνότητα και την τάση εστιάζει περαιτέρω τη δράση του φαρμάκου προς τον ταχέως ενεργοποιούμενο και μερικώς εκπολωμένο κολπικό ιστό από ότι προς την φυσιολογικώς πολωμένη κοιλία που χτυπά σε χαμηλότερους καρδιακούς ρυθμούς.
  - Μείωση της επαναπόλωσης των κοιλιών που προκαλείται από τον αποκλεισμό ρευμάτων καλίου στις κοιλίες
  - Οι εστιασμένες επιδράσεις στους κόλπους συνδυασμένες με αποκλεισμό όψιμων ρευμάτων νατρίου αποδεικνύει το χαμηλό προ-αρρυθμικό φορτίο της Βερνακαλάντης

Σύνοψη κλινικών μελετών (φάσης 3)

CARDIOME PHARMA CORP

		atients
		acebo/Control
ACT I Pivotal[1]	A	115
ACT III Pivotal[2]	A	1 (AFL: N=9)
ACT II Pivotal[3]	A	(AFL: N=4)
ACT IV[4]	A	NA
ACT V	A	68
AVRO Pivotal[5]	A	(amiodarone)

AF = atrial fibrillatio

ACT I and ACT III: Ταχεία ανάταξη ΚΜ με Vernakalant[a]

CARDIOME PHARMA CORP

Αποτελ/τα: Συνολικά στοιχεία από ACT I and ACT III[1]

CARDIOME PHARMA CORP

- Μέσος χρόνος ανάταξης: 10 λεπτά από την έναρξη της 1ης δόσης
- Στο 97% των αποκρινόμενων στην vernakalant, ο σταθερός φλεβοκομβικός ρυθμός διατηρήθηκε για τουλάχιστον 24 ώρες

1. EU Summary of Product Characteristics, BRINAVESS, MSD, 2010.

1. Roy D et al. *Circulation.* 2008;117:1518–1525; 2. Pratt CM et al. *Am J Cardiol.* 2010;106:1277–1283; 3. Kowey PR et al. *Circ Arrhythmia Electrophysiol.* 2009;2:652–659; 4. Stiell IG et al. *Am Heart J.* 2010;159:1095–1101; 5. Camm AJ et al. *J Am Coll Cardiol.* 2011;57:313–321.

Vernakalant: Incidence of Hypotension and Ventricular Arrhythmia During the First 2 Hours[1]

CARDIOME PHARMA CORP

	Placebo (%)	Vernakalant (%)
Hypotension		
All patients	5.1	7.6
Patients with CHF	4.7	16.1
-Serious/discontinuation	0	2.9
Patients without CHF	5.2	5.7
Ventricular arrhythmia		
Patients with CHF[a]	1.6	7.3
Patients without CHF	3.6	3.2

CHF = congestive heart failure

[a]These arrythmias typically presented as asymptomatic, monomorphic, non-sustained (average 3-4 beats) ventricular tachycardias

1. EU Summary of Product Characteristics, BRINAVESS, MSD, 2010.

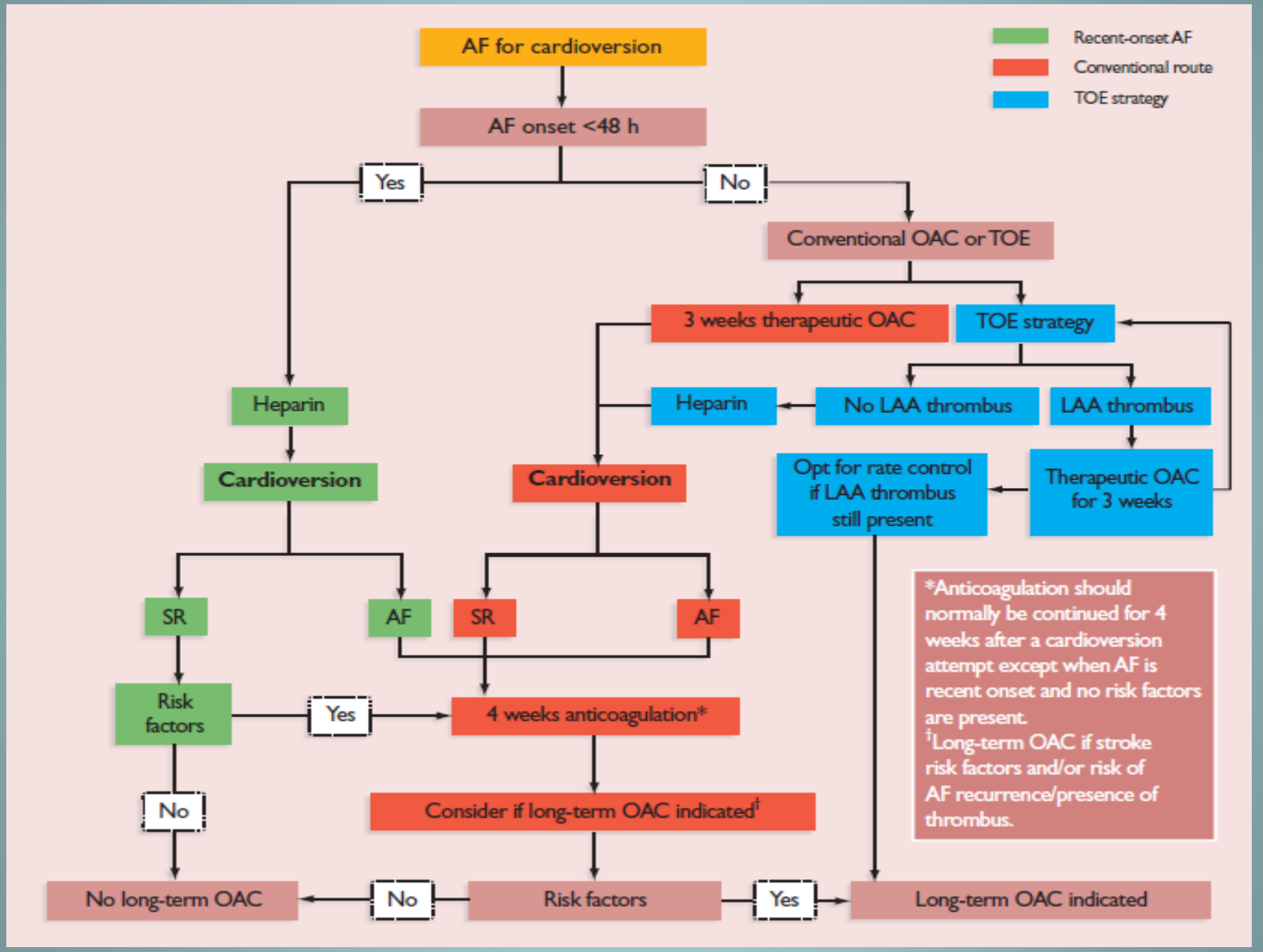
VERNAKALANT
Αντενδείξεις

Υπερευαισθησία στη δραστική ουσία

- Ασθενείς με σοβαρή στένωση της αορτής, ασθενείς με συστολική αρτηριακή πίεση < 100 mm Hg και ασθενείς με καρδιακή ανεπάρκεια κατηγορίας NYHA III και NYHA IV.
- Ασθενείς με παρατεταμένο διάστημα QT στην αρχική κατάσταση (μη διορθωμένο > 440 msec), ή σοβαρή βραδυκαρδία, δυσλειτουργία του φλεβόκομβου ή δεύτερου βαθμού και τρίτου βαθμού καρδιακό αποκλεισμό με απουσία βηματοδότη.
- Χρήση ενδοφλέβιων αντιαρρυθμικών που ελέγχουν το ρυθμό (κατηγορία I και κατηγορία III) εντός 4 ωρών πριν, καθώς και τις πρώτες 4 ώρες μετά, τη χορήγηση του
- Οξύ στεφανιαίο σύνδρομο (που περιλαμβάνει έμφραγμα του μυοκαρδίου) εντός των τελευταίων 30 ημερών.

Recommendations for direct current cardioversion

Recommendations	Class[a]	Level[b]	Ref.[c]
Immediate DCC is recommended when a rapid ventricular rate does not respond promptly to pharmacological measures in patients with AF and ongoing myocardial ischaemia, symptomatic hypotension, angina, or heart failure.	I	C	
Immediate DCC is recommended for patients with AF involving pre-excitation when rapid tachycardia or haemodynamic instability is present.	I	B	82
Elective DCC should be considered in order to initiate a long-term rhythm control management strategy for patients with AF.	IIa	B	46, 78, 83
Pre-treatment with amiodarone, flecainide, propafenone, ibutilide, or sotalol should be considered to enhance success of DCC and prevent recurrent AF.	IIa	B	79–81
Repeated DCC may be considered in highly symptomatic patients refractory to other therapy.	IIb	C	
Pre-treatment with β-blockers, diltiazem or verapamil may be considered for rate control, although the efficacy of these agents in enhancing success of DCC or preventing early recurrence of AF is uncertain.	IIb	C	
DCC is contraindicated in patients with digitalis toxicity.	III	C	


Recent-onset AF
Conventional route
TOE strategy
AF for cardioversion
AF onset <48 h
Yes
No
Conventional OAC or TOE
3 weeks therapeutic OAC
TOE strategy
Heparin
Heparin
No LAA thrombus
LAA thrombus
Cardioversion
Cardioversion
Opt for rate control if LAA thrombus still present
Therapeutic OAC for 3 weeks
SR
AF
SR
AF
Risk factors
Yes
4 weeks anticoagulation*
No
Consider if long-term OAC indicated†
No long-term OAC
No
Risk factors
Yes
Long-term OAC indicated
*Anticoagulation should normally be continued for 4 weeks after a cardioversion attempt except when AF is recent onset and no risk factors are present.
†Long-term OAC if stroke risk factors and/or risk of AF recurrence/presence of thrombus.

D.C.CARDIOVERSION

- The overall immediate success rate of DC cardioversion is greater than 90 %
- Commonly performed procedure with a high success rate and a low complication rate when performed by experienced clinicians.

- Synchronized DC cardioversion Biphasic shock should be performed while the patient is under the influence of procedural sedation

- Anteroposterior placement of electrodes more effective than anteriolateral.

- Arrhythmic complications — Bradyarrhythmias are occasionally seen after DC cardioversion; ventricular tachyarrhythmias are rare.
- 1-2% risk of thrombo-embolism

ESH 2010

RECURRENCE after DCC

- Immediate, within the first few minutes
- Early, during the first five days
- Late.

- Age
- AF duration before DCC
- Number of previous reccurences
- LA size, LA function
- Presence of Coronary disease,pulmonary,mitral disease
- Atrial ectopic beats

The recurrence rate of AF is high, particularly without maintenance antiarrhythmic therapy

DC cardioversion may be repeated if AF recurs acutely in patients who have not been pretreated with antiarrhythmic therapy

The combination of an atrioventricular (AV) nodal blocker plus intravenous loading with amiodarone, ibutilide, oral flecainide, sotalol, or propafenone may restore SR pharmacologically

Less than 14 % of patients remain in SR for a prolonged period after a third cardioversion

Tieleman,et all,J Am CollCard,1998 Bertaglia, Eur Heart J 2002

Advantages and Disadvantages

Electrical

- More effective (90%)
- Quick
- One procedure with TEE
- Cardioversion itself safe

Pharmacological

Works well for recent onset

Avoid sedation

Screen for a proarrhythmic response

AF may convert to atrial flutter, permit rapid one-to-one AV conduction, class IA,IC

CONCLUSIONS I

- Direct current cardioversion is the primary conversion strategy
- Pretreatment with amiodarone, flecainide, propafenone, ibutilide, or sotalol should be considered to enhance success and prevent recurrent AF

CONCLUSIONS II

When pharmacologic therapy is preferred to electrical cardioversion

- For those without structural heart disease: intravenous flecainide or propafenone or vernakalant or ibutilide

  A single, high oral dose of flecainide or propafenone may be considered

- For those with structural heart disease,

  intravenous amiodarone is preferred


ΕΥΧΑΡΙΣΤΩ ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ