From AF Management to Stroke Prevention

Taiwan Association of Lipid Educators 2014/01/26

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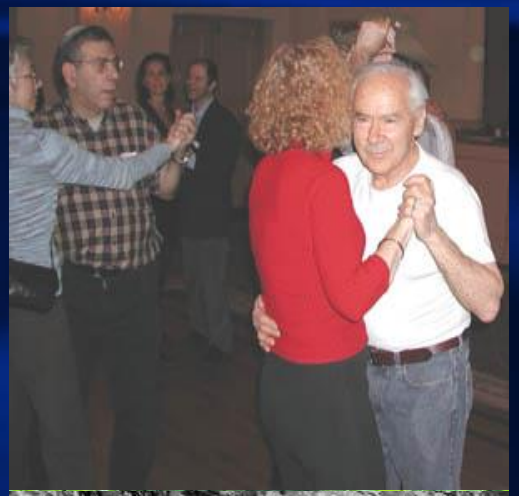
Stroke & Chronic Disability

Framingham Heart Study 2005

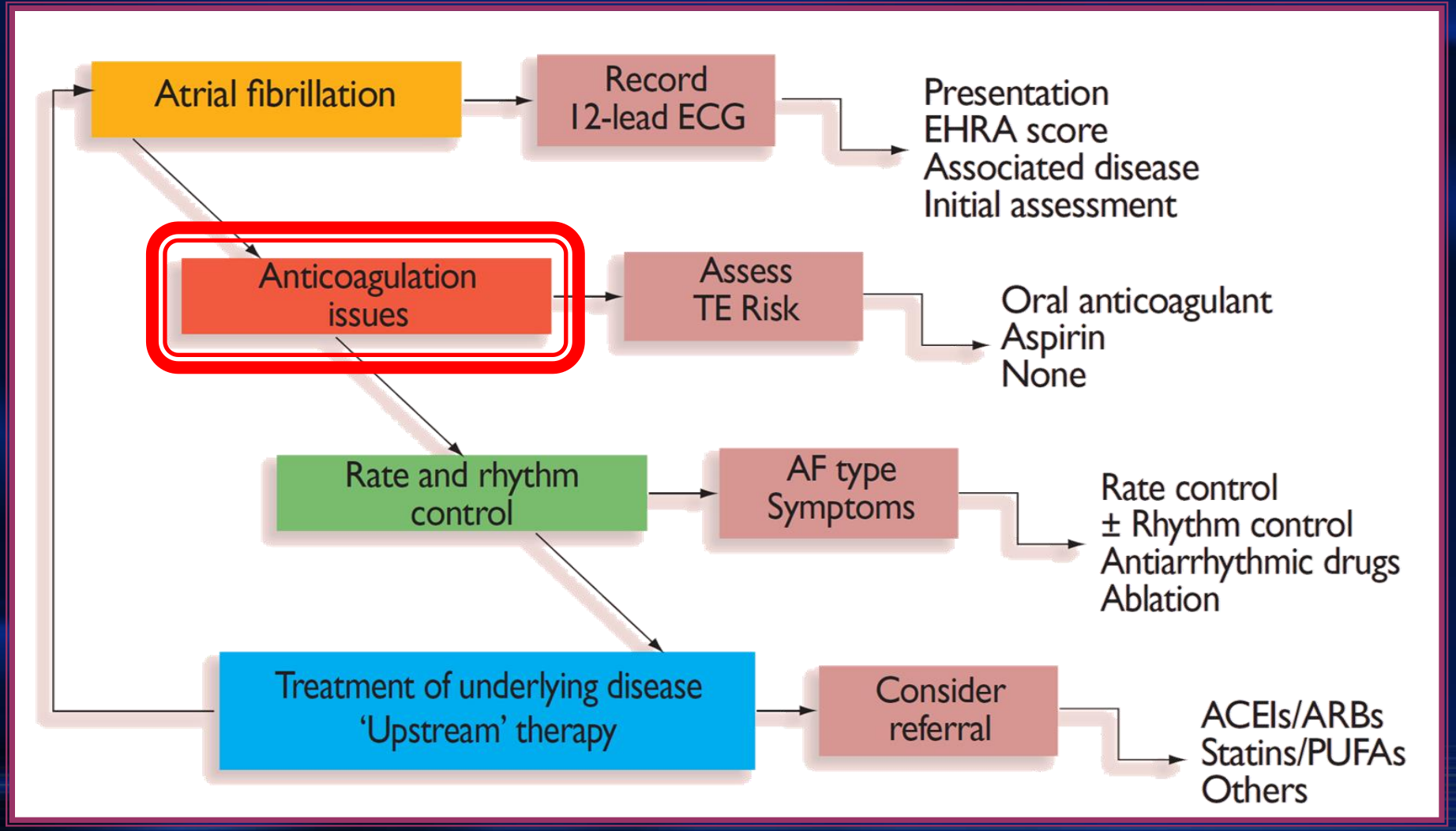
Six months post-stroke:

- **50 %** Hemiparesis
- **35 %** Depression
- **30 %** Unable to walk without some assistance
- **26 %** Dependent in ADL (activities of daily living: grooming, eating, bathing, etc)
- **26 %** Institutionalized in a nursing home
- **19 %** Aphasia (trouble speaking or understanding the speech of others)



Principles of Management

2010 ESC AF Guideline



Primary Endpoint of Stroke or Systemic Embolism: Non-inferiority Analysis

		HR	Non Inferiority p vs warfarin
RE-LY			
Dabigatran 110 mg	1.53% / yr	0.91	<0.001
Dabigatran 150 mg	1.11% / yr	0.66	<0.001
Warfarin	1.69% / yr		(ITT)
ROCKET AF			
Rivaroxaban 20 mg	1.7% / yr	0.79	<0.001
Warfarin	2.2% / yr		(Modified ITT)
ARISTOTLE			
Apixaban 5 mg	1.27% / yr	0.79	<0.001
Warfarin	1.60% / yr		(ITT)
ENGAGE AF			
Edoxaban 60 mg	1.18% / yr	0.79	<0.001
Edoxaban 30 mg	1.61% / yr	1.07	0.005
Warfarin	1.5% / yr		(Modified ITT)

Major Bleeding

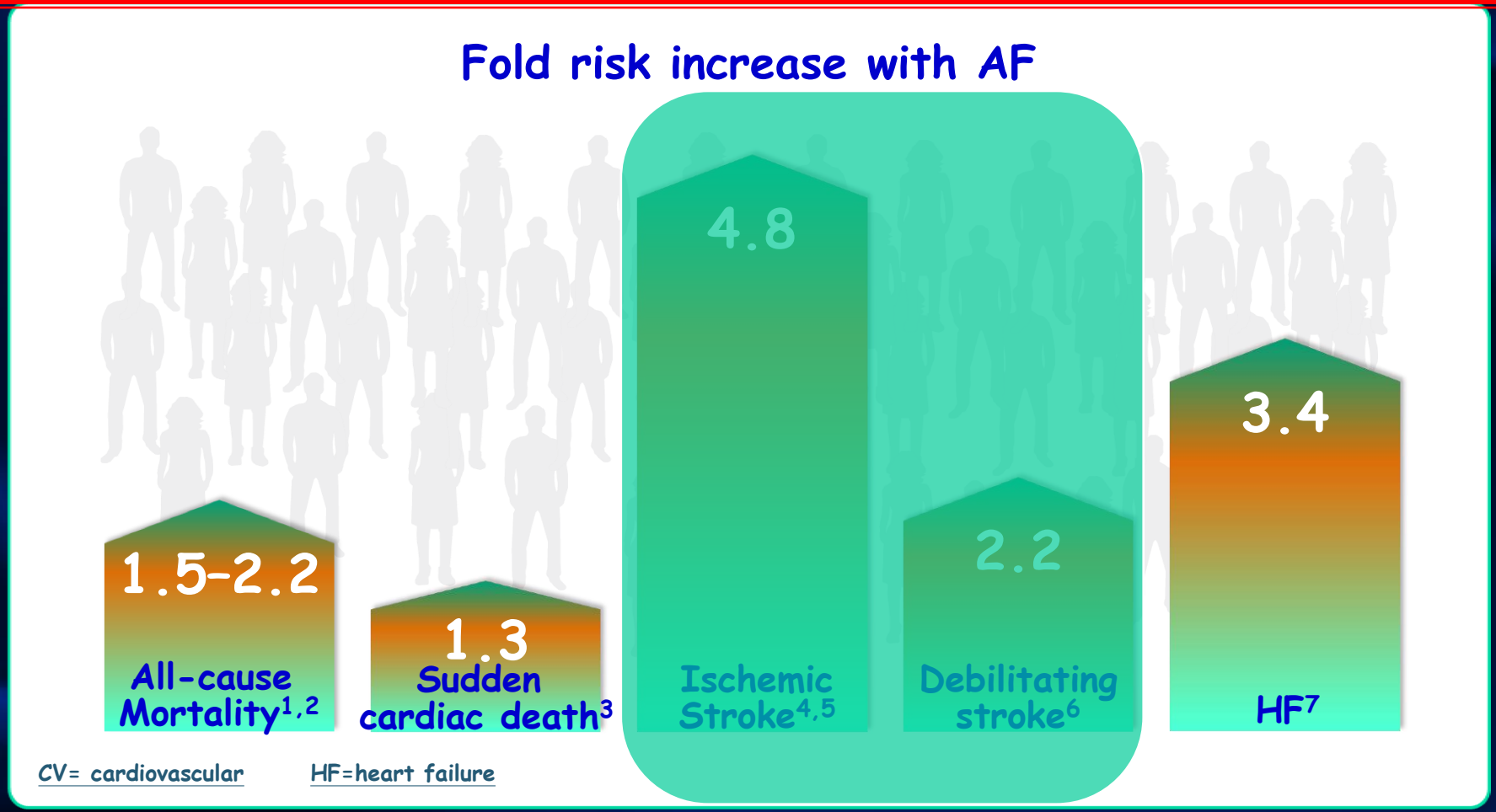
RE-LY		HR	ITT p vs warfarin
Dabigatran 110 mg	2.71% / yr	0.8	0.003
Dabigatran 150 mg	3.11% / yr	0.93	0.31
Warfarin	3.36% / yr		
ROCKET AF	150 mg Dabigatran vs 110 mg Dabigatran HR 1.16 (1.00–1.34) p = 0.052		
Rivaroxaban 20 mg	3.60% / yr	0.92	0.58* (On Treatment)
Warfarin	3.45% / yr		2 g drop
ARISTOTLE			
Apixaban 5 mg	2.13% / yr	0.69	<0.001
Warfarin	3.09% / yr		2 g drop in 24 hours
ENGAGE AF			
Edoxaban 60mg	2.75% / yr	0.8	<0.001
Edoxaban 30mg	1.61% / yr	0.47	<0.001
Warfarin	3.43% / yr		

Atrial Fibrillation

Goals of Acute and Chronic Therapy

- Prevent thromboembolic complication
- Improve symptoms / quality of life
- Treat / prevent heart failure
  - ✓ Stroke Prevention
- Reduce healthcare costs
- Prolong survival

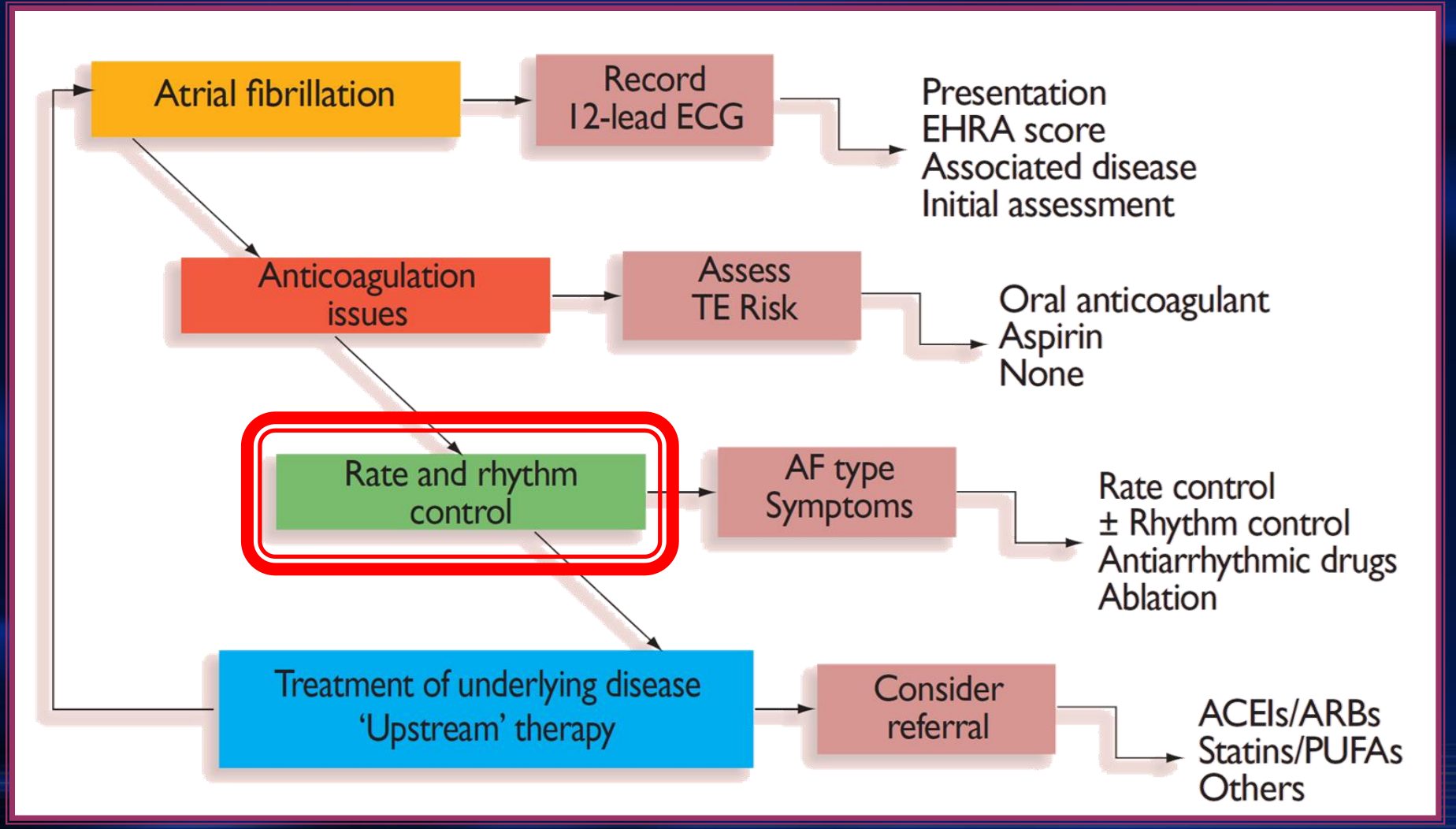
AF increases patients' risk of death, HF and CV events



1. The Task Force for the Management of Atrial Fibrillation of the ESC. Eur Heart J 2010;31(19):2369-429.
2. Stewart S, et al. Am J Med 2002;113:359-64.
3. Pedersen OD, et al. Eur Heart J 2006; 27: 290-5
4. Wolf PA, et al. Stroke 1991; 22: 983-8
5. Page RL, et al. Circulation 2003; 107: 1141-5
6. Dalli DA, et al. Neuroepidemiology 2003; 22: 118-23
7. Stewart S, et al. Am J Med 2002; 113: 359-64

Principles of Management

2010 ESC AF Guideline



Why is rhythm control indicated?

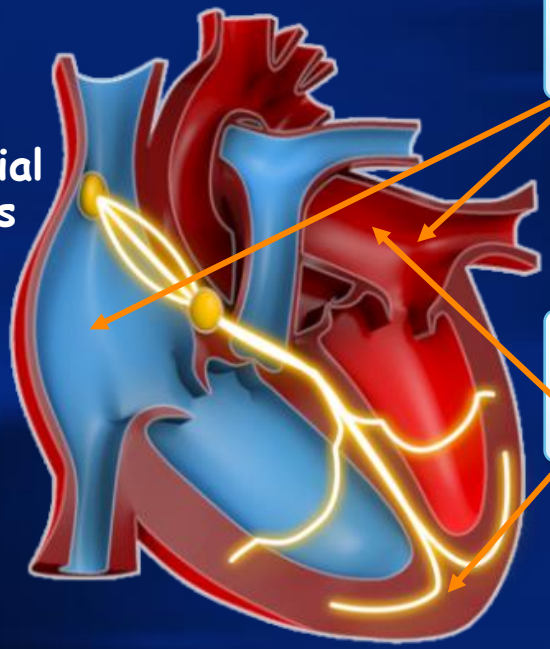
- Maintain atrioventricular synchrony.
- Control ventricular rate.
- Avoid atrial remodeling
- Avoid thromboembolic complications

- In some patients, continuous uninterrupted tachycardia leads to LV dysfunction.
- Multiple studies show that LV dysfunction in AF is reversible when NSR or VR slowing is achieved.

Atrial Fibrillation Begets Atrial Fibrillation

Electrical Remodeling

- Shortening of atrial refractory periods



Contractile Remodeling

- Reduced atrial contractility
- Sets the stage for thrombus formation

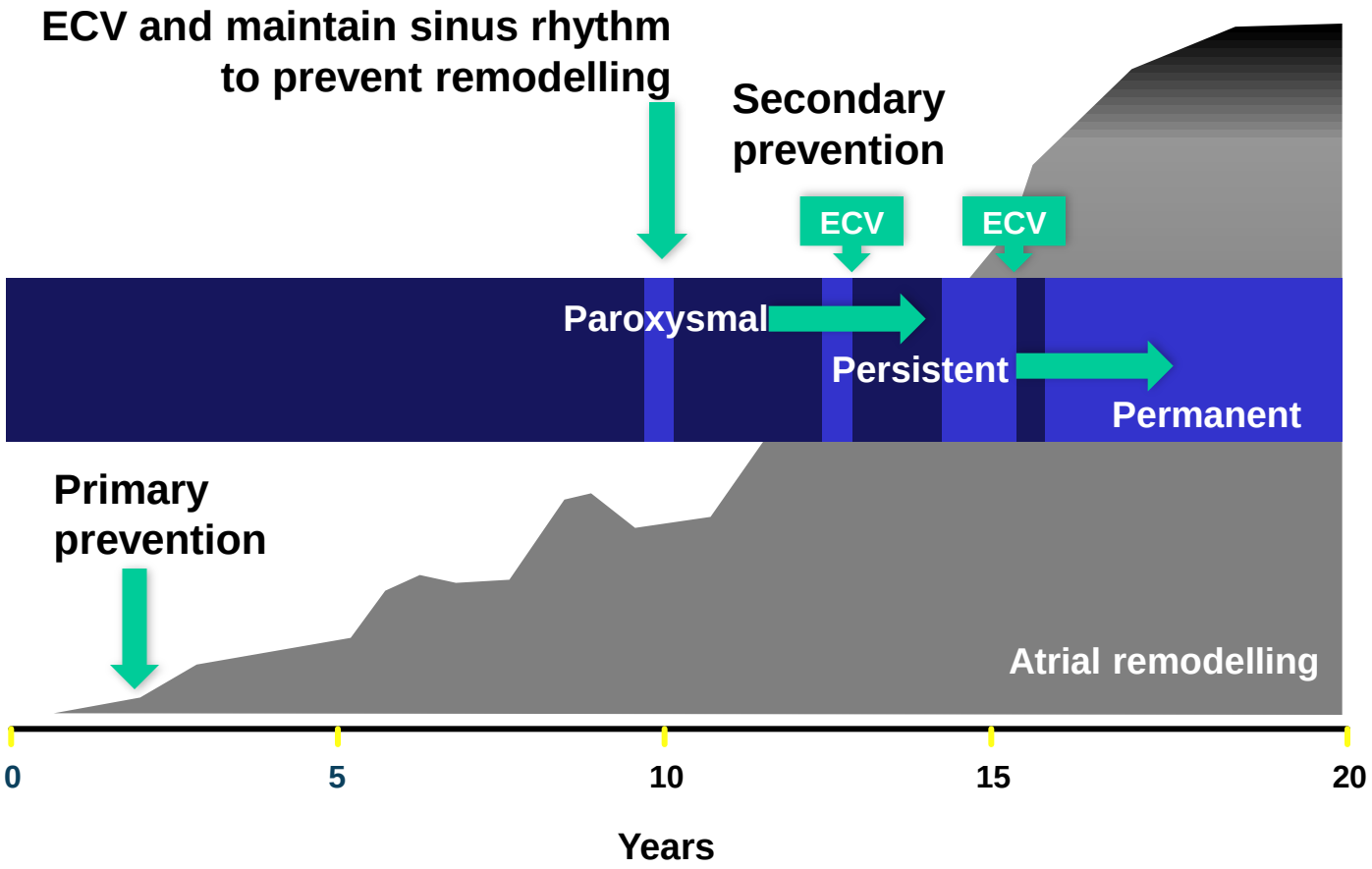
Structural Remodeling

- Left atrium & left atrial appendage enlargement
- Decrease in cardiac output

- The self-perpetuating nature of AF induces electrophysiologic changes that promote further AF.[1-3]
- These changes cause and result from electrical, contractile, & structural atrial remodeling, and can occur within days of initial AF onset.[4-6]

1. Kirchhof P, et al. Europace. 2007;9(11):1006-23
2. Dittrich HC, et al. Am J Cardiol. 1989;63(3):193-7
3. Wijffels MC, et al. Circulation. 1995;92(7):1954-68
4. Van Gelder IC, Hemels ME. Europace. 2006; 8(11):943-9
5. Schotten U, et al. Circulation. 2003;107(10):1433-9
6. Veenhuyzen et al. CMAJ 2004;171 (7):755-60

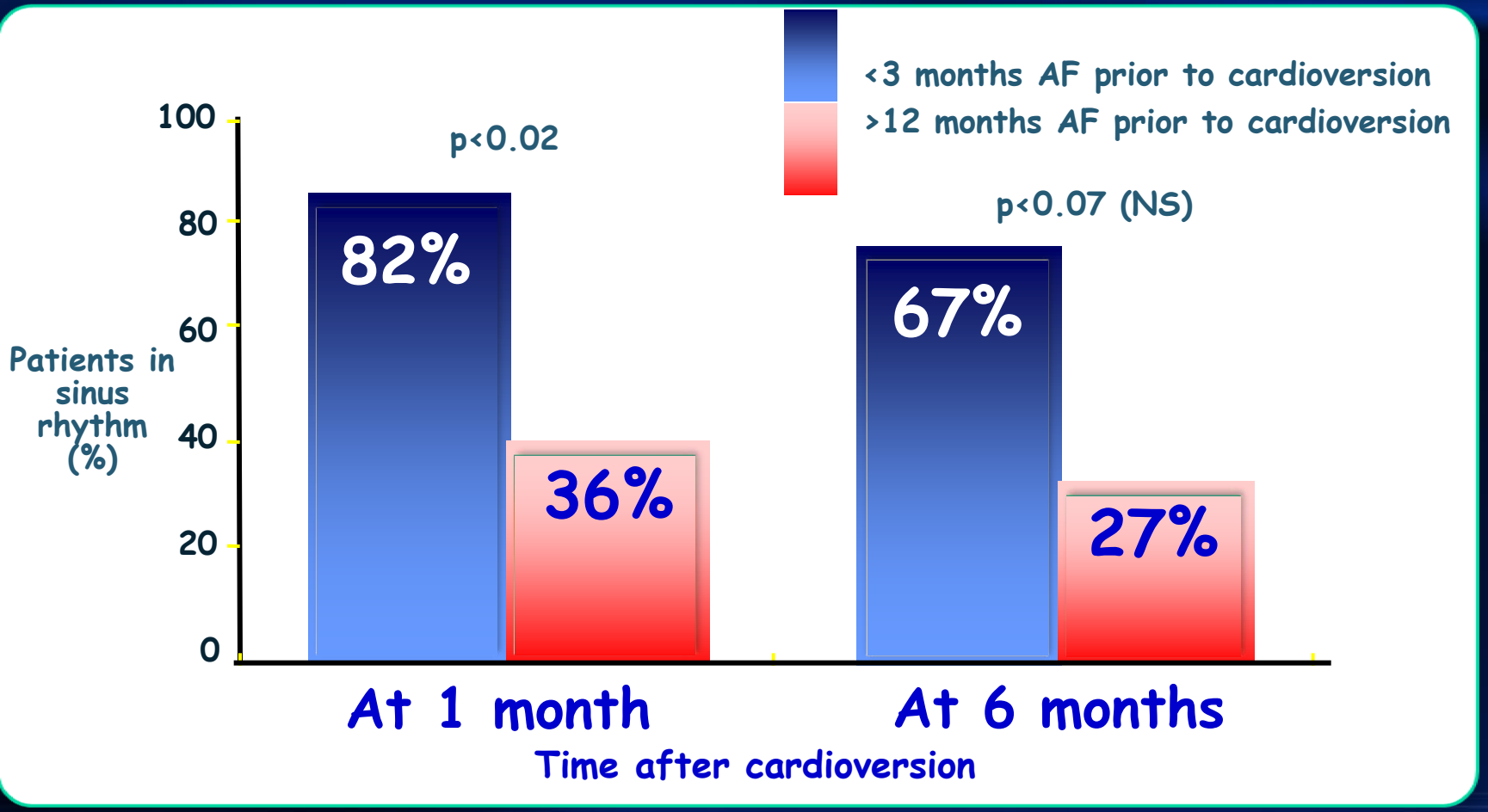
The chronic progressive nature of untreated AF suggests the need for early intervention



ECV=Electrical cardioversion

Cosio FG, et al. Europace. 2008;10:21-7

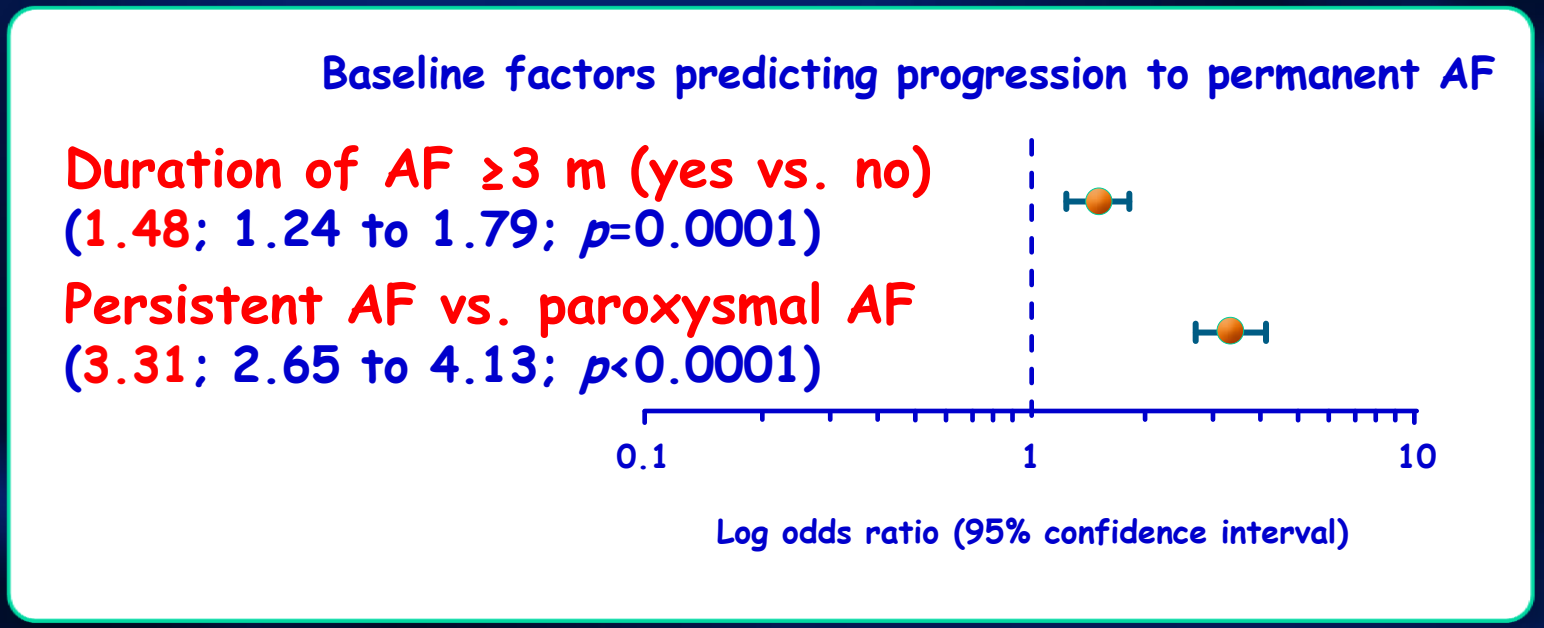
The longer the time spent in AF, the harder it is to restore and maintain sinus rhythm



Dittrich HC, et al. Am J Cardiol. 1989;63:193-7

Longer AF duration predicts AF progression

RECORD AF



- AF ≥3 months at baseline and persistent AF (vs. paroxysmal) increased the risk of permanent AF, indicating AF duration as an important predictor of progression

Camm J, et al. J Am Coll Cardiol. 2011 26;58:493-501

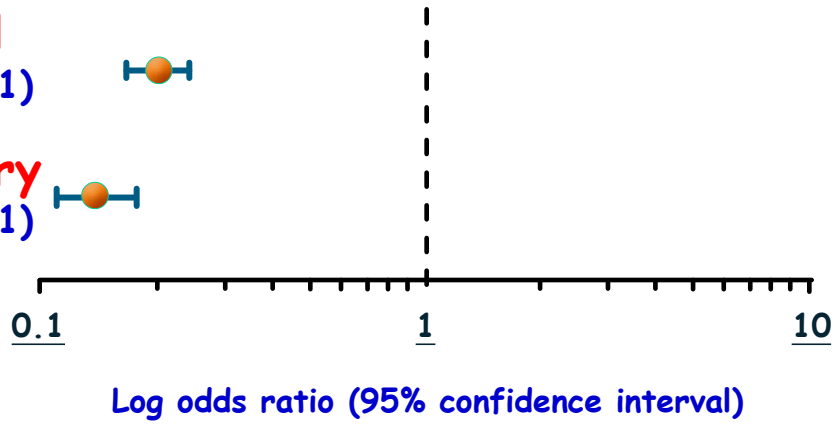
Maintenance of sinus rhythm reduces risk of AF progression

RECORD AF

Baseline factors predicting progression to permanent AF

Rhythm vs. rate control
(0.21; 0.17 to 0.25; $p<0.0001$)

SR vs. AF at study entry
(0.14; 0.11 to 0.18; $p<0.0001$)



- Entering the study in sinus rhythm and the choice of rhythm control strategy predicted that AF would not progress
- After 1 year only 13% of rhythm control patients had progressed to permanent AF, compared to 54% of rate control

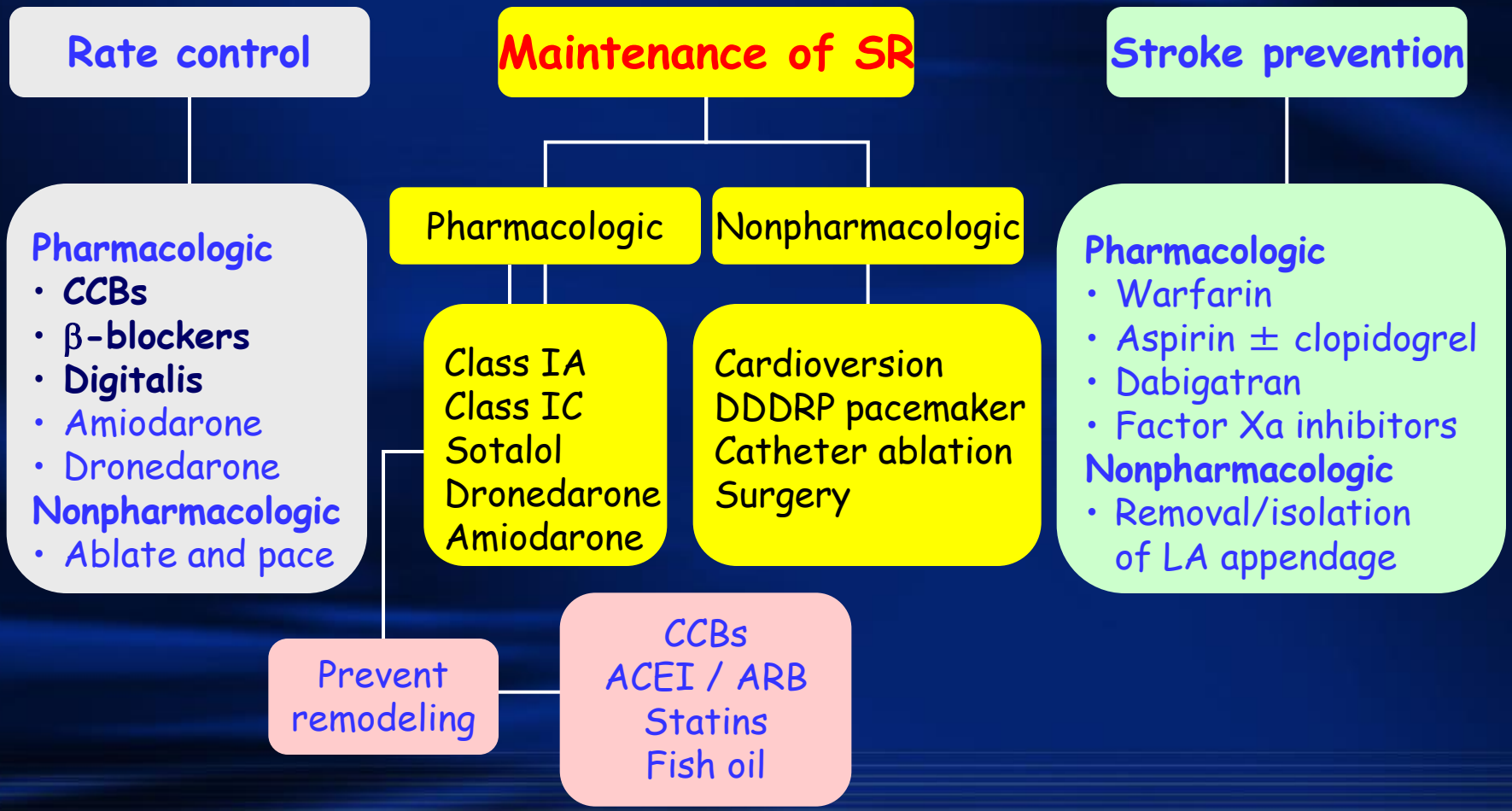
Camm J, et al. J Am Coll Cardiol. 2011 26;58:493-501

Canadian Cardiovascular Society Recommendations

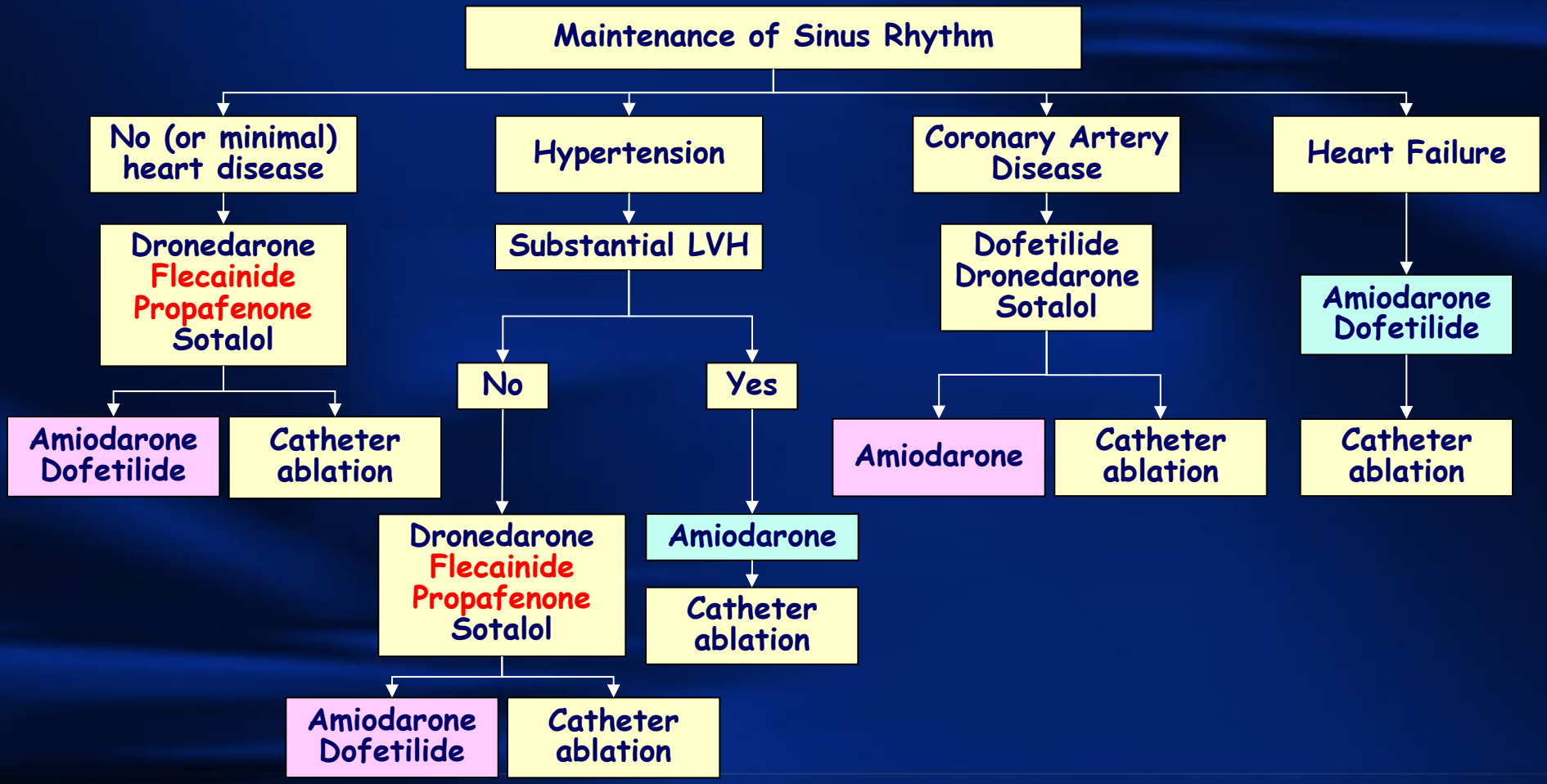
Favors Rate Control	Favors Rhythm Control
Persistent AF	Paroxysmal AF
	Newly Detected AF
Less Symptomatic	More Symptomatic
>65 years of age	< 65 years of age
Hypertension	No Hypertension
No History of CHF	CHF clearly exacerbated by AF
Previous AAD Failure	No Previous AAD Failure

Canadian Cardiovascular Society AF Guidelines. http://www.ccsguidelineprograms.ca/index.php. Accessed January 25, 2011.

Guideline-Based AF Treatment Options

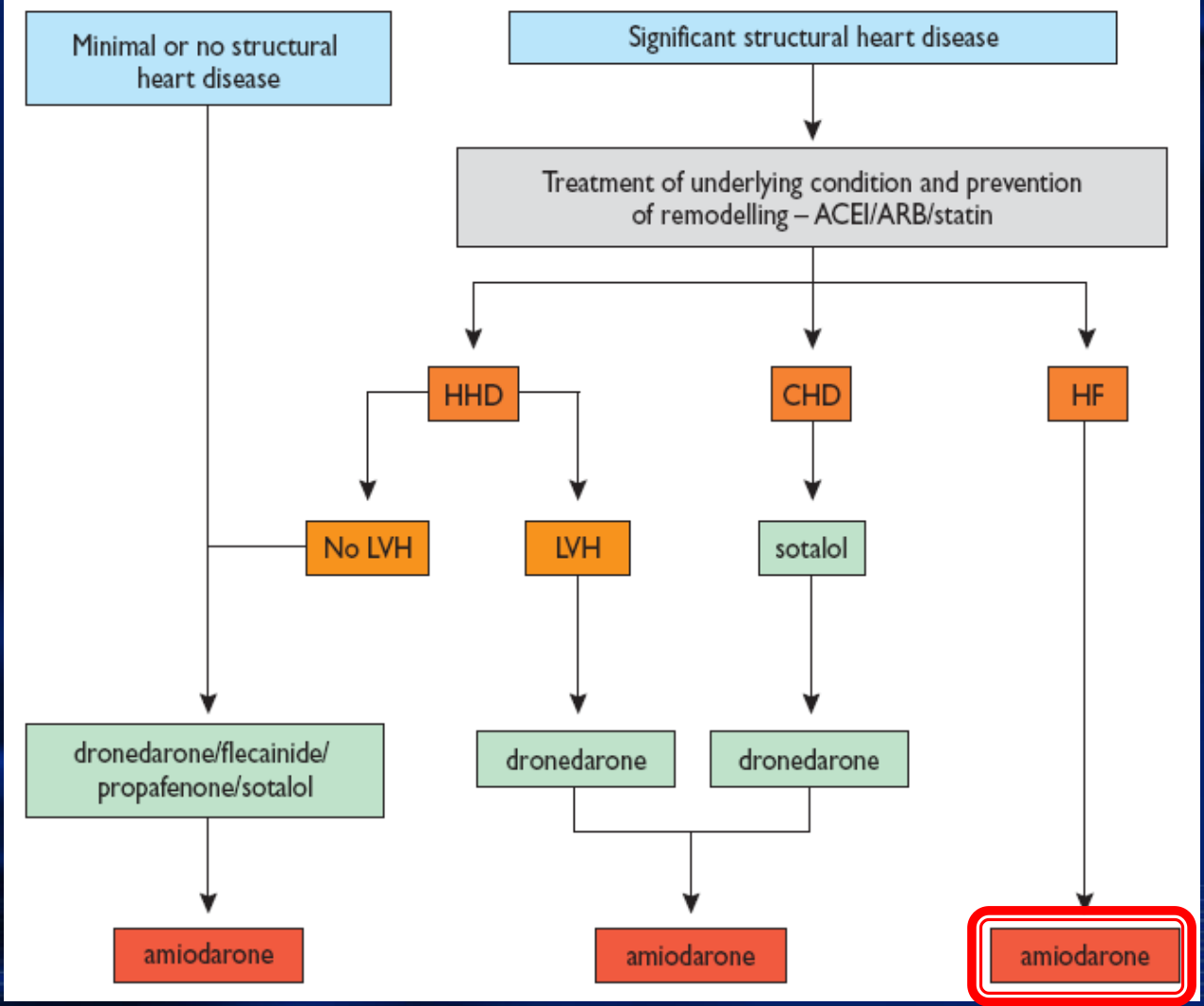


2011 ACCF/AHA/HRS Focused Update on the Management of Patients with AF



Drugs are listed alphabetically and not in order of suggested use. The seriousness of heart disease progresses from left to right, and selection of therapy in patients with multiple conditions depends on the most serious condition present. LVH indicates left ventricular hypertrophy.

2012 focused update of the ESC Guidelines for the management of AF



Europace 2012;14:1385–1413

Prescribing Amiodarone

An Evidence-Based Review of Clinical Indications

Vassallo P et al. JAMA 2007;298(11):1312-22

Adverse effects

• Corneal microdeposits	90%
• Optic neuropathy/neuritis	1~2%
• Blue-gray skin discoloration	4~9%
• Photosensitivity	25~75%
• Hypothyroidism	6%
• Hyperthyroidism	0.9~2%
• Pulmonary toxicity	1~17%
• Peripheral neuropathy	0.3% annually
• Hepatotoxicity	
– elevated enzyme levels	15~30%
– hepatitis and cirrhosis	3% [0.6% annually]

1970~2007 92 studies included in review

Amiodarone and Thyroid Function

Hypothyroidism - Iodine Induced

- Overt Hypothyroidism – 5%
- Subclinical Hypothyroidism – 25%

Hyperthyroidism - 3-5%

- Type 1- (Jod-Basedow, Iodine-Induced), Underlying MNG, Graves' Disease
- Type 2 – Chemical Destructive Thyroiditis

香港華人服用碘胺酮引致甲狀腺功能異常的研究

目的 探討服用碘胺酮引致甲狀腺功能異常的發病率、風險因素、臨床表現及處理方法。

設計 回顧性研究。

安排 香港一所分區醫院。

患者 2005年10月1日至2007年9月30日期間，曾服用碘胺酮不少於6個月的病人。

結果 共390位病人（平均年齡70歲；標準差9歲；54%為男性）參與研究，隨訪期中位數為43個月（四分位距：25-69個月）。其中87位病人（22%；平均年齡72歲；標準差7歲；56%為男性）出現因碘胺酮引致的甲狀腺功能不足，24位病人（6%；平均年齡65歲；標準差11歲；54%為男性）出現因碘胺酮引致的甲狀腺功能亢進。碘胺酮引致甲狀腺功能不足的預測因素為服藥前高促甲狀腺素（TSH）水平，當TSH水平≥4mIU/L時，其患病風險增加4.7倍（95%置信區間：1.9-11.7；P<0.001）。碘胺酮引致甲狀腺功能亢進的病人相對正常甲狀腺功能病人較為年輕。碘胺酮引致甲狀腺功能亢進的病人多數沒有典型症狀，但他們的心律失常或心臟病況轉差、體重下降及薄血指數上升可能是甲狀腺功能亢進的提示。碘胺酮引致甲狀腺功能異常皆為良性病例。碘胺酮引致甲狀腺功能亢進的病人對甲狀腺藥及類固醇藥治療均有良好反應。

CV Outcome Benefits:
Amiodarone & Dronedarone in Large AF Trials

	AFFIRM	AF-CHF	ATHENA
Amiodarone use	63% of patients	82% of patients	None
Total mortality	↑ *P* = .08	↔	↔
CV mortality	NA	↔	↓ *P* = .03
Hospitalization*	↑ *P* <.001	↑ *P* = .06	↓ *P*<.001
Stroke	↔	↔	↓ *P* = .027

** Hospitalization was not reported in the same way in ATHENA, AFFIRM, and AF-CHF trials.*
NA = not applicable.

Wyse DG, et al. N Engl J Med. 2002;347(23):1825-33. Roy D, et al. N Engl J Med. 2008;358(25):2667-77. Hohnloser SH, et al. N Engl J Med. 2009;360(7):668-78. Torp-Pedersen C, et al. Circulation.2008;118:S828. Connolly SJ, et al. Circulation. 2009;120(13):1174-1180.

Prescribing Amiodarone

An Evidence-Based Review of Clinical Indications

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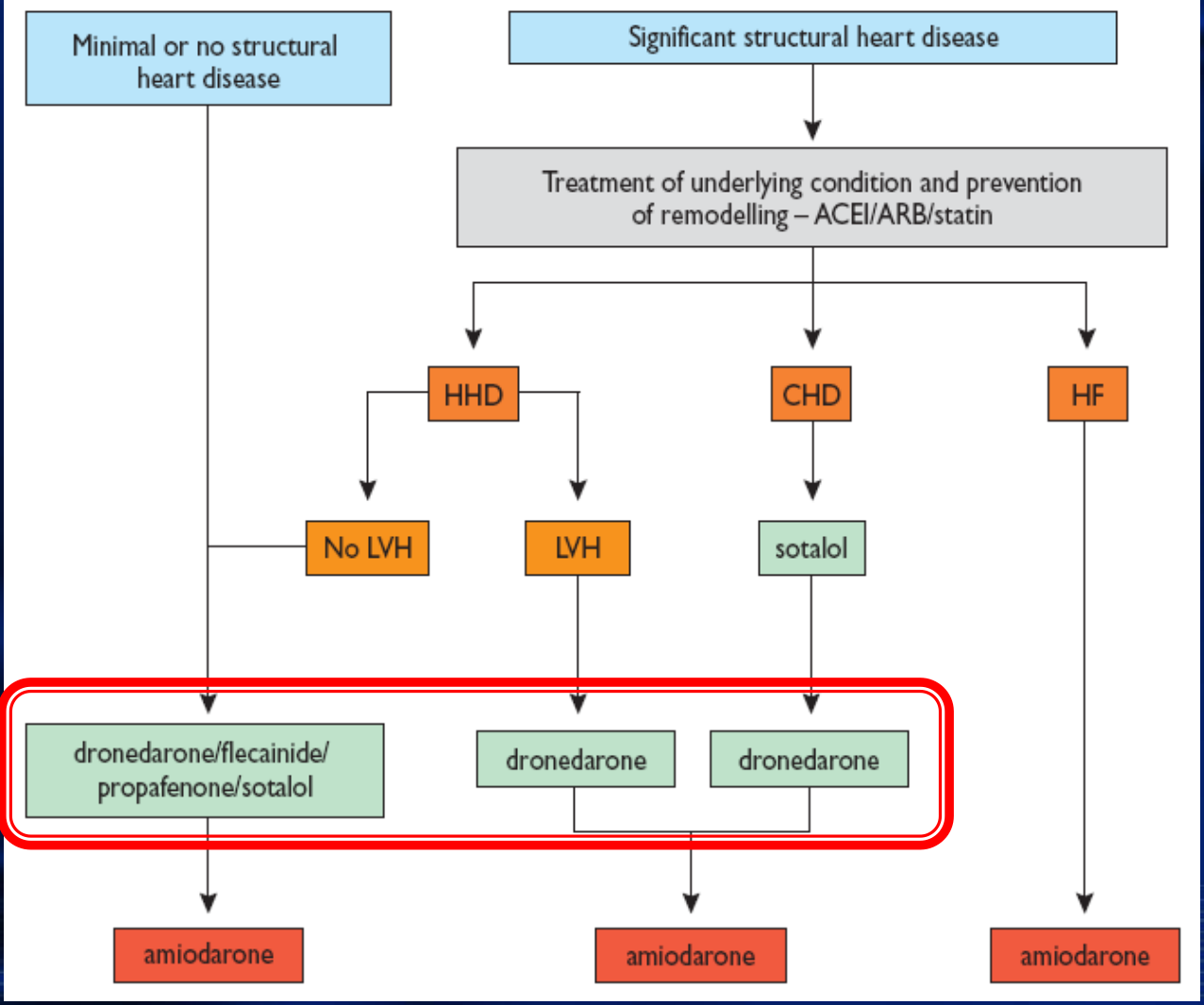
Amiodarone: Practical Advice for Clinicians & Patients

- Refer to cardiologist when amiodarone therapy is contemplated.
- Make every effort to use less toxic alternatives (other AADs or ablation).
- Do not use in patients with symptomatic conduction system disease, significant liver disease, hyperthyroidism, or significant pulmonary disease.
- Patients should wear sunscreen and limit sun exposure.
- To avoid adverse drug-drug interactions, patients taking amiodarone should consult their pharmacist/ cardiologist whenever a new drug is prescribed.

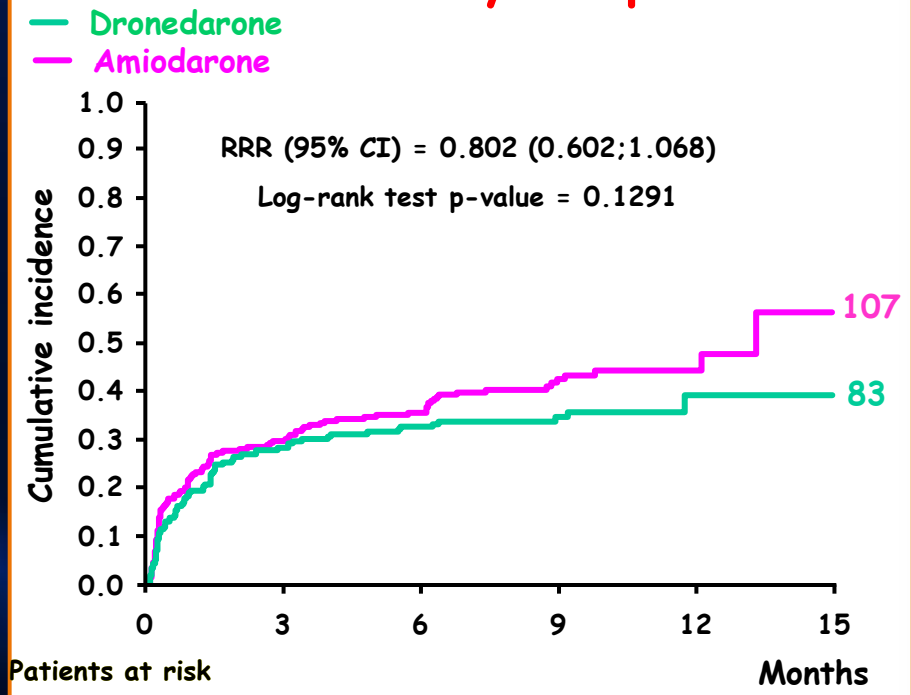
2012 focused update of the ESC Guidelines for the management of AF



Europace 2012;14:1385-1413

Safety Profile in DIONYSOS Study

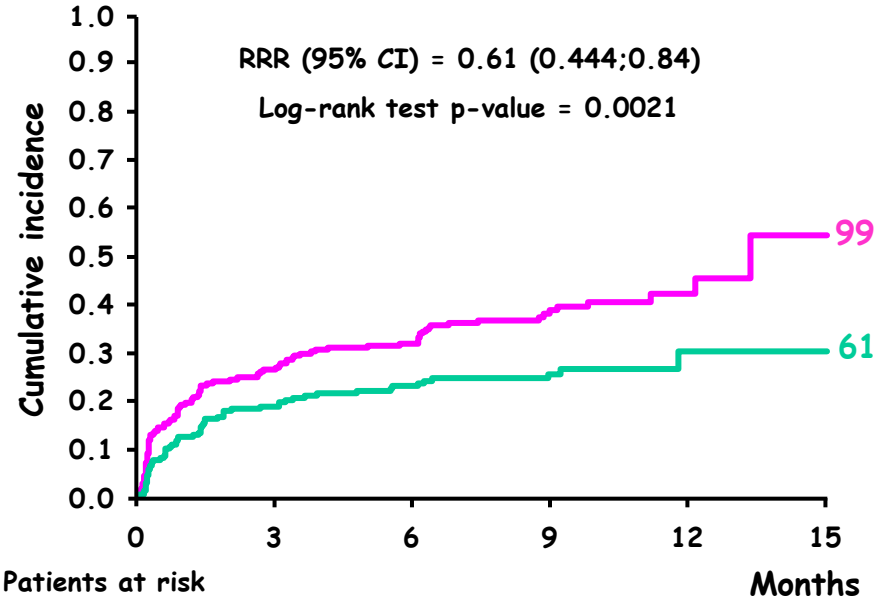
Main Safety Endpoint



Patients at risk

Dronedarone	249	157	127	63	12	0
Amiodarone	255	168	152	76	17	0

Main Safety Endpoint focusing on Organ Toxicity*



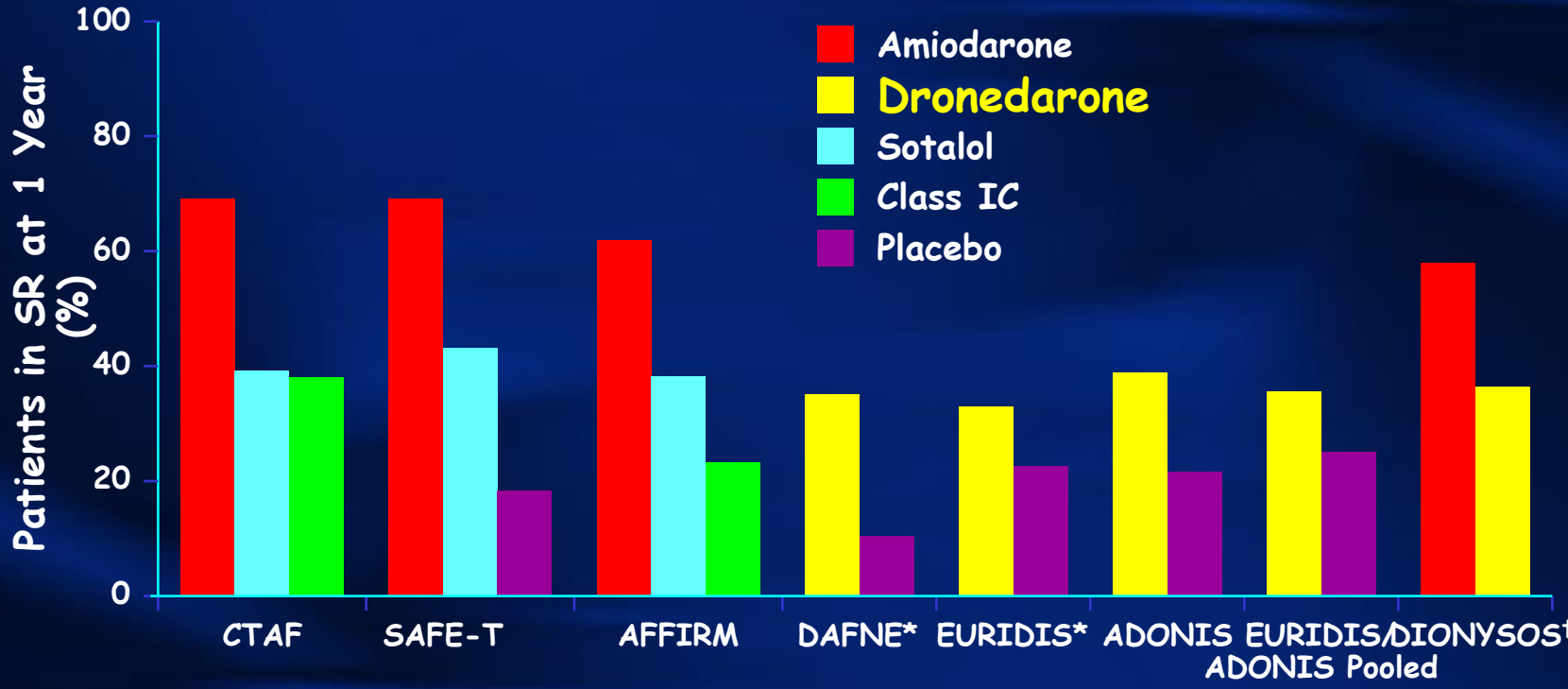
Patients at risk

Dronedarone	249	179	148	73	14	0
Amiodarone	255	175	160	82	19	0

- The incidence of the MSE was reduced by 20% in the dronedarone group compared with the amiodarone group (p=0.1291).
- The pre-specified safety endpoint that excluded GI side effects showed a statistically significant 39% decrease in favor of dronedarone (p=0.0021).

Le Heuzey JY et al. J Cardiovasc Electrophysiol. 2010;21:597-605.

Efficacy of AADs in AF Trials

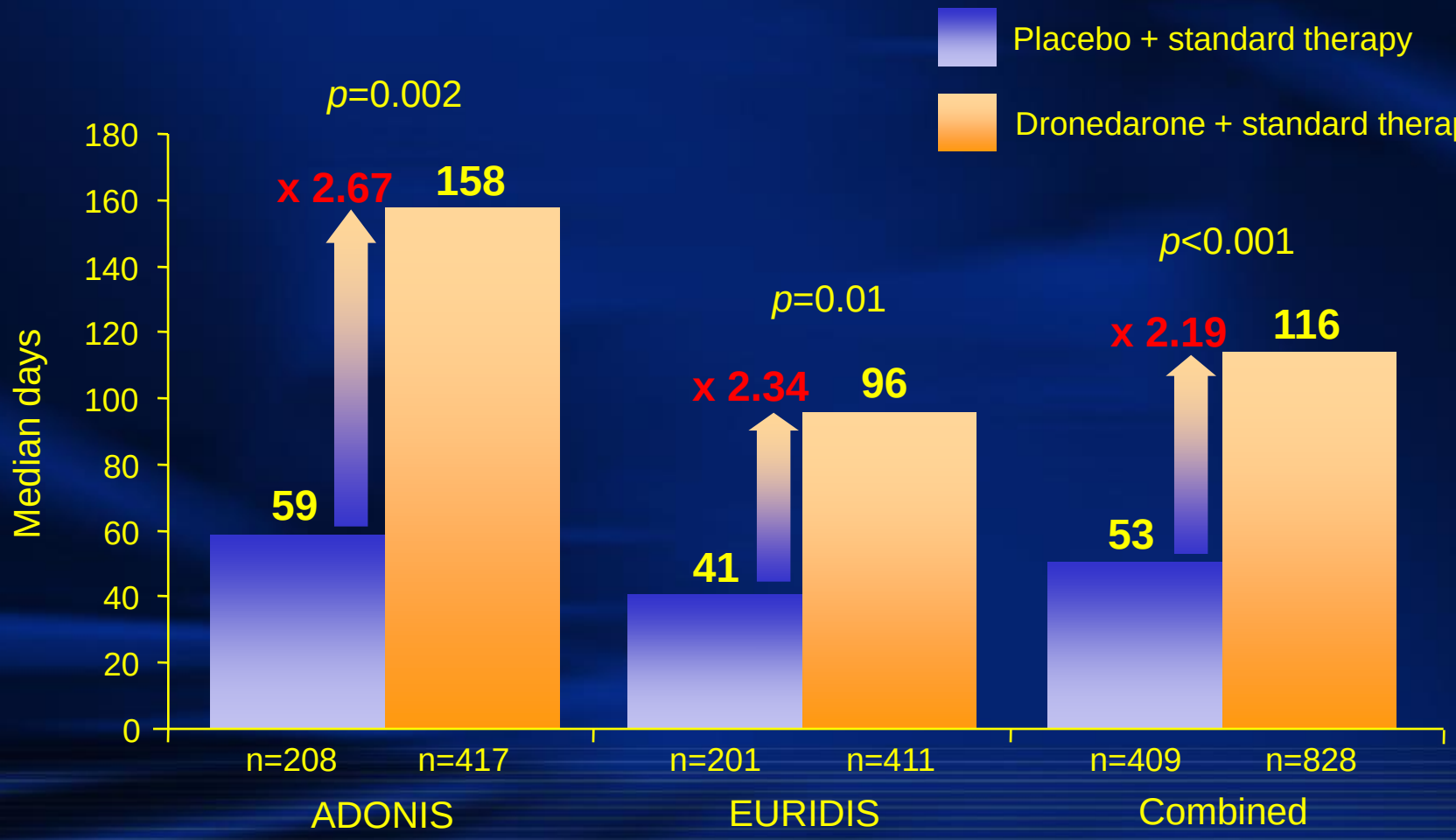


*At 6 months; †Mean follow-up 7 months.

CTAF = Canadian Trial of Atrial Fibrillation; SAFE-T = Sotalol Amiodarone Atrial Fibrillation Efficacy Trial; DAFNE = Dronedarone Atrial Fibrillation Study after Electrical Cardioversion;
EURIDIS = European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm;
ADONIS = American-Australian-African Trial with Dronedarone in Atrial Fibrillation or Flutter for the Maintenance of Sinus Rhythm;
DIONYSOS = Randomized, Double-blind Trial to Evaluate the Efficacy and Safety of Dronedarone vs Amiodarone for at Least 6 Months for the Maintenance of Sinus Rhythm in Patients with AF.

Roy D, et al. Am J Cardiol. 1997;80:464-8. Singh BN, et al. N EJM 2005;352(18):1861-72. AFFIRM Investigators. J Am Coll Cardiol. 2003;42:20-9. Touboul P, et al. Eur Heart J. 2003;24:1481-7. Singh BN, et al. N EJM 2007;357(10):987-99. Le Heuzey JY, et al. J Cardiovasc Electrophysiol. 2010;21:597-605.

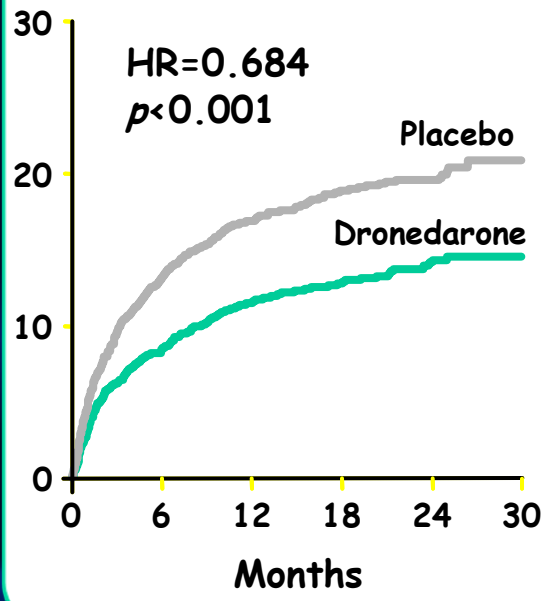
Dronedarone More Than Doubled Time to First Recurrence of AF/AFL



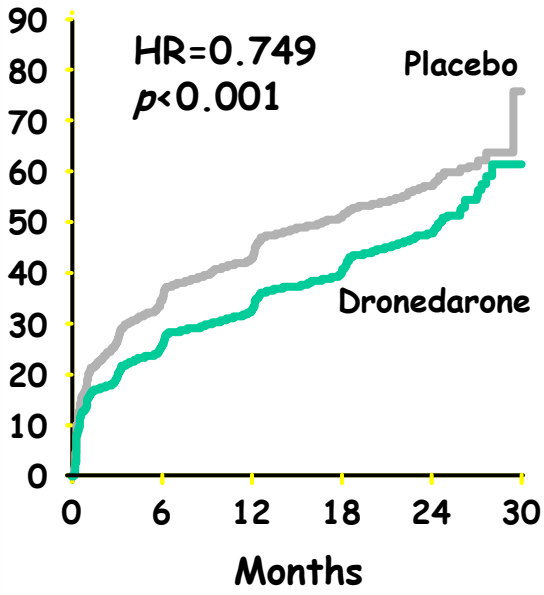
Singh BN, et al. N Engl J Med. 2007;357:987-99

Dronedarone antiarrhythmic effect in ATHENA

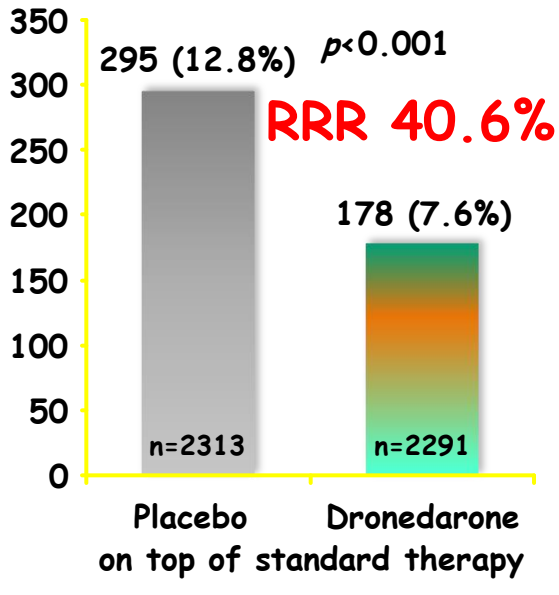
Time to 1st DCV



Time to 1st AF/AFL



% patients in "Permanent AF"

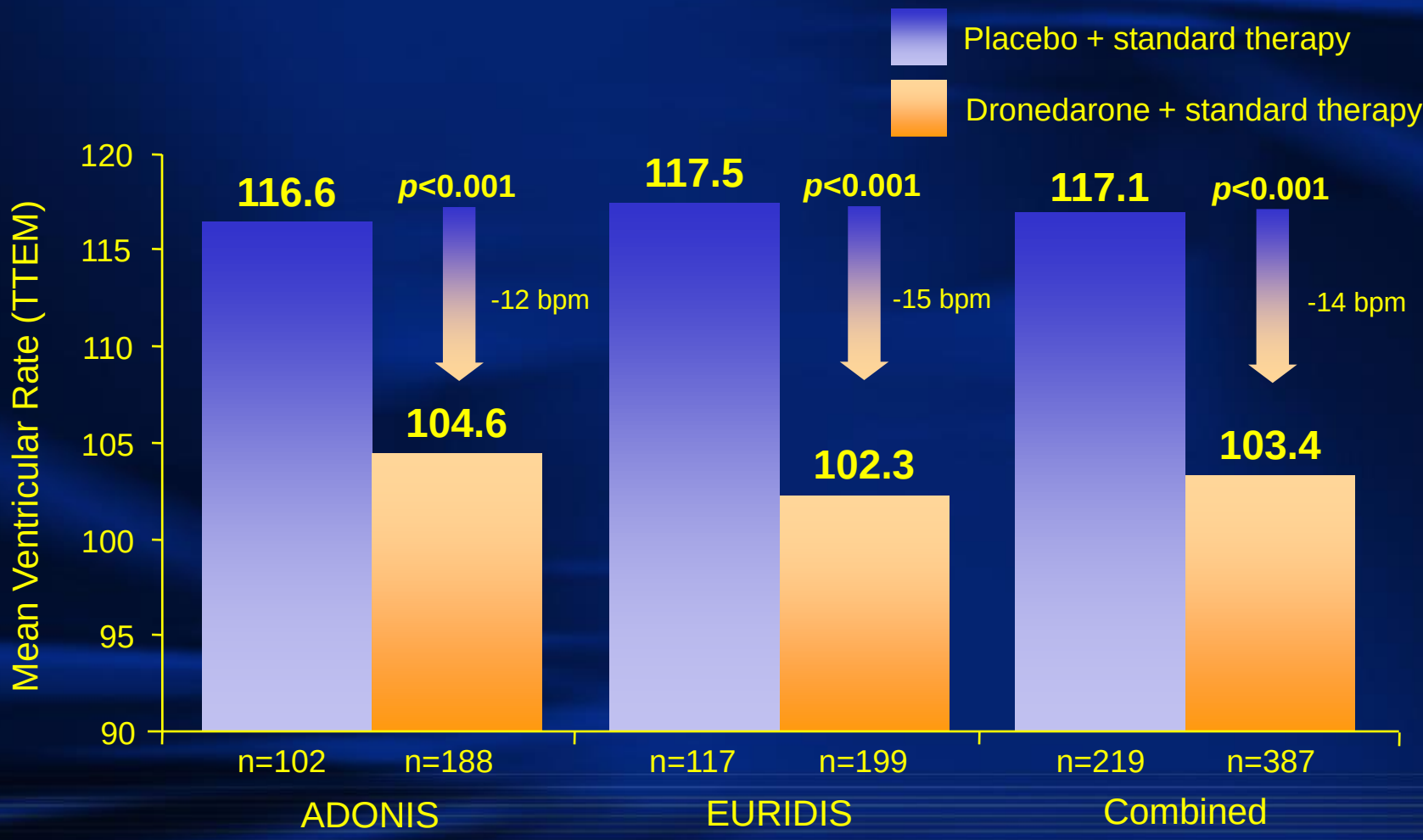


All AF related hospitalization: HR = 0.626; 95% CI = [.54; .73]
First AF related hospitalization: HR = 0.63; 95% CI = [.55; .72]

DCV=Direct cardioversion

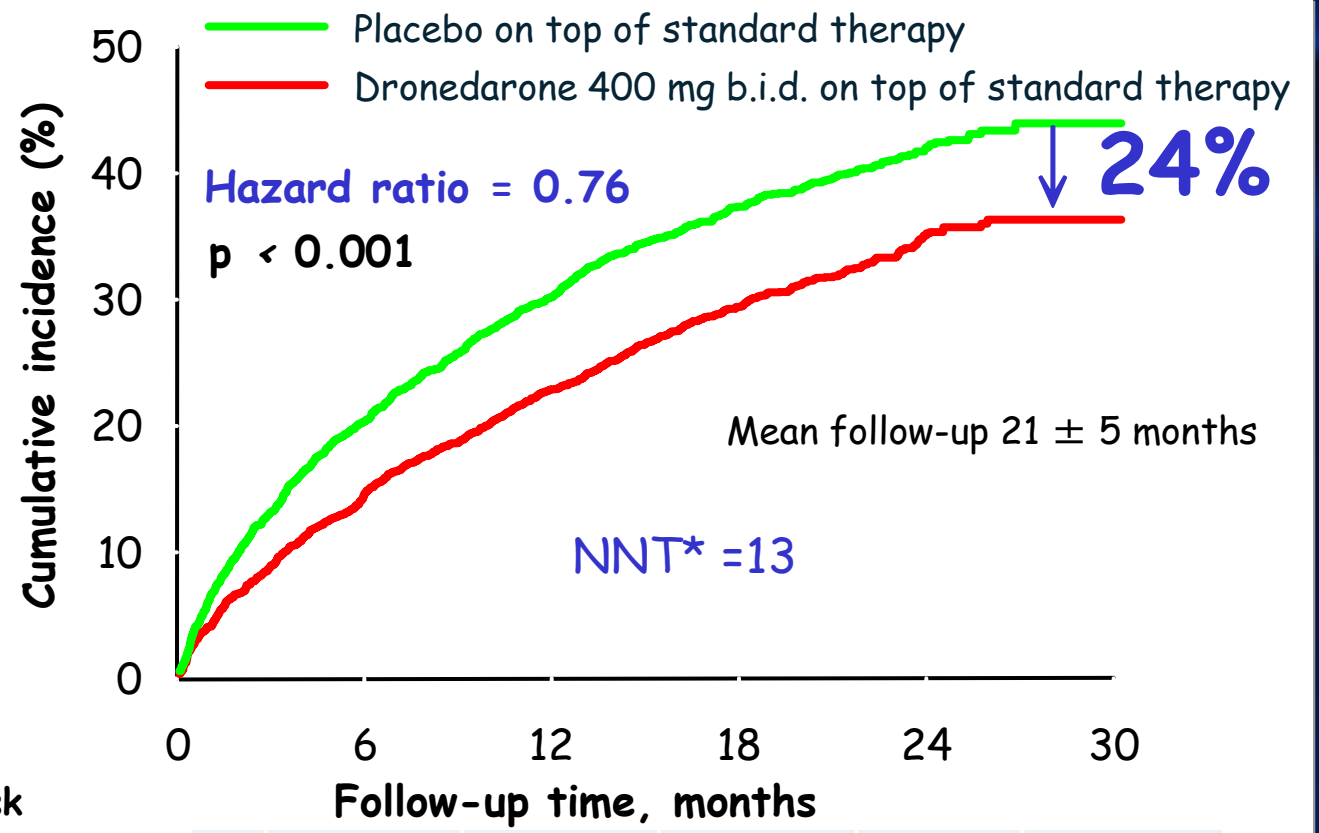
Hohnloser SH, et al. N Engl J Med 2009;360:668-78
Page et al. Am J Cardiol. 2011;107:1019-22

Dronedarone: Significant & Consistent Decrease in Ventricular Rate at First AF/AFL Recurrence



TTEM= Trans Telephonic Electrocardiogram Monitoring.
Singh BN, et al. N Engl J Med. 2007;357:987-99

Primary Outcome: Unplanned cardiovascular hospitalization or death



Patients at risk						
Placebo	2,327	1,858	1,625	1,072	385	3
Dronedarone 400 mg b.i.d.	2,301	1,963	1,776	1,177	403	2

*Number needed to treat (NNT) to save one first cardiovascular hospitalization or death for any cause during the on-study period

Hohnloser S, et al. N Engl J Med. 2009;360:668-78.

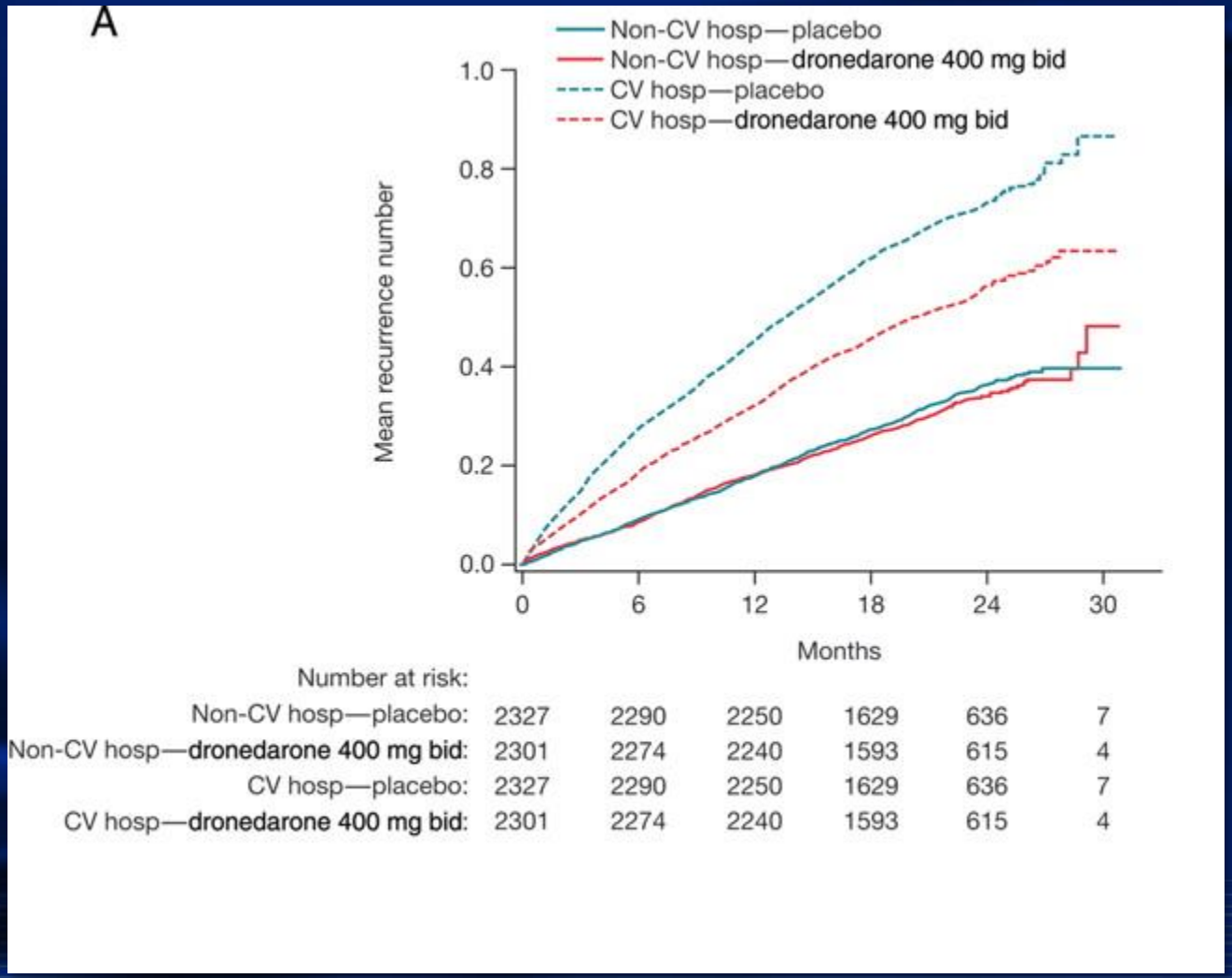
Significant reduction in CV events demonstrated in ATHENA

Outcome	Placebo n=2327	Dronedarone 400 mg b.i.d. n=2301	Hazard Ratio for dronedarone [95% CI]	Absolute Reduction*	*p* value
CV death (secondary endpoint)	94	65	0.71 [0.50-0.96]	0.9%	0.03
Events of Interest (post-hoc)					
Stroke	70	46	0.66 [0.45-0.96]	1.1%	0.027
Acute coronary syndrome (hospitalizations)	89	62	0.70 [0.51-0.97]	1.3%	0.03
Death, stroke or ACS	262	196	0.75 [0.62-0.90]	2.2%	0.002
Any Hospitalizations	1142	964	0.80 [0.74-0.87]	7.1%	<0.0001

Hohnloser SH, et al. N Engl J Med 2009;360:668-78; Connolly SJ, et al. Circulation 2009;120(13):1174-80

** 2-year absolute reduction between cumulative incidences of events in placebo and dronedarone groups*

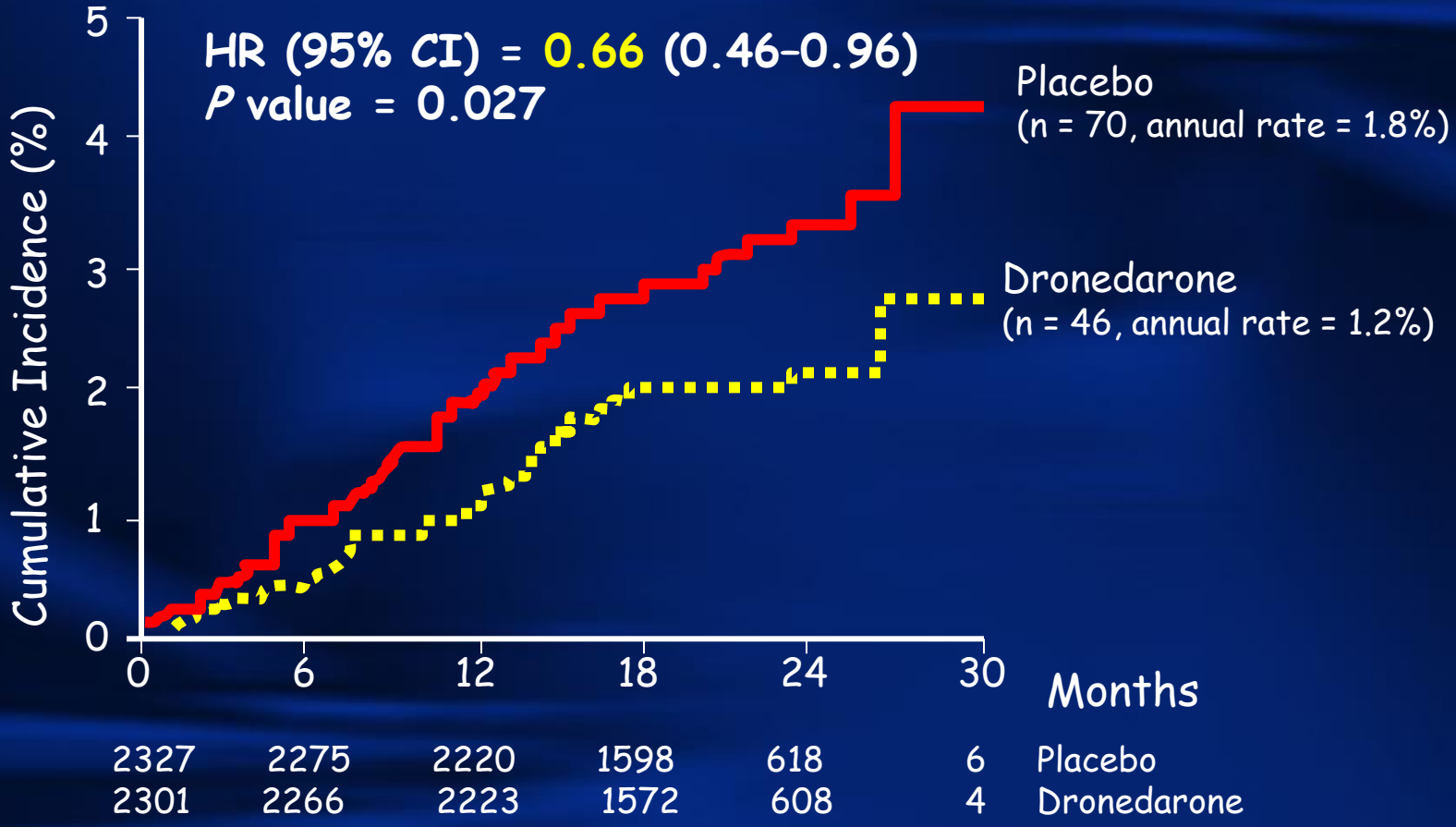
Incidence of CV & non-CV Hospitalizations



Number at risk:						
Non-CV hosp—placebo:	2327	2290	2250	1629	636	7
Non-CV hosp—**dronedarone 400 mg bid**:	2301	2274	2240	1593	615	4
CV hosp—placebo:	2327	2290	2250	1629	636	7
CV hosp—**dronedarone 400 mg bid**:	2301	2274	2240	1593	615	4

Torp-Pedersen C et al. Europace 2011;13:1118-1126

Post hoc Analysis of Stroke in ATHENA



Patients: N = 2327 placebo; N = 2301 dronedarone (400 mg BID)
Baseline mean $CHADS_2$ score: 2
Mean age: 72 yrs

Connolly S et al. Circulation. 2009;120:1174-80

Impact of choice of rhythm or rate control on short term clinical outcomes

RecordAF

Clinical events at 1 year	Rhythm-control strategy (%)	Rate-control strategy (%)	*p* value
Any clinical event	17.2	18.2	0.352
Cardiovascular death	0.9	2.8	<0.001
Stroke or transient ischemic attack	1.7	2.8	0.008
Myocardial infarction		0.9	0.078
Hospitalization/prolongation of hosp for arrhythmia/proarrhythmia		7.3	<0.001
Hospitalization/prolongation of hospitalization for other CV events/interventions	6.8	9.3	0.001
Congestive heart failure	2.4	4.8	<0.001
Unstable angina	1.3	1.5	0.436
Other	3.7	4.7	0.082
Hospitalization/prolongation of hospitalization for major complications of ablative procedure	0.5	0.6	0.626
Hospitalization for CV event	16.6	16.7	0.891

RRR: 39%

Camm AJ *et al.* J Am Coll Cardiol. 2011 26;58(5):493-501

ATHENA - Adverse events

Outcome	Placebo n = 2,313	Dronedarone n = 2,291	p value
Patients with any TEAE	1,603 (69%)	1,649 (72%)	0.048
Gastro-intestinal	508 (22%)	600 (26%)	< 0.001
Respiratory	337 (15%)	332 (15%)	0.97
Skin	176 (8%)	237 (10%)	0.001
Creatinine increase	31 (1%)	108 (4.7%)	< 0.001
Patients with any serious TEAE	489 (2%)	456 (20%)	0.31
Gastro-intestinal	68 (3%)	81 (4%)	0.28
Respiratory	45 (2%)	41 (2%)	0.74
Skin	6 (0.3%)	7 (0.3%)	0.79
Creatinine increase	1 (< 0.1%)	5 (0.2%)	0.12

TEAE = treatment-emergent adverse event.

Hohnloser S, et al. N Engl J Med. 2009;360:668-78.

Dronedarone for the Prevention of Recurrent AF (2011 New Section)

ACCF/AHA 2013 Practice Guideline

Class IIa

1. *Dronedarone is reasonable* to decrease the need for hospitalization for CV events in patients with paroxysmal AF or after conversion of persistent AF. Dronedarone can be initiated during outpatient therapy. *(LoE: B)*

Class III: Harm

1. *Dronedarone should not* be administered to patients with class IV HF or patients who have had an episode of decompensated HF in the past 4 weeks, especially if they have depressed left ventricular function (LVEF<35%). *(LoE: B)*

ATHENA: Fatal Outcomes

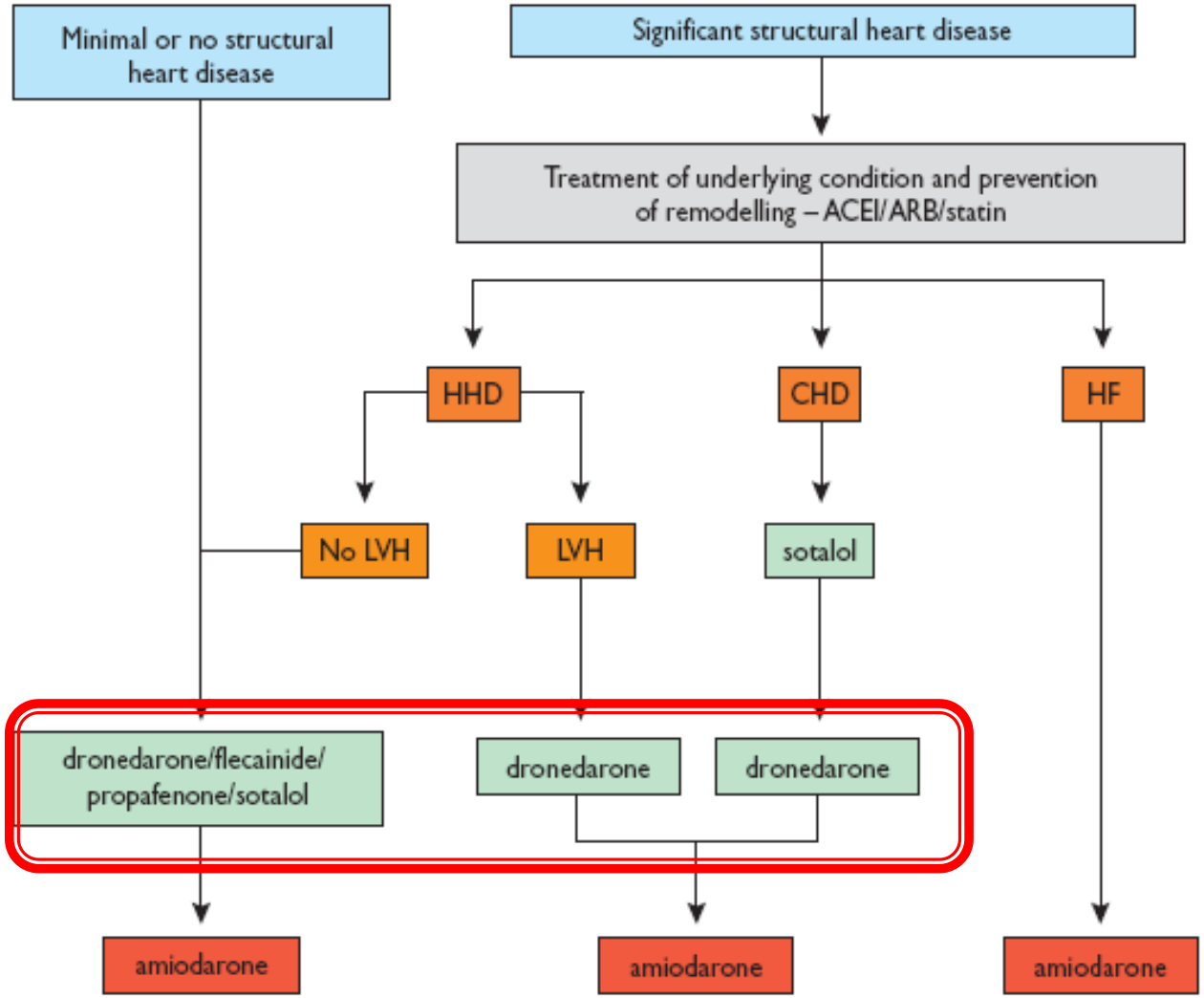
Outcome	Placebo (N=2327)	Dronedarone (N=2301)	Hazard Ratio	95% CI	*P* Value
All death	139	116	0.84	0.66-1.08	.18
Non-CV death	49	53	1.10	0.74-1.62	.65
CV death	90	63	0.71	0.51-0.98	.03
Non-arrhythmic death	18	17	0.95	0.49-1.85	.89
Arrhythmic death	48	26	0.55	0.34-0.88	.01
Vascular non-cardiac	24	20	0.84	0.47-1.52	.57

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

Recommendations for oral antiarrhythmic agents

Recommendations	Class[a]	Level[b]	Ref[c]
Dronedarone is recommended in patients with recurrent AF as a moderately effective antiarrhythmic agent for the maintenance of sinus rhythm.	I	A	142, 144, 153
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	145
Dronedarone is not recommended in patients with permanent AF.	III	B	5

2012 Focused Update of the ESC Guidelines for the Management of Atrial Fibrillation



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. Antiarrhythmic agents are listed in alphabetical order within each treatment box.

Contraindications

- 第2或第3級房室傳導阻滯或病竇症候群(sick sinus syndrome)之患者 (使用功能性節律器者除外)
- 心搏徐緩<50 bpm者
- 心房顫動持續六個月以上之永久性心房顫動患者(或未知其心房顫動發作持續時間)，且醫師不再認為可恢復竇性節律之患者
- 具不穩定性血液動力學之患者
- 有症狀的心衰竭患者且最近曾因心臟代償不全而住院或紐約心臟學會（NYHA）分類為第IV類的心衰竭患者
- 併用CYP3A之強效抑制劑者，例如ketoconazole、itraconazole、voriconazole、cyclosporine 、telithromycin、clarithromycin、nefazodone及ritonavir
- 併用會延長QT間隔及可能增加Torsades de Pointes風險的藥物或草藥，如phenothiazines抗精神病藥物、三環抗憂鬱劑、某些口服的巨環類抗生素（macrolide）及第 I類和第III類抗心律不整藥物
- QTc Bazett 間隔 ≥ 500 msec或PR間隔 >280 msec者
- 嚴重肝功能不全者
- 懷孕（第X類）或授乳婦女

Multaq Taiwan labeling

Multaq 衛生署 藥品適應症

Multaq適用於最近6個月內有陣發性或持續性心房纖維顫動(AF)或心房撲動(AFL)，且目前處於竇性節律（sinus rhythm）狀態或即將接受治療成為正常節律的患者，可降低病患發生心血管疾病而住院的風險:

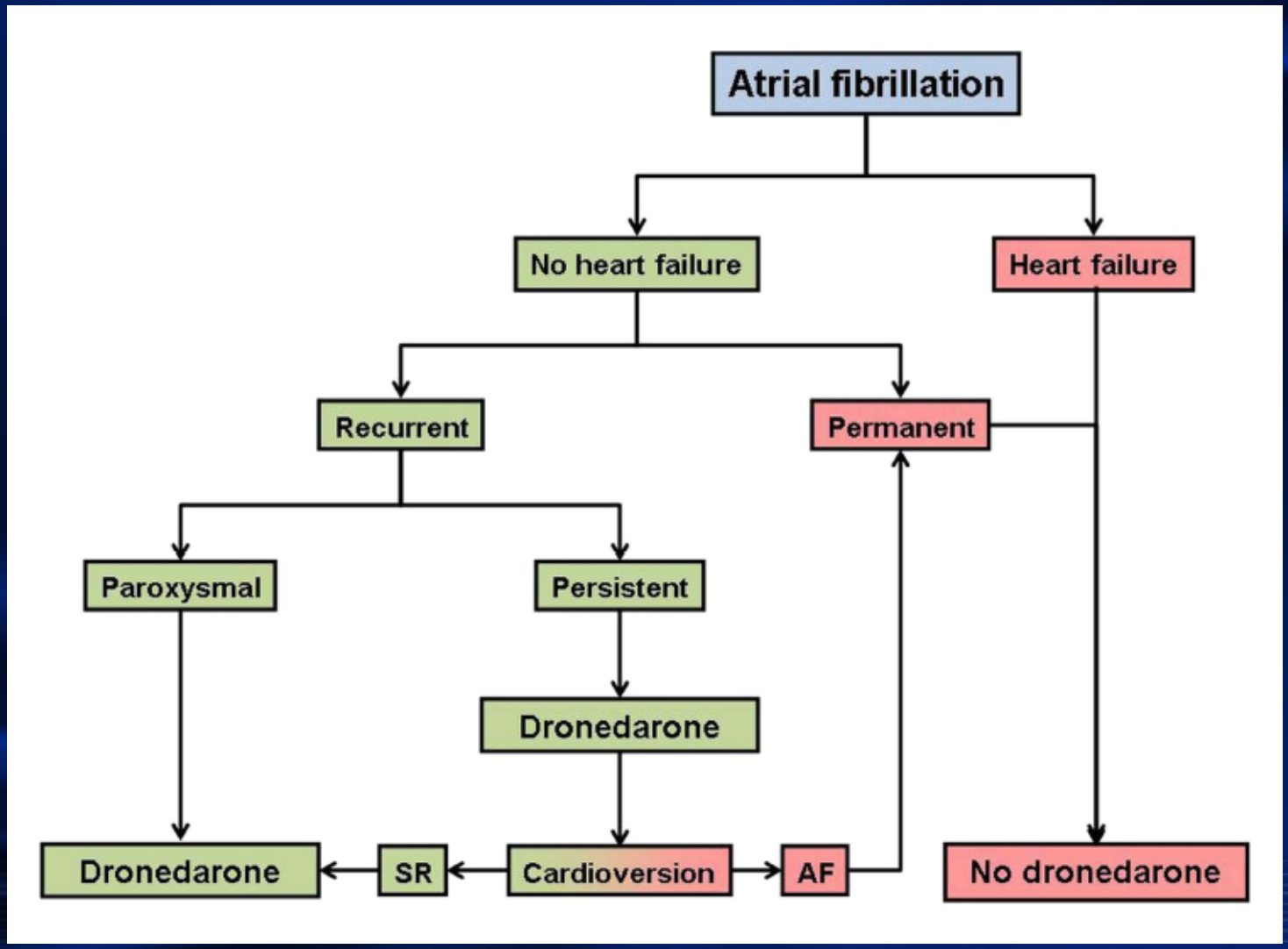
1.年齡≧70歲以上，曾有過心房纖維顫動（AF）或心房撲動(AFL)之病患

2.65≦年齡＜70歲，且帶有下列心血管相關危險因子之一的患者（高血壓、糖尿病、曾發生過腦血管意外、左心房直徑≧50mm

Multaq 全民健康保險藥品給付規定

1. Multaq適用於最近6個月內有陣發性或持續性心房纖維顫動(AF)或心房撲動(AFL)，且目前處於竇性節律（sinus rhythm）狀態或即將接受治療成為正常節律的患者，可降低病患發生心血管疾病而住院的風險：
   - 年齡≧70歲以上，曾有過心房纖維顫動（AF）或心房撲動(AFL)之病患；
   - 65≦年齡＜70歲，且帶有下列心血管相關危險因子之一的患者（例如：高血壓、糖尿病、曾發生過腦血管意外、左心房直徑≧50mm或左心室射出率【LVEF】＜40%）。
2. 不得使用於有心衰竭住院診斷史病人。

Dronedarone for the Rx of non-permanent Af:
National Institute for Health & Clinical Excellence guidance



Camm,AJ, Savelieva I. Heart 2013;99:1476-80


Thank you for
your attention!