HOW TO CONTROL ATRIAL FIBRILLATION IN 2013 ?

THE IDEAL PATIENT FOR A RHYTHM CONTROL STRATEGY

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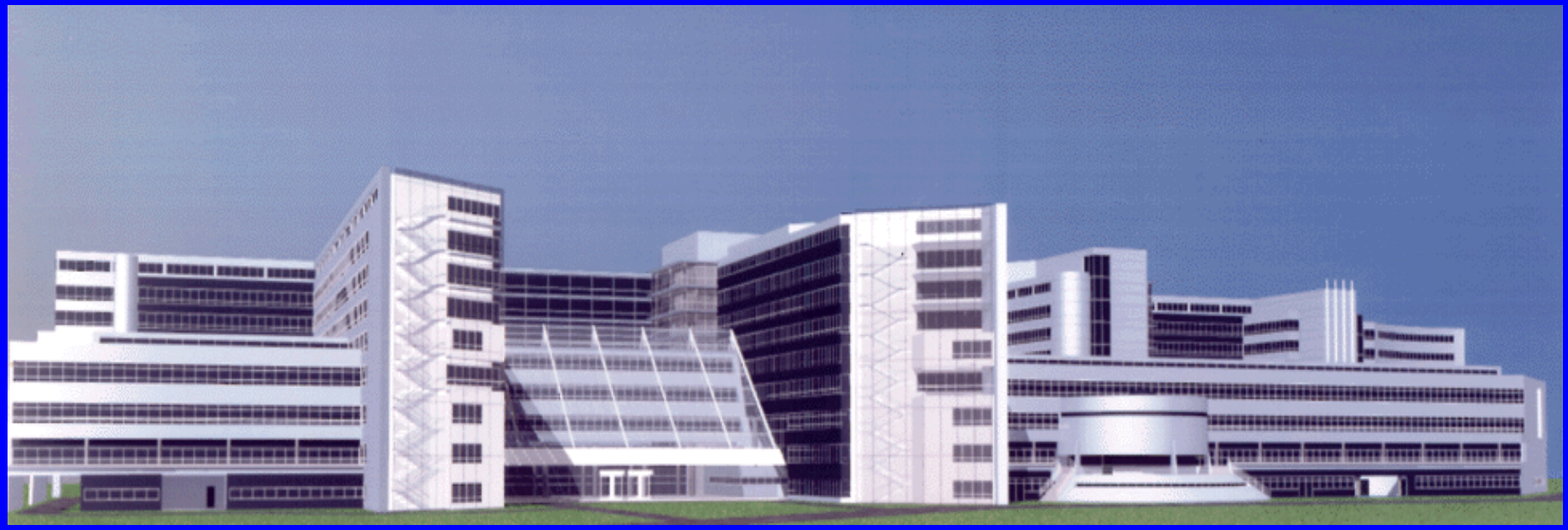


Turin, September 28, 2013

Disclosure

Consultant / Conferences / Advisory Board fees from Sanofi - Aventis, Bristol Myers Squibb / Pfizer, Meda, Boehringer – Ingelheim, MSD, Bayer, Servier and Daiichi – Sankyo.

European Heart Journal
doi:10.1093/eurheartj/ehq278

ESC GUIDELINES

Eur. Heart J. 2010; 31 : 2369 - 429

Guidelines for the management of atrial fibrillation

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

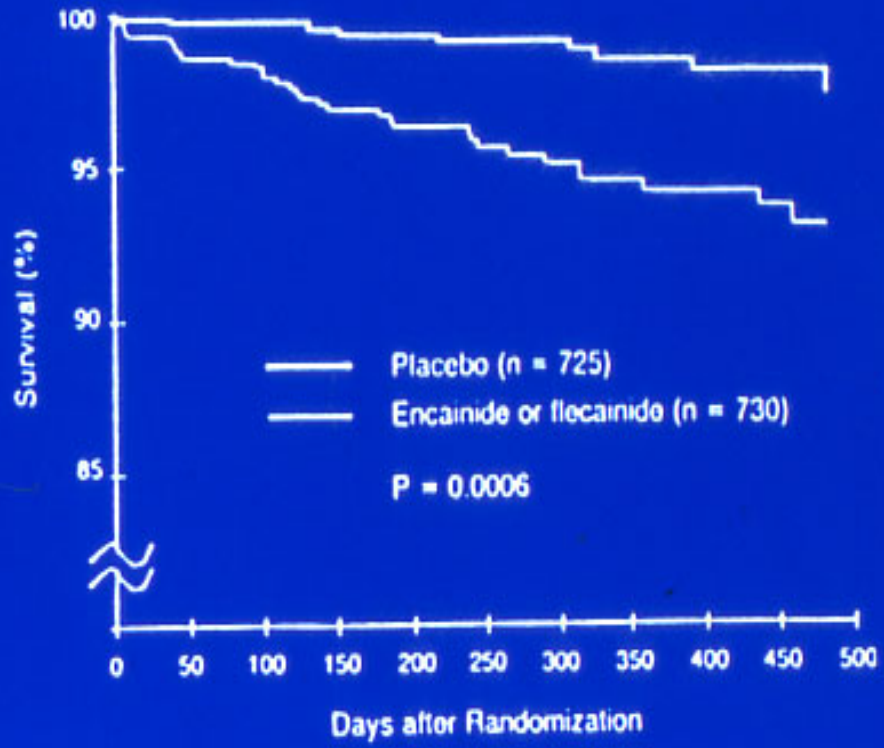
Developed with the special contribution of the European Heart Rhythm Association (EHRA)†

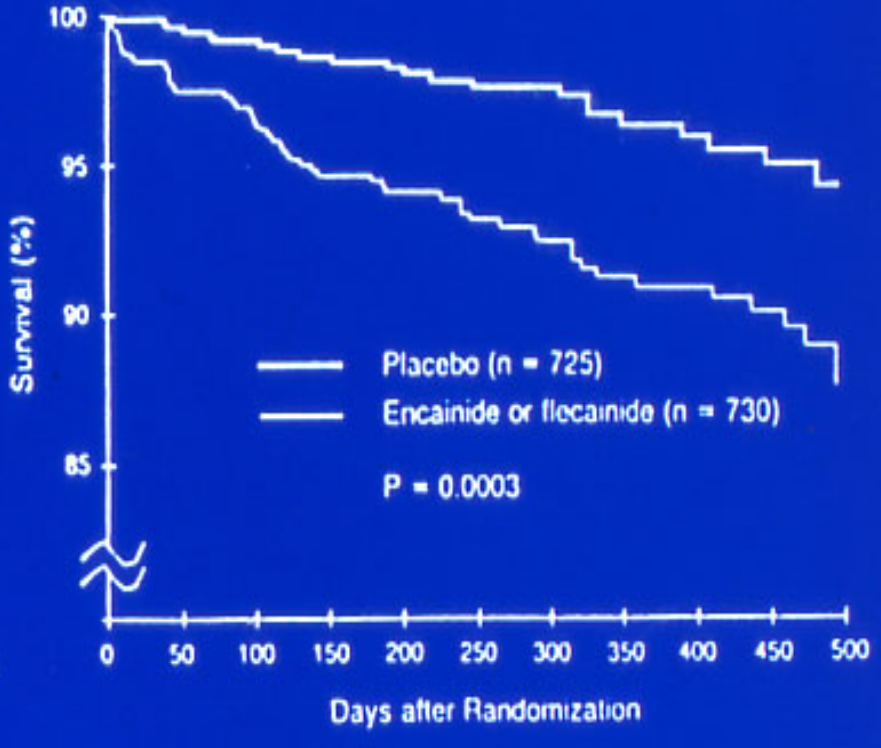
Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS)

Eur. Heart J. 2012; 33 : 2713 - 47

Potential advantages of sinus rhythm maintenance

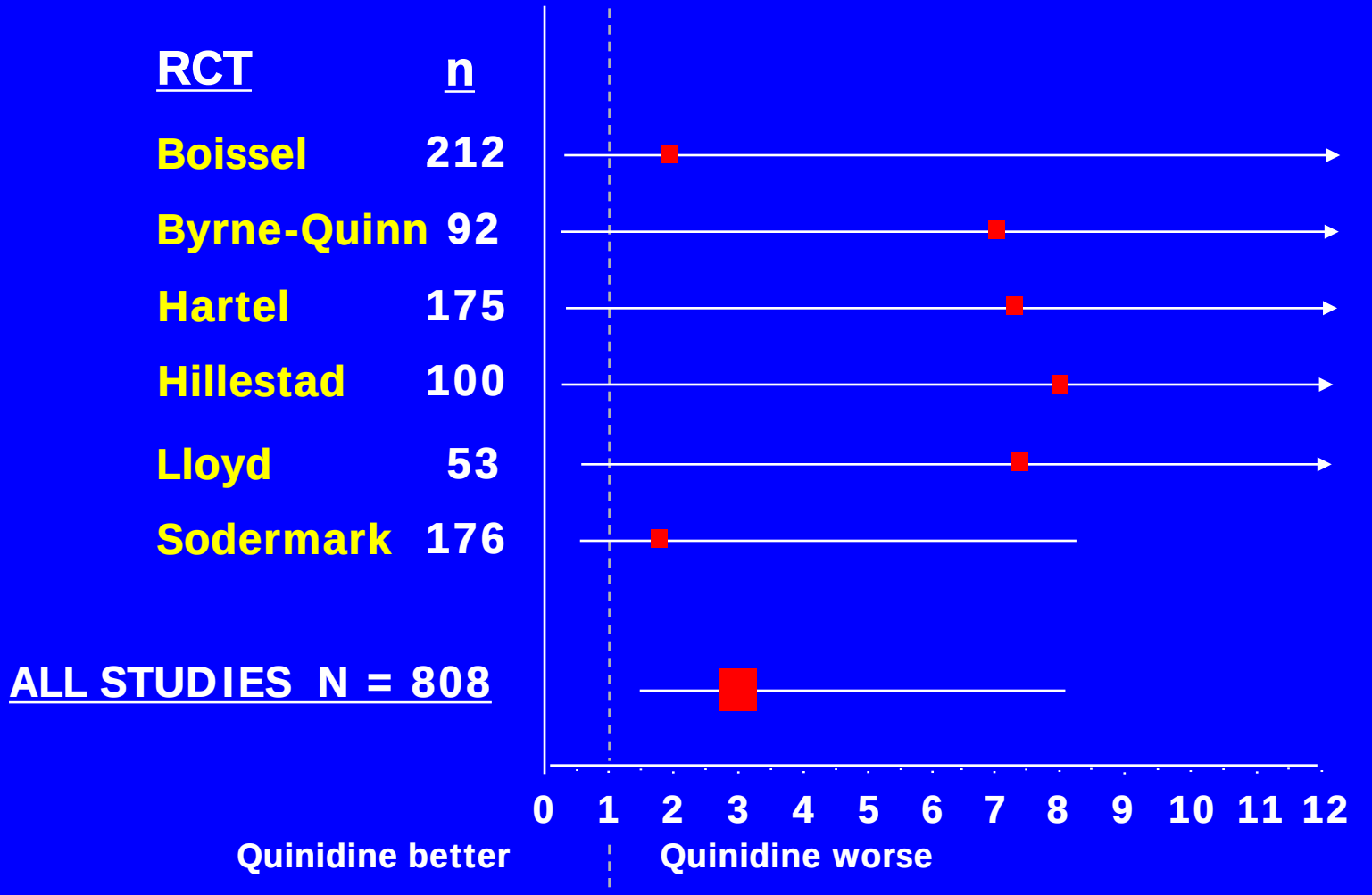
1. Restores a physiological rhythm
2. Allows atrial systole to play its role
3. Ensures optimal haemodynamic functioning
4. Avoids electrophysiological remodelling
5. Avoids the evolution towards chronicity
6. Prevents the occurrence of tachycardiomyopathy
7. Controls the symptomatology
8. Offers a better quality of life
9. Prevents thromboembolic events


100
95
90
85
Survival (%)
Placebo (n = 725)
Encainide or flecainide (n = 730)
P = 0.0006
0
50
100
150
200
250
300
350
400
450
500
Days after Randomization


100
95
90
85
Survival (%)
Placebo (n = 725)
Encainide or flecainide (n = 730)
P = 0.0003
0
50
100
150
200
250
300
350
400
450
500
Days after Randomization

CAST 1989

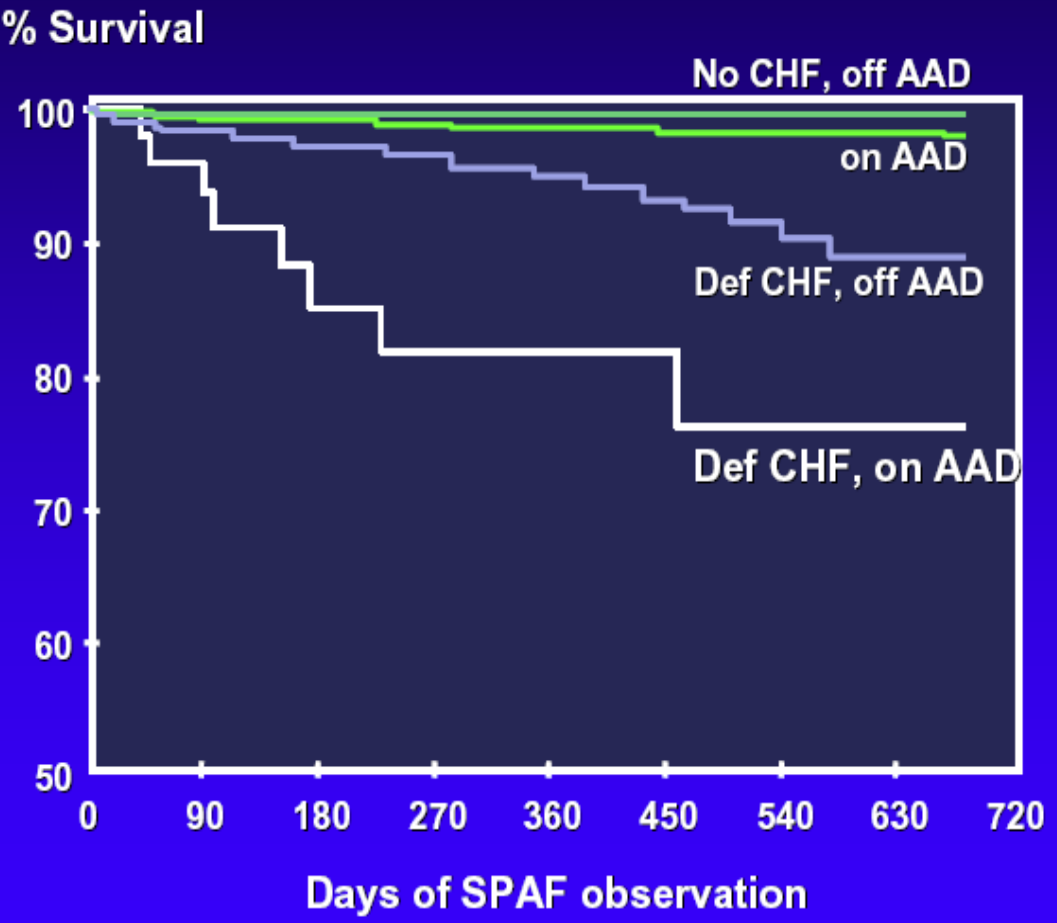
Odds Ratio/ Total Mortality in patients treated by quinidine /Control



Coplen SE. Circulation. 1990;82:1106-1116.

Antiarrhythmic Agents Cardiac Mortality SPAF trial

- **Stroke prevention in AF 1330 pts**
- **AAD** (class I)
- **RR of cardiac death in pts with CHF: 4.7** ($p < 0.001$, CI 1.9 -11.6)

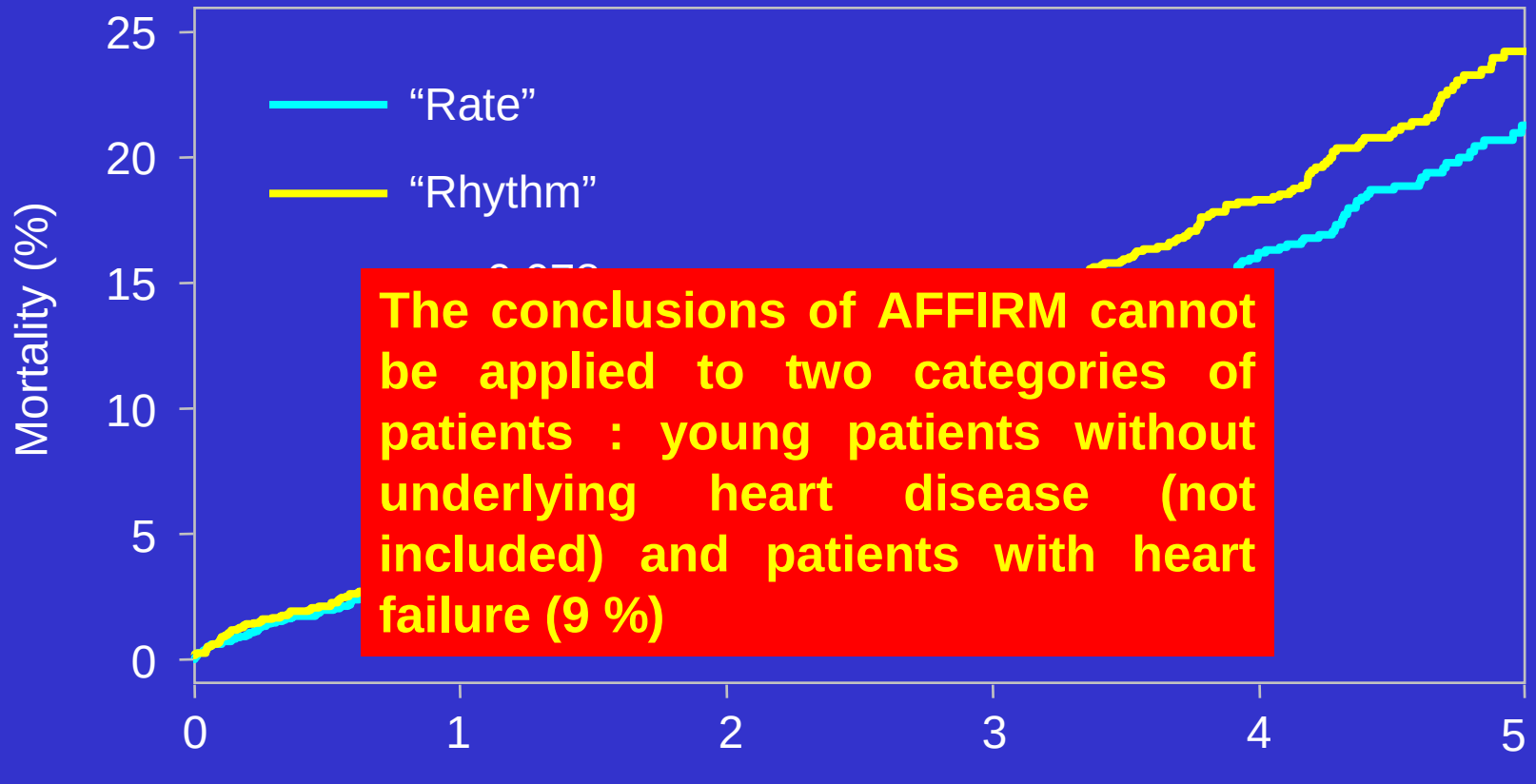


Flaker et al J ACC 1992; 20: 527

CLASS I ANTI-ARRHYTHMIC DRUGS IN DEVELOPMENT (1984)

- Encainide
- Lorcainide
- Moricizine
- Pirmenol
- Penticainide
- Mesocainide
- Carocainide
- Tocainide
- Indocainide
- Recainam
- Diprafenone
- Nicainoprolol

Primary end point : total mortality (all causes)



The conclusions of AFFIRM cannot be applied to two categories of patients : young patients without underlying heart disease (not included) and patients with heart failure (9 %)

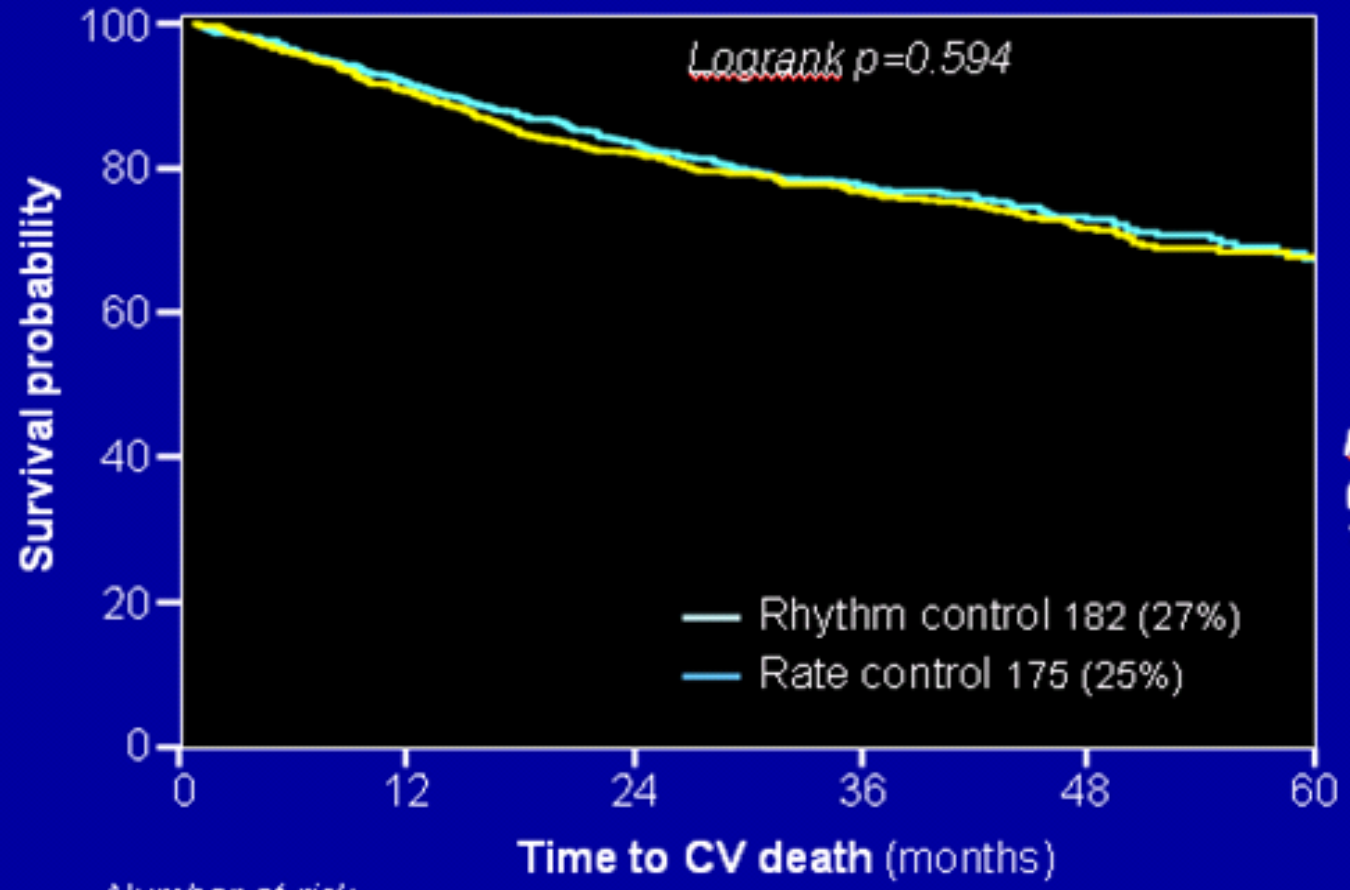
"Rate" n :	2027,0	1926,78	1827,148	1329,210	774,275	236,306
"Rhythm" n :	2033,0	1932,80	1807,175	1316,257	780,314	255,352

AFFIRM

Atrial Fibrillation Follow-up Investigation of Rhythm Management

H E G P

Primary End Point: Cardiovascular Death



Hazard ratio: 1.058 (95% CI, 0.86 to 1.30)

Number at risk

Rhythm control	593	514	378	228	82
Rate control	604	521	381	219	69

D. Roy et al., New Engl. J. Med. 2008; 358 : 2667 - 77

H E G P

Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study

TABLE 3. Covariates Significantly Associated With Survival Results With Echocardiographic Data Excluded

Covariate	*P*	HR	HR: 99% Confidence Limits	
			Lower	Upper
Age at enrollment*	<0.0001	1.06	1.04	1.08
Coronary artery disease	<0.0001	1.65	1.31	2.07
Congestive heart failure	<0.0001	1.83	1.45	2.32
Diabetes	<0.0001	1.56	1.22	2.00
Stroke or transient ischemic attack	<0.0001	1.54	1.17	2.05
Smoking	<0.0001	1.75	1.29	2.39
First episode of atrial fibrillation	0.0067	1.27	1.01	1.58
Sinus rhythm	<0.0001	0.54	0.42	0.70
Warfarin use	<0.0001	0.47	0.36	0.61
Digoxin use	<0.0001	1.50	1.18	1.89
Rhythm-control drug use	0.0005	1.41	1.10	1.83

*Per year of age.

The AFFIRM investigators, Circulation 2004; 109 : 1509-1513

H E G P

Rhythm Versus Rate Control Therapy and Subsequent Stroke or Transient Ischemic Attack in Patients With Atrial Fibrillation

Meytal Avgil Tsadok, PhD; Cynthia A. Jackevicius, PharmD, MSc; Vidal Essebag, MD, PhD; Mark J. Eisenberg, MD, MPH; Elham Rahme, PhD; Karin H. Humphries, DSc; Jack V. Tu, MD, PhD; Hassan Behlouli, PhD; Louise Pilote, MD, PhD

1999 - 2007

n = 16,325
n = 41,193

Conclusions—In comparison with rate control therapy, the use of rhythm control therapy was associated with lower rates of stroke/TIA among patients with atrial fibrillation, in particular, among those with moderate and high risk of stroke. (***Circulation*. 2012;126:2680-2687.**)

The RecordAF Study: Design, Baseline Data, and Profile of Patients According to Chosen Treatment Strategy for Atrial Fibrillation

Jean-Yves Le Heuzey, MD[a,*], Günter Breithardt, MD[b], John Camm, MD[c], Harry Crijns, MD[d], Paul Dorian, MD[e], Peter R. Kowey, MD[f], Ihsen Merioua, MD[g], Eric N. Prystowsky, MD[h], Peter J. Schwartz, MD[i], Christian Torp-Pedersen, MD[j], and William Weintraub, MD[k]

(Am J Cardiol 2010;105:687–693)

Real-Life Observations of Clinical Outcomes With Rhythm- and Rate-Control Therapies for Atrial Fibrillation

RECORDAF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation)

A. John Camm, MD,* Günter Breithardt, MD,† Harry Crijns, MD,‡ Paul Dorian, MD,§ Peter Kowey, MD,‖ Jean-Yves Le Heuzey, MD,¶ Ihsen Merioua, MD,# Laurence Pedrazzini, MD,# Eric N. Prystowsky, MD,** Peter J. Schwartz, MD,†† Christian Torp-Pedersen, MD,‡‡ William Weintraub, MD§§

London, United Kingdom; Muenster, Germany; Maastricht, the Netherlands; Toronto, Ontario, Canada; Wynnewood, Pennsylvania; Paris, France; Indianapolis, Indiana; Pavia, Italy; Hellerup, Denmark; and Wilmington, Delaware

(J Am Coll Cardiol 2011;58:493–501)

RecordAF Registry – Design

- **International, observational, prospective 1-year longitudinal cohort study**
- **3 continents, 21 countries (Austria, Belarus, Brazil, Colombia, Denmark, France, Germany, Greece, Hungary, Italy, Korea, Mexico, Philippines, Poland, Portugal, Russia, Spain, Sweden, Thailand, United Kingdom, United States)**
- **~ 600 randomized general cardiologists**
- **n = 5,604 eligible pts included from May 2007 to April 2008.**

- **Main Inclusion criteria**
  - –Age ≥ 18 y
  - –History of AF<1y or newly diagnosed AF
  - –Treated or not
  - –In SR or not
  - –Eligible for a pharmacological treatment of AF
- **Main Exclusion criteria:**
  - – AF due to a transient cause
  - – Post-operative AF

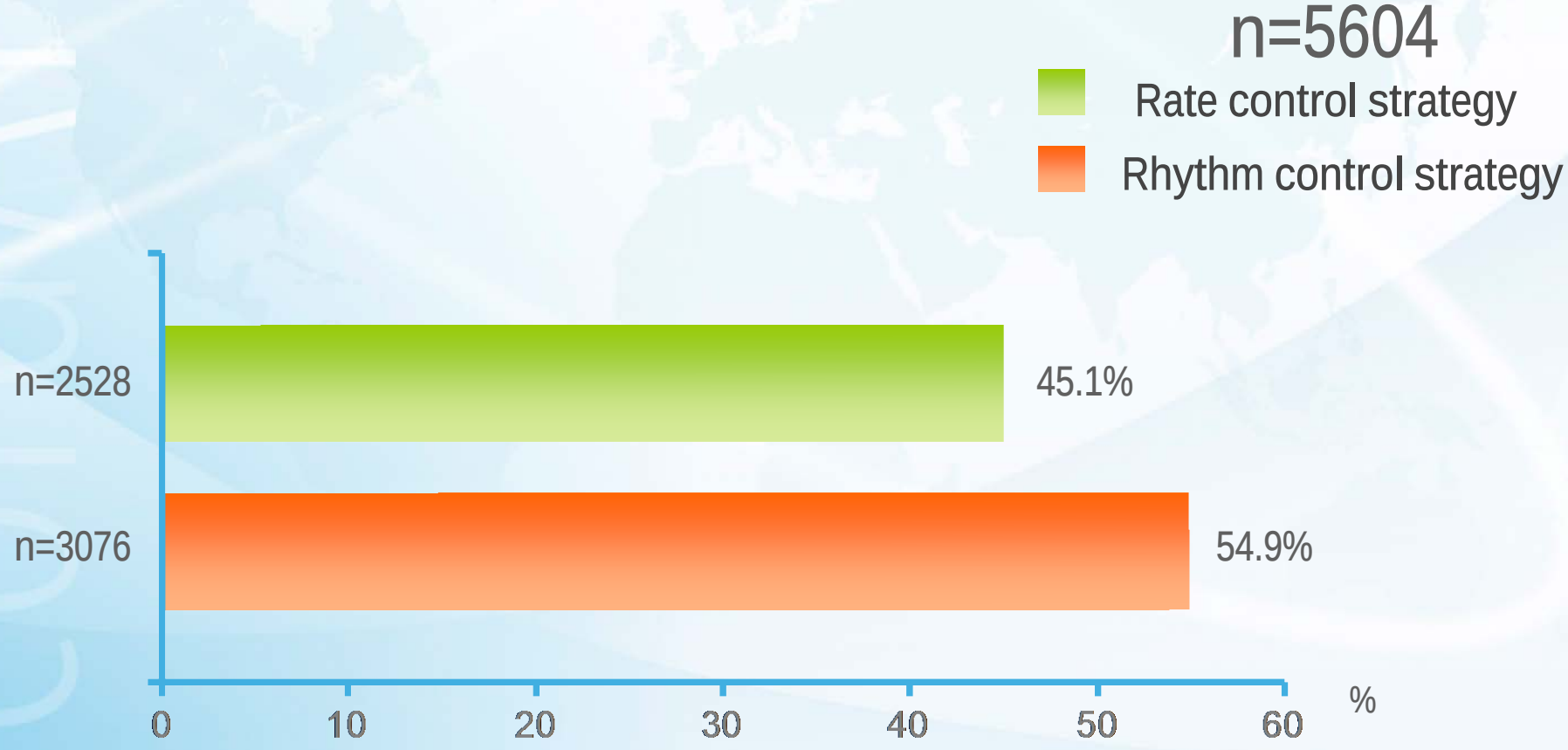
CRF:
- Demographics
- CV & AF history
- Current AF (type, symptoms…)
- AF drug therapy: (strategy, drug allocation)
- Other CV drugs
- QoL evaluation

Co-primary endpoints at 12 months
- Rate of therapeutic success of AF management (patient in SR or at rate control target / no major CV event / no strategy switch)
- To compare the major CV events* in the 2 strategies

**** CV death, myocardial Infarction, stroke, TIA leading to hospitalization, hospitalization or prolongation of hospitalization (arrhythmic or proarrhythmic events, other CV events, major complications of ablative procedure)***

RecordAF
REGISTRY ON CARDIAC RHYTHM DISORDERS

Choice of Strategy at Baseline by Cardiologists



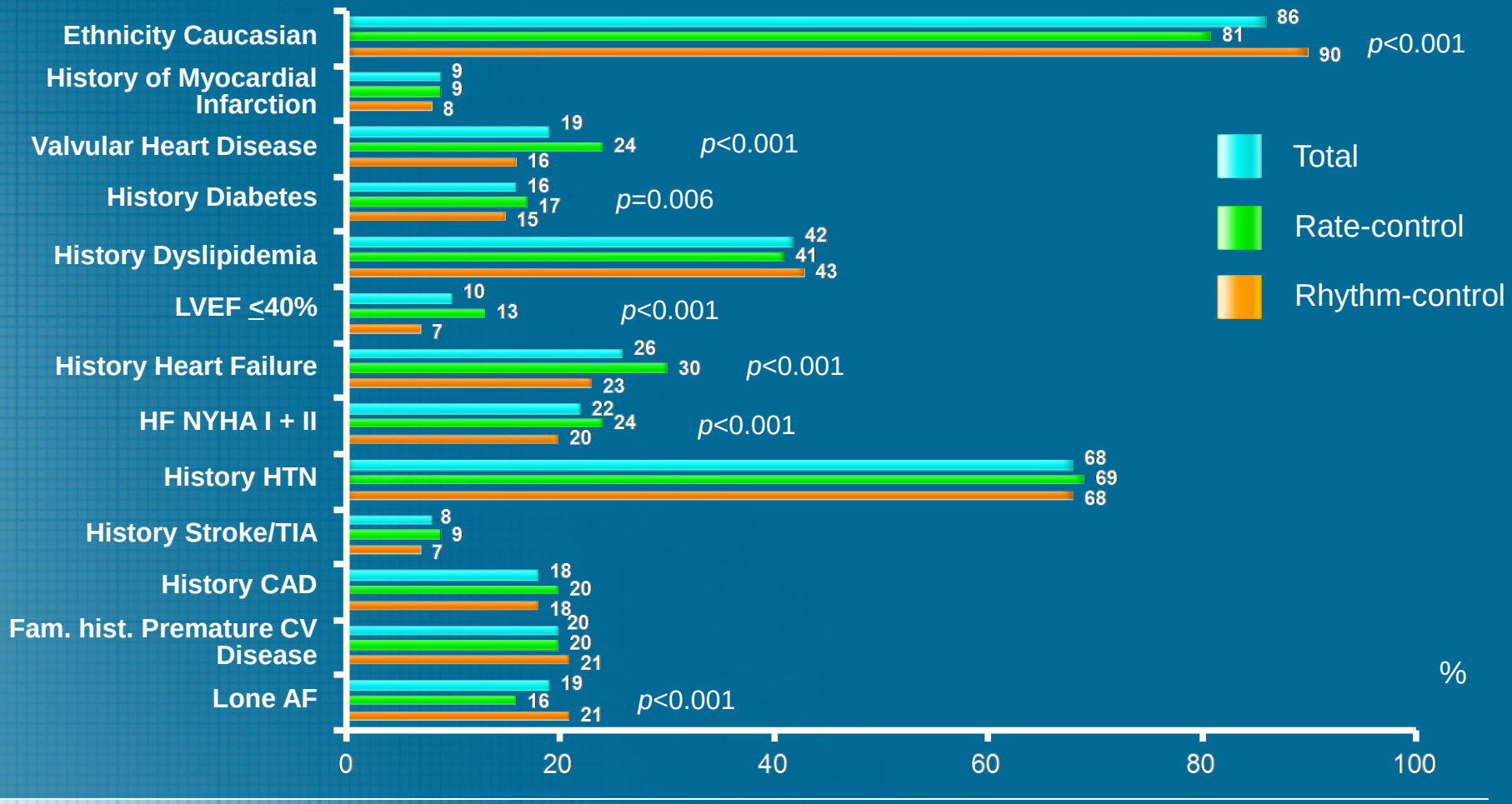
Le Heuzey J.Y. et al. Am.J. Cardiol. 2010; 105 : 687 - 93

RecordAF
REGISTRY ON CARDIAC RHYTHM DISORDERS

Baseline Demographics and Comorbidities

n=5604

	n=3076	n=2528	n=5604
Mean age years (SD)	64.2 (12.0)	67.3 (11.6)	65.6 (11.9) *p*<0.001
Female	43%	43%	43%
Resting heart rate	76.6 bpm	80.6 bpm	78.4 bpm *p*<0.001



*p value compares the percentage of the condition between rhythm control vs. rate control

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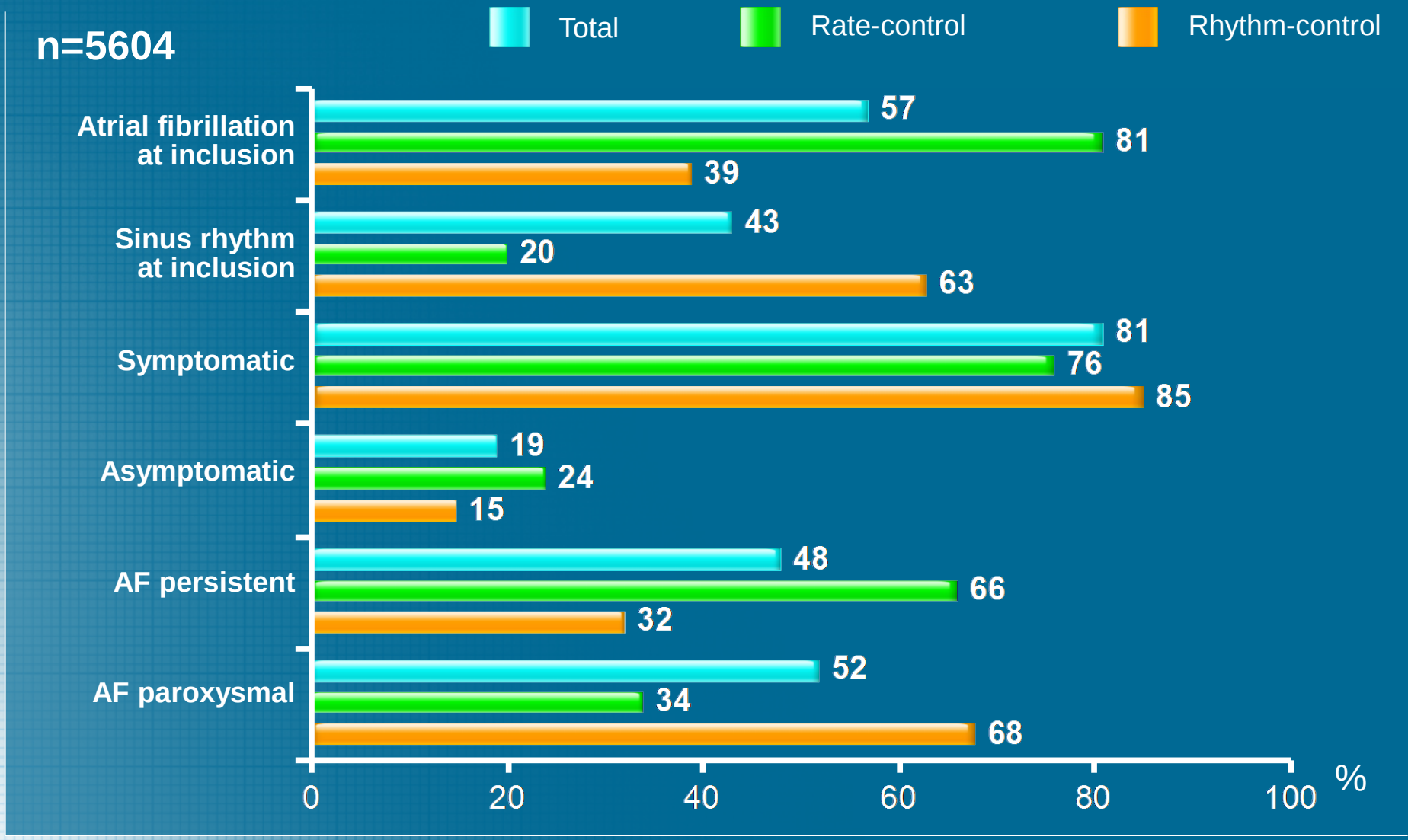
Clinical Presentation of AF at Baseline

p< 0.001*



**p* value <0.001 for all comparisons

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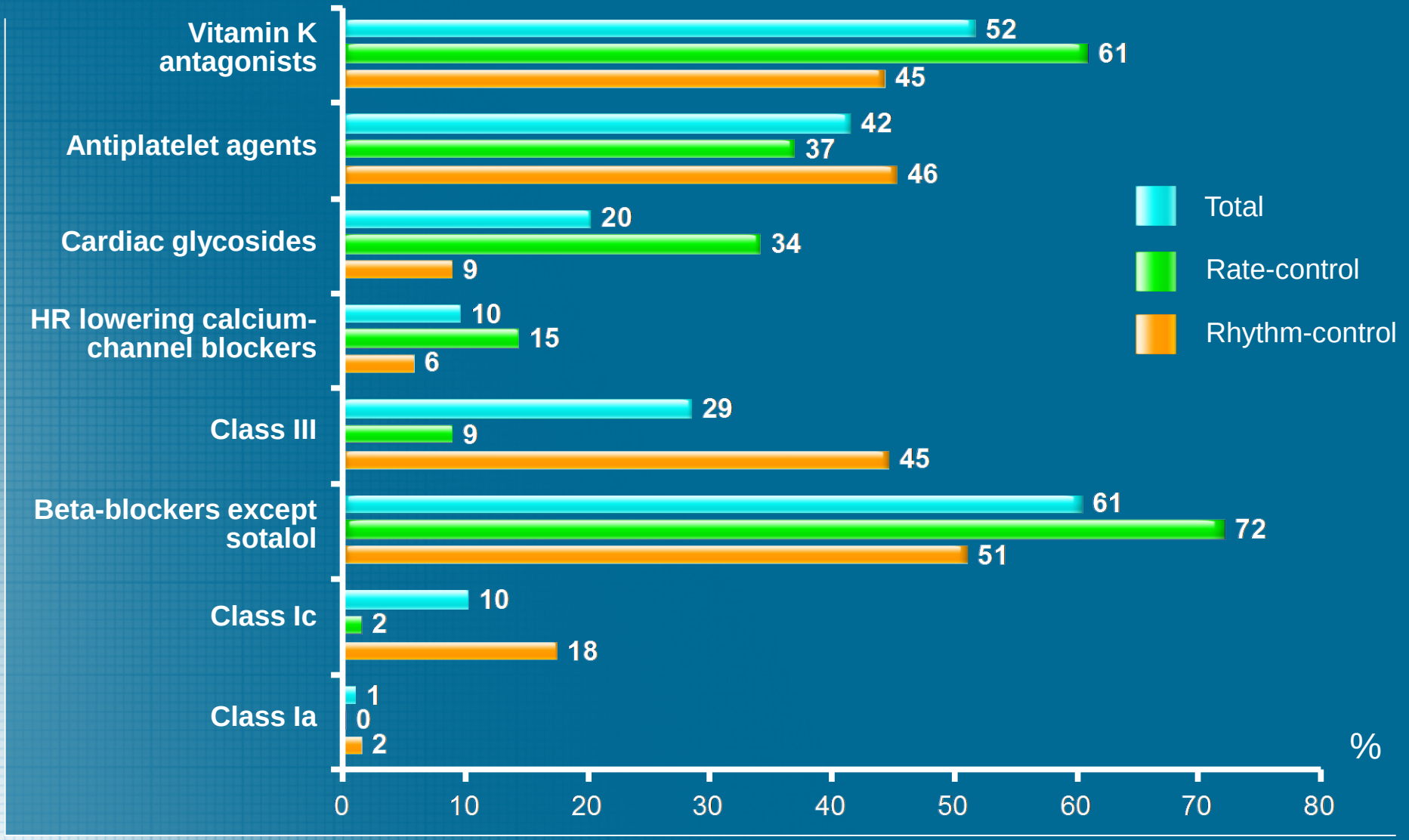
AF Treatments at Baseline

n=5604

p< 0.001*



*p value <0.001 for all comparisons

RecordAF
REGISTRY ON CARDIAC RHYTHM DISORDERS

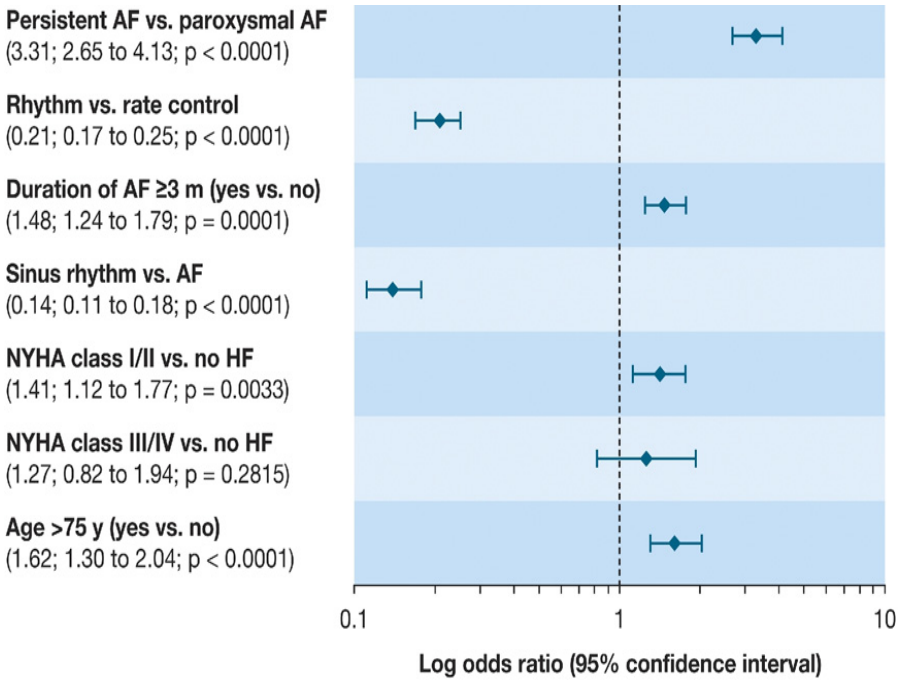
RECORD AF baseline data

- RecordAF is a real-life prospective international registry including 5604 patients conducted in 3 continents to evaluate management and clinical outcomes in paroxysmal and persistent AF patients over 1 year.
- Patients with ECG evidence of AF, heart failure and valvulopathy were more likely to be started on rate control.
- Being in sinus rhythm, symptomatic or Caucasian was associated with more use of rhythm control.
- A rhythm control strategy remains the preferred therapeutic option (55%).
- Class III antiarrhythmics were the main drugs prescribed for rhythm control and beta blockers were the drugs of choice for a majority of patients in whom rate control strategy was chosen.

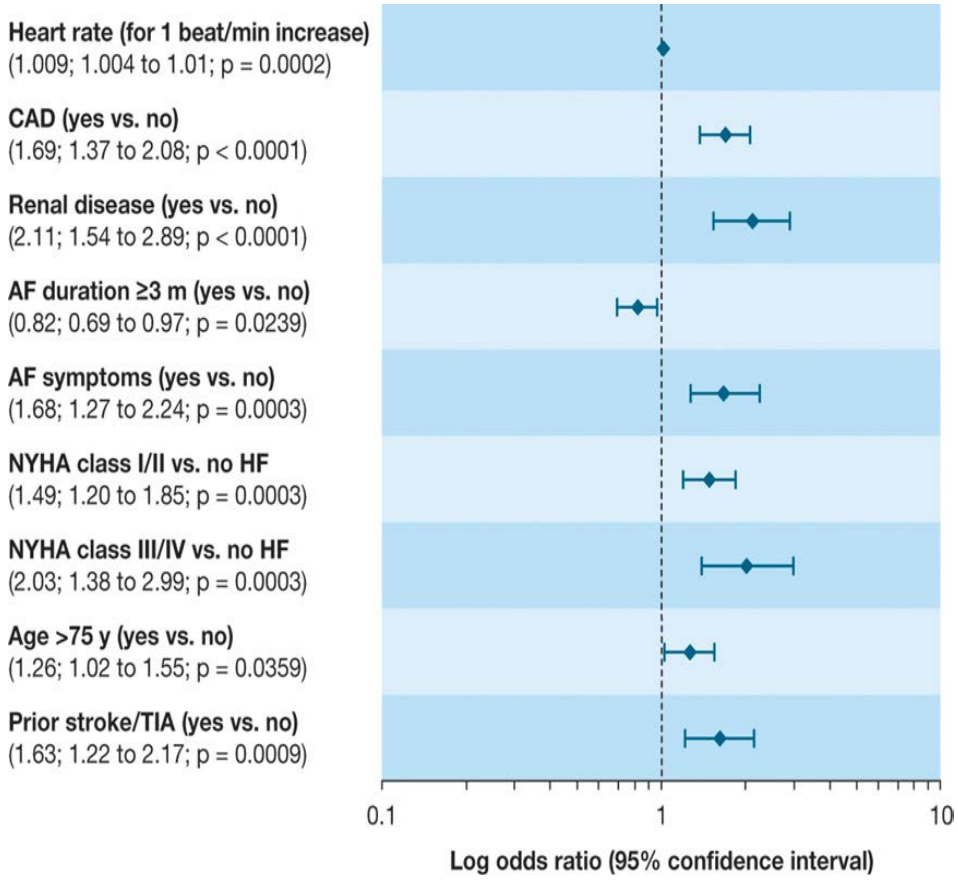
RecordAF
REGISTRY ON CARDIAC RHYTHM DISORDERS

RECORD AF

A.J. Camm et al.

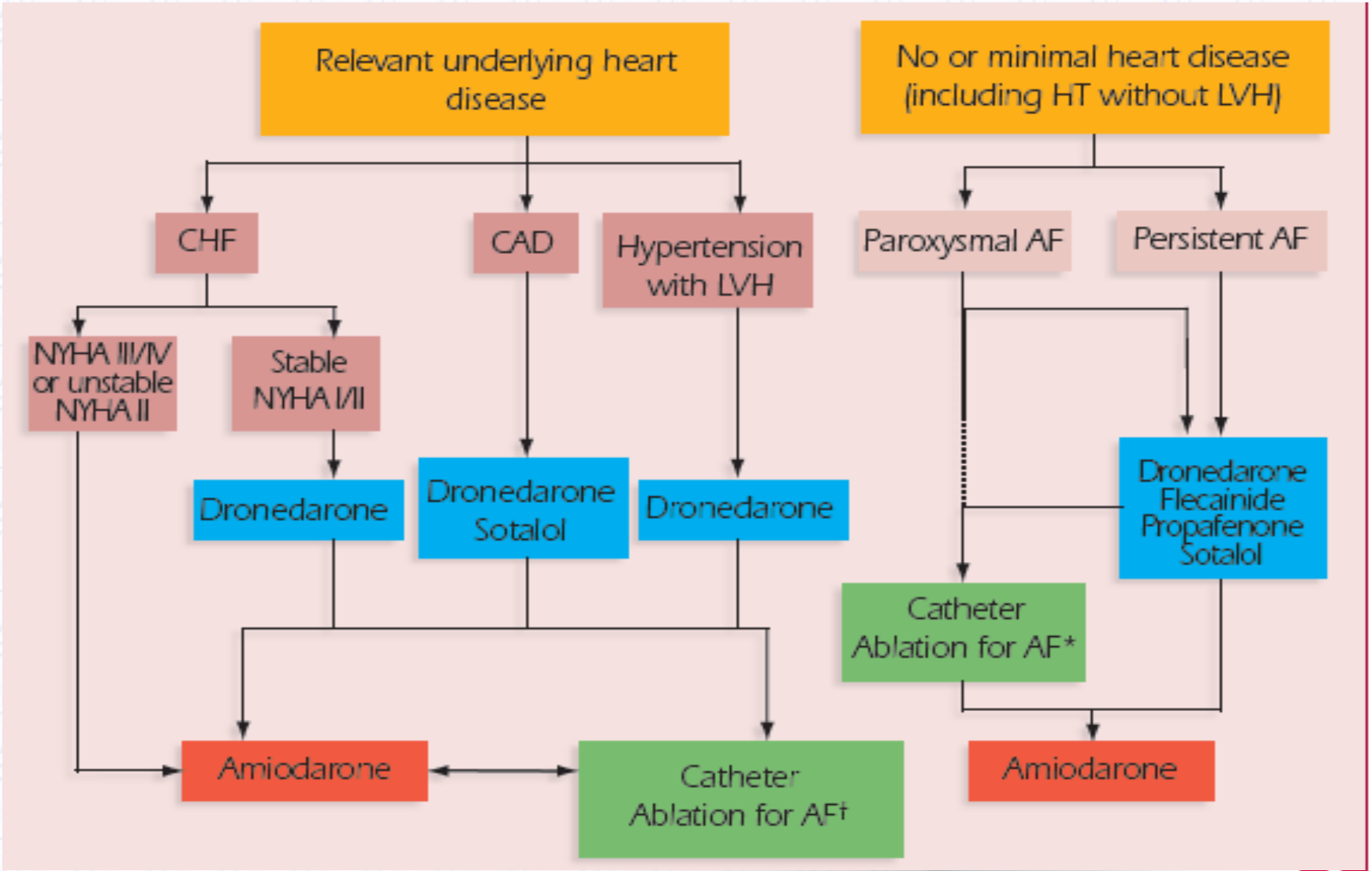


Baseline Factors Predicting Progression to Permanent AF



Baseline Factors Predicting Clinical Outcomes

(J Am Coll Cardiol 2011;58:493–501)



Eur. Heart J. 2010, 31 : 2369 - 469

ATHENA Baseline Patient Characteristics

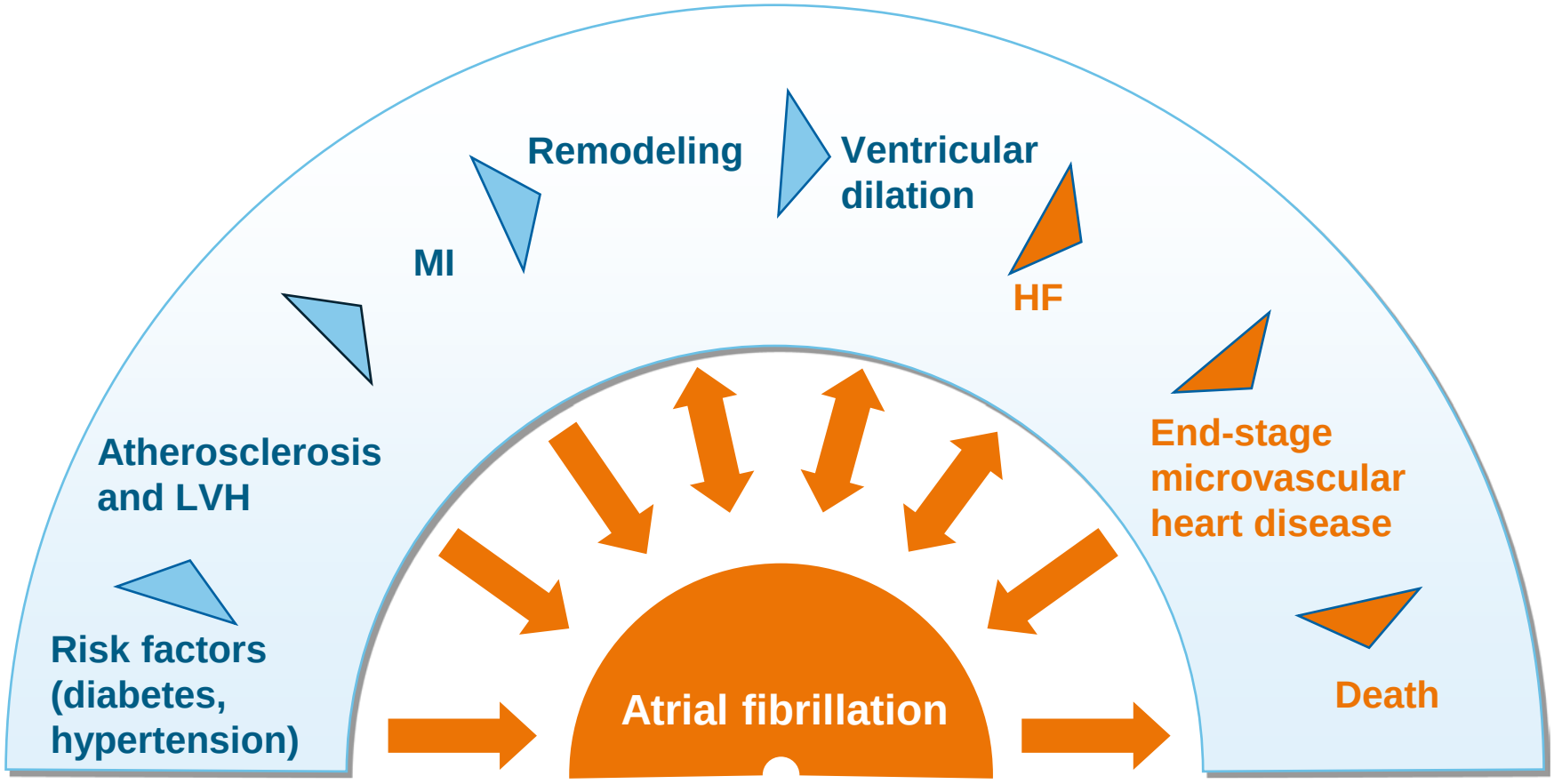
	Placebo n=2327	Dronedarone n=2301	All patients n=4628
Age (mean ±SD, years)	71.7 ±9.0	71.6 ±8.9	72 ±9.0
<65yr	442 (19.0%)	431 (18.7%)	873 (18.9%)
65 to 75yr	907 (39.0%)	923 (40.1%)	1830 (39.5%)
≥75yr	978 (42.0%)	947 (41.2%)	1925 (41.6%)
Female gender	1038 (44.6%)	1131 (49.2%)	2169 (46.9%)
AF/AFL at baseline	586 (25.2%)	569 (24.7%)	1155 (25.0%)
Structural heart disease	1402 (60.9%)	1330 (58.3%)	2732 (59.6%)
Hypertension	1996 (85.8%)	1999 (86.9%)	3995 (86.3%)
Coronary heart disease	737 (31.7%)	668 (29.0%)	1405 (30.4%)
Valvular heart disease	380 (16.3%)	379 (16.5%)	759 (16.4%)
Non-ischemic cardiomyopathy	131 (5.6%)	123 (5.3%)	254 (5.5%)
History of CHF NYHA II/III	515 (22.1%)	464 (20.2%)	979 (21.2%)
LVEF <0.45	285/2281 (12.5%)	255/2263 (11.3%)	540/4544 (11.9%)
LVEF <0.35	87/2281 (3.8%)	92/2263 (4.1%)	179/4544 (3.9%)
Lone atrial fibrillation	139 (6.0%)	140 (6.1%)	279 (6.0%)
Pacemaker	243 (10.4%)	214 (9.3%)	457 (9.9%)

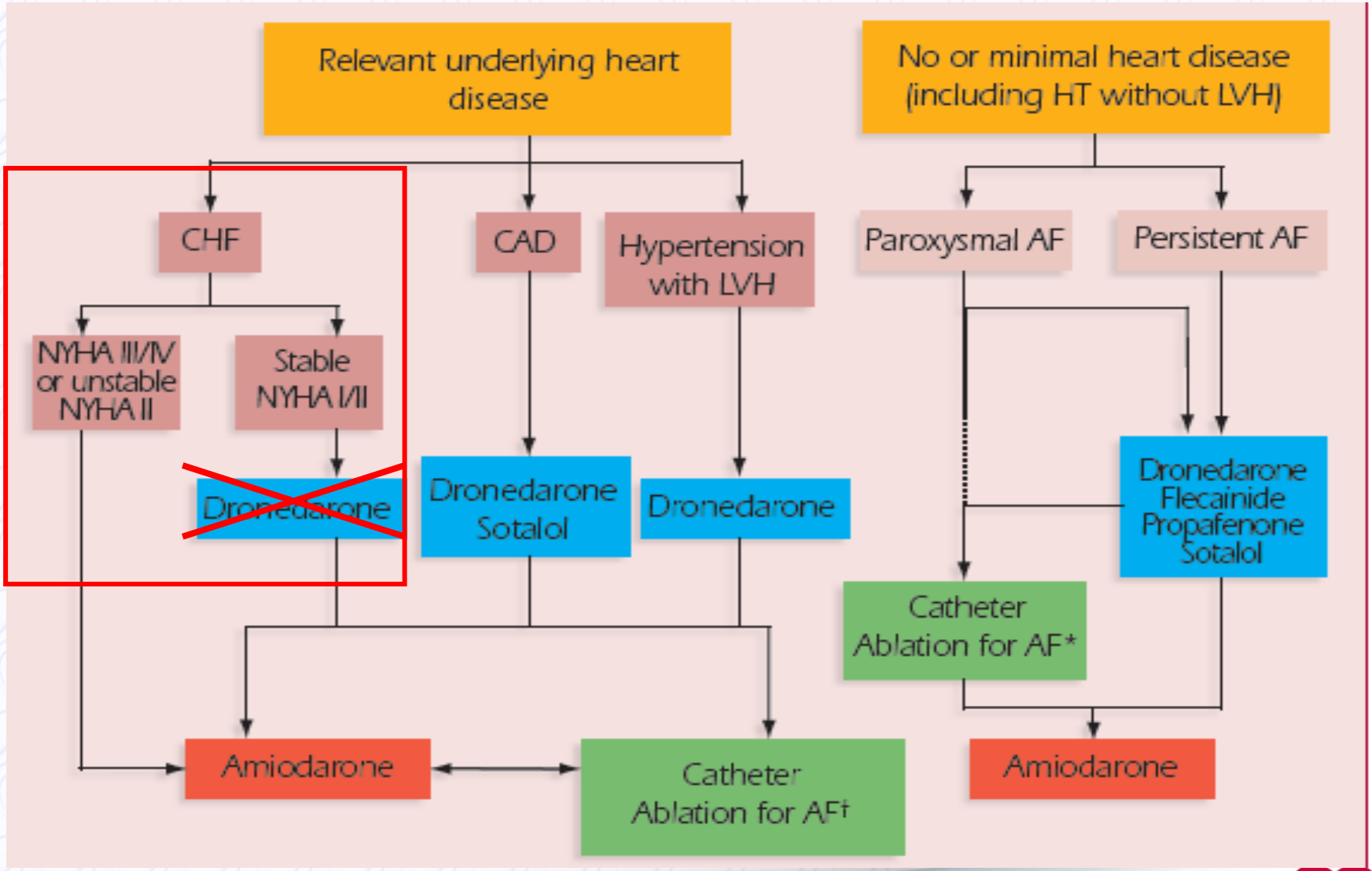
Hohnloser SH, *et al. J Cardiovasc Electrophysiol* 2008;19:69-73.

Baseline Characteristics

	Dronedarone N=1619	Placebo N=1617
Age years mean (SD)	75.0 (5.9)	75.0 (5.9)
Duration of permanent AF > 2 years	1119 (69.1%)	1124 (69.5%)
Coronary artery disease	661 (40.8%)	666 (41.2%)
Peripheral arterial disease	187 (11.6%)	213 (13.2%)
Prior Stroke or TIA	436 (26.9%)	458 (28.3%)
History of heart failure	1139 (70.4%)	1117 (69.1%)
Left ventricular ejection fraction ≤ 40%	345 (21.3%)	335 (20.7%)
Baseline use of a Beta-blocker	1201 (74%)	1201 (74%)
Baseline use of Vitamin K antagonist	1359 (84%)	1363 (84%)

Antiarrhythmic drugs in atrial fibrillation : do not cross the red line !





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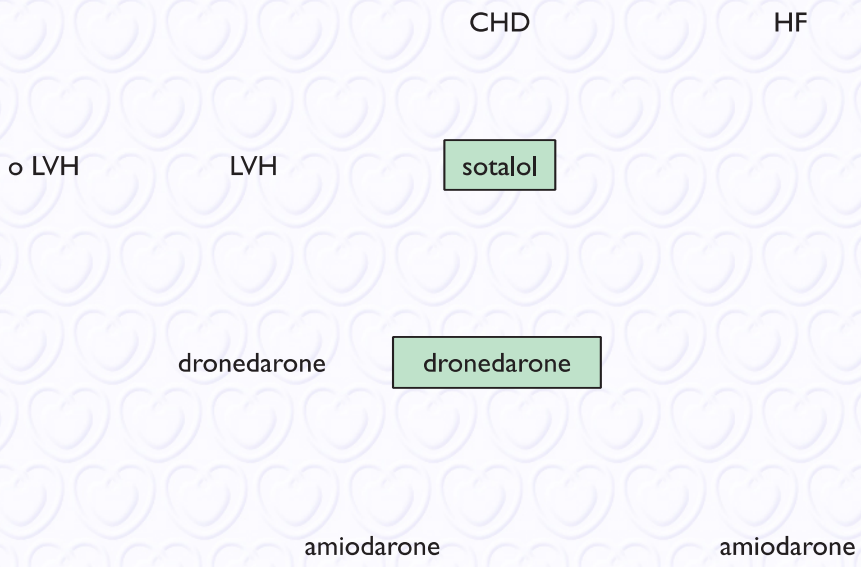

Figure 4 Choice of antiarrhythmic drug according to underlying pathology.

Europace (2009) **11**, 840–841
doi:10.1093/europace/eup175

EDITORIAL

The risk of antiarrhythmic drugs in atrial fibrillation: 20 years of controversies

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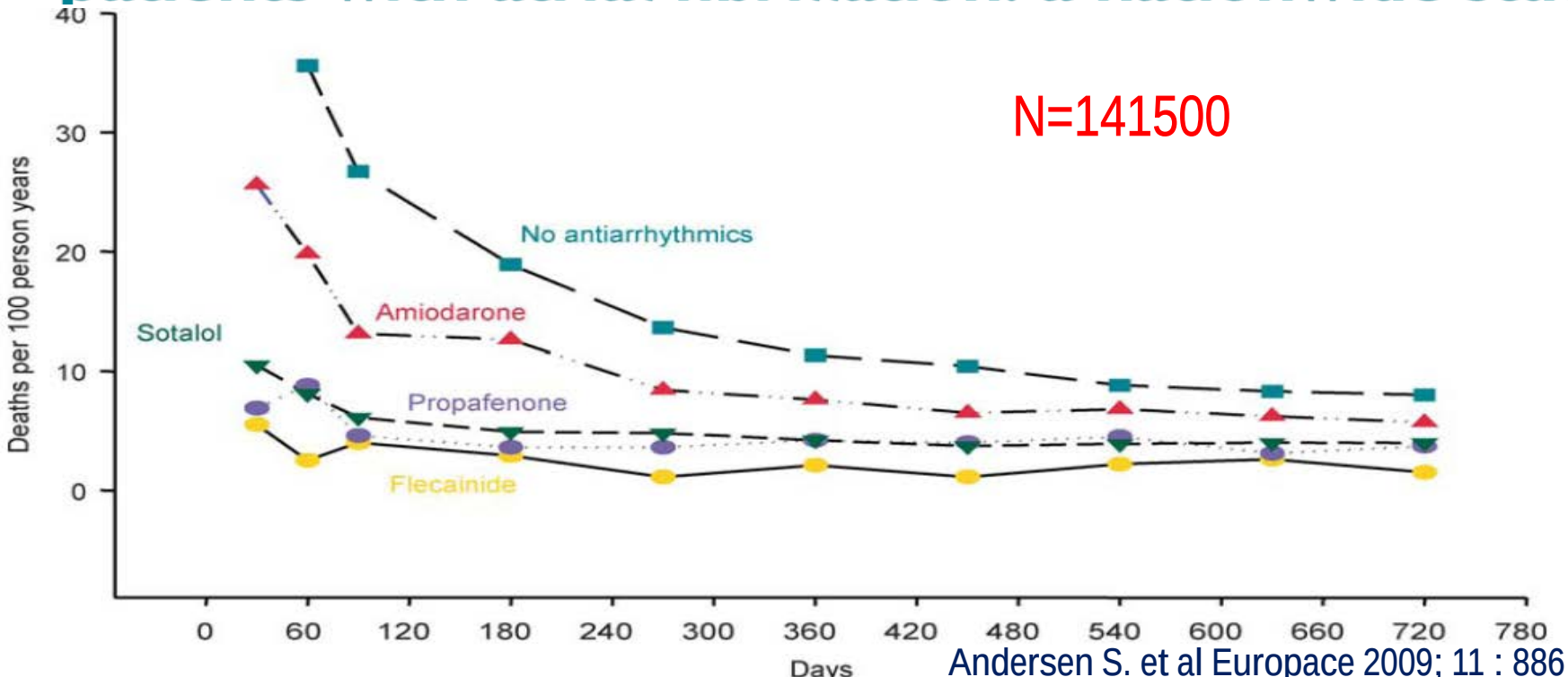
Received 8 June 2009; accepted after revision 9 June 2009

Antiarrhythmic therapy and risk of death in patients with atrial fibrillation: a nationwide study



N=141500

Andersen S. et al Europace 2009; 11 : 886 - 91

Mr L… 84 years, persistent atrial fibrillation (around 25 days), history of hypertension and coronary artery disease, 2 electrical cardioversion in 2010 and 2011, heart failure class II / III, treatment amiodarone

RATE

Le vieillard

Mr V… 42 years, persistent lone atrial fibrillation (10 days), second episode (spontaneous termination of the first episode on December 31, 2012), new episode of« saturday night atrial fibrillation » three months later

RHYTHM

Le fêtard

CONCLUSION

- **Rate control better choice for :**
  older patients, asymptomatic patients or patients with few symptoms, patients with advanced underlying heart disease

- **Rhythm control better choice for :**
  younger patients, patients without (or minimal) underlying heart disease, highly symptomatic patients or patients with few risk factors of relapse

but it is a continuum, the majority of patients are between these two extremes … and the choice must be made case by case

H E G P