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Fibrillazione atriale:
cosa c'è di nuovo nella terapia antiaritmica?

Fibrillazione atriale: cosa c'è di nuovo nella terapia antiaritmica?

E' un grave problema di salute pubblica

- Pericolosa per la vita ?
- Influenza la qualità della vita (funzionale, emozionale, sociale)
- Causa diretta o indiretta di gravi conseguenze anatomo-funzionali, emocoagulative, emodinamiche (tromboembolie, emorragie, dilatazione camere, portata cardiaca, ecc.)
- Molto frequente nella pratica clinica

Fibrillazione atriale: cosa c'è di nuovo nella terapia antiaritmica?

Epidemiologia FA in Europa

2014 (popolazione 500 milioni)

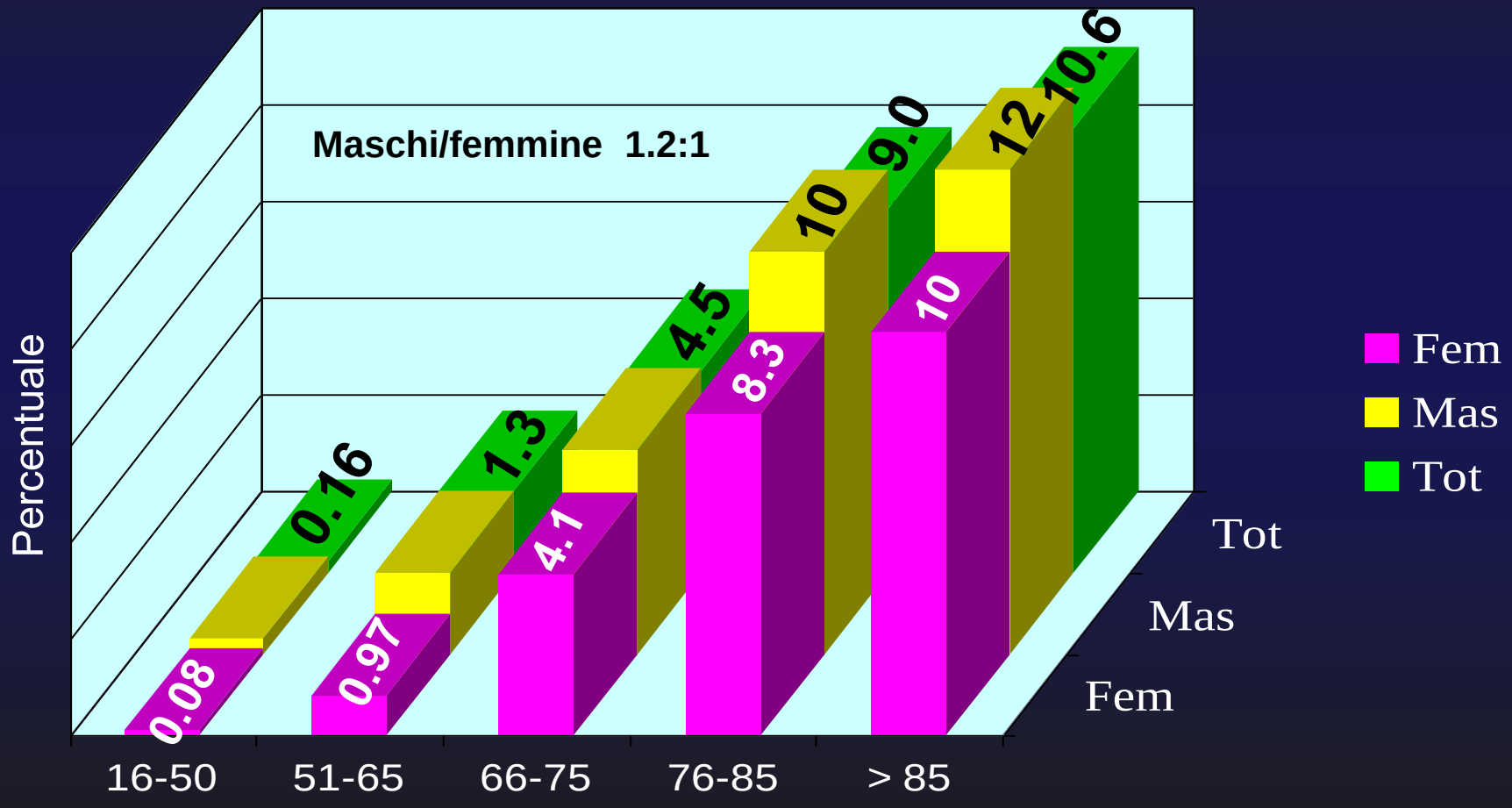
- Prevalenza 10 milioni
- Incidenza 100-200.000 nuovi casi x anno

2030 (popolazione 517-525 milioni)

- Prevalenza 14-17 milioni
- Incidenza 120-220.000 nuovi casi x anno

Fibrillazione atriale: cosa c'è di nuovo nella terapia antiaritmica?

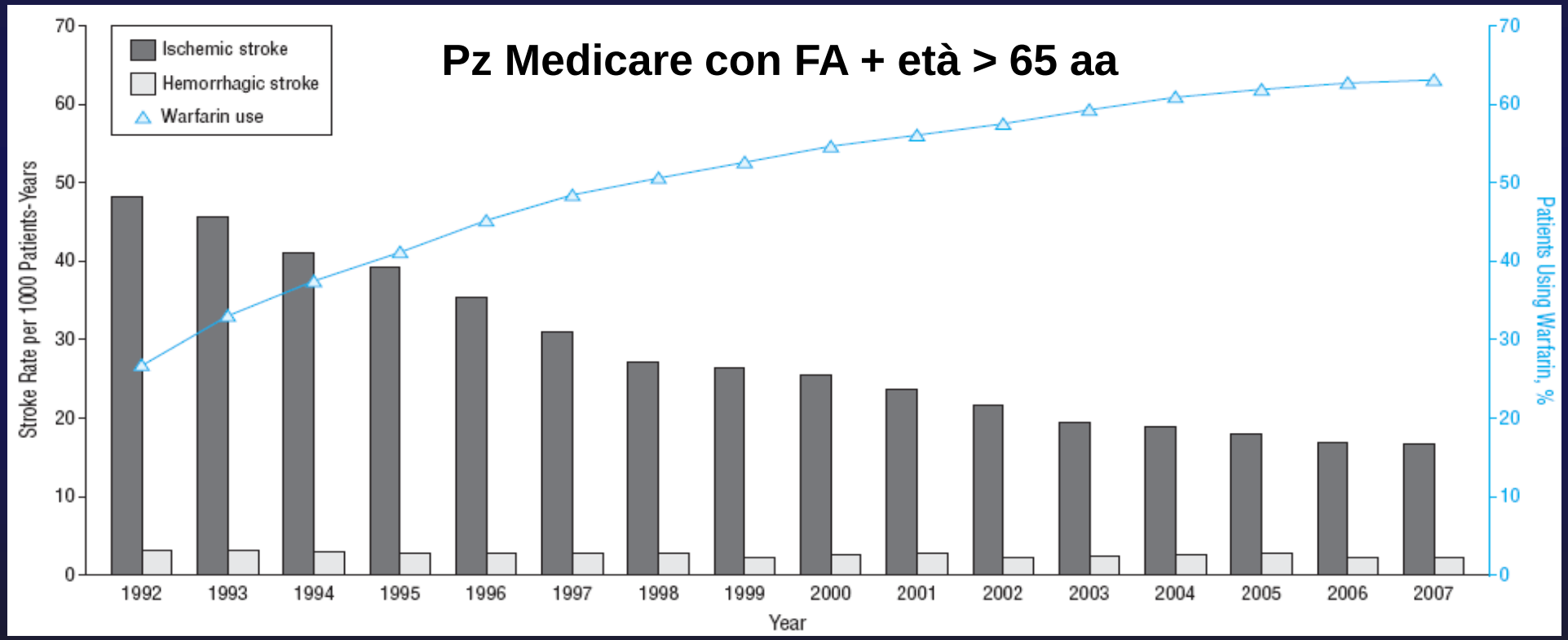
Distribuzione per età e sesso



Zoni Berisso et al Studio ISAF Am J Cardiol 2013;111:705

Fibrillazione atriale: cosa c'è di nuovo nella terapia antiaritmica?

Ictus ischemico/emorragico



Shroff JAMA Intern Med 2013;173:159

Inama G[1], Fornari C[2], Botto G[3], Tondo C[4], Chiodini V[2], Mantovani LG[2], Madotto F[2], Conti S[2], Cesana G[2]

Epidemiologia della Fibrillazione Atriale e del Flutter in Lombardia: una Coorte di Soggetti Ospedalizzati Progetto O.R.M.E.

1 Istituto Clinico F. S. Camillo, Cremona; 2 Università degli Studi di Milano - Bicocca, Monza; 3 Ospedale S.Anna, Como; 4 Centro Cardiologico Monzino, Milano

Epidemiologia della Fibrillazione Atriale e del Flutter in Lombardia: una Coorte di Soggetti Ospedalizzati

- ✓ Studio **dell'epidemiologia della fibrillazione atriale** (FA) **e del flutter** in Lombardia
  - **Tassi** di ospedalizzazione
- ✓ Analisi di una **coorte di pazienti ospedalizzati per FA e flutter** in Lombardia
  - **Caratteristiche demografiche e cliniche** al primo ricovero (evento indice)
  - **Indagine degli outcome**
    - **Sopravvivenza**
    - **Riospedalizzazione per FA**
    - **Ospedalizzazione** per:
      - Stroke
      - Attacco ischemico transitorio (TIA)
      - Complicanze emorragiche

Epidemiologia della Fibrillazione Atriale e del Flutter in Lombardia: una Coorte di Soggetti Ospedalizzati

Identificazione delle ospedalizzazioni per FA e flutter durante il periodo 2000-2010.

Diagnosi	Procedure
FA (ICD9-CM 427.31) **Flutter** (ICD9-CM 427.32)	**Cardioversione** (ICD9-CM 99.61, 99.62, 99.69) **Ablazione** (ICD9-CM 37.33, 37.34)

Criteri di inclusione

- Almeno **3 anni** di follow-up **prima** del primo ricovero
- Almeno **un anno** di follow-up potenziale **dopo** il primo ricovero.

Identificazione della coorte 2003 - 2009

Divisione in 3 gruppi

- **Gruppo FA** → Solo diagnosi di FA.
- **Gruppo flutter** → Solo diagnosi di flutter.
- **Gruppo FA e flutter** → Almeno una diagnosi di FA ed una di flutter.

Epidemiologia della Fibrillazione Atriale e del Flutter in Lombardia: una Coorte di Soggetti Ospedalizzati

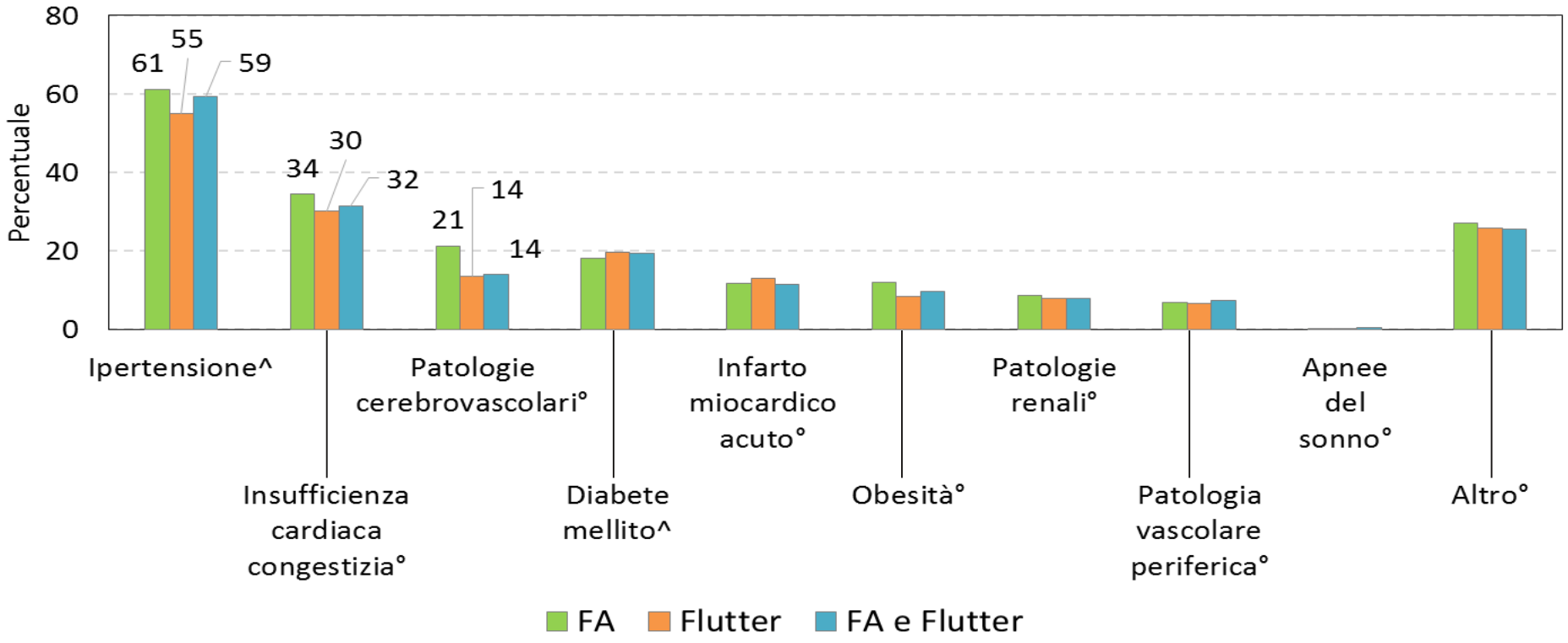
Tabella 1. Principali caratteristiche della coorte di soggetti ospedalizzati (2003 – 2009), stratificate per gruppo.

	FA	Flutter	FA e Flutter	Totale
N	143022	9100	10834	162956
Uomini (%)	70.198 (49,08)	5.637 (61,95) [a]	6.541 (60,37)[a]	82.376 (50,55)
Età in anni – Media ± DS*	75,07 ± 11,69	71,96 ± 12,97 [a]	71,26 ± 11,55 [ab]	74,64 ± 11,81
Tempo di follow-up in anni - Media ± DS*	3,19 ± 2,30	3,23 ± 2,20 [a]	4,07 ± 2,20 [ab]	3,25 ± 2,30

** Deviazione Standard*
[a] p-value vs gruppo FA < 0.05
[b] p-value vs group flutter < 0.05

Epidemiologia della Fibrillazione Atriale e del Flutter in Lombardia: una Coorte di Soggetti Ospedalizzati

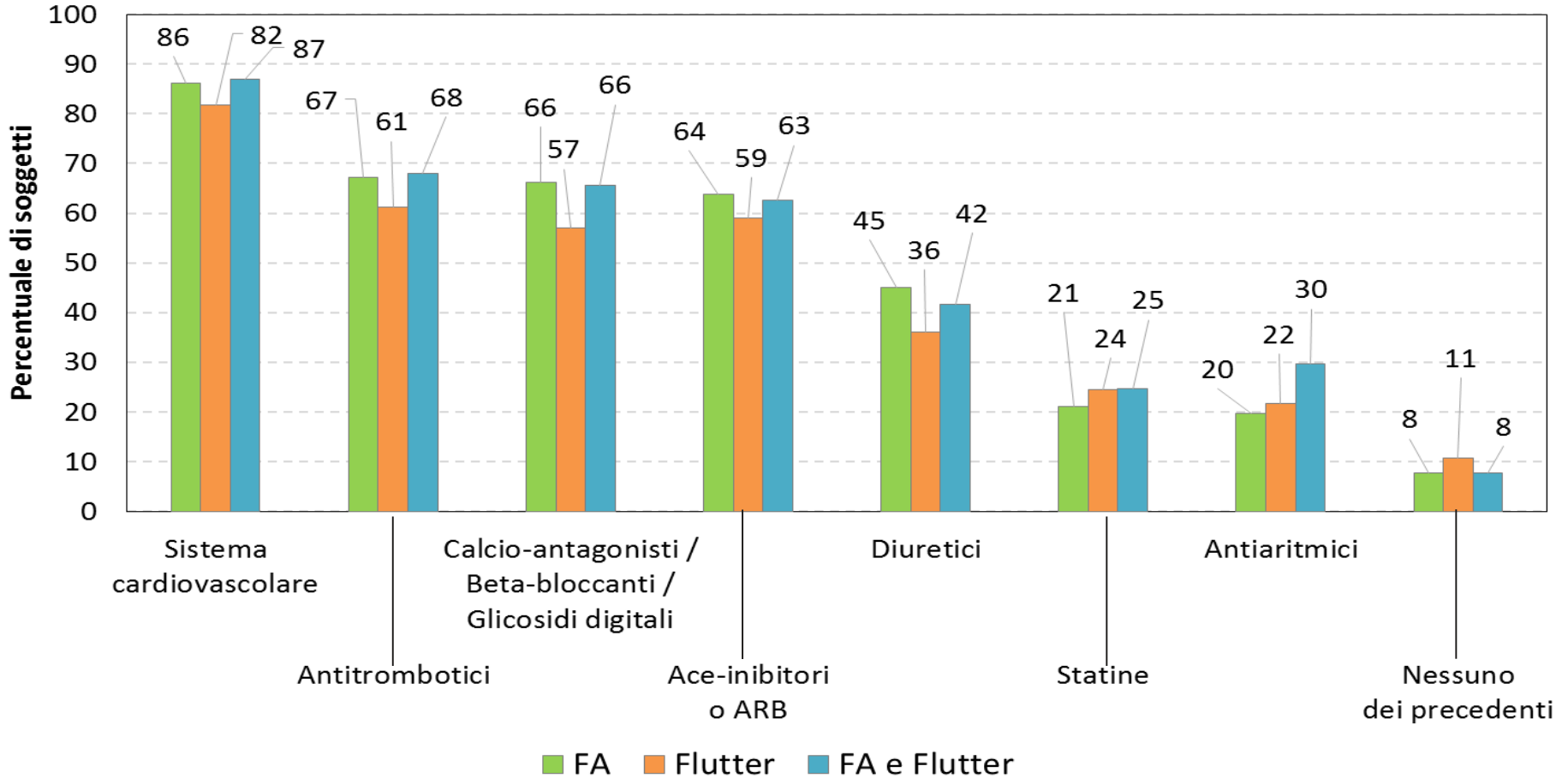
Comorbosità nei tre anni precedenti l'evento indice.



^ *Calcolato su ospedalizzazioni ed esenzioni*
°*Calcolato solo su ospedalizzazioni*

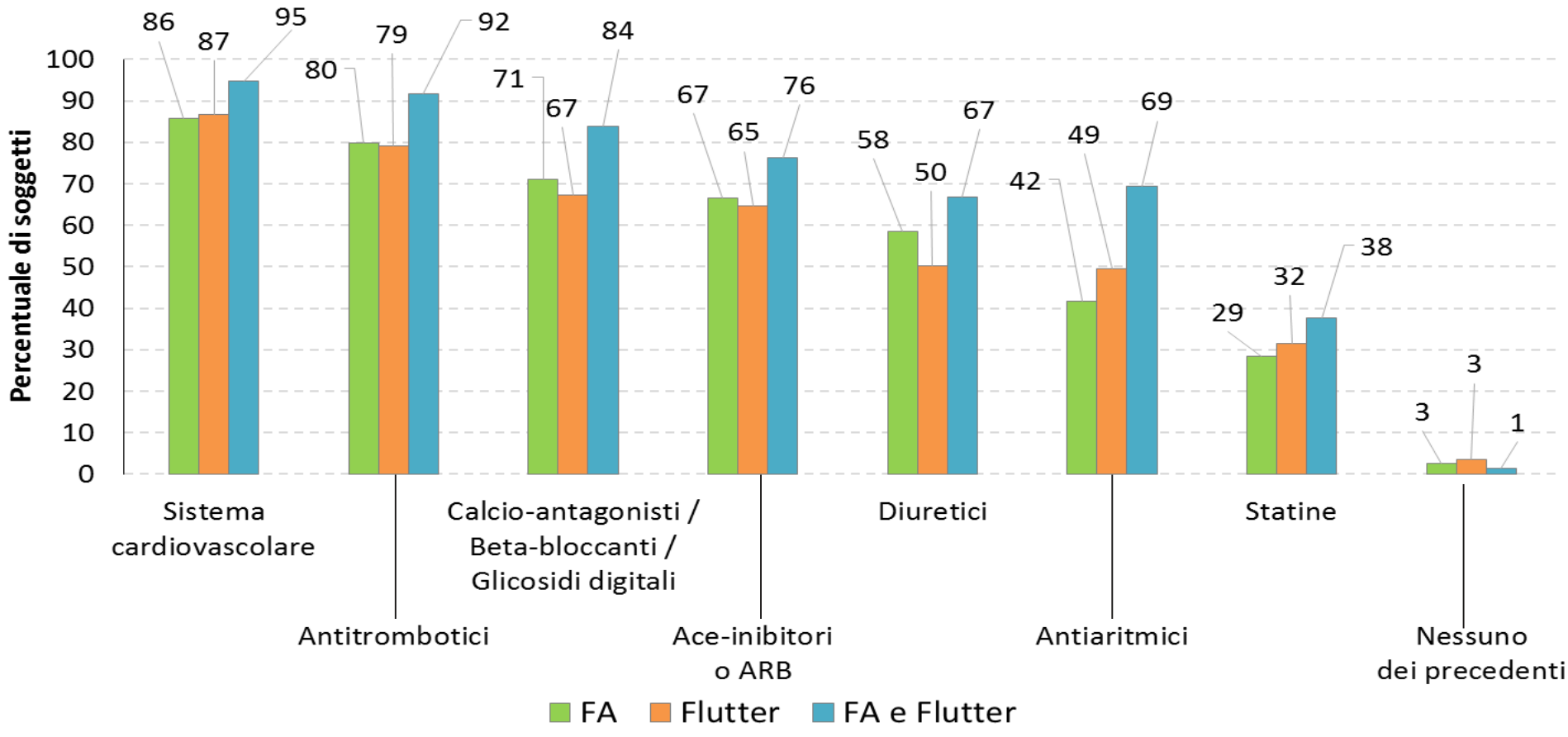
Epidemiologia della Fibrillazione Atriale e del Flutter in Lombardia: una Coorte di Soggetti Ospedalizzati

Prescrizioni farmacologiche nei tre anni precedenti l'evento indice. Percentuale di soggetti con almeno una prescrizione.



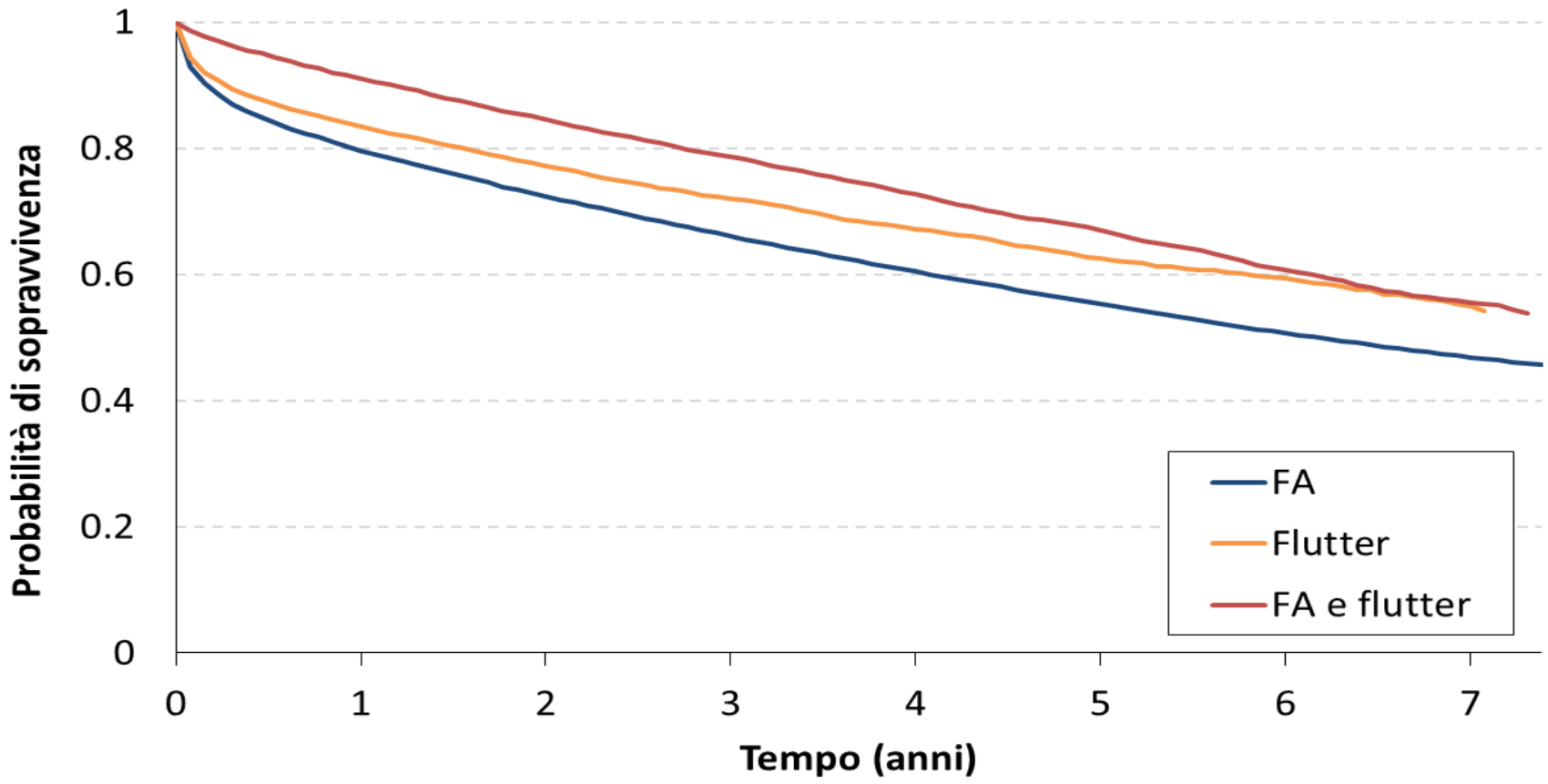
Epidemiologia della Fibrillazione Atriale e del Flutter in Lombardia: una Coorte di Soggetti Ospedalizzati

Prescrizioni farmacologiche nel follow-up. Percentuale di soggetti con almeno una prescrizione.



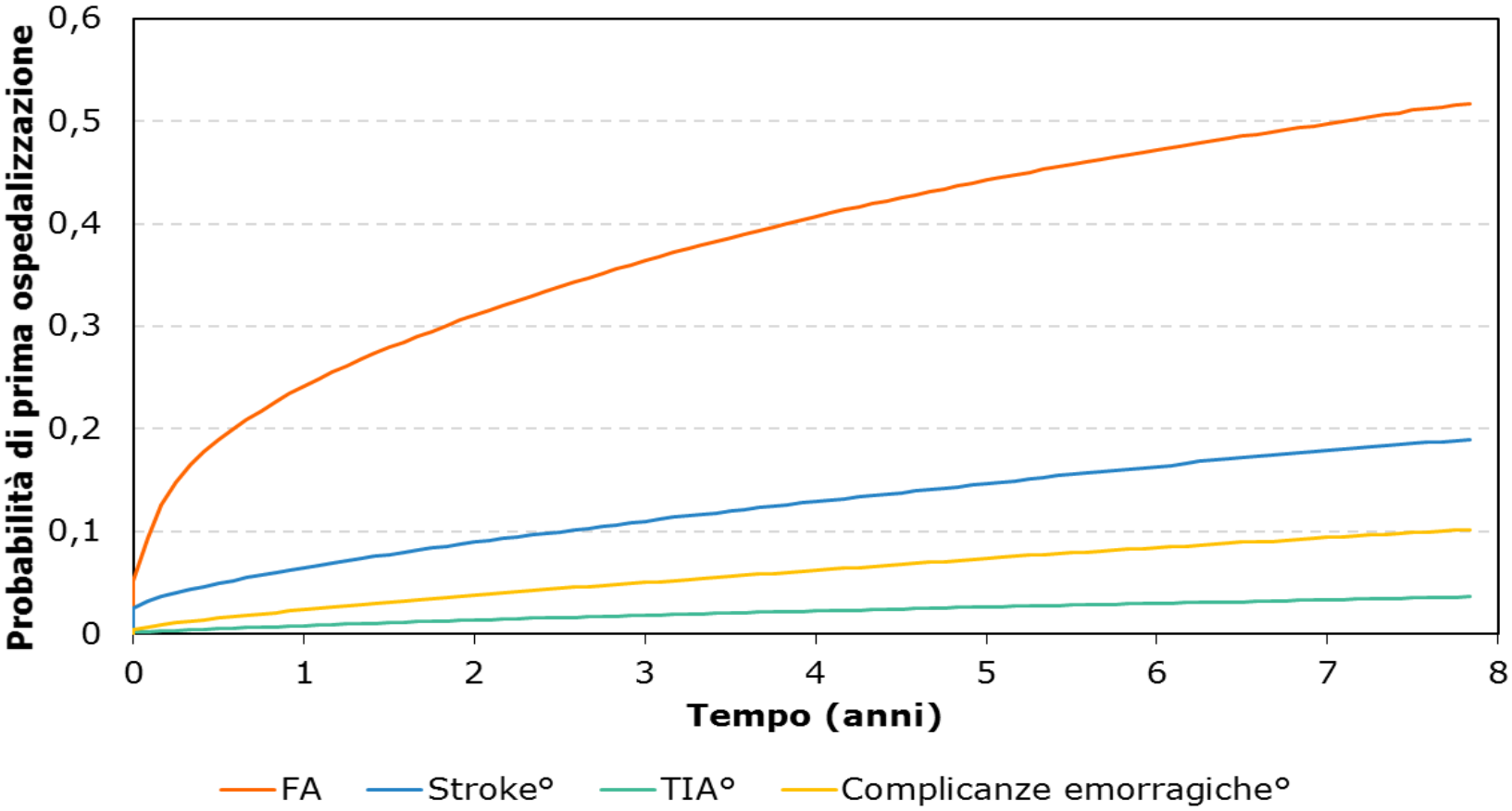
Epidemiologia della Fibrillazione Atriale e del Flutter in Lombardia: una Coorte di Soggetti Ospedalizzati

Curve di sopravvivenza nel follow-up, per ciascuno dei gruppi analizzati.



INDAGINE DEGLI OUTCOME - OSPEDALIZZAZIONI

Probabilità di sperimentare una prima ospedalizzazione di interesse nel corso del follow-up.



° *Tutte le diagnosi di dimissione.*

Fibrillazione atriale: cosa c'è di nuovo nella terapia antiaritmica?

1921	Chinidina
1953	Procainamide
1959	Lidocaina
1964	Fentoina
1966	Bretilio Tosilato
1969	Sotalolo Disopiramide Amiodarone
1973	Mexiletina Bunaftine
1975	Propafenone
1976	Tocainide
1978	Encainide
1979	Flecainide
1980	Etmozina
1990	Dofetilide (USA)
1991	Ibutilide (i.v.)
1992	**CAST**
1995	Dronedarone
2004	Ranolazina
2007	Vernakalant (i.v.)

Fibrillazione atriale: cosa c'è di nuovo nella terapia antiaritmica?

European Heart Journal (2016) **37**, 2893–2962
doi:10.1093/eurheartj/ehw210

ESC GUIDELINES

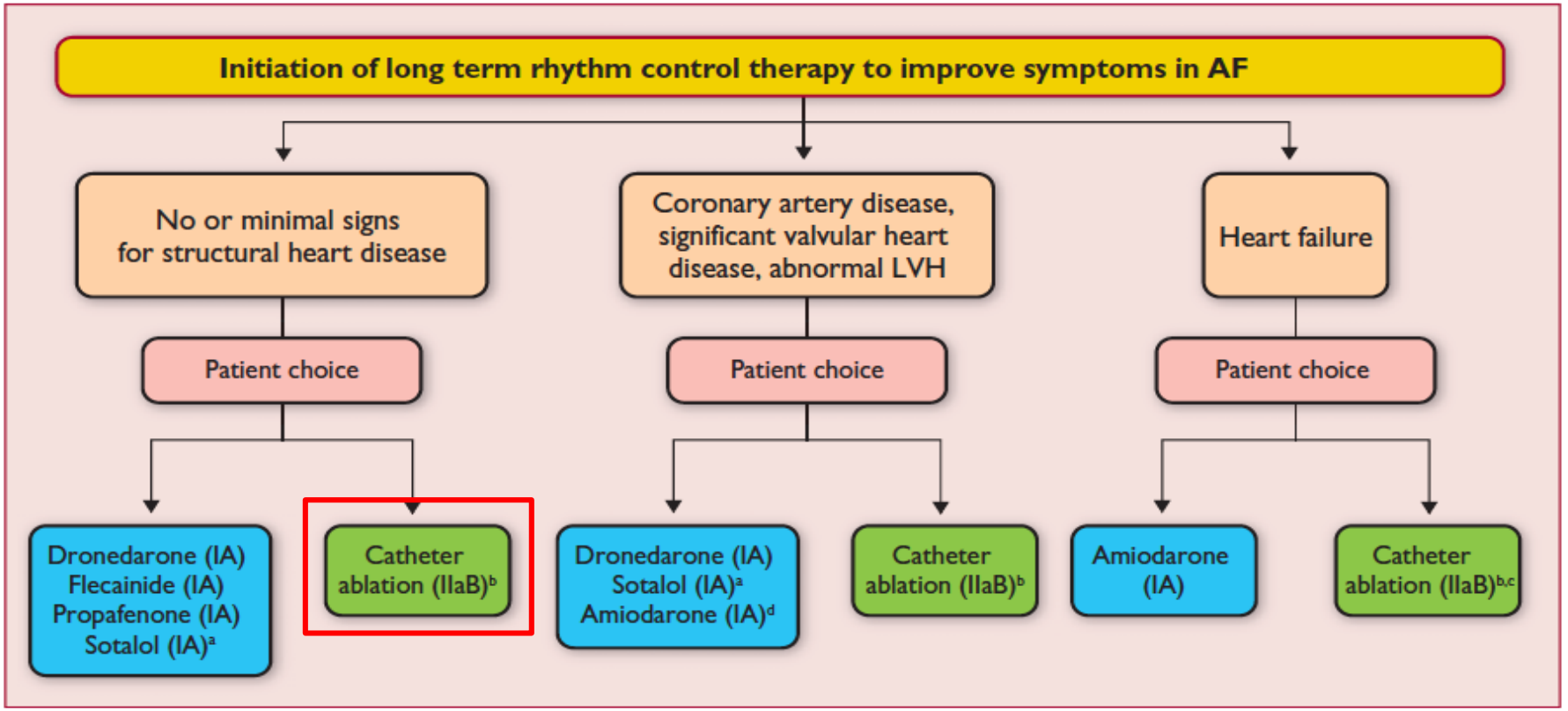
2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

The Task Force for the Management of AF of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:2893-2962

European Heart Journal (2016) 37, 2893–2962
doi:10.1093/eurheartj/ehw210

Fibrillazione atriale: cosa c'è di nuovo nella terapia antiaritmica?

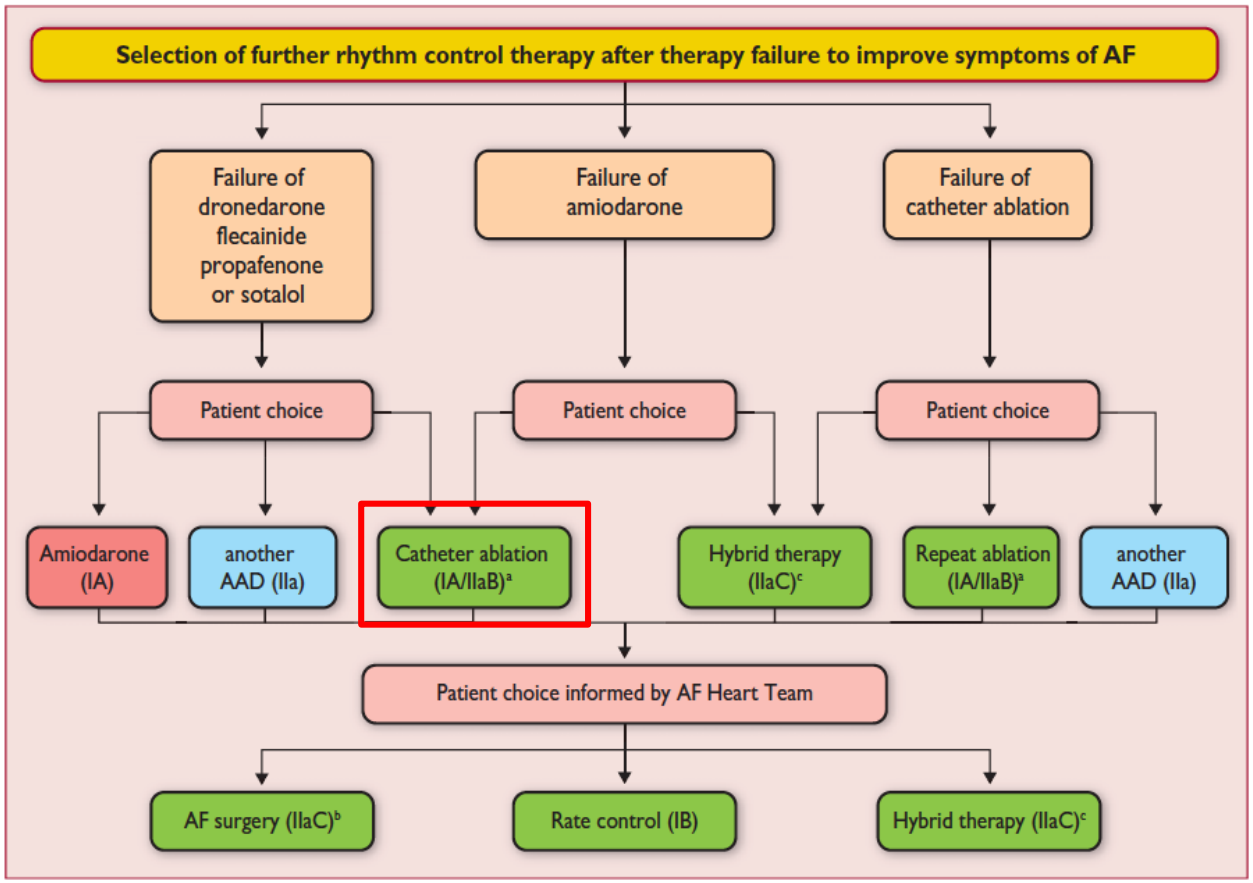


AF = atrial fibrillation; HF = heart failure; LVH = left ventricular hypertrophy;
[a]Sotalol requires careful evaluation of proarrhythmic risk.
[b]Catheter ablation should isolate pulmonary veins and can be performed using radiofrequency or cryoballoon catheters.
[c]Catheter ablation as a first-line therapy is usually reserved for heart failure patients with tachycardiomyopathy.
[d]Amiodarone is a second-choice therapy in many patients because of its extracardiac side-effects.

Figure 17 Initiation of long-term rhythm control therapy in symptomatic patients with atrial fibrillation.

European Heart Journal (2016) 37, 2893–2962
doi:10.1093/eurheartj/ehw210

Fibrillazione atriale: cosa c'è di nuovo nella terapia antiaritmica?



AAD = antiarrhythmic drug; AF = atrial fibrillation; PVI = pulmonary vein isolation.
[a]catheter ablation should target PVI. IA for paroxysmal AF, IIaB for persistent and long-standing persistent AF.
[b]AF surgery may be PVI (e.g. in paroxysmal AF) or maze surgery (e.g. in therapy-refractory or persistent and long-standing persistent AF).
[c]Hybrid therapy involves combination of antiarrhythmic drugs, catheter ablation, and/or AF surgery.

Figure 20 Choice of rhythm control therapy following treatment failure.

ATHENA, PALLAS, ANDROMEDA

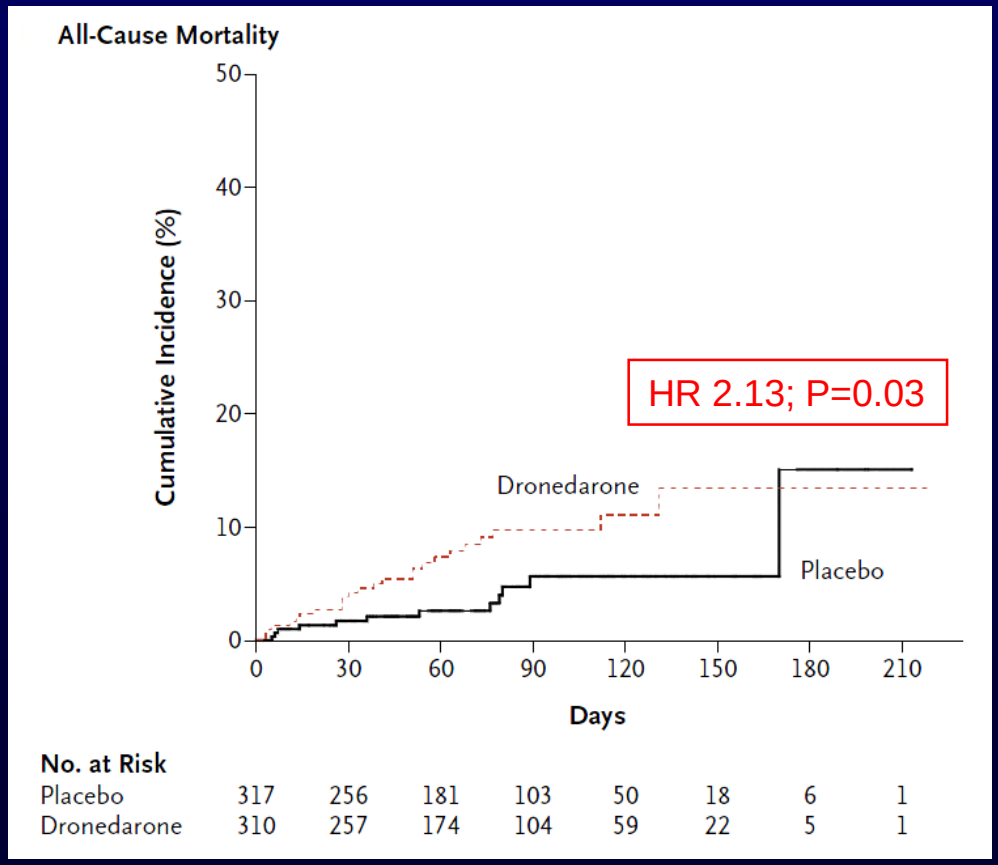
Demographics, *Clinical Characteristics and Outcomes of Study Pts*

Variable	ATHENA	PALLAS	ANDROMEDA
Mean age (ys)	72	75 (52% ≥ 75y)	72
Baseline AF	25	100 (70% perm AF > 2ys)	25
Hypertension	86	83	37
Coronary Artery D.	30	41	65
Heart Failure II-III	21	54	97
LVEF	12 <45%	20<40%	100 < 35%
Previous stroke	13	27	NA
Beta-blocker ACE-i or AT-II-i Digoxin	71 70 14	74 78 33	61 86 31
Oral anticoagulant	60	84	31
Death Any Death CV Death Arrhythmic	0.84 0.71 0.55	1.94 2.11 3.26	2.13 2.75 1.68
Stroke	0.66	2.32	NA
Congestive HF	0.86	1.89	1.22

Morbidity/Mortality Studies With Dronedarone

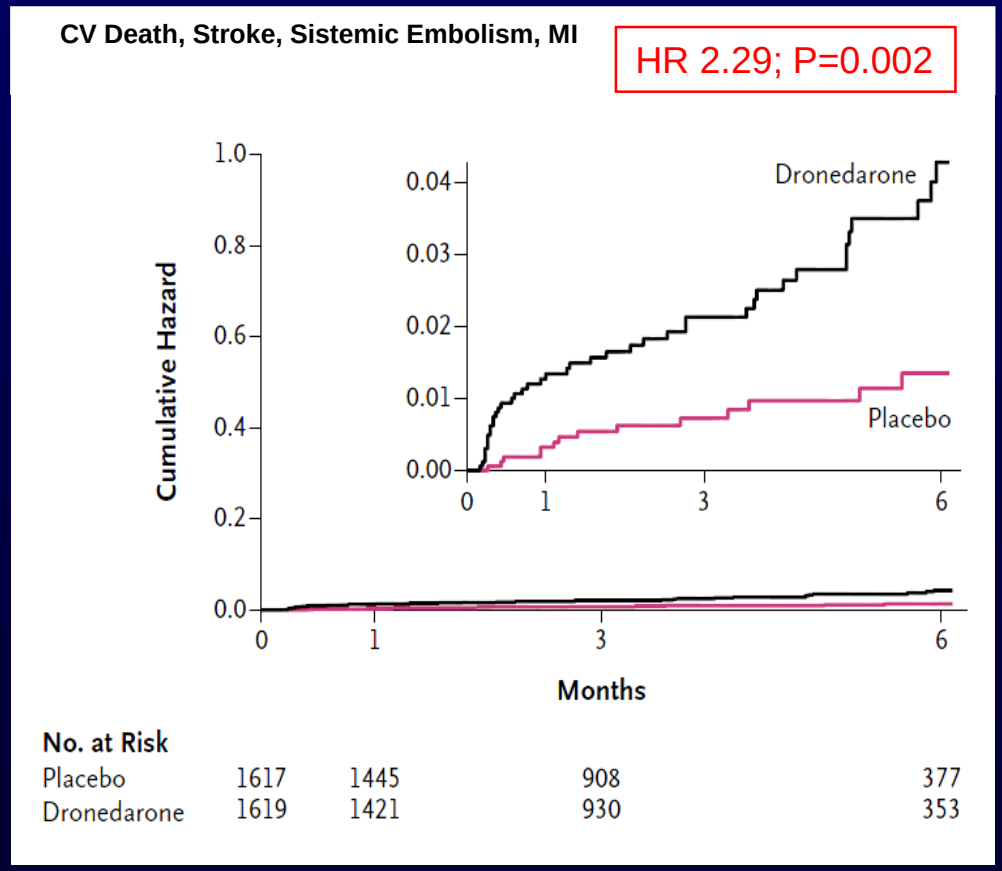
Antiarrhythmic Effect Not The Main Espected Driver

ANDROMEDA
Severe HF population (25% AF)



Kober L. N Engl J Med 2008

PALLAS
High Risk Permanent AF population



Connolly S. New Engl J Med 2011

2012 Update of the ESC Guidelines on The Management of Atrial Fibrillation

Dronedarone IS NOT Recommended

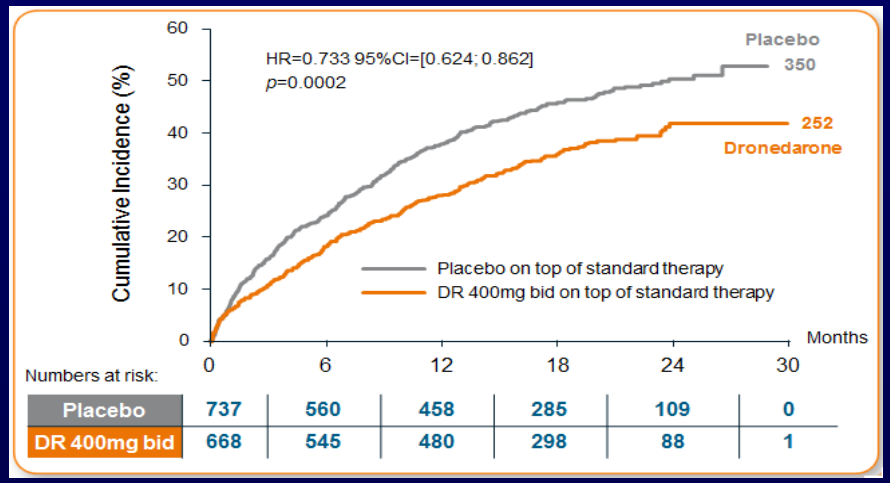
Recommendations (not recommended)	Class	Level
Dronedarone is not recommended for treatment of AF in patients with NYHA class III and IV, or with recently unstable (decompensation within the prior month) NYHA class II heart failure.	III	B
Dronedarone is not recommended in patients with permanent AF	III	B

Camm AJ. Eur Heart J 2012; 33: 2719-2747 (modif.)

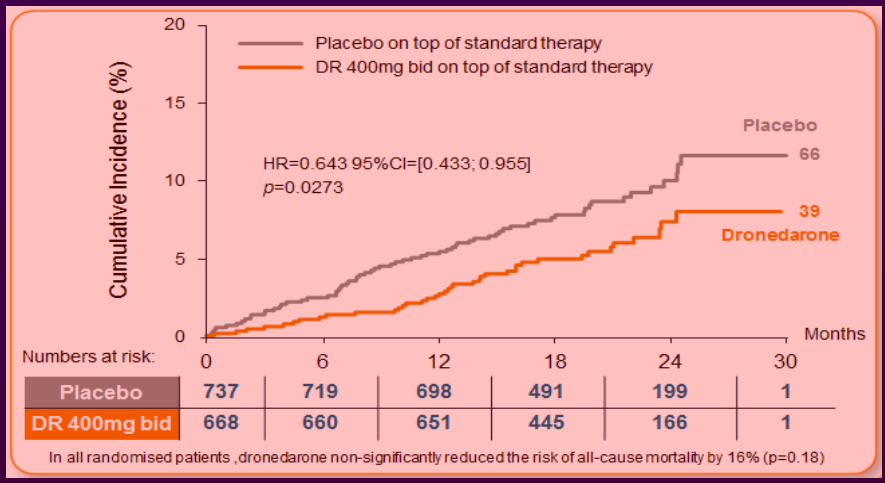
ATHENA: Coronary Heart Disease Sub-Group

Dronedarone Reduced …

…the risk of unplanned CV hospitalisation or death by 27%

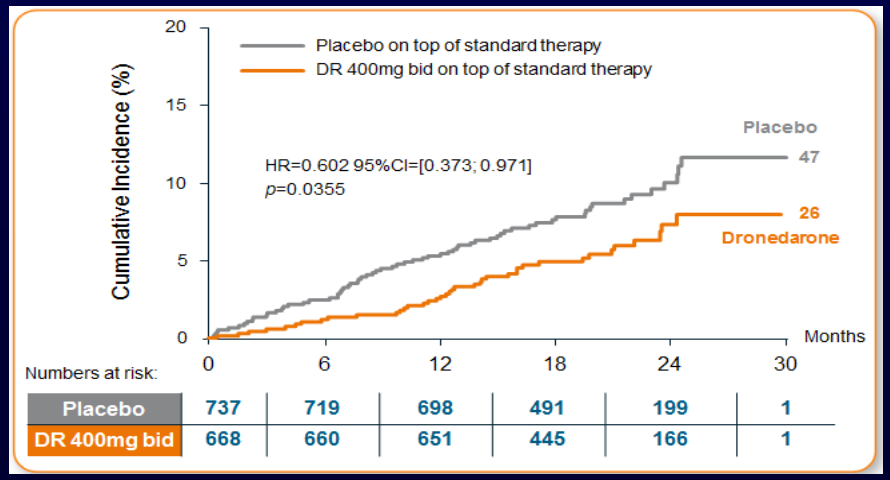


…the risk of overall mortality by 36%

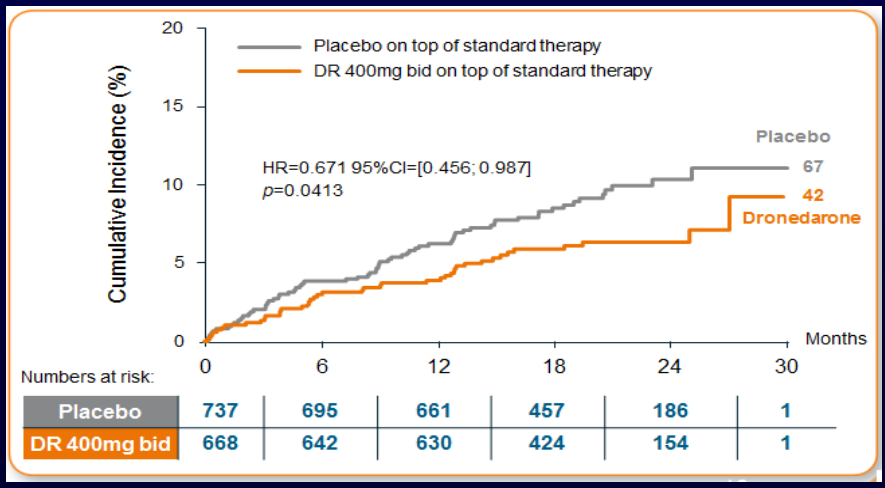


In all randomised patients ,dronedarone non-significantly reduced the risk of all-cause mortality by 16% (p=0.18)

…the risk of CV mortality by 40%

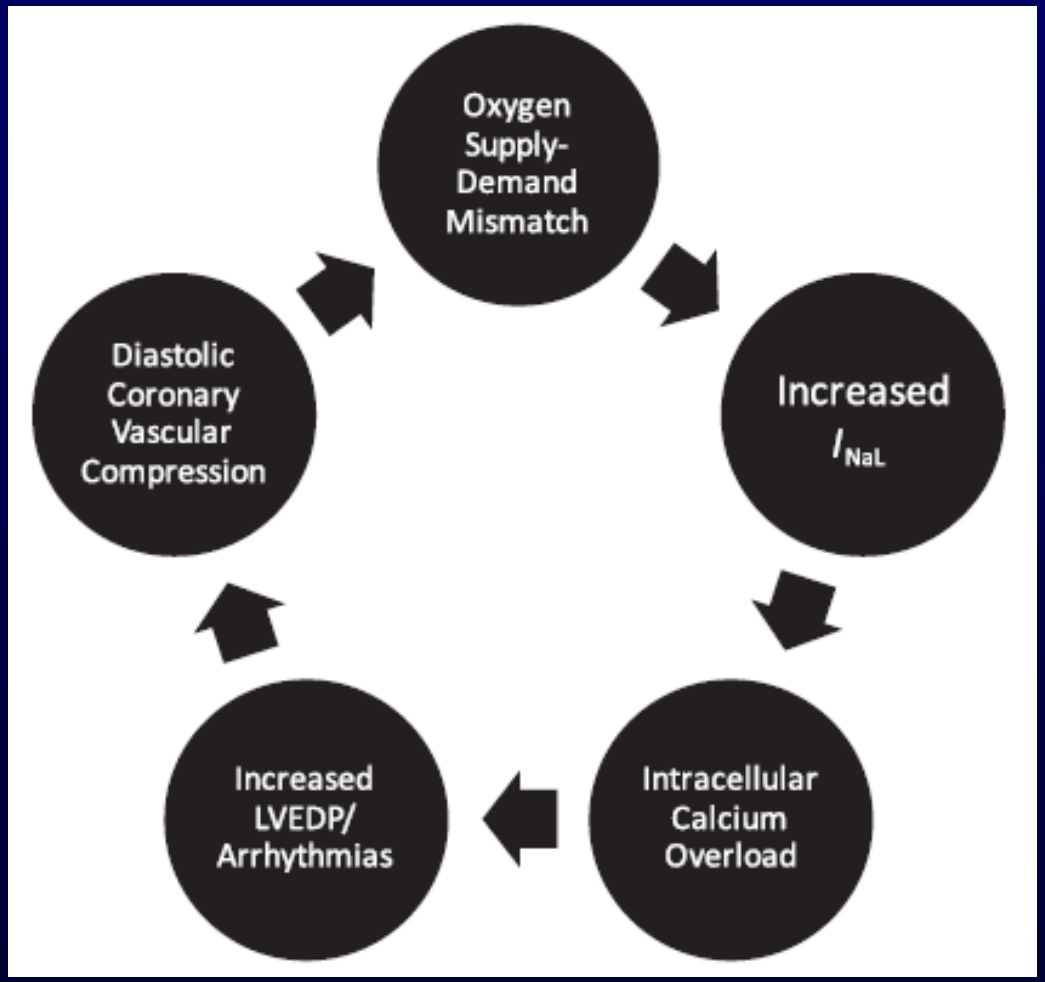


…the time to first ACS



Pisters R. Europace Advance Access published September 26, 2013

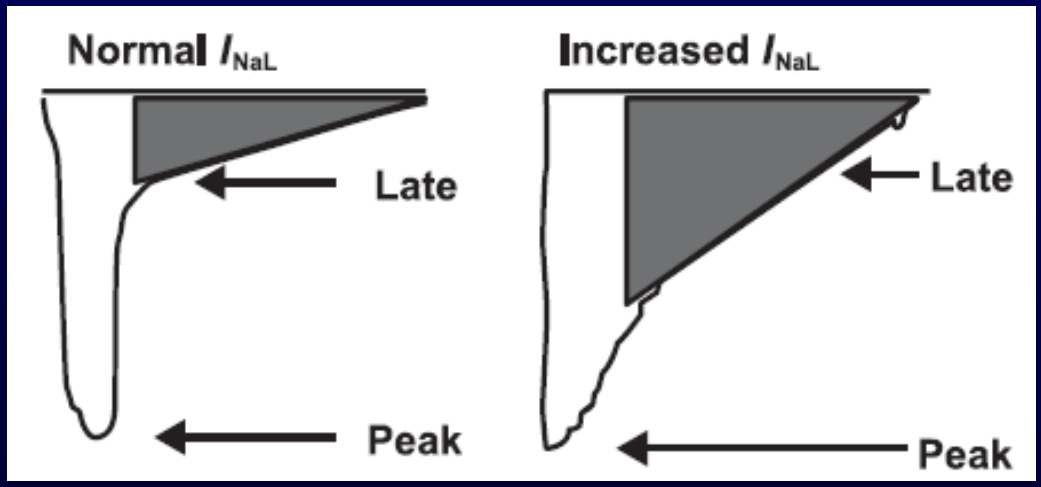
Fibrillazione atriale: cosa c'è di nuovo nella terapia antiaritmica?



Stone PH Cardiol Clin 2008; 26: 603-614

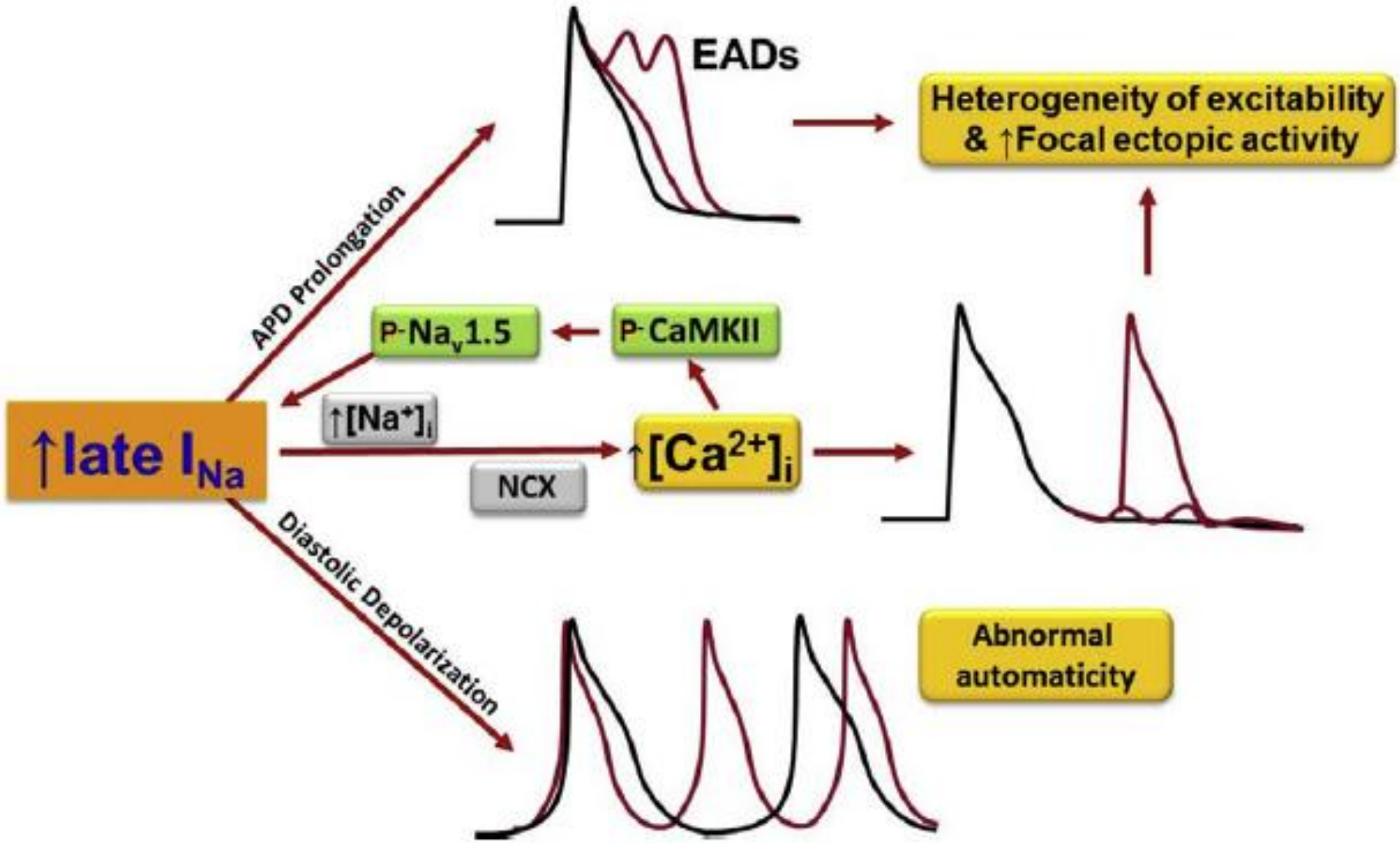
Effect of Ranolazine

Late inhibition of inward Na current (I_{Na}) under normal and pathologic increased state



Hasenfuss G.
Clin Res Cardiol 2008; 97: 222-6

Mechanisms of Late I_{Na} induced Arrhythmia

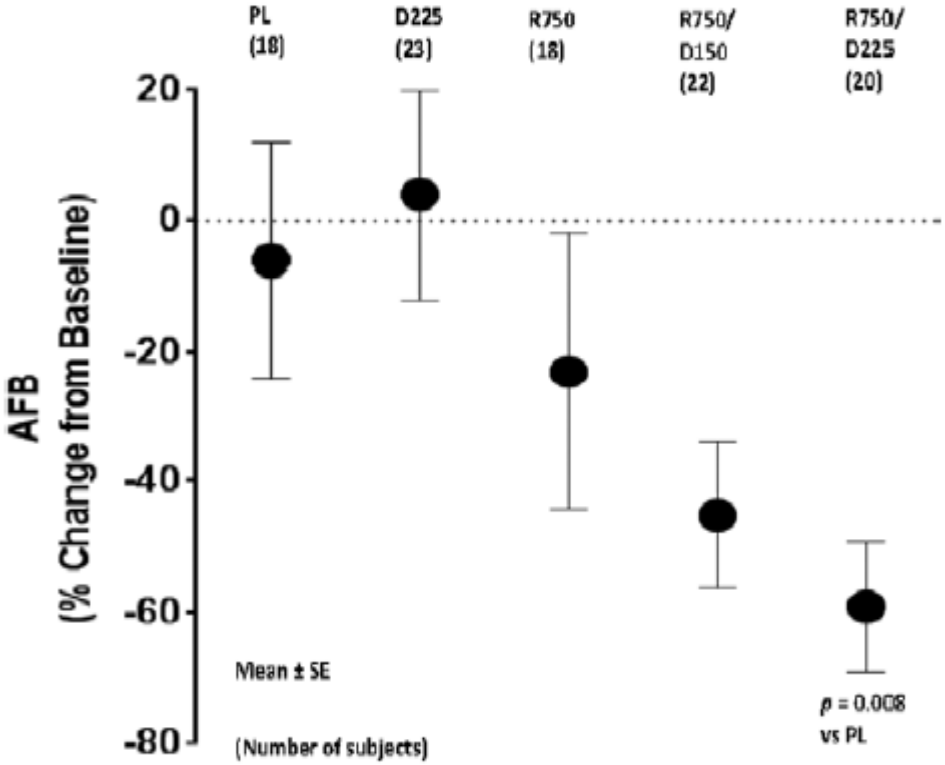


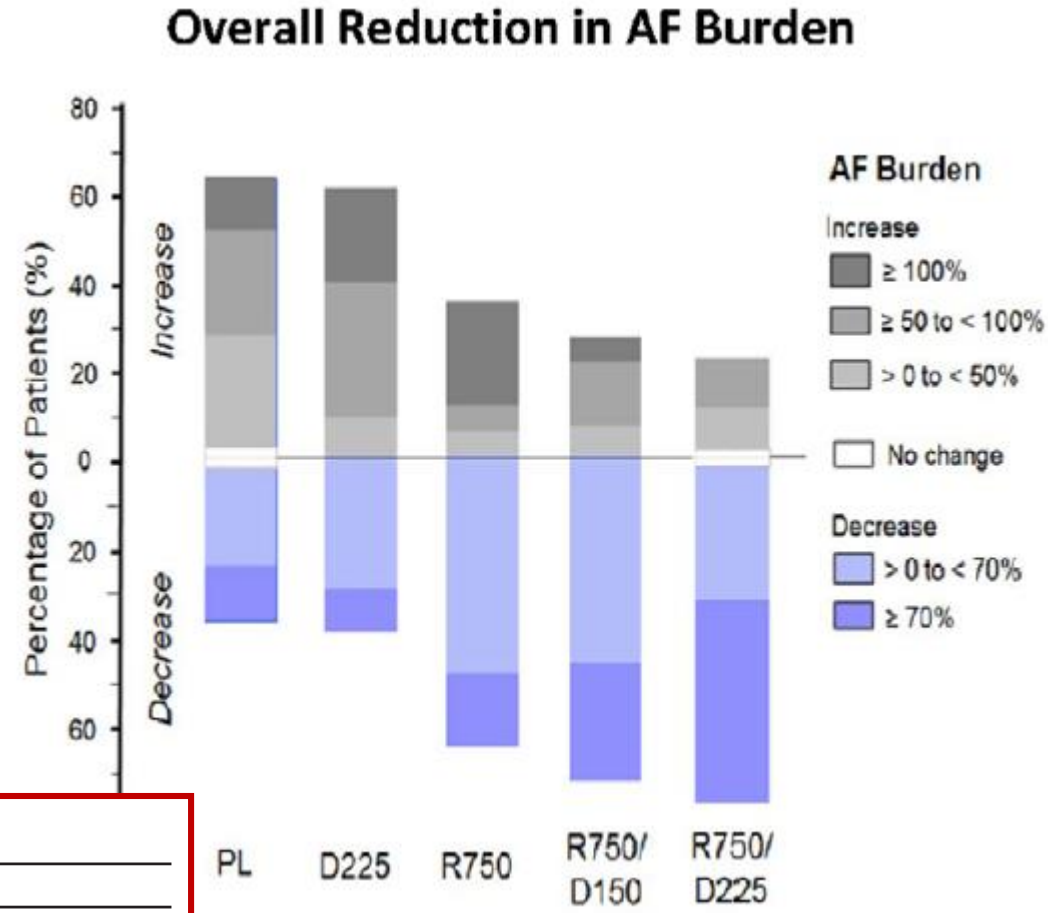
Shryock JC. Cardiovasc Res 2013; 99: 603

Clinical Trial on Ranolazine

Trial Name	Type	No. of Patients	Dosage	Endpoints	Results
MERLIN-TIMI 36[5,6] 2007	Multinational, double-blind, randomized, placebo-controlled, parallel-group clinical trial	6560	*Ranolazine IV* + *Oral extended release:* 1000 mg twice a day (3279 patients) OR *Placebo* (3281 patients)	*Primary endpoint:* Cardiovascular death, recurrent ischemia, myocardial infarction, or documented arrhythmias	Additional ranolazine to standard treatment of ACS did not reduce major cardiovascular events or all-cause mortality; ranolazine did not adversely affect all-cause death or symptomatic documented arrhythmias; ranolazine was effective as an antianginal agent in a high-risk patient group; ranolazine did not pose any proarrhythmic effect; ranolazine significantly reduced episodes of VT, SVT, and new-onset AF
RAFFAELLO[44] 2015	Double-blind, randomized, double-dummy, placebo-controlled, dose-ranging phase II study	238	*Ranolazine:* 375 mg (65 patients), 500 mg (60 patients), 750 mg (58 patients) *Placebo* (55 patients)	*Primary endpoint:* Time to recurrence after successful cardioversion	Ranolazine was safe in all 3 doses; 500-mg and 750-mg groups combined reduced AF recurrences; ranolazine did not prolong the QTc interval; no proarrhythmic effects in the ranolazine-treated groups
RAID In progress	Double-blind, randomized, placebo-controlled, phase III study	Currently Recruiting (est. 1440)	*Ranolazine:* 500 mg BID for 1 wk and then increase to 1000 mg BID *Placebo*	*Primary endpoint:* Reduction in ventricular tachycardia or fibrillation requiring ICD interventions (ie, antitachycardia pacing therapy, ICD shocks, or death)	In progress
Ranolazine New Onset AF in Post-OP Cardiac Surgery	Double-blind, randomized, placebo-controlled, 1:1	54	*Ranolazine:* 1000 mg BID *Placebo*	*Primary endpoint:* AF up to 14 d postoperatively *Secondary endpoint:* Readmission 30 d postoperatively	38% reduction in the incidence of postoperative AF compared with 30% on placebo
Heart & Rhythm Medical Group 2014	Retrospective observational study	31	*Ranolazine:* 500 mg BID *Placebo*	Incidence, duration of AF/AFL, number of PAC/PVC couples, and VT	Ranolazine at 500 mg BID significantly reduced atrial and ventricular arrhythmias; no significant change in ECG interval; no proarrhythmic effects

Combined Ranolazine and Dronedarone in Paroxysmal AF: *The HARMONY Trial*





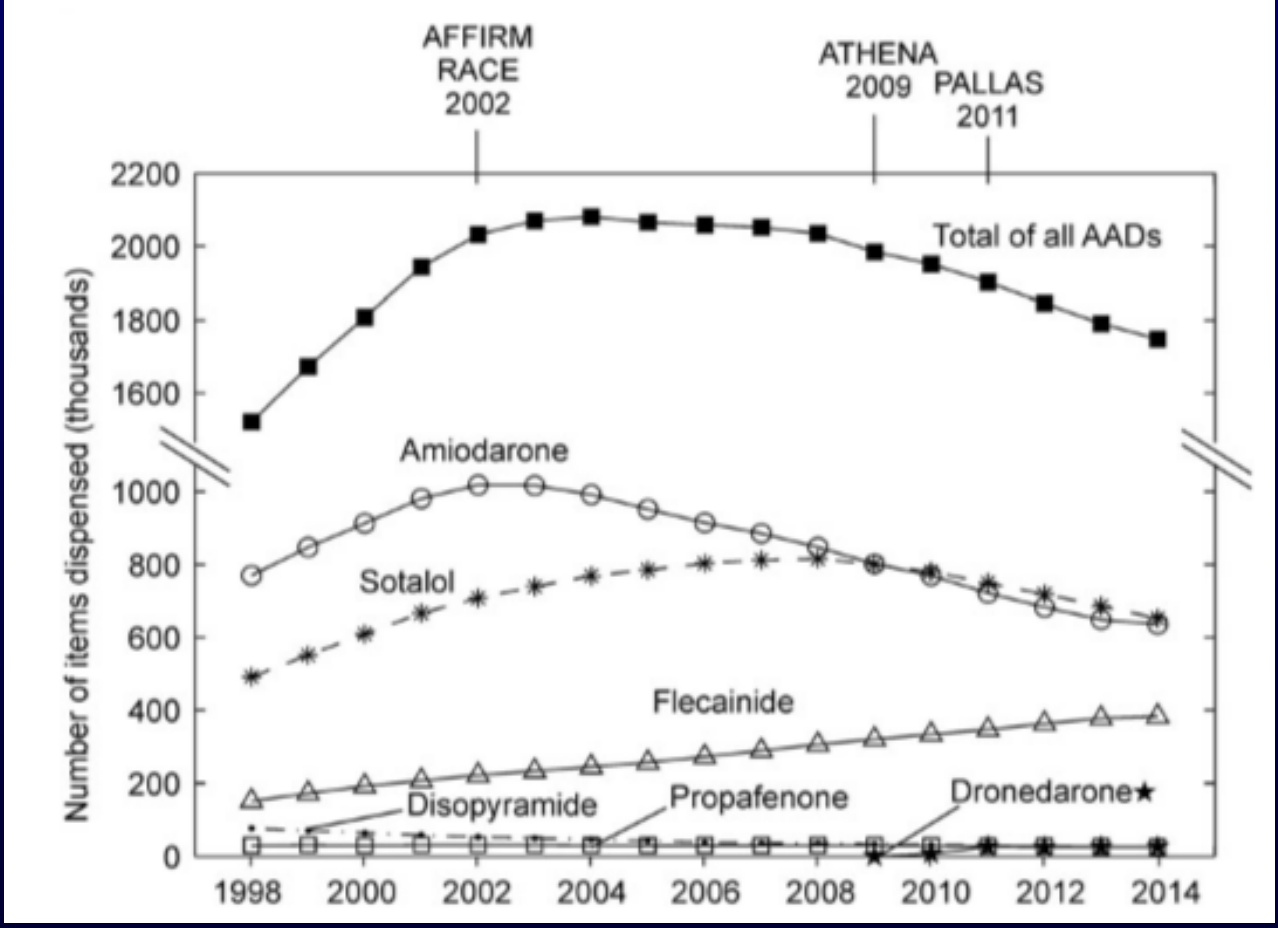
Summary of Treatment Emergent Adverse Events (TEAE)

	No (%) of Patients With Any Event				
	PL (N=26)	D225 (N=26)	R750 (N=26)	R750/D150 (N=26)	R750/D225 (N=27)
Patients with any TEAE					
AE	15 (58)	18 (69)	17 (65)	16 (62)	20 (74)
SAE	1 (4)	2 (8)	7 (27)	1 (4)	5 (19)
AE leading to discontinuation	3 (12)	4 (15)	5 (19)	5 (19)	5 (19)

Reiffel JA.
Circ AEP. 2015; 8: 1048-1056

Fibrillazione atriale: cosa c'è di nuovo nella terapia antiaritmica?

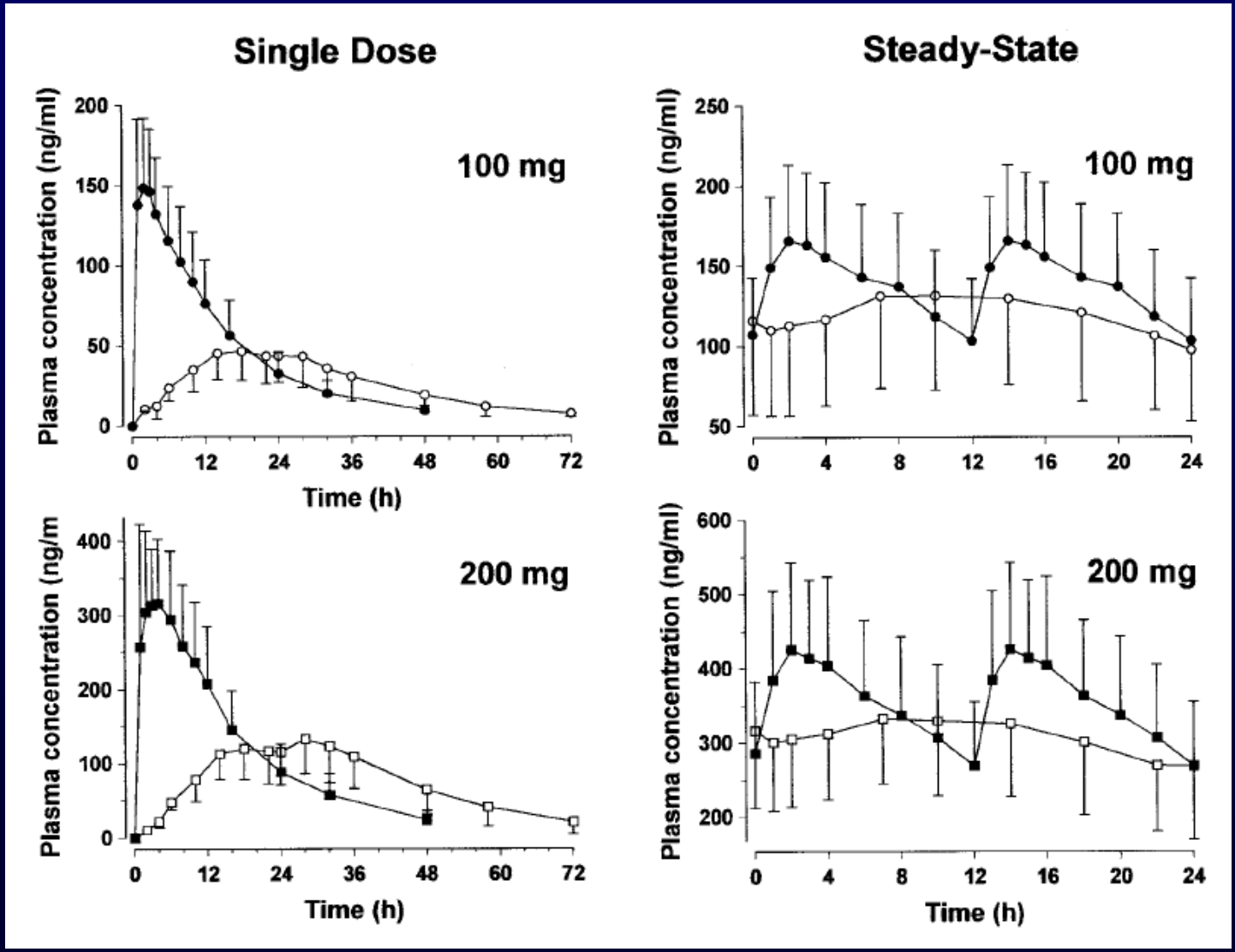
Trend in AADs Dispensations in England1998–2014



EHJ Cardiovascular Pharmacotherapy 2016; 2, 90–94

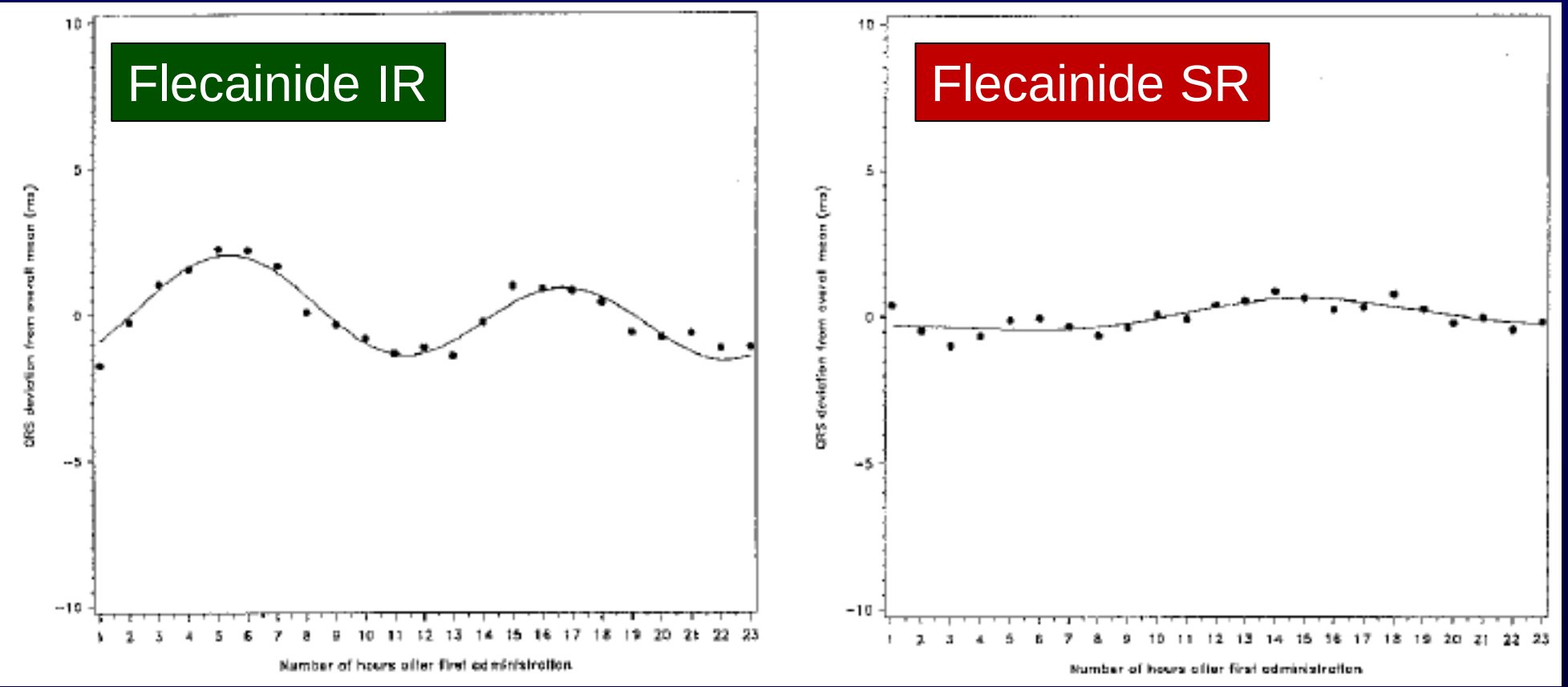
PK and EKGraphic effects of a new controlled-release form of flecainide acetate:

Comparison with the standard form



Tennezè L. Clin Pharmacol Ther 2002; 72: 112-22

PD Equivalence of Two Flecainide Acetate Formulations in Patients With Paroxysmal AF by QRS Analysis of Ambulatory EKG



Coumel P. J Cardiovasc Pharmacol 2003; 41: 771-779

Fibrillazione atriale: cosa c'è di nuovo nella terapia antiaritmica?

Europace (2016) **18**, 1698–1704
doi:10.1093/europace/euv462

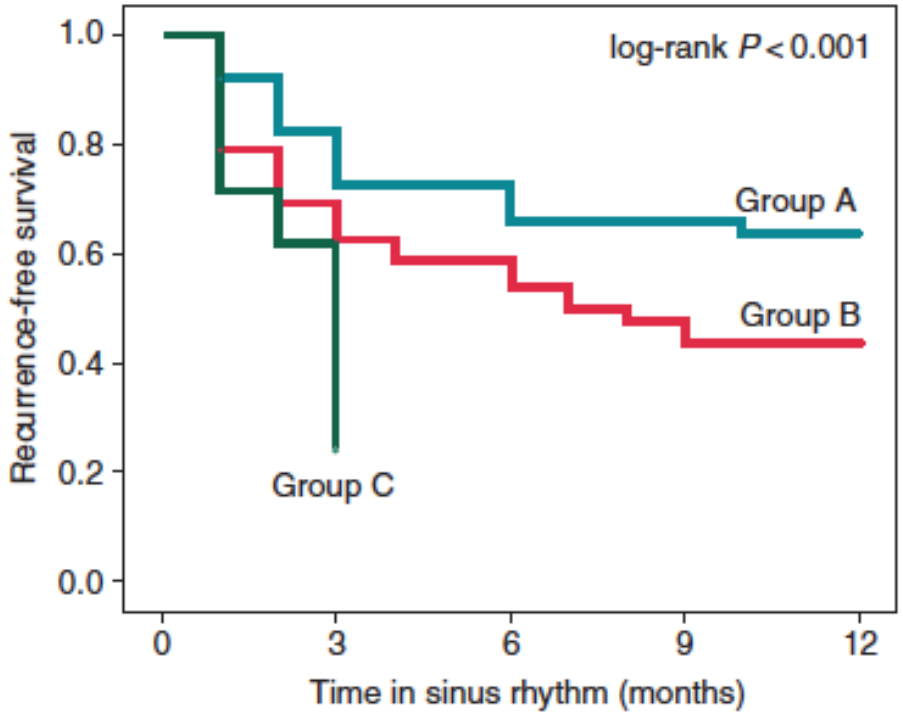
CLINICAL RESEARCH
Atrial fibrillation

Flecainide–metoprolol combination reduces atrial fibrillation clinical recurrences and improves tolerability at 1-year follow-up in persistent symptomatic atrial fibrillation

Alessandro Capucci[1], Luca Piangerelli[1], Jenny Ricciotti[1], Domenico Gabrielli[2], and Federico Guerra[1]*

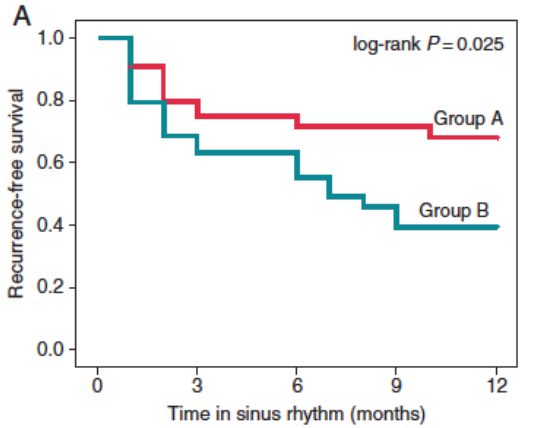
Europace (2016) **18**, 1698–1704
doi:10.1093/europace/euv462

Fibrillazione atriale: cosa c'è di nuovo nella terapia antiaritmica?

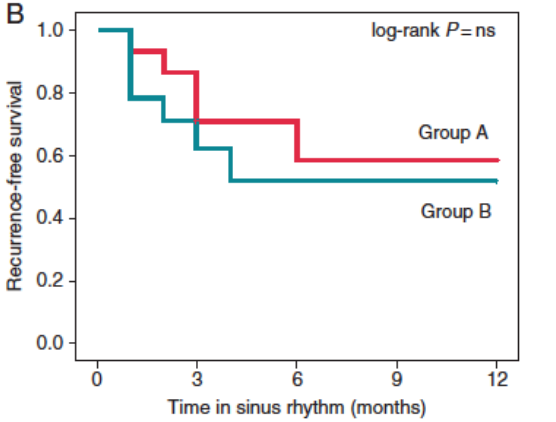


Group A	80	53 (0.73)	37 (0.69)	33 (0.69)	32 (0.67)
Group B	72	38 (0.63)	28 (0.54)	21 (0.47)	20 (0.47)
Group C	21	5 (0.76)	–	–	–

Figure 1 Recurrence-free survival during the 12-month follow-up period.



Group A	47	34 (79.7)	23 (75.2)	19 (75.2)	17 (71.1)
Group B	45	26 (68.9)	18 (55.0)	15 (43.6)	13 (43.6)



Group A	33	25 (0.87)	17 (0.60)	13 (0.60)	11 (0.60)
Group B	27	16 (0.69)	11 (0.52)	9 (0.52)	8 (0.52)

Figure 3 Recurrence-free survival during 12-month follow-up in patients with (*A*) persistent AF and (*B*) paroxysmal AF.

Fibrillazione atriale: cosa c'è di nuovo nella terapia antiaritmica?

Conclusion

Metoprolol and flecainide combination therapy improves effectiveness of rhythm control, reducing recurrences in persistent symptomatic AF up to 30% over 1-year follow-up period. Combination therapy leads to a better tolerability, with reduction of side effects and overall improved compliance. Combination therapy with flecainide and metoprolol positively affects physical aspects of quality of life when compared with a flecainide-only regimen.

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Fibrillazione atriale: cosa c'è di nuovo nella terapia antiaritmica?

Conclusioni

- La scelta terapeutica va decisa nel singolo paziente
- Il farmaco antiaritmico è la prima scelta. In casi particolari anticipare l'ablazione
- Considerare la frequenza, la durata, la severità dei singoli episodi aritmici
- Isolate recidive non vanno considerate fallimento della terapia
- La disponibilità di nuovi AA è scarsa mentre lo sviluppo delle tecniche ablative è incalzante

Fibrillazione atriale: cosa c'è di nuovo nella terapia antiaritmica?

SPECIAL ARTICLES

The End of the Disease Era

Mary E. Tinetti, MD, Terri Fried, MD

The time has come to abandon disease as the focus of medical care. The changed spectrum of health, the complex interplay of biological and nonbiological factors, the aging population, and the interindividual variability in health priorities render medical care that is centered on the diagnosis and treatment of individual diseases at best out of date and at worst harmful. A primary focus on disease may inadvertently lead to undertreatment, overtreatment, or mistreatment. The numerous strategies that have evolved to address the limitations of the disease model, although laudable, are offered only to a select subset of persons and often further fragment care. Clinical decision making for all patients should be predicated on the attainment of individual goals and the identification and treatment of all modifiable biological and nonbiological factors, rather than solely on the diagnosis, treatment, or prevention of individual diseases. Anticipated arguments against a more integrated and individualized approach range from concerns about medicalization of life problems to "this is nothing new" and "resources would be better spent determining the underlying biological mechanisms." The perception that the disease model is "truth" rather than a previously useful model will be a barrier as well. Notwithstanding these barriers, medical care must evolve to meet the health care needs of patients in the 21st century. **Am J Med. 2004;116:179–185.** ©2004 by Excerpta Medica Inc.

(Tinetti M.E, Fried T. **Am J Med 2004;116:179–185)**

Fibrillazione atriale: cosa c'è di nuovo nella terapia antiaritmica?

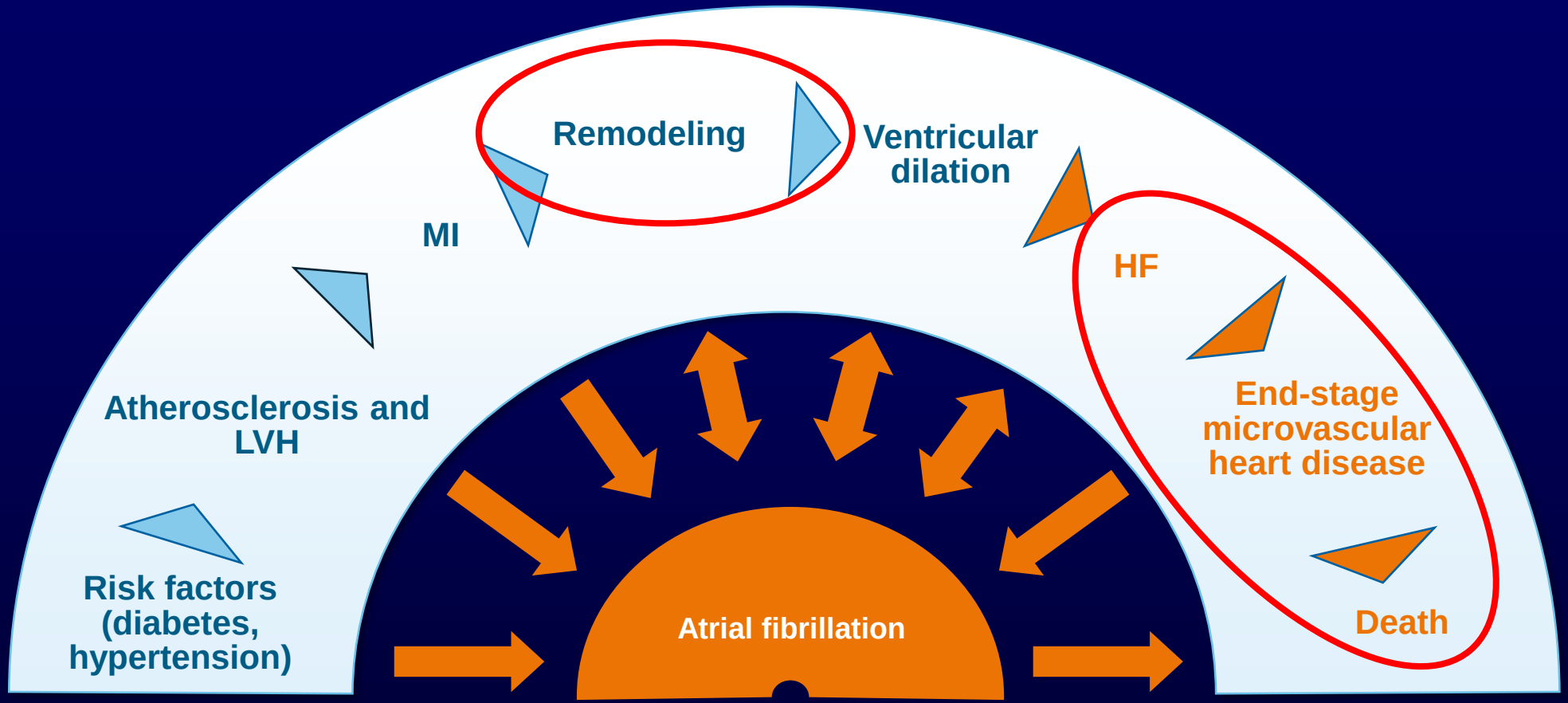
Non è più tempo di pensare ad una sola condizione nei nostri pazienti

Table 1. Characteristics of Two Models of Medical Care

Disease-Oriented Model	Integrated, Individually Tailored Model
Clinical decision making is focused primarily on the diagnosis, prevention, and treatment of individual diseases.	Clinical decision making is focused primarily on the priorities and preferences of individual patients.
Discrete pathology is believed to cause disease; psychological, social, cultural, environmental and other factors are secondary factors, not primary determinants of disease.	Health conditions are believed to result from the complex interplay of genetic, environmental, psychological, social, and other factors.
Treatment is targeted at the pathophysiologic mechanisms thought to cause the disease(s).	Treatment is targeted at the modifiable factors contributing to the health conditions impeding the patient's health goals.
Symptoms and impairments are best addressed by diagnosing and treating "causative" disease(s).	Symptoms and impairments are the primary foci of treatment even if they cannot be ascribed to a discrete disease.
Relevant clinical outcomes are determined by the disease(s).	Relevant clinical outcomes are determined by individual patient preference.
Survival is the usual primary focus of disease prevention and treatment.	Survival is one of several competing goals.

(Tinetti M.E, Fried T. **Am J Med 2004;116:179–185)**

AFIB Within The Cardiovascular Continuum



AF is NOT a DISEASE, but rather a manifestation of a number of **CLINICAL SYNDROMES,** some of which are curable