Atrial fibrillation: new patho-physiological concepts and novel pharmacological approaches:

Update on rate control strategies which are the real targets?

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ESC GUIDELINES

Guidelines for the management of atrial fibrillation

The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)

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

Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS)

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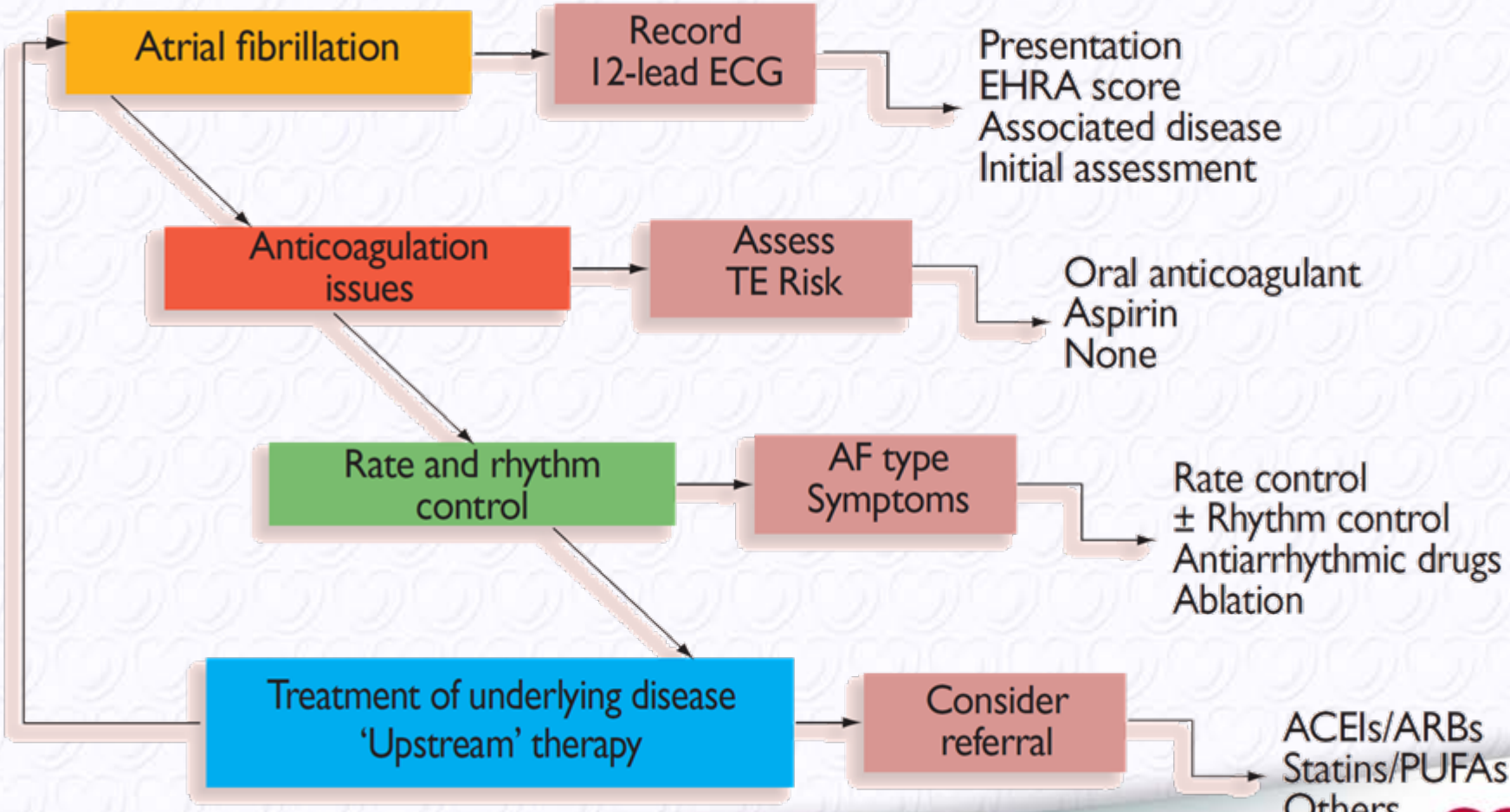
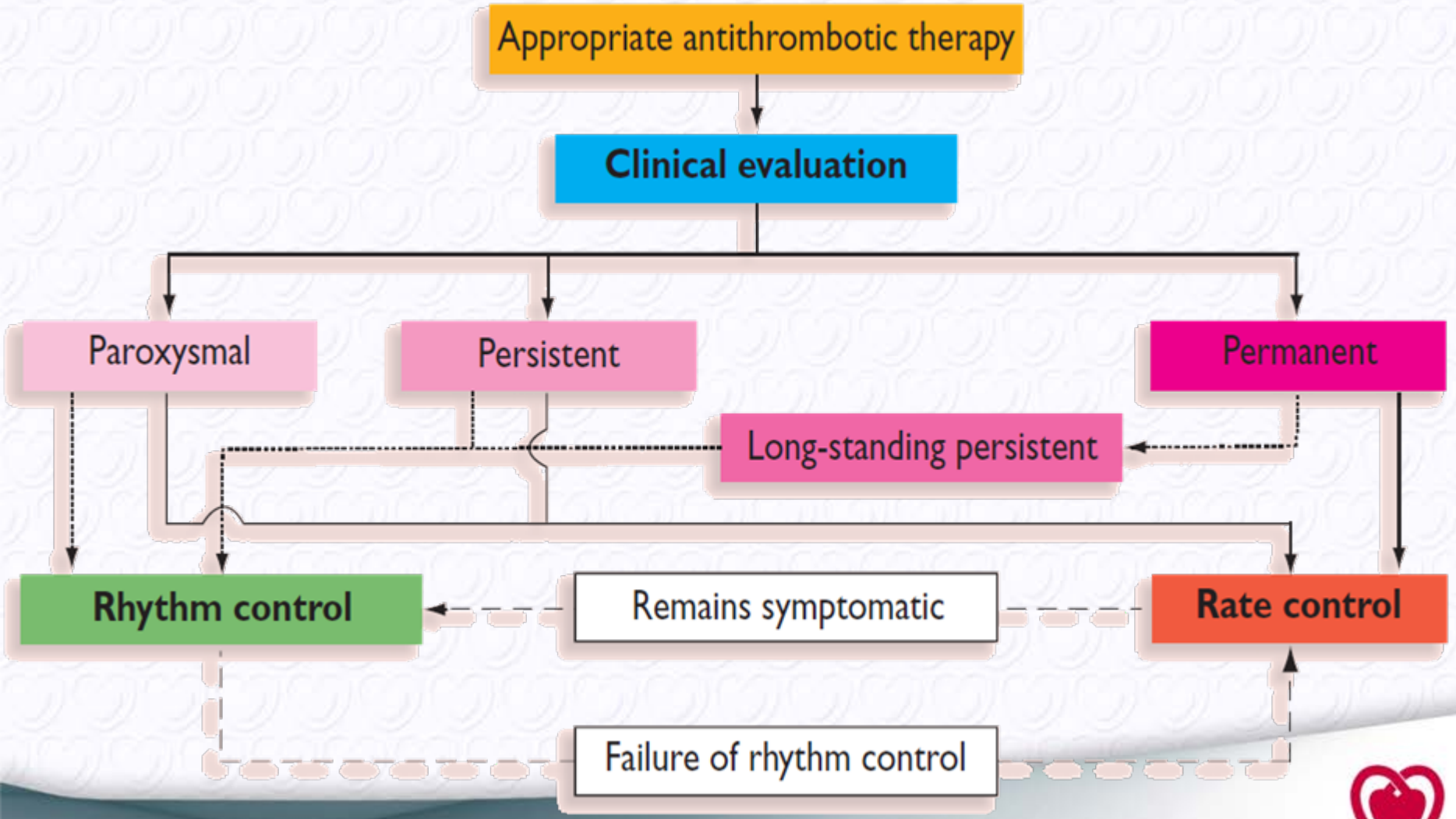
Principles of Management



EUROPEAN SOCIETY OF CARDIOLOGY®

Rate and Rhythm Control



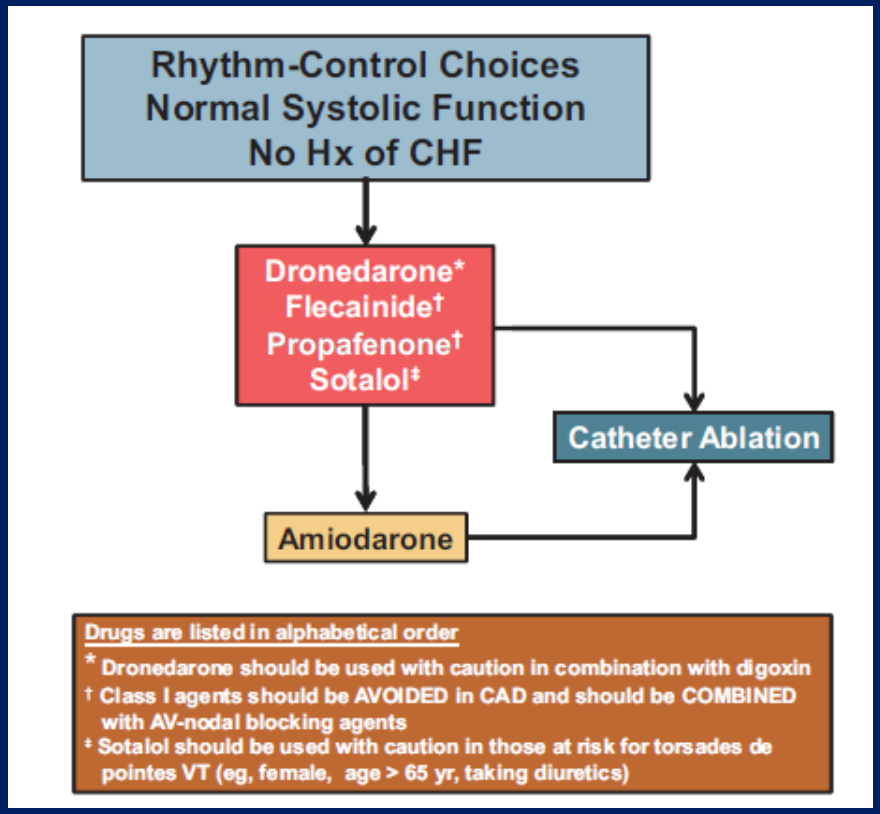
Principles of Antiarrhythmic Drug Therapy to Maintain Sinus Rhythm

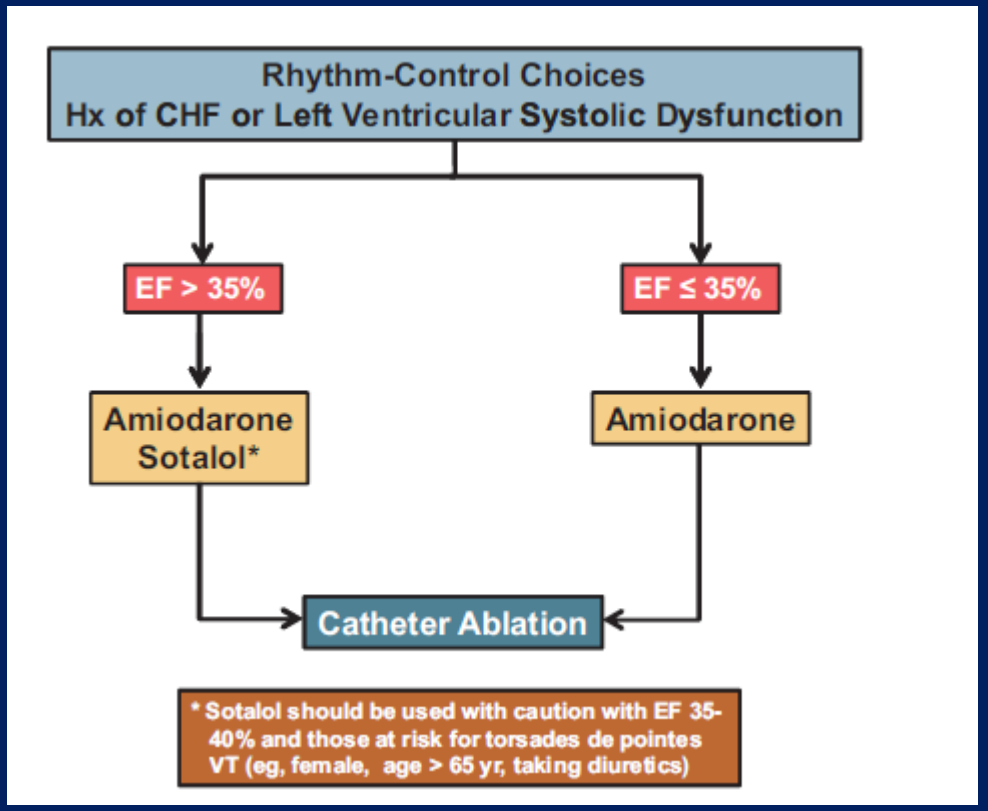
1. Treatment is motivated by attempts to reduce AF-related symptoms
2. Efficacy of antiarrhythmic drugs to maintain sinus rhythm is modest
3. Clinically successful antiarrhythmic drug therapy may reduce rather than eliminate recurrence of AF
4. If one antiarrhythmic drug 'fails' a clinically acceptable response may be achieved with another agent
5. Drug-induced proarrhythmia or extra-cardiac side-effects are frequent
6. Safety rather than efficacy considerations should primarily guide the choice of antiarrhythmic agent

Canadian Journal of Cardiology 28 (2012) 125–136

Society Guidelines

Focused 2012 Update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines: Recommendations for Stroke Prevention and Rate/Rhythm Control





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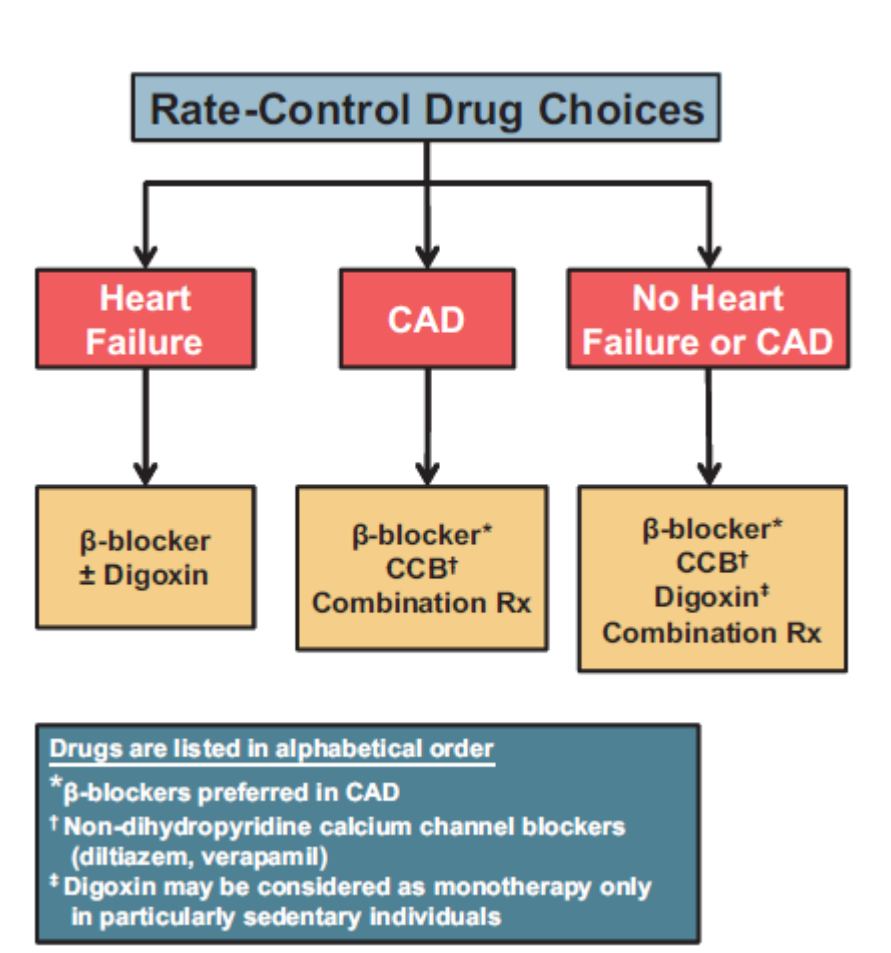


Table 13 General characteristics of rhythm control and rate control trials in patients with AF[86–92]

Trial	Ref	Patients (*n*)	Mean age (years)	Mean follow-up (years)	Inclusion criteria	Primary outcome parameter	Patients reaching primary outcome (*n*)		
							Rate control	Rhythm control	*P*
PIAF (2000)	92	252	61.0	1.0	Persistent AF (7–360 days)	Symptomatic improvement	76/125 (60.8%)	70/127 (55.1%)	0.32
AFFIRM (2002)	86	4060	69.7	3.5	Paroxysmal AF or persistent AF, age ≥65 years, or risk of stroke or death	All-cause mortality	310/2027 (25.9%)	356/2033 (26.7%)	0.08
RACE (2002)	87	522	68.0	2.3	Persistent AF or flutter for <1 years and 1–2 cardioversions over 2 years and oral anticoagulation	Composite: cardiovascular death, CHF, severe bleeding, pacemaker implantation, thrombo-embolic events, severe adverse effects of antiarrhythmic drugs	44/256 (17.2%)	60/266 (22.6%)	0.11
STAF (2003)	88	200	66.0	1.6	Persistent AF (>4 weeks and <2 years), LA size >45 mm, CHF NYHA II–IV, LVEF <45%	Composite: overall mortality, cerebrovascular complications, CPR, embolic events	10/100 (10.0%)	9/100 (9.0%)	0.99
HOT CAFÉ (2004)	89	205	60.8	1.7	First clinically overt persistent AF (≥7 days and <2 years), age 50–75 years	Composite: death, thrombo-embolic events; intracranial/major haemorrhage	1/101 (1.0%)	4/104 (3.9%)	>0.71
AF-CHF (2008)	90	1376	66	3.1	LVEF ≤35%, symptoms of CHF, history of AF (≥6 h or DCC <last 6 months)	Cardiovascular death	175/1376 (25%)	182/1376 (27%)	0.59
J-RHYTHM (2009)	91	823	64.7	1.6	Paroxysmal AF	Composite of total mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalization for heart failure, or physical/ psychological disability	89/405 (22.0%)	64/418 (15.3%)	0.012

AF = atrial fibrillation; AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management; CHF = congestive heart failure; CPR = cardiopulmonary resuscitation; DCC = direct current cardioversion; HOT CAFÉ = How to Treat Chronic Atrial Fibrillation; J-RHYTHM = Japanese Rhythm Management Trial for Atrial Fibrillation; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PIAF = Pharmacological Intervention in Atrial Fibrillation; RACE = RAte Control versus Electrical cardioversion for persistent atrial fibrillation; STAF = Strategies of Treatment of Atrial Fibrillation.

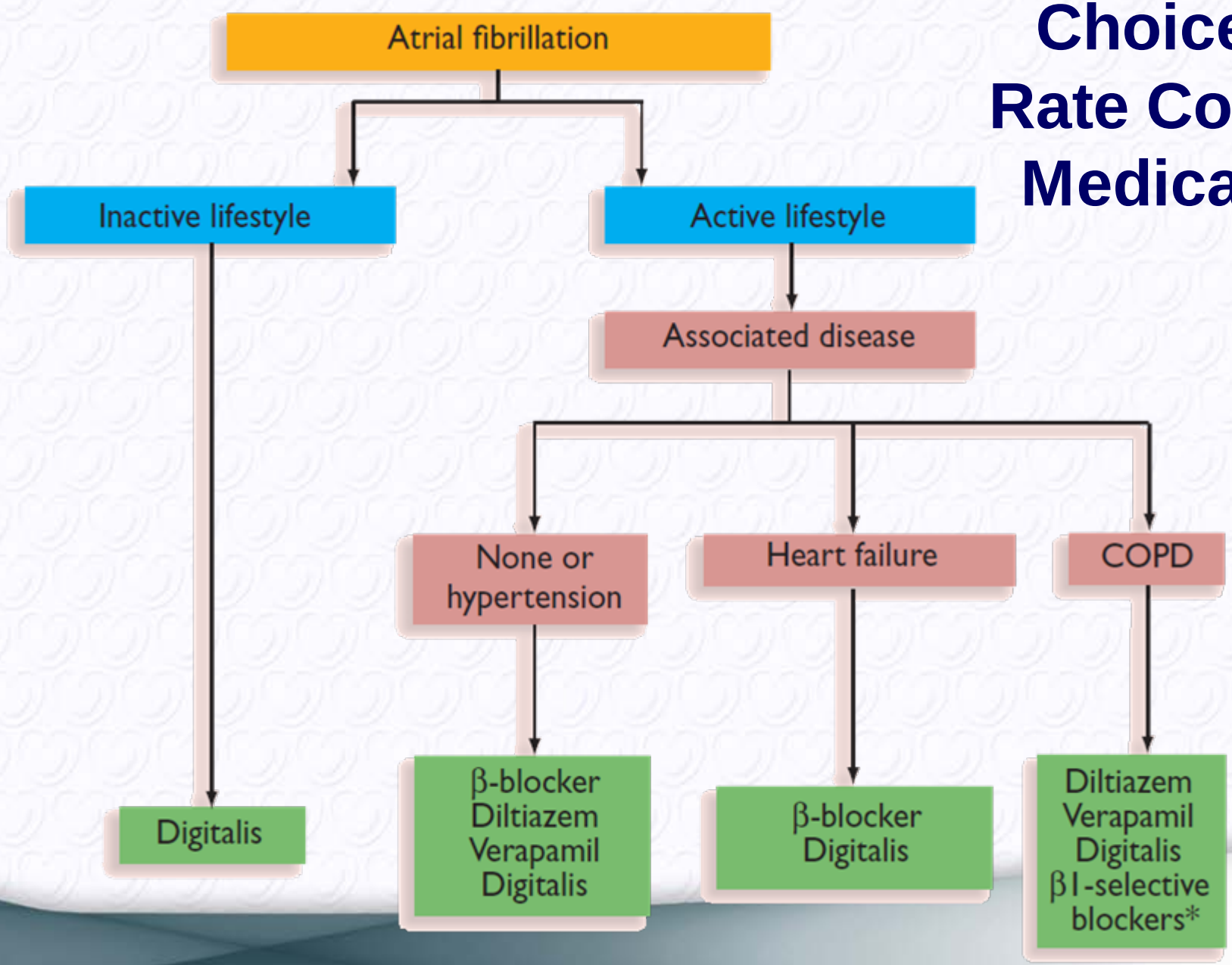
Table 14 Comparison of adverse outcomes in rhythm control and rate control trials in patients with AF

Trial	Ref	Deaths from all causes (in rate/rhythm)	Deaths from cardiovascular causes	Deaths from non-cardiovascular causes	Stroke	Thrombo-embolic events	Bleeding
PIAF (2000)	92	4	1/1	1[a]	ND	ND	ND
AFFIRM (2002)	86	666 (310/356)	167/164	113/165	77/80	ND	107/96
RACE (2002)	87	36	18/18	ND	ND	14/21	12/9
STAF (2003)	88	12 (8/4)	8/3	0/1	1/5	ND	8/11
HOT CAFÉ (2004)	89	4 (1/3)	0/2	1/1	0/3	ND	5/8
AF-CHF (2008)	90	228/217	175/182	53/35	11/9	ND	ND

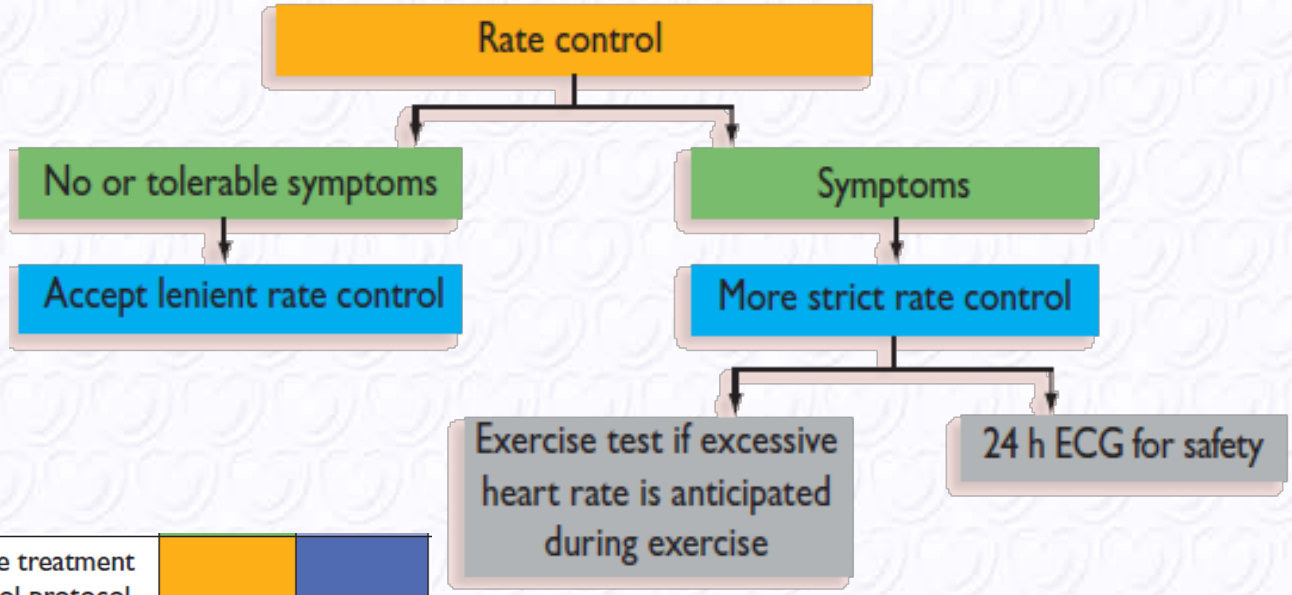
[a]Total number of patients not reported.

AF = atrial fibrillation; AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management; HOT CAFÉ = HOw to Treat Chronic Atrial Fibrillation; ND = not determined; PIAF = Pharmacological Intervention in Atrial Fibrillation; RACE = RAte Control versus Electrical cardioversion for persistent atrial fibrillation; STAF = Strategies of Treatment of Atrial Fibrillation.

Choice of Rate Control Medication



Optimal Rate Control



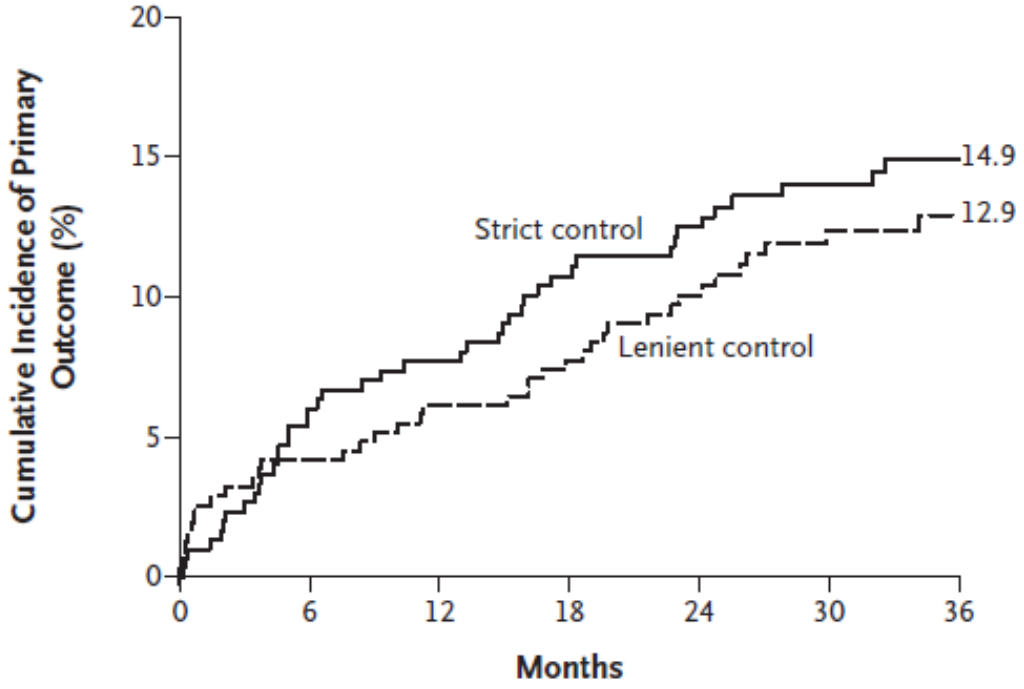
It is reasonable to initiate treatment with a lenient rate control protocol aimed at a resting heart rate <110 bpm.	IIa	B
It is reasonable to adopt a stricter rate control strategy when symptoms persist or tachycardiomyopathy occurs, despite lenient rate control: resting heart rate <80 bpm and heart rate during moderate exercise <110 bpm. After achieving the strict heart rate target, a 24 h Holter monitor is recommended to assess safety.	IIa	B

In patients who experience symptoms related to AF during activity, the adequacy of rate control should be assessed during exercise, and therapy should be adjusted to achieve a physiological chronotropic response and to avoid bradycardia.	I	C

Lenient versus Strict Rate Control in Patients with Atrial Fibrillation

Van Gelder et al, NEJM 2010

Characteristic	Lenient Rate Control (N=311)	Strict Rate Control (N=303)	Total Population (N=614)
Rate-control medications in use — no. (%)			
None	36 (11.6)	27 (8.9)	63 (10.3)
Beta-blocker alone	140 (45.0)	136 (44.9)	276 (45.0)
Verapamil or diltiazem alone	18 (5.8)	19 (6.3)	37 (6.0)
Digoxin alone	20 (6.4)	24 (7.9)	44 (7.2)
Beta-blocker and either verapamil or diltiazem	7 (2.3)	11 (3.6)	18 (2.9)
Beta-blocker and digoxin	53 (17.0)	49 (16.2)	102 (16.6)
Digoxin and either verapamil or diltiazem	14 (4.5)	14 (4.6)	28 (4.6)
Beta-blocker, digoxin, and either verapamil or diltiazem	2 (0.6)	5 (1.7)	7 (1.1)
Sotalol	18 (5.8)	13 (4.3)	31 (5.0)
Amiodarone	3 (1.0)	5 (1.7)	8 (1.3)
Echocardiographic variables			
Left atrial size, long axis — mm	46±6	46±7	46±7
Left ventricular end-diastolic diameter — mm	51±7	51±8	51±7
Left ventricular end-systolic diameter — mm	36±8	36±9	36±8
Left ventricular ejection fraction — %	52±11	52±12	52±12
Left ventricular ejection fraction ≤40% — no. (%)	45 (14.5)	48 (15.8)	93 (15.1)



No. at Risk

Strict control	303	282	273	262	246	212	131
Lenient control	311	298	290	285	255	218	138

Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of the Primary Outcome, According to Treatment Group.

The numbers at the end of the Kaplan–Meier curves are the estimated cumulative incidence of the primary outcome at 3 years.

Van Gelder et al, NEJM 2010

Table 3. Cumulative Incidence of the Composite Primary Outcome and Its Components during the 3-Year Follow-up Period, According to Treatment Group.*

Outcome	Lenient Rate Control (N=311)	Strict Rate Control (N=303)	Hazard Ratio (90% CI)
	no. of patients (%)		
Composite primary outcome	38 (12.9)	43 (14.9)	0.84 (0.58–1.21)
Individual components			
Death from cardiovascular cause	9 (2.9)	11 (3.9)	0.79 (0.38–1.65)
From cardiac arrhythmia	3 (1.0)	4 (1.4)	
From cardiac cause other than arrhythmia	1 (0.3)	2 (0.8)	
From noncardiac vascular cause	5 (1.7)	5 (1.9)	
Heart failure	11 (3.8)	11 (4.1)	0.97 (0.48–1.96)
Stroke	4 (1.6)	11 (3.9)	0.35 (0.13–0.92)
Ischemic	3 (1.3)	8 (2.9)	
Hemorrhagic	1 (0.3)	4 (1.5)	
Systemic embolism	1 (0.3)	0	
Bleeding	15 (5.3)	13 (4.5)	1.12 (0.60–2.08)
Intracranial	0	3 (1.0)	
Extracranial	15 (5.3)	10 (3.5)	
Syncope	3 (1.0)	3 (1.0)	
Life-threatening adverse effect of rate-control drugs	3 (1.1)	2 (0.7)	
Sustained ventricular tachycardia or ventricular fibrillation	0	1 (0.3)	
Cardioverter–defibrillator implantation	0	1 (0.3)	
Pacemaker implantation	2 (0.8)	4 (1.4)	

Van Gelder et al, NEJM 2010

Effect of Lenient Versus Strict Rate Control on Cardiac Remodeling in Patients With Atrial Fibrillation

Data of the RACE II (RAte Control Efficacy in permanent atrial fibrillation II) Study

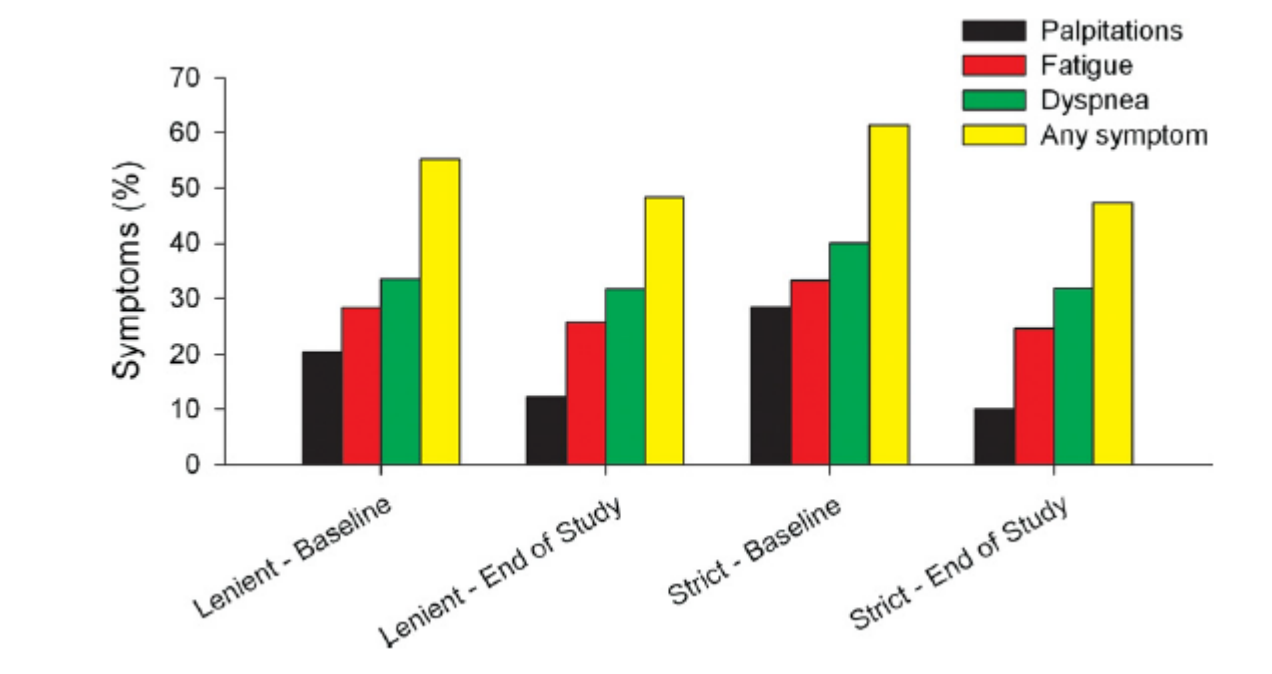
Clinical Factors Associated With Changes in Echocardiographic Parameters

Change in LV end-diastolic diameter, mm				
Lenient rate control	1.1 (−0.8 to 3.0)	0.24	1.0 (−0.8 to 2.8)	0.27
Age	0.1 (0 to 0.2)	0.03		
Female	5.8 (3.9 to 7.6)	<0.0001	6.5 (4.6 to 8.4)	<0.0001
Duration of any AF	0 (−0.1 to 0)	0.82		
Valvular heart disease	−1.9 (−4.2 to 0.4)	0.10	−3.8 (−6.0 to −1.5)	0.001
Previous heart failure hospitalization	−4.7 (−7.8 to −1.6)	0.003	−3.9 (−6.9 to −0.8)	0.01
Body mass index, kg/m^2	−0.3 (−0.5 to −0.1)	0.007	−0.3 (−0.5 to −0.1)	0.004
QRS duration, 5 ms	−0.4 (−0.7 to −0.2)	0.001		
Creatinine, 10 μmol/l	−0.3 (−0.8 to 0.1)	0.10		
Verapamil/diltiazem	1.6 (−0.5 to 3.8)	0.13		
Digoxin	−1.6 (−3.4 to 0.3)	0.10		
RAAS inhibitor	−3.3 (−5.2 to −1.5)	<0.0001	−2.8 (−4.6 to −0.9)	0.003
Change in heart rate	0 (0 to 0)	0.80		

Smit et al, JACC 2011

The Effect of Rate Control on Quality of Life in Patients With Permanent Atrial Fibrillation

Data From the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) Study



Groenveld et al, JACC 2011

2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management

6.2. The cardiac resynchronization therapy patient with atrial fibrillation

In patients with atrial fibrillation, it is imperative to ensure a high rate of biventricular pacing for the patient to extract maximum benefit from CRT. Unlike in NSR, in atrial fibrillation patients this task may be challenging. **Relying on the per cent biventricular pacing data stored in the CRT device may be misleading** as these rates would include fusion and pseudo-fusion between pacing from the device and conduction through the patient's intrinsic conduction system. This is one of the reasons implicated in the improved outcomes of CRT patients with atrial fibrillation with AV nodal ablation compared to rate control with medications. [238] Other mechanisms implicated in the improved outcomes after AV ablation include more complete rate control and regularization without the need for medications that may induce fatigue and tiredness and exacerbate other symptoms of heart failure.[329]

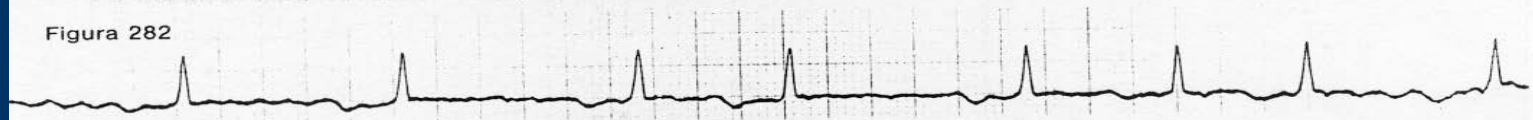
Heart Rhythm 2012

Recommendation for atrioventricular node ablation in AF patients

Recommendations	Class[a]	Level[b]	Ref.[c]
Ablation of the AV node to control heart rate should be considered when the rate cannot be controlled with pharmacological agents and when AF cannot be prevented by antiarrhythmic therapy or is associated with intolerable side effects, and direct catheter-based or surgical ablation of AF is not indicated, has failed, or is rejected.	IIa	B	106,107
Ablation of the AV node should be considered for patients with permanent AF and an indication for CRT (NYHA functional class III or ambulatory class IV symptoms despite optimal medical therapy, LVEF ≤35%, QRS width ≥130 ms).	IIa	B	105, 108–110
Ablation of the AV node should be considered for CRT non-responders in whom AF prevents effective biventricular stimulation and amiodarone is ineffective or contraindicated.	IIa	C	
In patients with any type of AF and severely depressed LV function (LVEF ≤35%) and severe heart failure symptoms (NYHA III or IV), biventricular stimulation should be considered after AV node ablation.	IIa	C	
Ablation of the AV node to control heart rate may be considered when tachycardia-mediated cardiomyopathy is suspected and the rate cannot be controlled with pharmacological agents, and direct ablation of AF is not indicated, has failed, or is rejected.	IIb	C	
Ablation of the AV node with consecutive implantation of a CRT device may be considered in patients with permanent AF, LVEF ≤35%, and NYHA functional class I or II symptoms on optimal medical therapy to control heart rate when pharmacological therapy is insufficient or associated with side effects.	IIb	C	
Catheter ablation of the AV node should not be attempted without a prior trial of medication, or catheter ablation for AF, to control the AF and/or ventricular rate in patients with AF.	III	C	

Different ventricular response during AF

Figura 282

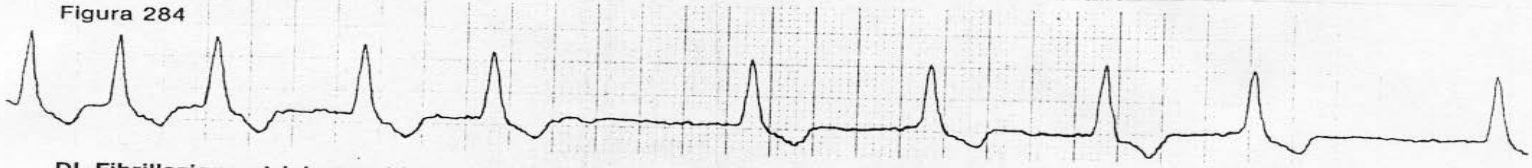


V1. Fibrillazione atriale. Non vi sono onde P e la linea di base è irregolare. I QRS hanno durata normale (0,07 sec). La frequenza ventricolare è variabile (cioè, l'intervallo R-R è variabile) con una frequenza media lenta (circa 42 battiti/min).

Figura 283

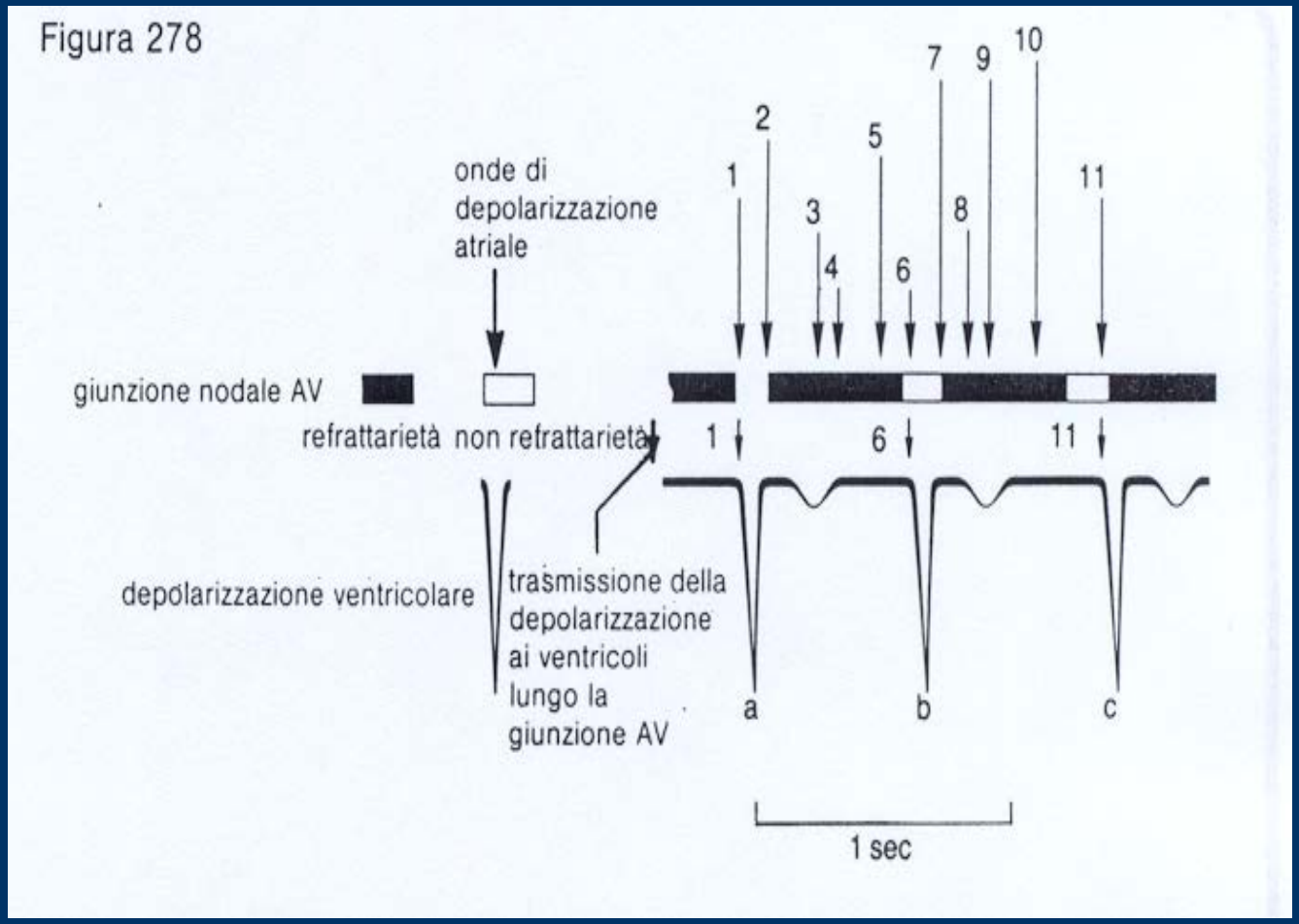
DII. Fibrillazione atriale. Non vi sono onde P e la linea di base è irregolare. I QRS mostrano una morfologia normale. L'intervallo R-R è variabile con una frequenza ventricolare media molto lenta. Il quadro è chiaramente indicativo di una disfunzione del nodo AV. È possibile che la depressa funzione del nodo AV sia causata da una condizione patologica, da farmaci o da una combinazione di questi fattori.

Figura 284

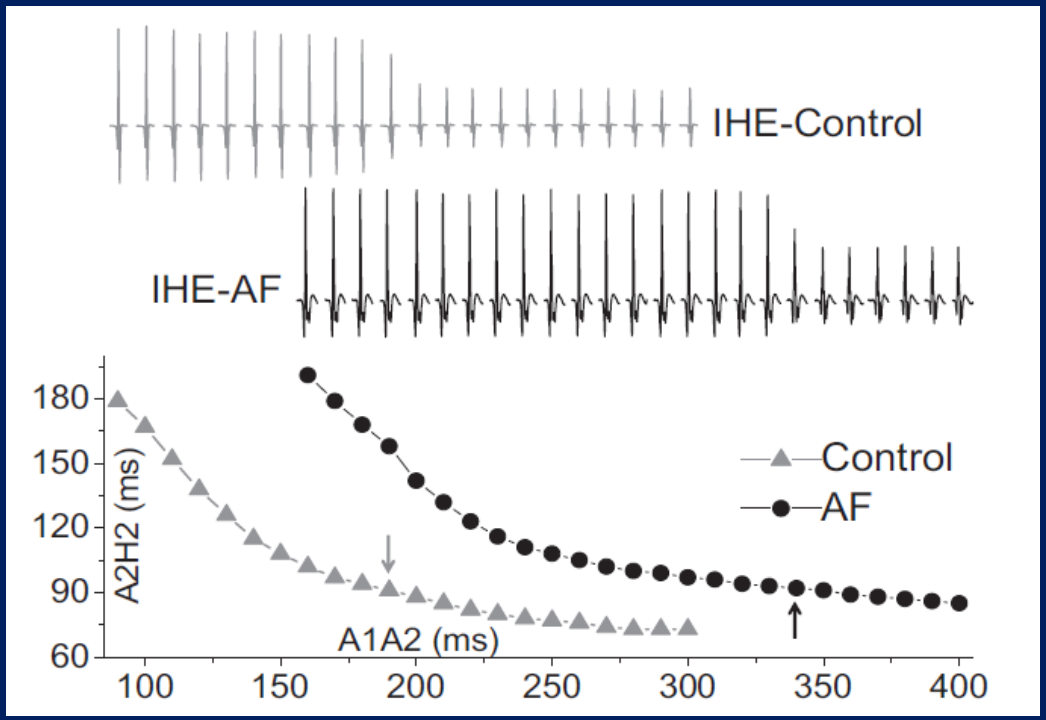


DI. Fibrillazione atriale con blocco di branca sinistra. Non vi sono onde P e la linea di base è irregolare. La frequenza ventricolare è irregolare. Tutti i QRS (e i loro corrispondenti S-T e T) mostrano una morfologia del tipo blocco di branca sinistra.

The AV node is subjected to the impact of atrial impulses during AF which leads to summation and/or cancellation of wave-fronts in AV node and, accordingly, a high level of disorganization of the penetrating impulses. Different properties such as intrinsic refractoriness of the AV node and concealed conduction determine the characteristics of the ventricular response. The existence of two pathways through the AV node, each with different electrophysiological properties, also affect ventricular response.



Atrioventricular node functional remodeling induced by atrial fibrillation



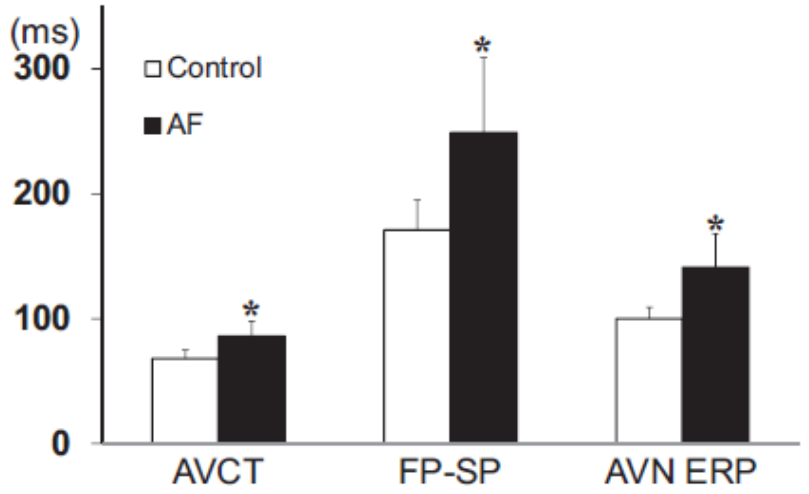


Figure 3 Basic atrioventricular node (AVN) conduction time (AVCT), the prematurities at which a transition from fast-pathway (FP) to slow-pathway (SP) conduction occurred (FP-SP), and AVN effective refractory period (AVN ERP) in the control and atrial fibrillation (AF) rabbit groups. *$P < .01$.

Zhang & Mazgalev, Heart Rhythm 2012

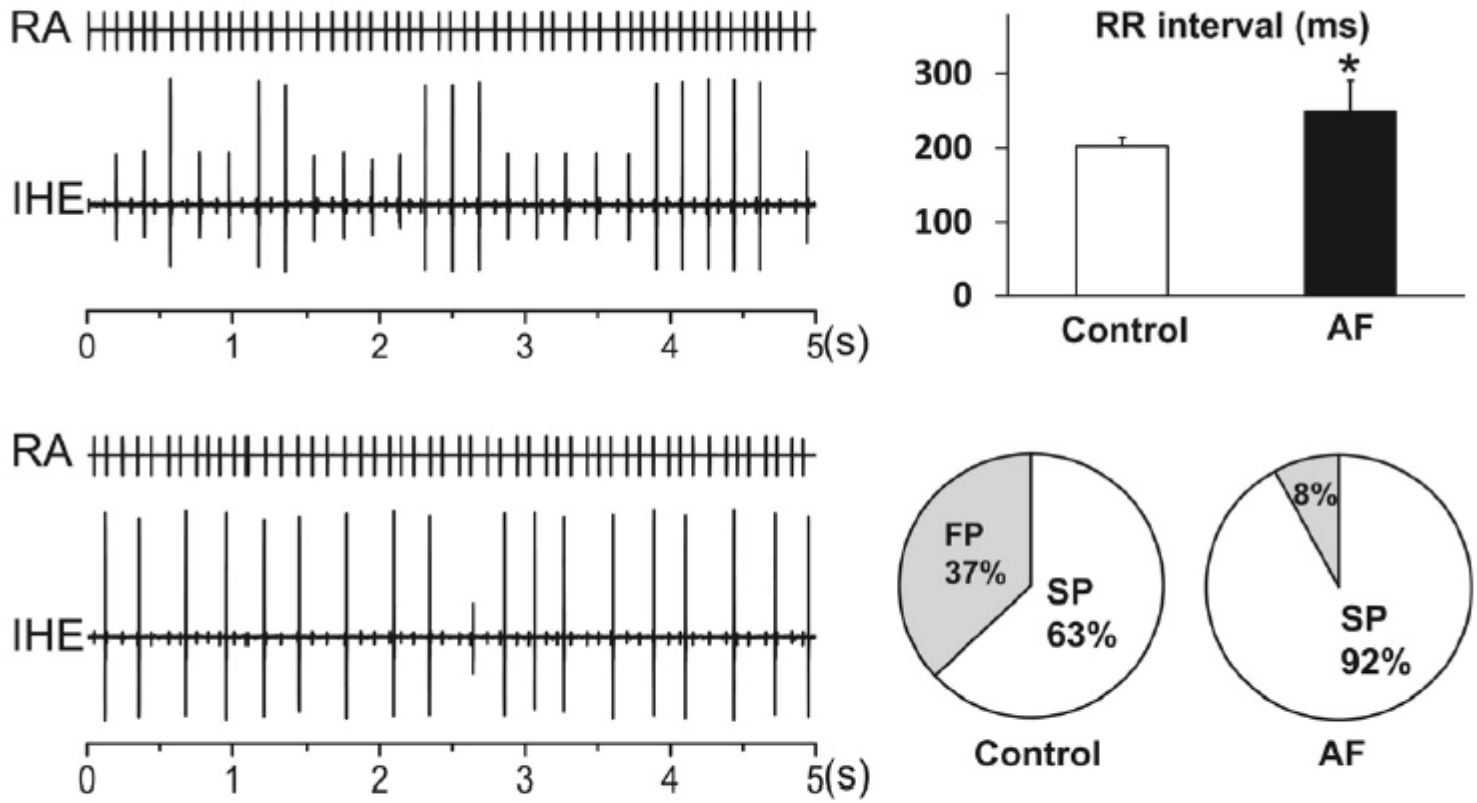
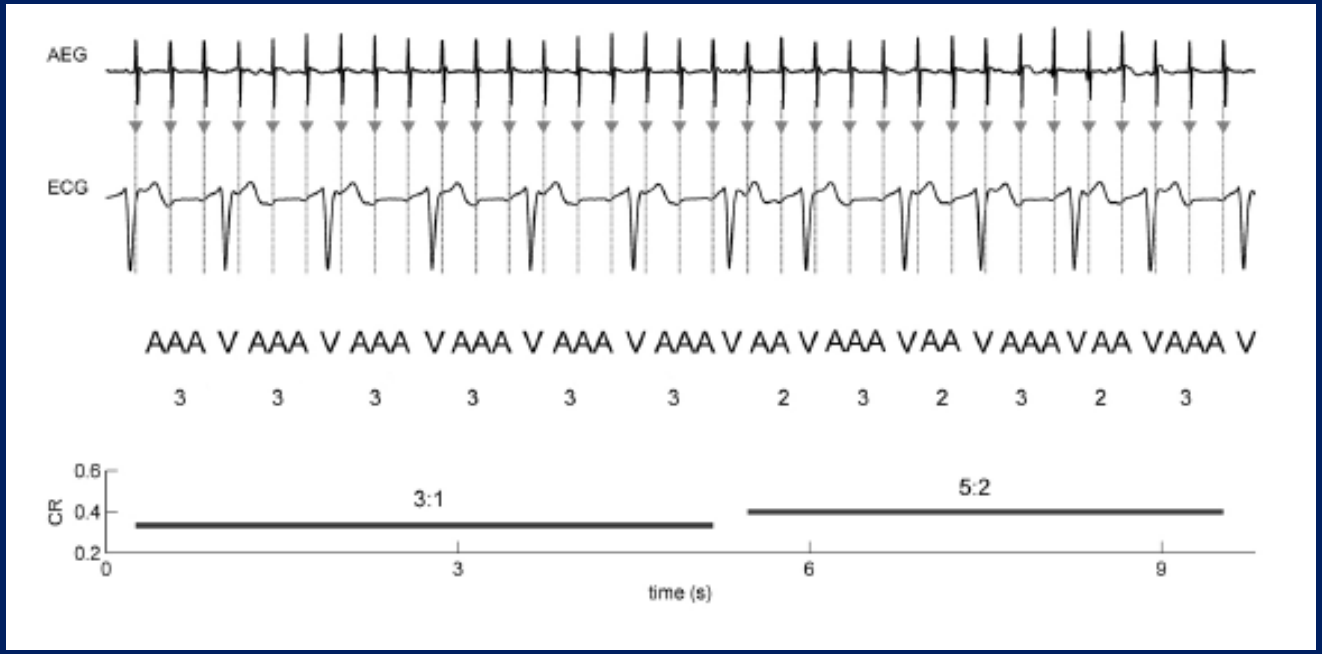
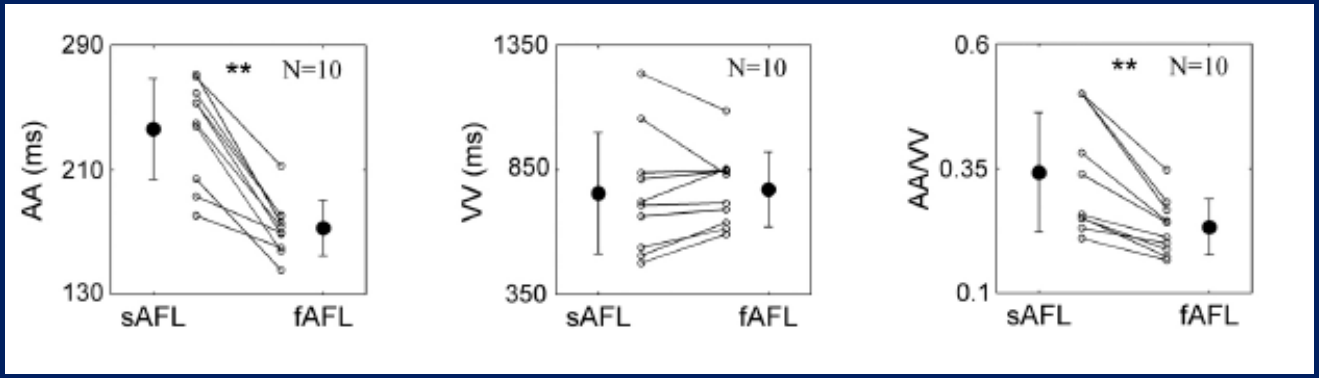


Figure 4 The left panel shows the original traces recorded during atrial fibrillation (AF) from a control (upper) and an AF rabbit preparation (bottom). Note the shorter HH intervals and frequent low-amplitude inferior His electrograms (IHE) in the control preparation. The right bar graph shows the longer average HH intervals during AF in the AF group than in the control group. The pie chart shows the percentage of beats conducted by the fast pathway (FP) and the slow pathway (SP) during AF in the 2 groups. RA = right atrium. *P <.01.

Zhang & Mazgalev, Heart Rhythm 2012

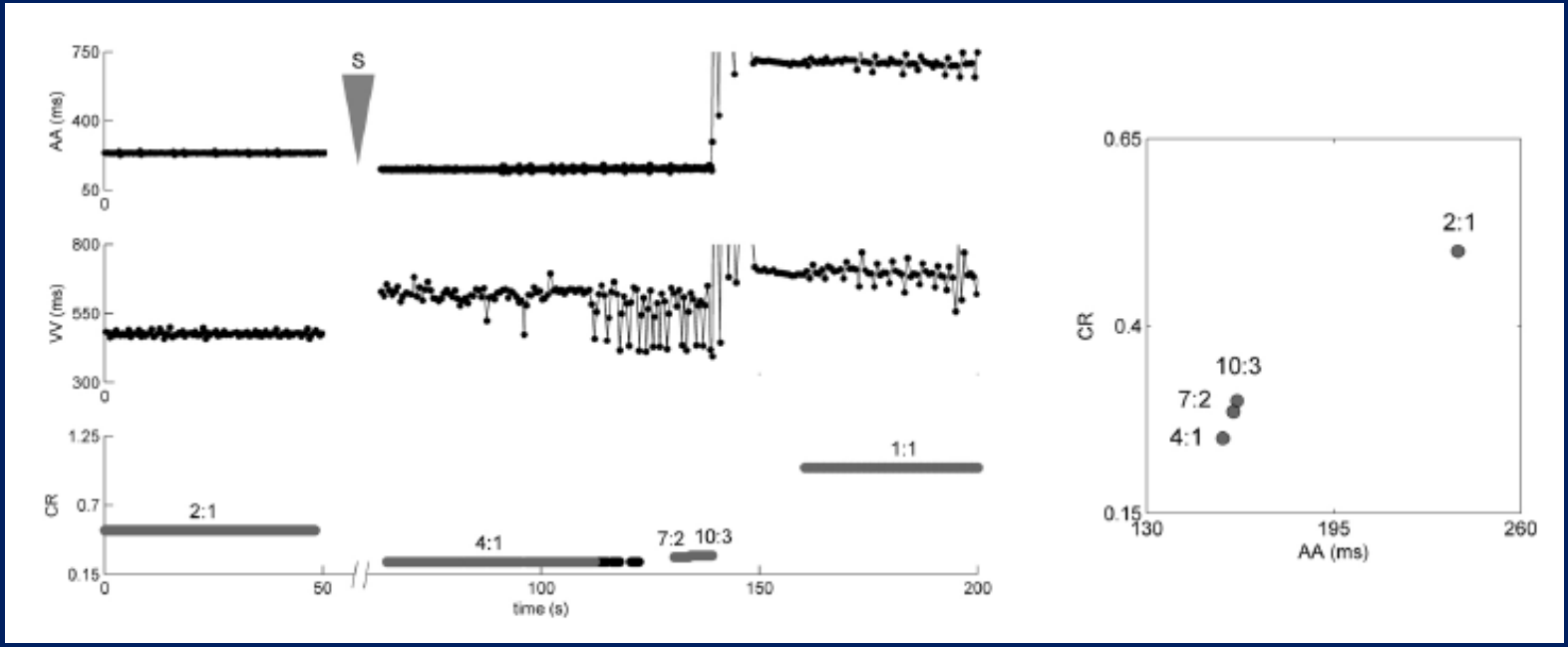
Nodal recovery, dual pathway physiology and concealed conduction determine complex AV dynamics in human atrial tachyarrhythmias





Masè et al, Am J Physiol 2012

Transitions between AV coupling patterns at changing atrial cycle length



Masè et al, Am J Physiol 2012

Atrioventricular Nodal Function during Atrial Fibrillation: Model Building and Robust Estimation

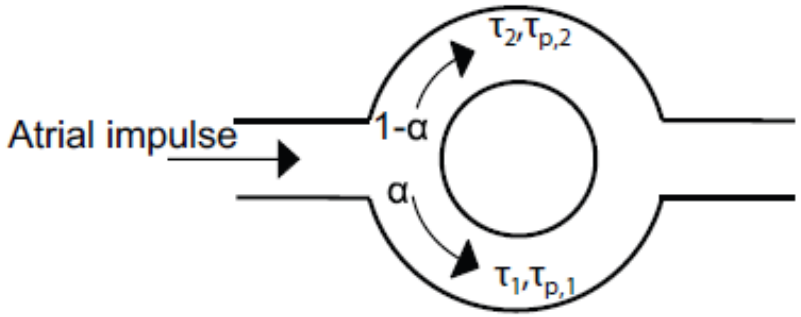


Figure 1: Modeling of the AV node in the proposed model. An atrial impulse arriving to the AV node passes through the slow pathway with a level of probability α and is characterized by the refractory period τ_1, whereas the corresponding parameters of the fast pathway are $(1 - \alpha)$ and τ_2. The refractory periods τ_1 and τ_2 can be prolonged by, at most, $\tau_{p,1}$ and $\tau_{p,2}$, respectively.

Corino et al, Biomed Sign Proc & Control in press

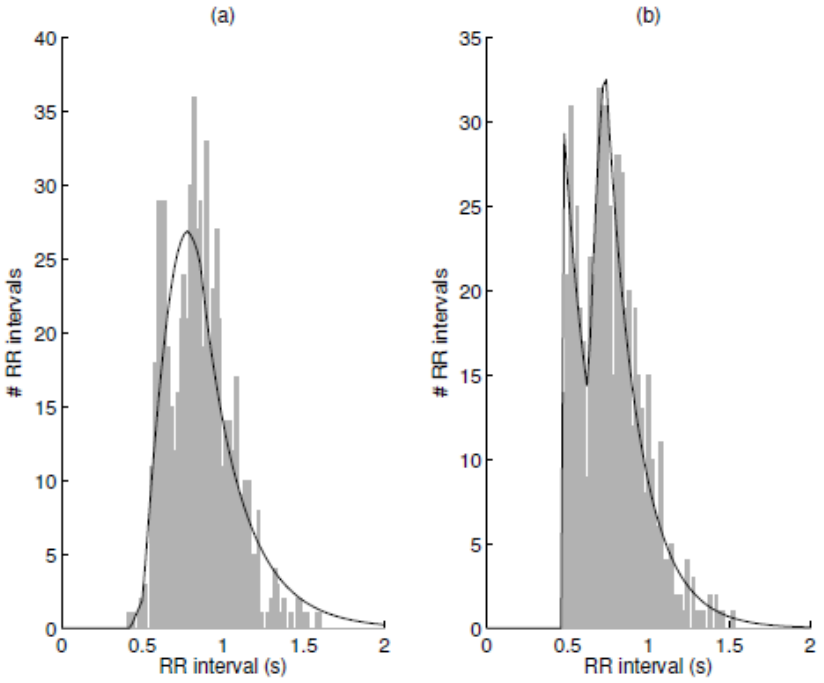


Figure 7: Histogram of transformed RR intervals and the estimated model PDF from the same patient using (a) the original and (b) the new AV node model.

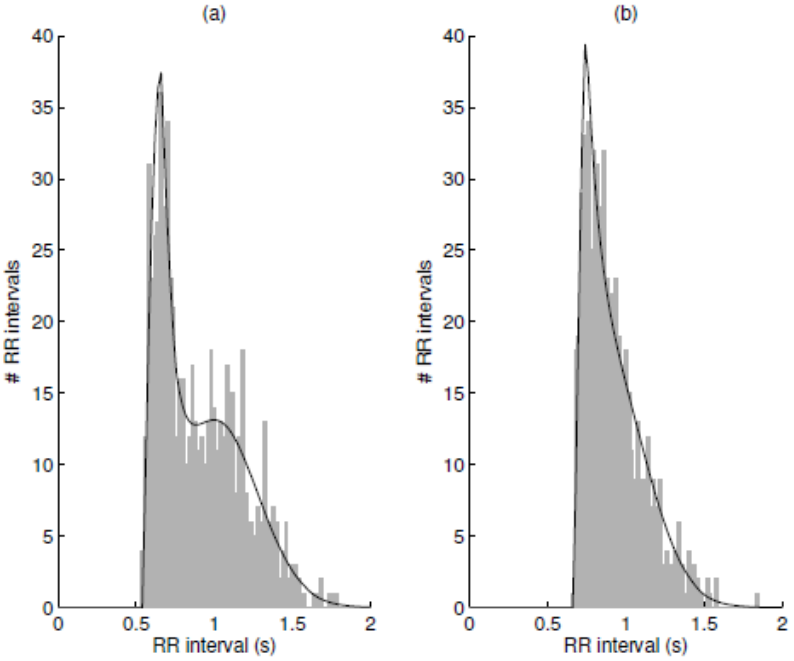
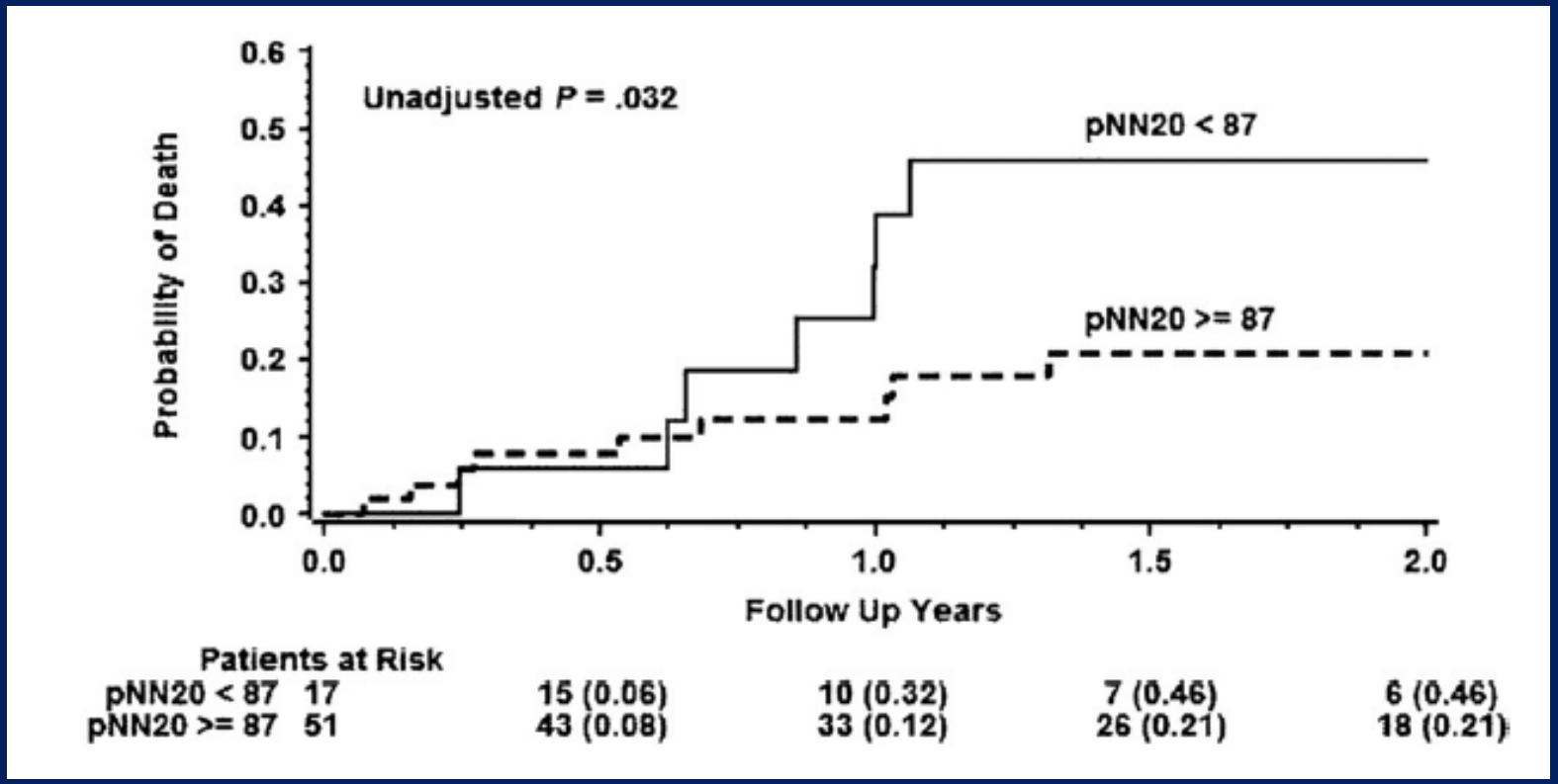


Figure 8: Histogram of transformed RR intervals and the estimated model PDF from the same patient during (a) rest and (b) tilt phase.

Corino et al, Biomed Sign Proc & Control in press

Atrial fibrillatory rate and irregularity of ventricular response as predictors of clinical outcome in patients with atrial fibrillation

MADIT II population; at multivariate Cox analysis, pNN20 was associated with HR 3.03; 95% CI 1.21-7.11; p= 0.018



Platonov & Holmqvist, J Electrocardiol 2011

Conclusions:

Control of ventricular response can be obtained in most patients with atrial fibrillation and is associated with symptoms' reduction.

Available evidence suggests that the efficacy of a lenient control strategy is not inferior to the strict one.

At variance with rhythm control, available drugs are safe and effective for rate control.

Control of ventricular response in CRT patients is still a critical issue, which needs to be properly addressed to reduce the number of non responders.

A compete understanding of AV physiology in AF patients is still missing and is now object of investigation of several bio-medical groups.