Atrial Fibrillation: Part II

Pharmacological therapies in Atrial Fibrillation: how well do randomised trials translate into clinical practice

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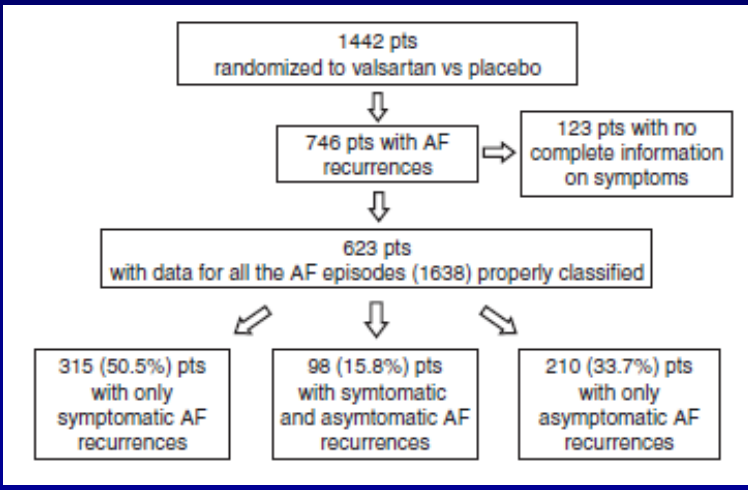
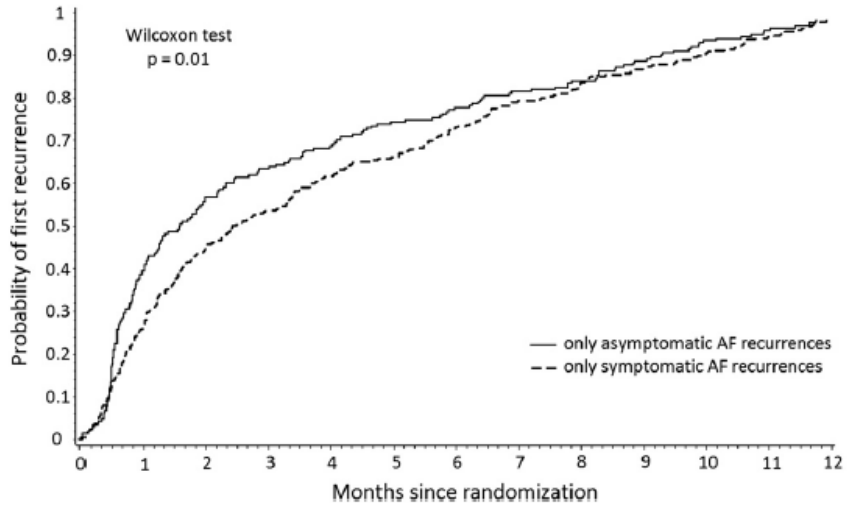
1: Is there a role for symptoms to guide the management of pts with AF

Clinical characteristics of patients with asymptomatic recurrences of atrial fibrillation in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Atrial Fibrillation (GISSI-AF) trial



AF recurrence episodes (n)	Patients with only symptomatic AF episodes (n = 315)	Patients with only asymptomatic AF episodes (n = 210)	Patients with symptomatic and asymptomatic AF episodes (n = 98)	P
<5 episodes	279 (88.6%)	193 (91.9%)	54 (55.1%)	<.0001
≥5 episodes	36 (11.4%)	17 (8.1%)	44 (44.9%)	

Figure 2



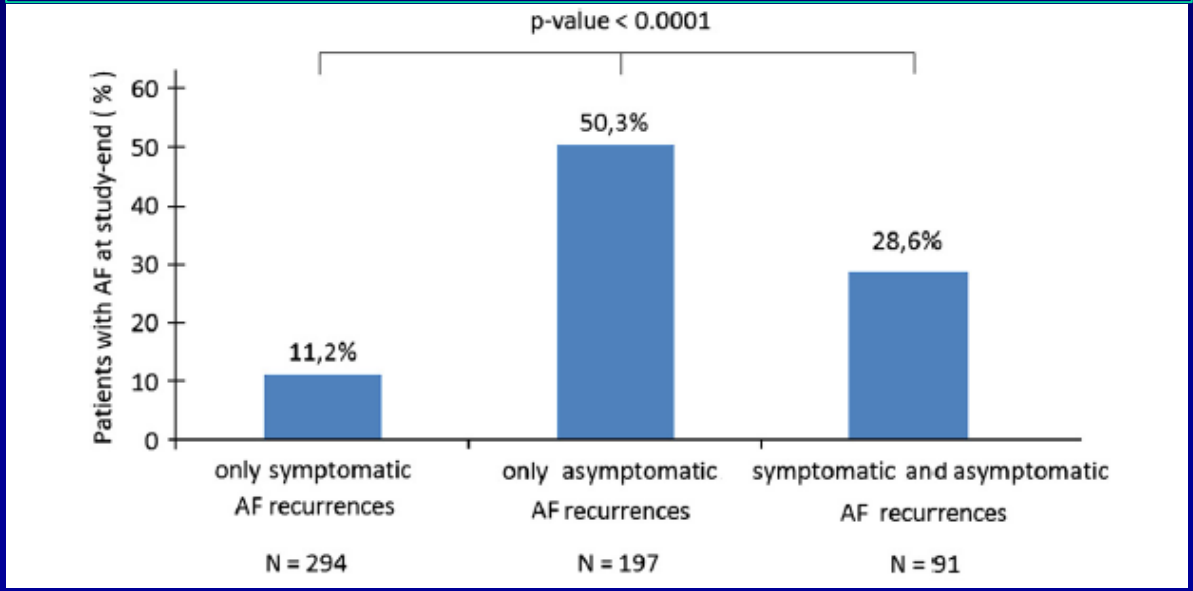
Kaplan-Meier curves for the time to first recurrence of AF. Patients having experienced a recurrence of AF are considered.

Disertori, Lombardi et al,
Am Heart J 2011

	Patients with only asymptomatic AF recurrences (n = 210)		
	OR (95% CI)	Wald χ^2	P
Duration of last qualifying episode of AF	1.57 (1.26-1.95)	16.23	<.0001
≤5 y of education	2.19 (1.33-3.61)	9.38	.0022
Digitalis	5.58 (1.56-20.00)	6.96	.0083
Sotalol	0.26 (0.10-0.72)	6.83	.0089
SR restoration (spontaneous vs pharmacologic)	2.74 (1.27-5.91)	6.59	.0103
Current smoker	2.73 (1.16-6.43)	5.30	.0213
Hypercholesterolemia	0.59 (0.36-0.96)	4.59	.0321
Class I antiarrhythmic agents	0.53 (0.30-0.94)	4.68	.0306

Multivariable logistic regression analysis was performed.

Relationship between symptomatic and asymptomatic AF recurrences and rhythm at study end-visit

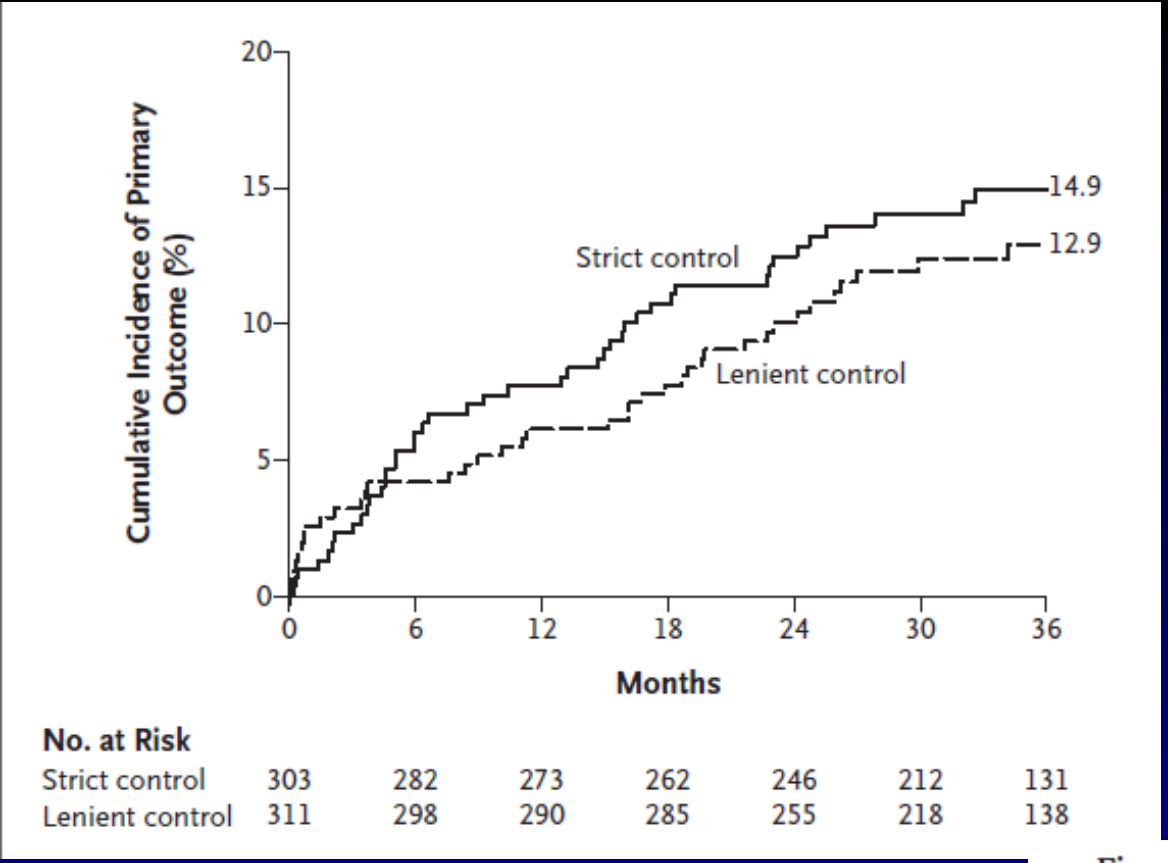


Disertori, Lombardi et al, Am Heart J 2011

Lenient versus Strict Rate Control in Patients with Atrial Fibrillation

Variable	Lenient Rate Control (N=311)	Strict Rate Control (N=303)	P Value
Rate-control target or targets achieved — no. (%)	304 (97.7)	203 (67.0)	<0.001
Resting heart rate — no. (%)			
<70 beats/min	1 (0.3)	67 (22.1)	<0.001
70–80 beats/min	5 (1.6)	161 (53.1)	<0.001
81–90 beats/min	112 (36.0)	39 (12.9)	<0.001
91–100 beats/min	123 (39.5)	20 (6.6)	<0.001
>100 beats/min	70 (22.5)	16 (5.3)	<0.001
Resting heart-rate target achieved — no. (%)	304 (97.7)	228 (75.2)	<0.001
Rate-control medication — no. (%)			
None	32 (10.3)	3 (1.0)	<0.001
Beta-blocker alone	132 (42.4)	61 (20.1)	<0.001
Verapamil or diltiazem alone	18 (5.8)	16 (5.3)	0.78
Digoxin alone	21 (6.8)	5 (1.7)	0.002
Beta-blocker and either verapamil or diltiazem	12 (3.9)	38 (12.5)	<0.001
Beta-blocker and digoxin	60 (19.3)	113 (37.3)	<0.001
Digoxin and either verapamil or diltiazem	18 (5.8)	29 (9.6)	0.08
Beta-blocker, digoxin, and either verapamil or diltiazem	3 (1.0)	27 (8.9)	<0.001

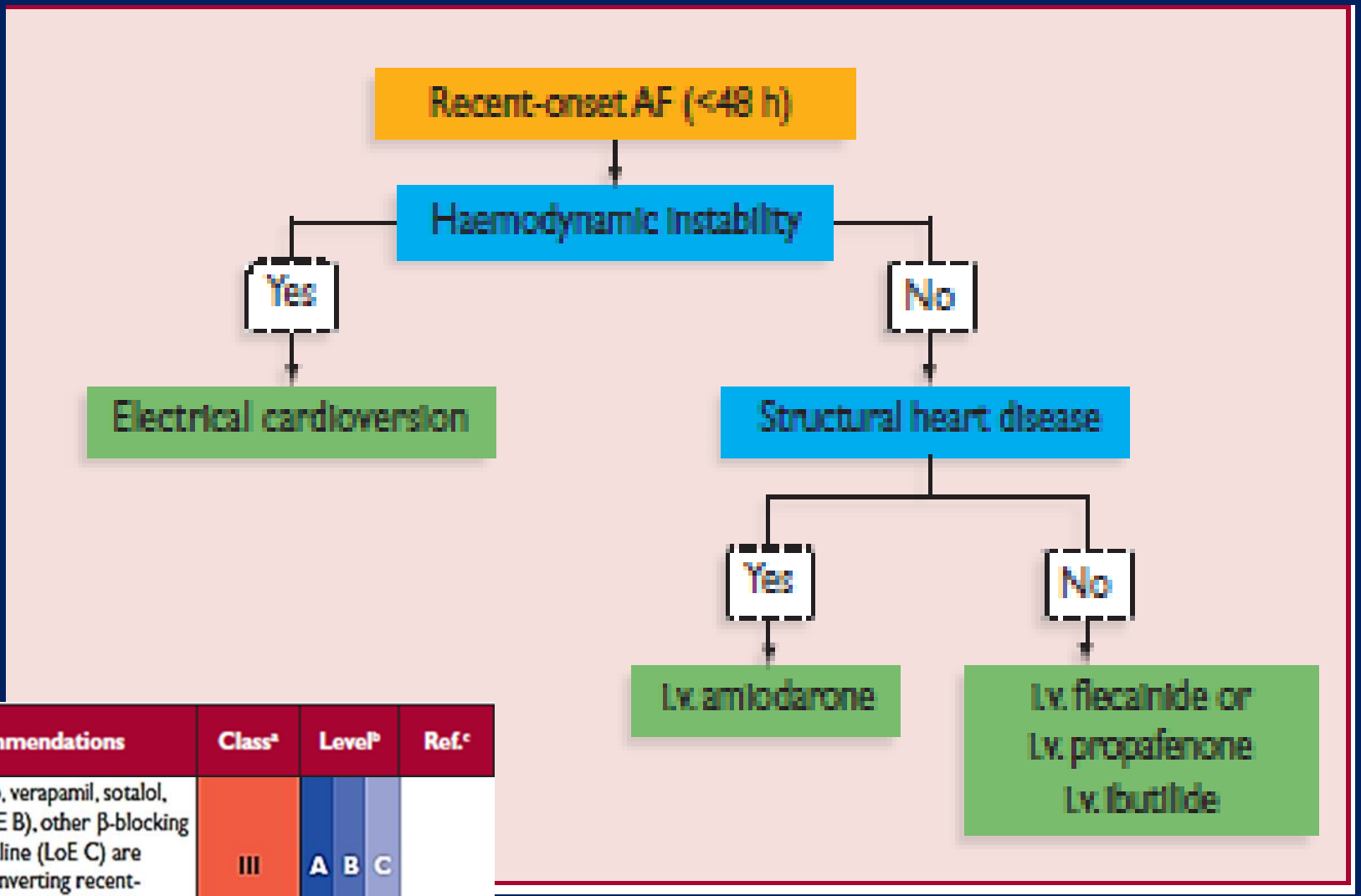
Van Gelder et al, NEJM 2010



Finally, we did not find significant differences in the prevalence of symptoms associated with atrial fibrillation. Almost 60% of the patients in both groups were symptomatic at baseline; this fraction decreased to 46% by the end of the follow-up period, a decline that may be related to underlying disease rather than to the heart rate driving symptoms.[18] Although the prevalence of symptoms was similar in the two groups in our study, we cannot rule out potential differences in the severity of symptoms between the groups.

Van Gelder et al, NEJM 2010

2: Is there a role for digoxin for recent onset AF ?



Recommendations	Class[a]	Level[b]	Ref.[c]
Digoxin (LoE A), verapamil, sotalol, metoprolol (LoE B), other β-blocking agents and ajmaline (LoE C) are ineffective in converting recent-onset AF to sinus rhythm and are not recommended.	III	A B C	

207 Participating Hospitals

FIRE

5734
ENROLLED PATIENTS

1185 (20.7%)
Planned admission in cardiology

4549 (79.3%)
Managed by the Emergency Room

2749 (60.4%) Admitted to hospital

- **1174 (42.7%)** Cardiology
- **1034 (37.6%)** Internal Medicine
- **541 (19.7%)** Other ward

1706 (37.5%) Discharged
89 (2.0%) Transferred
5 (0.1%) Dead

Cardioversion by ward of admissions (data on 2179 pts)

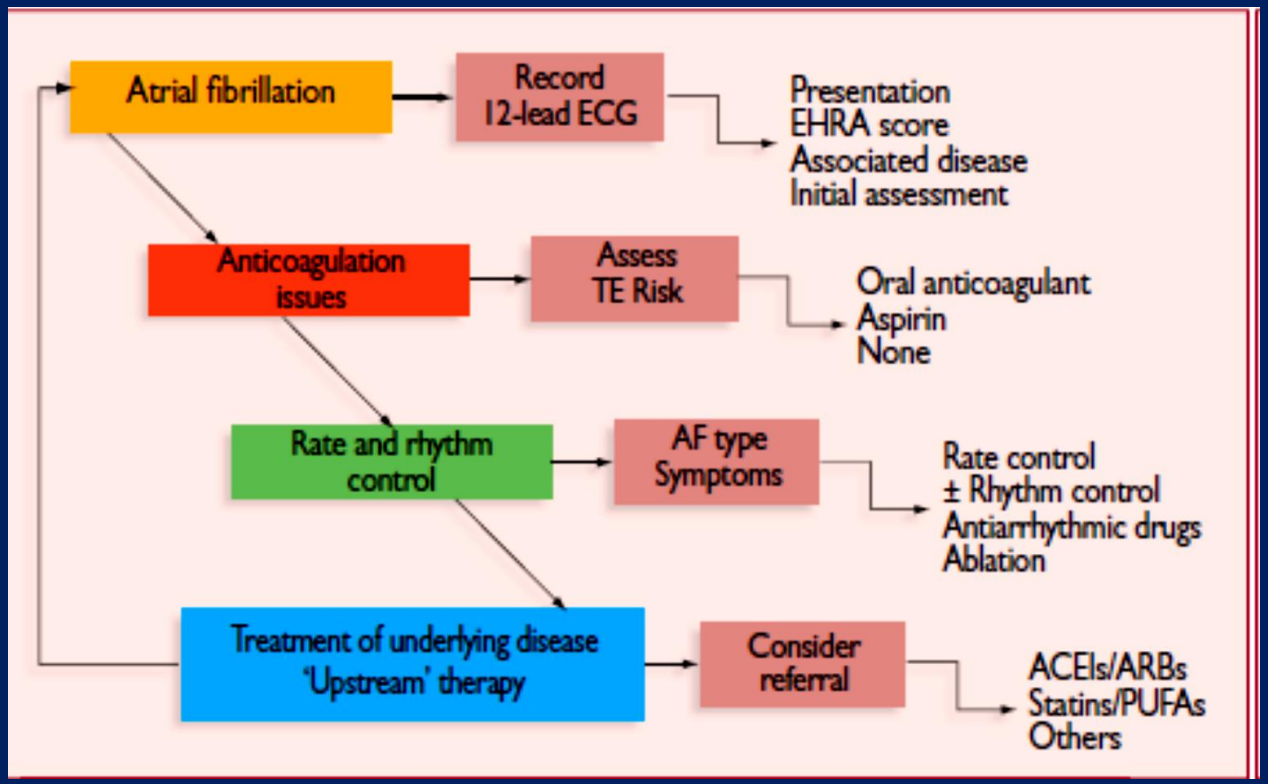
	Cardiology (%)	Internal Medicine (%)	Other wards (%)	p	Total (%)
CV-Electrical	15.8	1.4	7.1	0.001	8.9
CV-Pharmacological	62.7	47.5	52.1	0.001	55.2
CV-E or CV-Ph	72.5	48.1	56.5	0.001	60.6

Treatments in the first 24 hours by ward of admissions

	Cardiology (%)	Internal Medicine (%)	Other wards (%)	p	Total (%)
Digitalis	38.0	61.6	41.4	0.001	47.3
Amiodarone	36.1	22.8	26.6	0.001	29.4
Quinidine	3.9	2.8	1.9	NS	3.1
Flecainide	4.3	0.3	3.2	0.001	2.6
Propafenone	24.9	19.5	24.7	0.008	22.9

3: Is there a role for ACE inhibitors ?

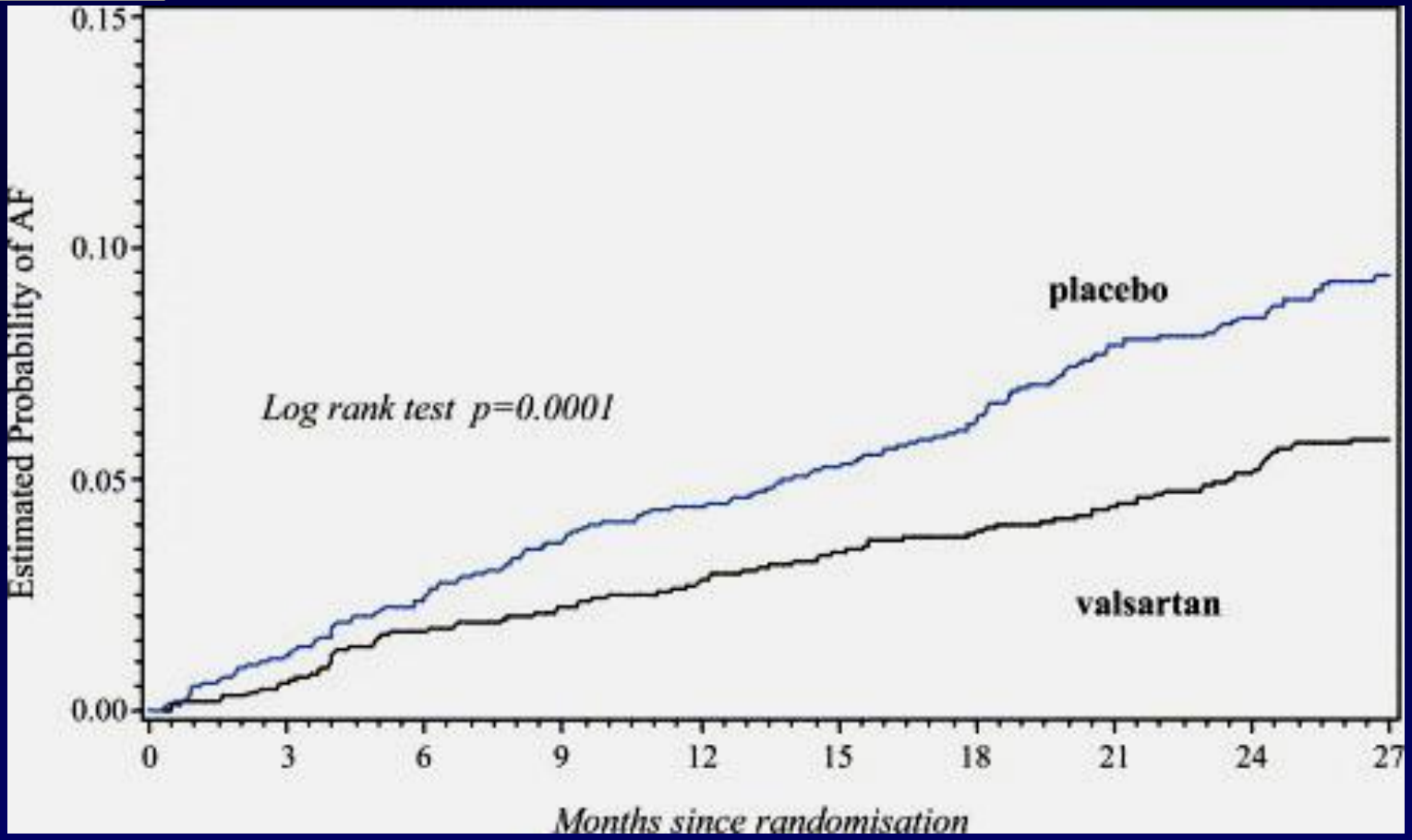
The management cascade for patients with AF



ESC 2010

In the Val-Heft study, valsartan administration was associated with a reduced incidence of AF.

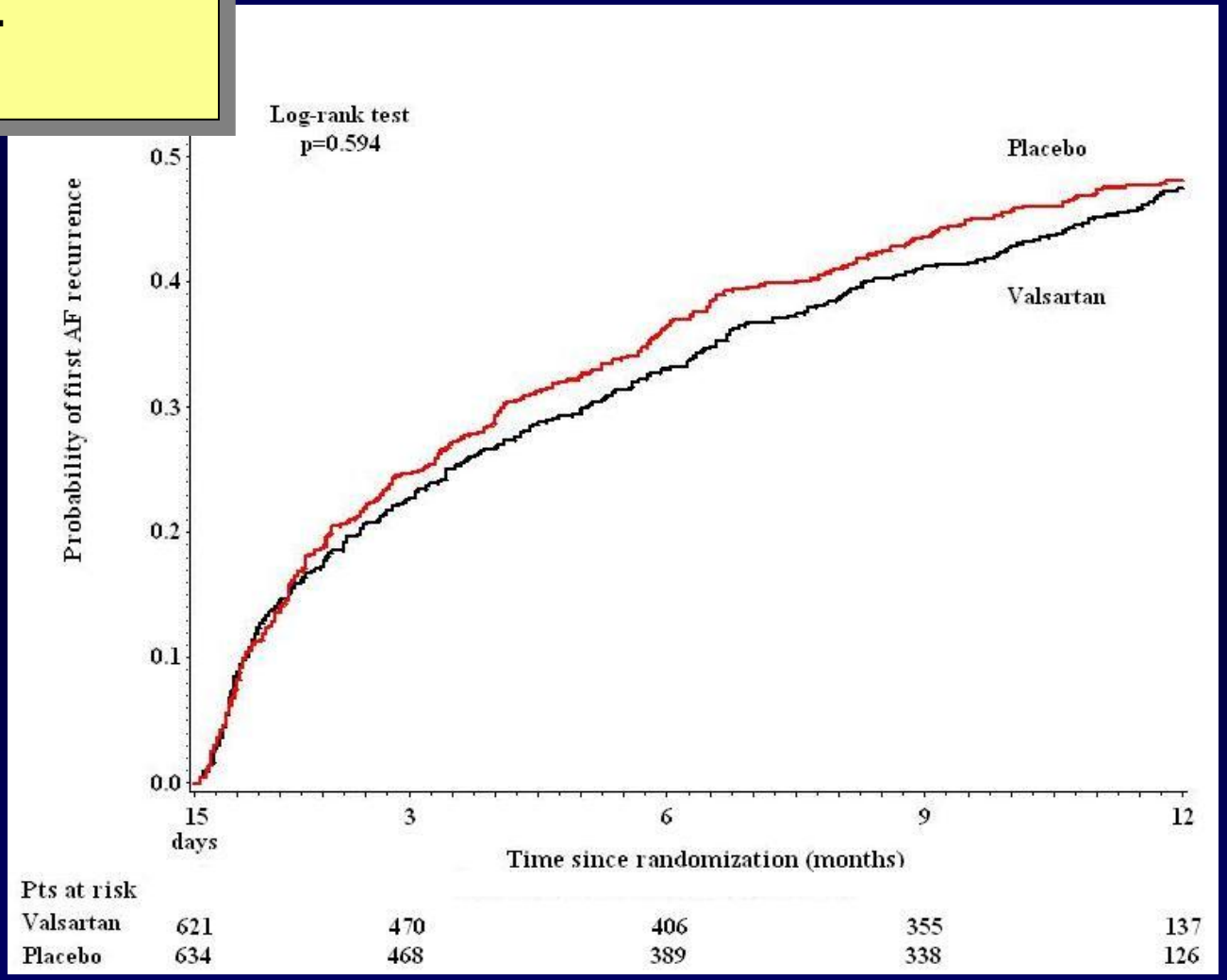
tan reduces the incidence of atrial ation in patients with heart failure (Val-Heft Study)



Maggioni et al, 2005

The results of GISSI-AF trial did not show a beneficial effect of Valsartan on AF recurrences during 1 year follow-up period.

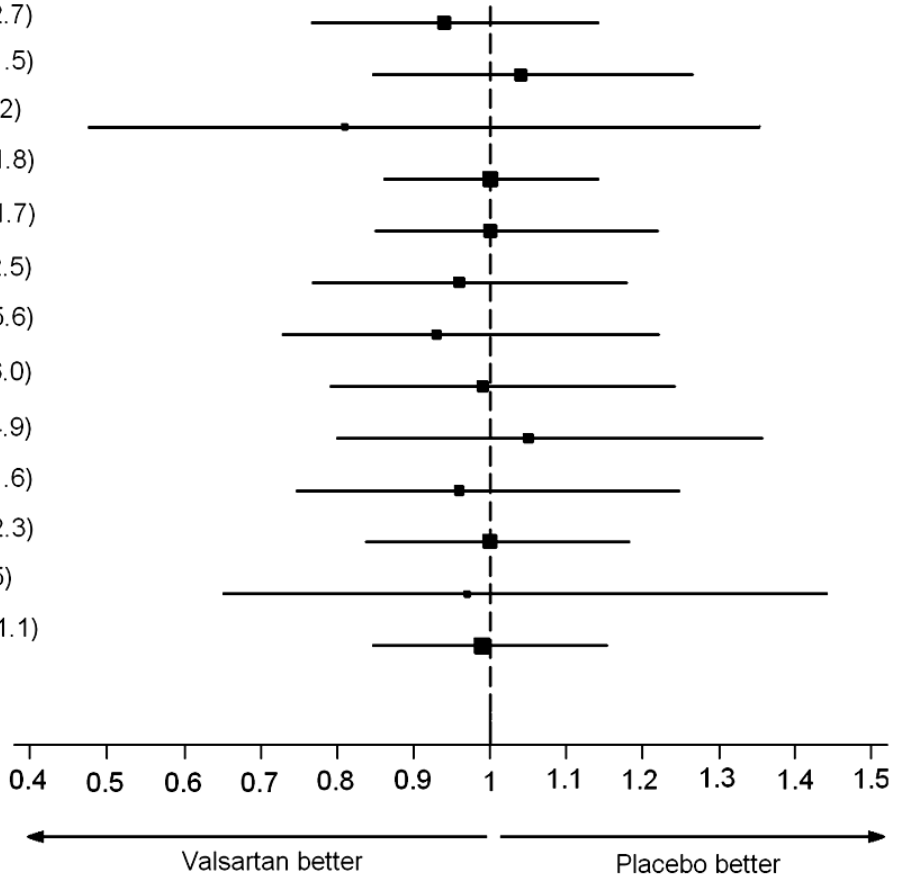
rial on the Angiotensin Receptor Blocker revention of Atrial Fibrillation Recurrence GISSI-AF Investigators*



Disertori et al. NEJM 2009

There were no subgroups in which Valsartan was better than placebo.

	Valsartan Events/Patients (%)	Placebo Events/patients (%)
	183 / 368 (49.7)	186 / 353 (52.7)
Age >= 69 years	188 / 354 (53.1)	189 / 367 (51.5)
HF and/or LVD	27 / 56 (48.2)	32 / 58 (55.2)
No HF and/or LVD	344 / 666 (51.7)	343 / 662 (51.8)
ACE-I	217 / 420 (51.7)	208 / 402 (51.7)
No ACE-I	154 / 302 (51.0)	167 / 318 (52.5)
Amiodarone	109 / 253 (43.1)	113 / 248 (45.6)
Other antiarrhythmics	154 / 277 (55.6)	150 / 268 (56.0)
No antiarrhythmics	108 / 192 (56.3)	112 / 204 (54.9)
Betablockers	110 / 223 (49.3)	110 / 213 (51.6)
No Betablockers	261 / 499 (52.3)	265 / 507 (52.3)
Lone AF	42 / 78 (53.9)	55 / 94 (58.5)
No lone AF	329 / 644 (51.1)	320 / 626 (51.1)



Disertori et al. NEJM 2009

4: Is there a role for ASA in AF ?

The management cascade for patients with AF

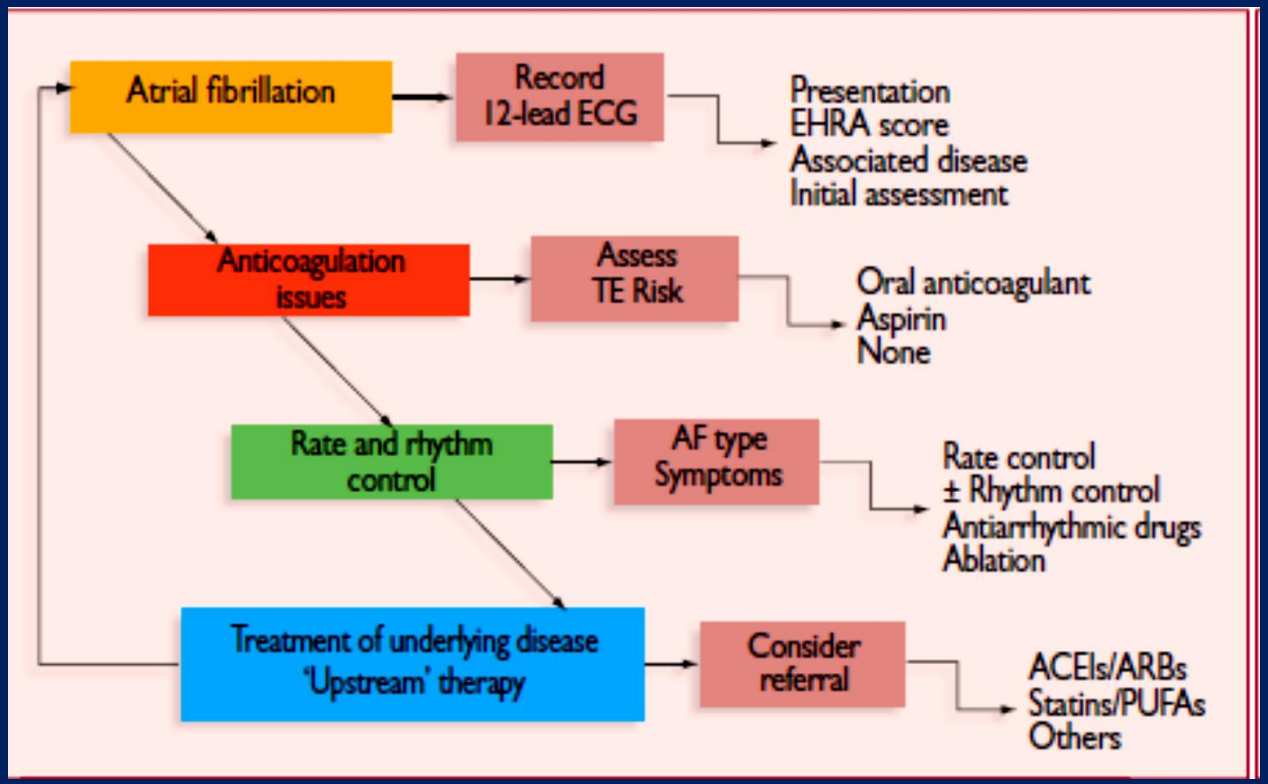


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Table 8 CHA_2DS_2VASc score and stroke rate

(a) Risk factors for stroke and thrombo-embolism in non-valvular AF	
'Major' risk factors	**'Clinically relevant non-major' risk factors**
Previous stroke, TIA, or systemic embolism Age ≥75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤40%) Hypertension - Diabetes mellitus Female sex - Age 65–74 years Vascular disease[a]

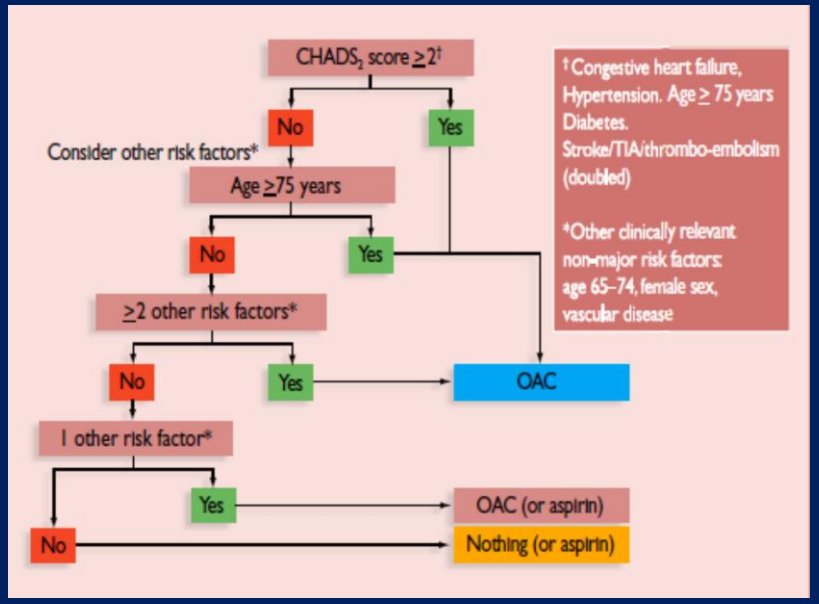
(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)	
Risk factor	**Score**
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score

CHA_2DS_2-VASc score	Patients (n=7329)	Adjusted stroke rate (%/year)[b]
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

Table 9 Approach to thromboprophylaxis in patients with AF

Risk category	CHA_2DS_2-VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥2 'clinically relevant non-major' risk factors	≥2	OAC[a]
One 'clinically relevant non-major' risk factor	1	Either OAC[a] or aspirin 75–325 mg daily. Preferred: OAC rather than aspirin.
No risk factors	0	Either aspirin 75–325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.



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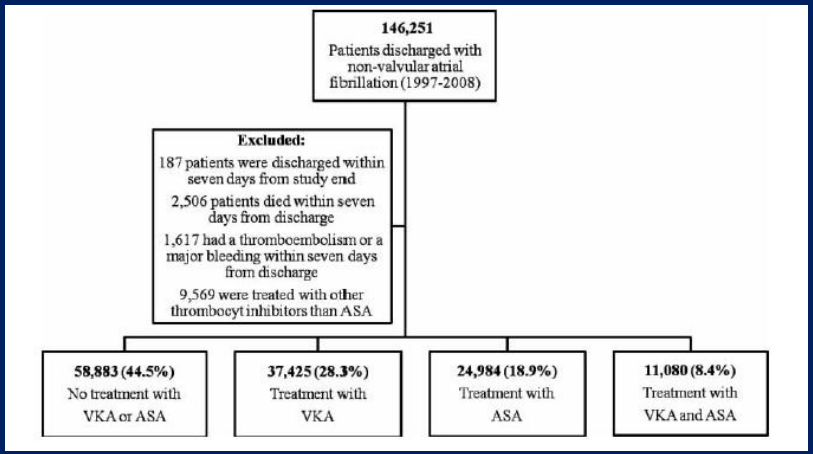
Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: A net clinical benefit analysis using a 'real world' nationwide cohort study



	No treatment (n=58,883)	VKA alone (n=37,425)	ASA alone (n=24,984)	VKA+ASA (n=11,080)
$CHADS_2$				
Low (score 0)	17,078 (29.0)	9,434 (25.2)	3,211 (12.9)	1,486 (13.4)
Intermediate (score 1)	20,174 (34.3)	12,281 (32.8)	8,137 (32.6)	3,310 (29.9)
High (score 2–6)	21,631 (36.7)	15,710 (42.0)	13,636 (54.6)	6,284 (56.7)
CHA_2DS_2-VASc				
Low (score 0)	6,915 (11.7)	3,881 (10.4)	917 (3.7)	451 (4.1)
Intermediate (score 1)	8,427 (14.3)	6,088 (16.3)	1,945 (7.8)	1,130 (10.2)
High (score 2–9)	43,541 (73.9)	27,456 (73.4)	22,122 (88.5)	9,499 (85.7)
HAS-BLED				
Low (score 0–1)	28,868 (49.0)	17,085 (45.7)	1,730 (6.9)	776 (7.0)
Intermediate (score 2)	19,043 (32.3)	13,416 (35.9)	9,328 (37.3)	3,580 (32.3)
High (score ≥3)	10,972 (18.6)	6,924 (18.5)	13,926 (55.7)	6,724 (60.7)

AF: atrial fibrillation; ASA: acetylsalicylic acid; NSAID: non-steroidal anti-inflammatory drug; SD: Standard deviation; VKA: vitamin K antagonist

Olesen et al Tromb Haemost 2011

	No treatment (n=58,883)	VKA alone (n=37,425)	ASA alone (n=24,984)	VKA+ASA (n=11,080)
Age, mean (SD)	72.8 (± 14.4)	70.6 (± 11.1)	78.1 (± 11.2)	73.1 (± 9.6)
Male gender (%)	29,338 (49.8)	23,011 (61.5)	11,552 (46.2)	6,766 (61.1)
Comorbidity (%)				
Heart failure	8,930 (15.2)	6,691 (17.9)	5,427 (21.7)	2,480 (22.4)
Hypertension	17,477 (29.7)	17,477 (46.7)	11,371 (45.5)	6,903 (62.3)
Age ≥75 years	31,450 (53.4)	15,339 (41.0)	17,016 (68.1)	5,414 (48.9)
Age 65–74 years	12,366 (21.0)	11,752 (31.4)	4,645 (18.6)	3,584 (32.4)
Diabetes mellitus	4,451 (7.6)	3,268 (8.3)	2,801 (11.2)	1,414 (12.8)
Previous thromboembolism	7,286 (12.4)	5,191 (13.9)	4,181 (16.7)	2,047 (18.5)
Vascular disease	7,637 (13.0)	3,776 (10.1)	5,565 (22.3)	2,478 (22.4)
Previous bleeding	4,938 (8.4)	1,974 (5.3)	2,199 (8.8)	579 (5.2)
Concomitant medication (%)				
Adrenergic α-antagonist	698 (1.2)	505 (1.4)	414 (1.7)	226 (2.0)
Non-loop-diuretics	15,643 (26.6)	11,354 (30.3)	8,872 (35.5)	4,200 (37.9)
Vasodilators	1,828 (3.1)	1,086 (2.9)	858 (3.4)	342 (3.1)
Beta blockers	19,299 (32.8)	19,842 (53.0)	11,660 (46.7)	6,990 (63.1)
Calcium channel blockers	13,585 (23.1)	12,284 (32.8)	7,739 (31.0)	4,146 (37.4)
Renin-angiotensin system inhibitors	11,695 (19.9)	12,480 (33.4)	7,787 (31.2)	5,065 (45.7)
Loop-diuretics	19,314 (32.8)	14,510 (38.8)	11,245 (45.0)	5,017 (45.3)
Statins	3,975 (6.8)	4,617 (12.3)	4,194 (16.8)	3,369 (30.4)
NSAID	12,432 (21.1)	7,142 (19.1)	5,586 (22.4)	2,374 (21.4)
Digoxin	22,454 (38.1)	22,645 (60.5)	11,845 (47.4)	6,234 (56.3)
Amiodarone	1,333 (2.3)	1,527 (4.1)	796 (3.2)	616 (5.6)

Hazard ratios of thromboembolism at maximum 12 years follow-up; results from time-dependent Cox proportional-hazard analyses.

	Whole cohort (n=132,372)		unadjusted	Age & gender	Baseline ch.	HAS-BLED score ≤2 (n=93,826)	HAS-BLED score ≥3 (n=38,546)	No preMI (n=112,916)	With preMI (n=19,456)
	Years of exposure	TE events	Hazard ratio (CI)*	Hazard ratio (CI)†	Hazard ratio (CI)‡	Hazard ratio (CI)‡	Hazard ratio (CI)‡	Hazard ratio (CI)‡	Hazard ratio (CI)‡
$CHADS_2$									
Low (score 0)									
VKA only	40,960	428	Reference	Reference	Reference	Reference	Reference	Reference	Reference
No treatment	82,214	1,280	1.53 (1.37–1.71)	2.05 (1.84–2.29)	2.09 (1.86–2.34)	2.08 (1.85–2.33)	1.83 (0.96–3.49)	2.09 (1.86–2.35)	2.10 (1.42–3.10)
ASA only	22,310	439	1.90 (1.66–2.17)	1.95 (1.71–2.23)	1.92 (1.67–2.20)	1.92 (1.67–2.20)	1.36 (0.68–2.75)	2.04 (1.77–2.35)	1.34 (0.88–2.05)
VKA + ASA	6,269	77	1.15 (0.90–1.47)	1.10 (0.86–1.40)	1.07 (0.84–1.37)	1.10 (0.86–1.41)	0.38 (0.08–1.72)	1.05 (0.80–1.38)	1.08 (0.61–1.92)
Intermediate (1)									
VKA only	45,132	781	Reference	Reference	Reference	Reference	Reference	Reference	Reference
No treatment	69,005	2,781	2.38 (2.20–2.58)	2.00 (1.84–2.16)	1.99 (1.83–2.16)	1.97 (1.80–2.15)	2.15 (1.71–2.71)	2.02 (1.86–2.21)	1.71 (1.34–2.17)
ASA only	37,247	1,554	2.45 (2.25–2.67)	1.99 (1.82–2.17)	1.98 (1.82–2.16)	1.96 (1.78–2.16)	1.94 (1.53–2.46)	2.06 (1.88–2.27)	1.47 (1.15–1.89)
VKA + ASA	9,685	230	1.34 (1.16–1.55)	1.41 (1.21–1.63)	1.41 (1.22–1.64)	1.45 (1.23–1.71)	1.20 (0.86–1.68)	1.47 (1.25–1.73)	1.09 (0.76–1.56)
High (2–6)									
VKA only	48,879	2,159	Reference	Reference	Reference	Reference	Reference	Reference	Reference
No treatment	60,550	5,100	1.92 (1.82–2.01)	1.75 (1.66–1.84)	1.82 (1.73–1.92)	1.91 (1.77–2.05)	1.74 (1.62–1.88)	1.88 (1.78–1.99)	1.56 (1.38–1.76)
ASA only	42,984	3,512	1.86 (1.76–1.96)	1.66 (1.57–1.75)	1.73 (1.64–1.83)	1.93 (1.76–2.11)	1.58 (1.47–1.70)	1.79 (1.69–1.91)	1.47 (1.30–1.67)
VKA + ASA	12,590	606	1.00 (0.92–1.10)	1.01 (0.93–1.11)	1.05 (0.96–1.15)	1.08 (0.90–1.28)	0.98 (0.88–1.10)	1.05 (0.94–1.17)	1.00 (0.84–1.20)

What is known about this topic?

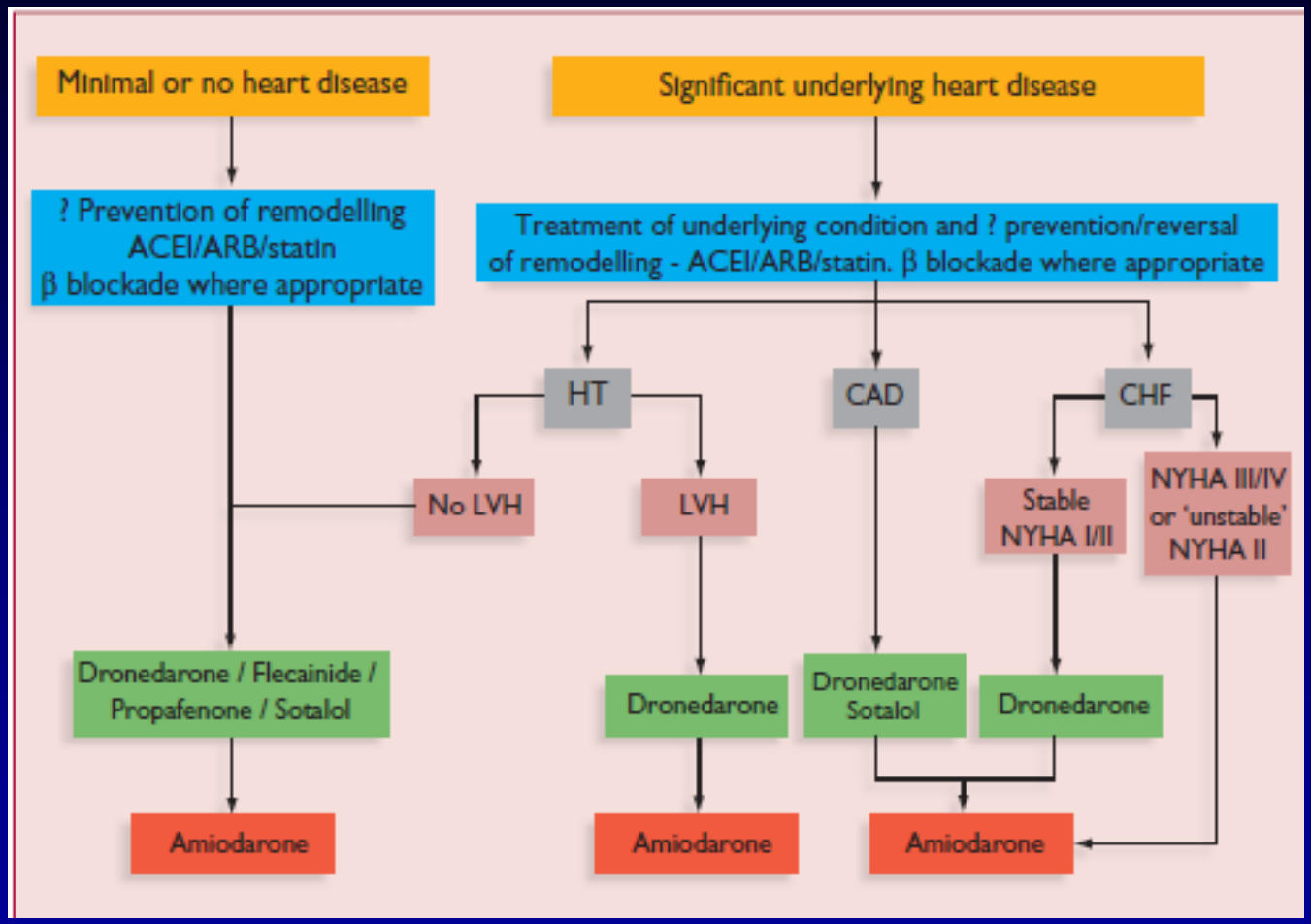
- The 2010 European guidelines on atrial fibrillation (AF) suggest that: AF patients with CHA_2DS_2-VASc score = 0 should receive acetylsalicylic acid or no antithrombotic treatment, AF patients with CHA_2DS_2-VASc score = 1 should receive oral anticoagulation or acetylsalicylic acid, and AF patients with CHA_2DS_2-VASc score ≥ 2 should receive oral anticoagulation.

What does this paper add?

- Regardless of HAS-BLED score, there is negative net clinical benefit of oral anticoagulation if patients are 'truly low risk' (i.e. CHA2DS2-VASc score = 0) and, a neutral or positive net clinical benefit of oral anticoagulation for patients with CHADS2 score ≥ 0 or CHA2DS2-VASc score ≥ 1.
- Acetylsalicylic acid should not be used for thromboprophylaxis in any patient with atrial fibrillation.

Olesen et al Tromb Haemost 2011

4: Is there still a role for dronedarone?



ESC 2010

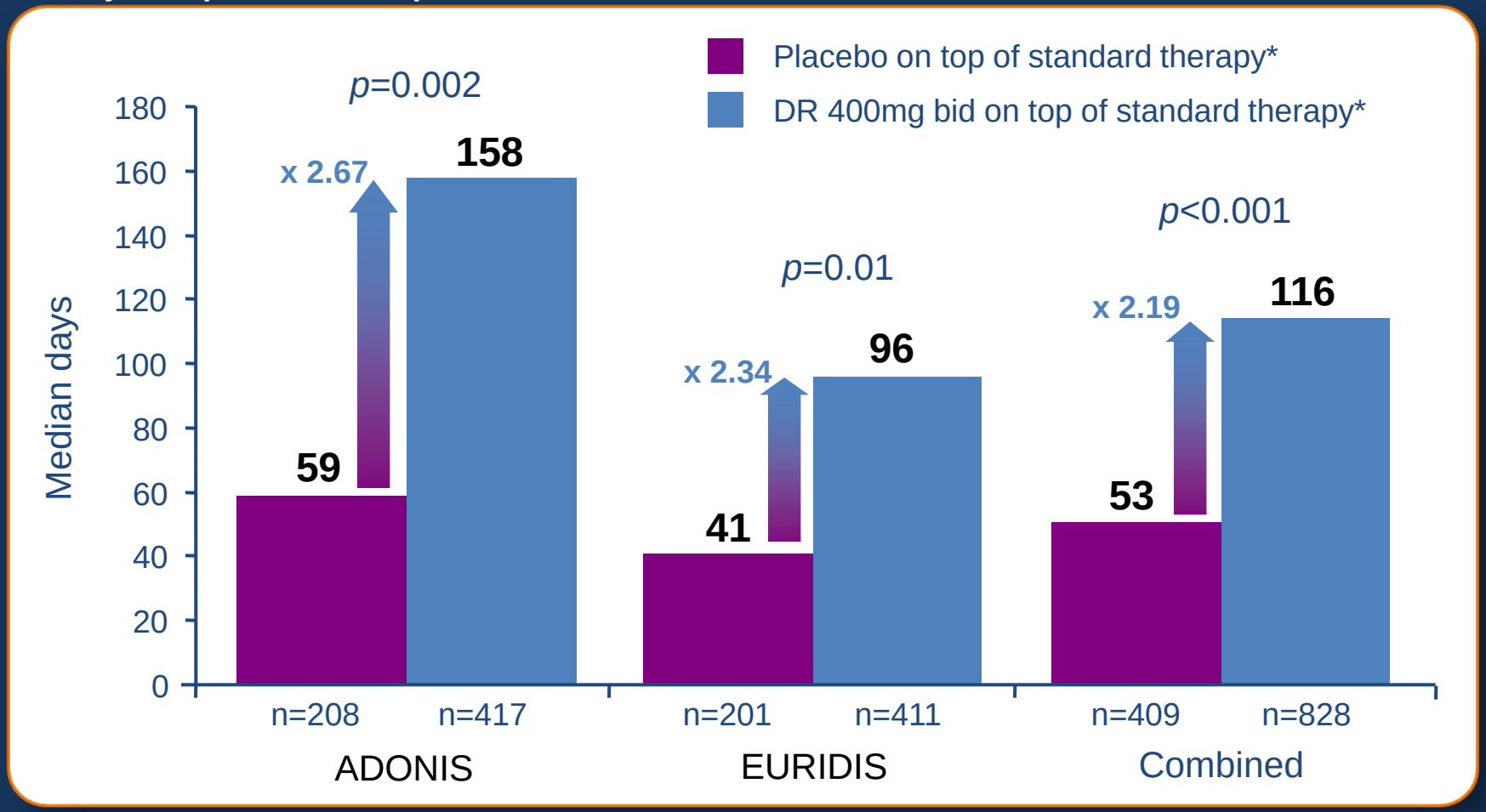
Dronedarone is a multichannel blocker

- Dronedarone Possesses Electrophysiologic Characteristics of all Four Vaughan Williams Classes
  - Outward currents
    - Ikr: rapidly activating delayed rectifier potassium current
    - Iks: slowly activating delayed rectifier potassium current
    - Ito: transient outward current
    - Ik(Ach): muscarinic receptor-operated K+ current (atria)
  - Inward currents
    - Fast sodium currents
    - Calcium channel antagonist
- Dronedarone has anti-fibrillatory effects in the ventricles and atria

Gautier P, *et al. J Cardiovasc Pharmacol.* 2003;41(2):191-202.
Doggrell SA, Hancox JC, *Expert Opin Investig Drugs* 2004;13:415-426.

Dronedarone more than doubled time to first recurrence of AF/AFL

Paroxysmal/persistent AF patients



*Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonists and/or digoxin) and/or anti-thrombotic therapy (oral anticoagulation and/or long-term antiplatelet therapy) and/or other CV therapy such as ACE inhibitors and statins

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

The ATHENA study

- The largest single antiarrhythmic drug trial conducted in AF
  - >4,600 patients with a history of atrial fibrillation or atrial flutter
  - More than 550 investigational sites in 37 countries

--- To evaluate the efficacy and safety of dronedarone 400mg bid vs placebo on top of standard therapy* in the prevention of CV hospitalisation or death from any cause over a minimum treatment and follow-up duration of 12 months in patients with paroxysmal or persistent AF/AFL

* Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonist and/or digoxin) and/or anti-thrombotic therapy (Vit. K antagonists and /or aspirin and other antiplatelets therapy) and/or other CV agents such as ACEIs/ARBs and statins

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

Inclusion criteria

- High-risk patients with a history of paroxysmal or persistent AF/AFL
- Aged ≥75 years with or without additional risk factors
- Aged ≥70 years and ≥1 risk factor (hypertension; diabetes; prior stroke/TIA; LA ≥50 mm; LVEF <0.40)

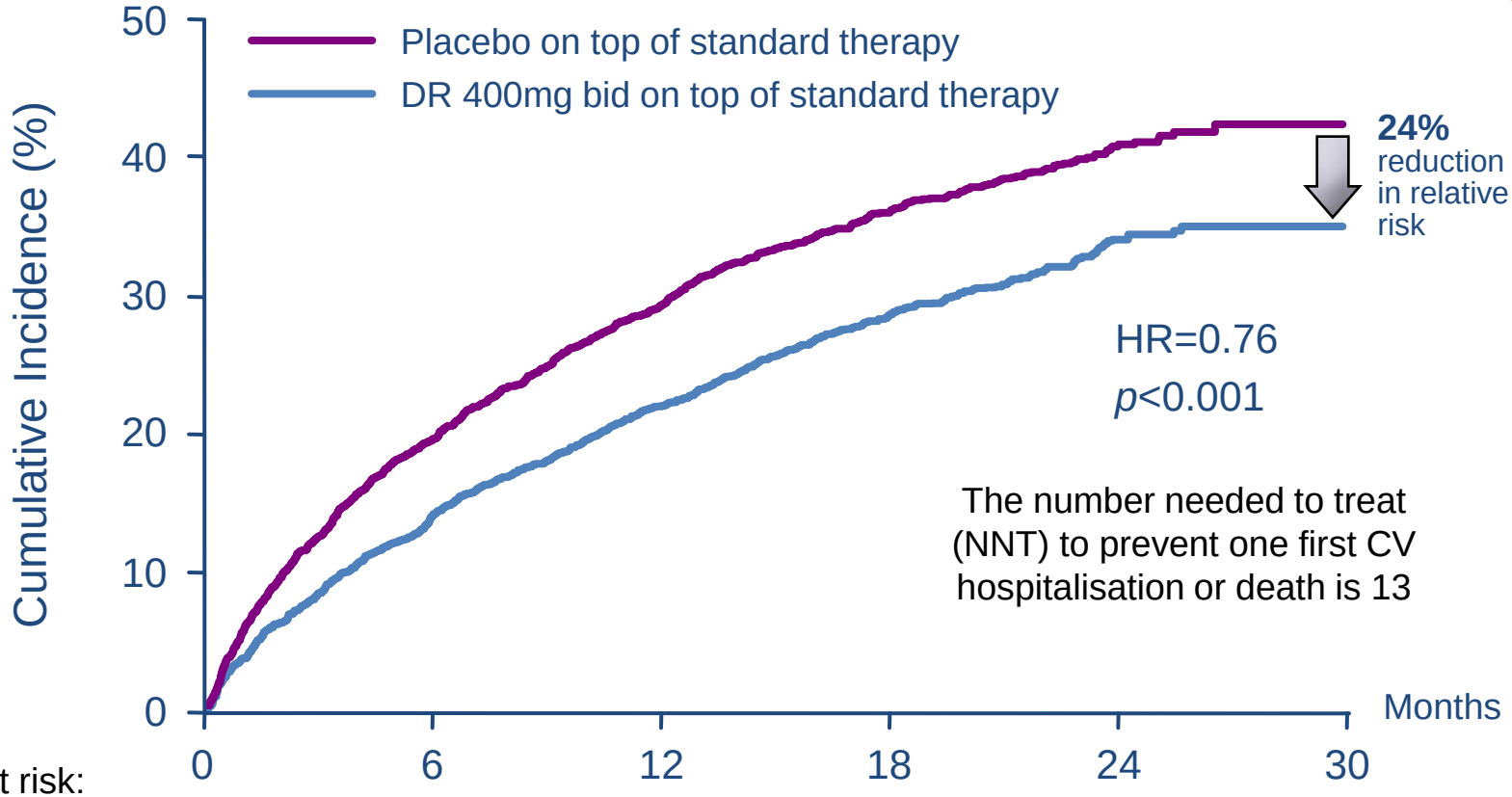
- Originally the protocol had allowed patients <70 years of age with additional risk factors into the study
- The protocol was subsequently amended to include only patients ≥70 years of age

Exclusion criteria

- Permanent AF
- Unstable hemodynamic situation (i.e. recently decompensated CHF)
- CHF NYHA class IV
- Bradycardia <50 bpm and/or PR >0.28 sec
- Sick sinus syndrome
- Calculated GFR at baseline <10 ml/min
- Potassium <3.5 mmol/L
- Concomitant antiarrhythmic drug Rx
- Severe illness limiting life expectancy
- Pregnancy or breastfeeding
- Refusal or inability to give informed consent

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

Dronedarone significantly decreased risk of CV hospitalisation or death from any cause by 24%



Patients at risk:

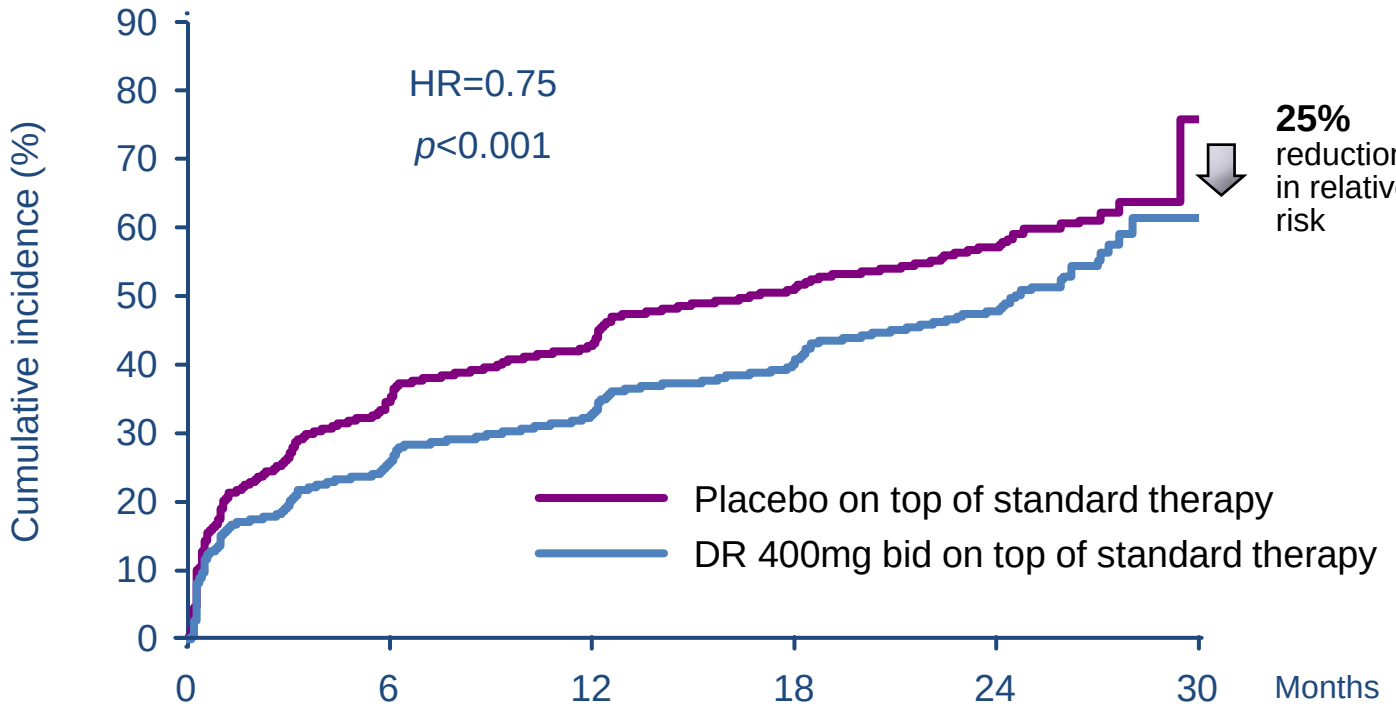
Placebo	2327	1858	1625	1072	385	3
DR 400mg bid	2301	1963	1776	1177	403	2

Any unplanned hospitalisation (i.e., admission with an overnight stay in the hospital) was classified by the investigator as a hospitalisation due to either CV or non-CV causes

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

Dronedarone reduced AF/AFL recurrence in patients with sinus rhythm at baseline

Paroxysmal/persistent AF patients



Placebo	**1741**	**1123**	**970**	**610**	**200**	**1**
DR 400mg bid	**1732**	**1272**	**1136**	**716**	**243**	**1**

- More than 50% of patients included in sinus rhythm and treated with dronedarone were free of AF recurrence after 2 years

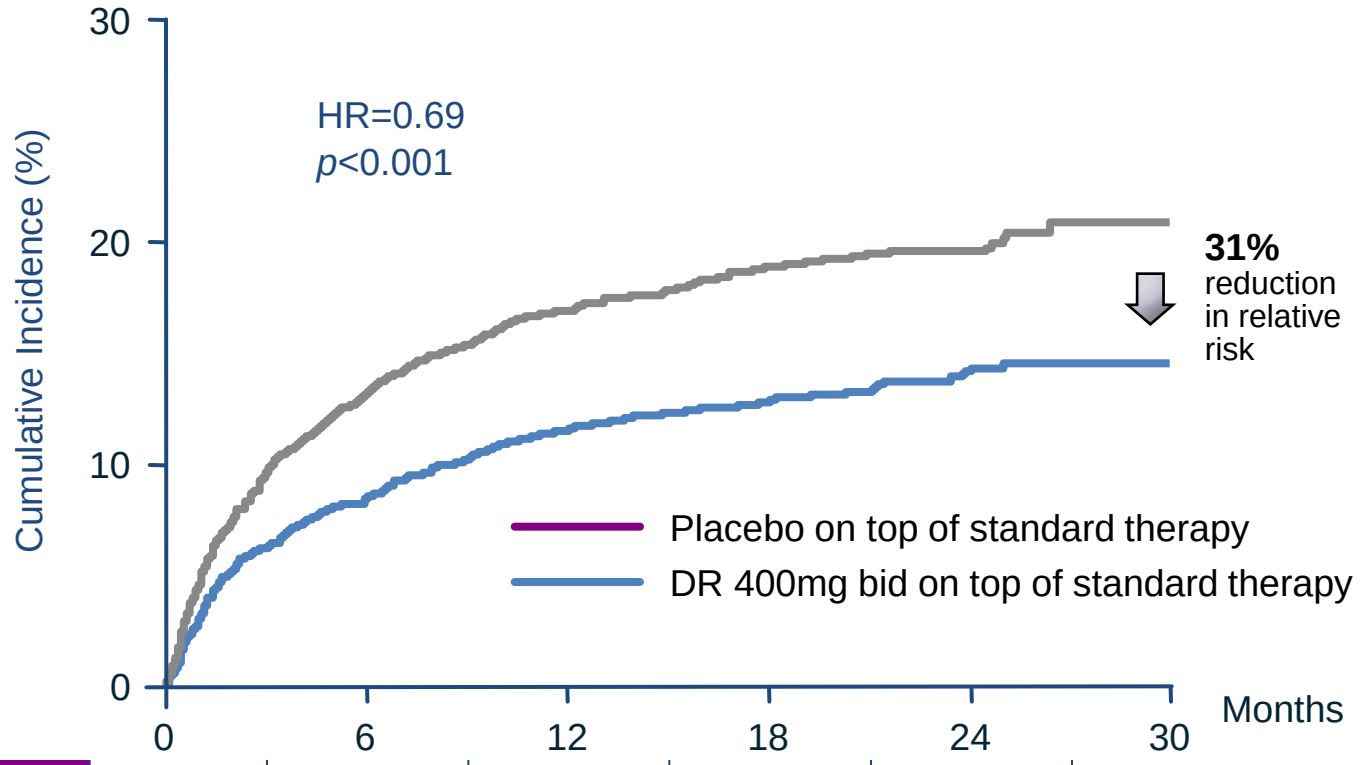
Page R, *et al. AHA Scientific Sessions* 2008
Page R, *et al. Circulation.* 2008;118:S_827.

On study analysis.

Mean follow-up 21 ± 5 months

Dronedarone significantly prolonged time to first electrical cardioversion

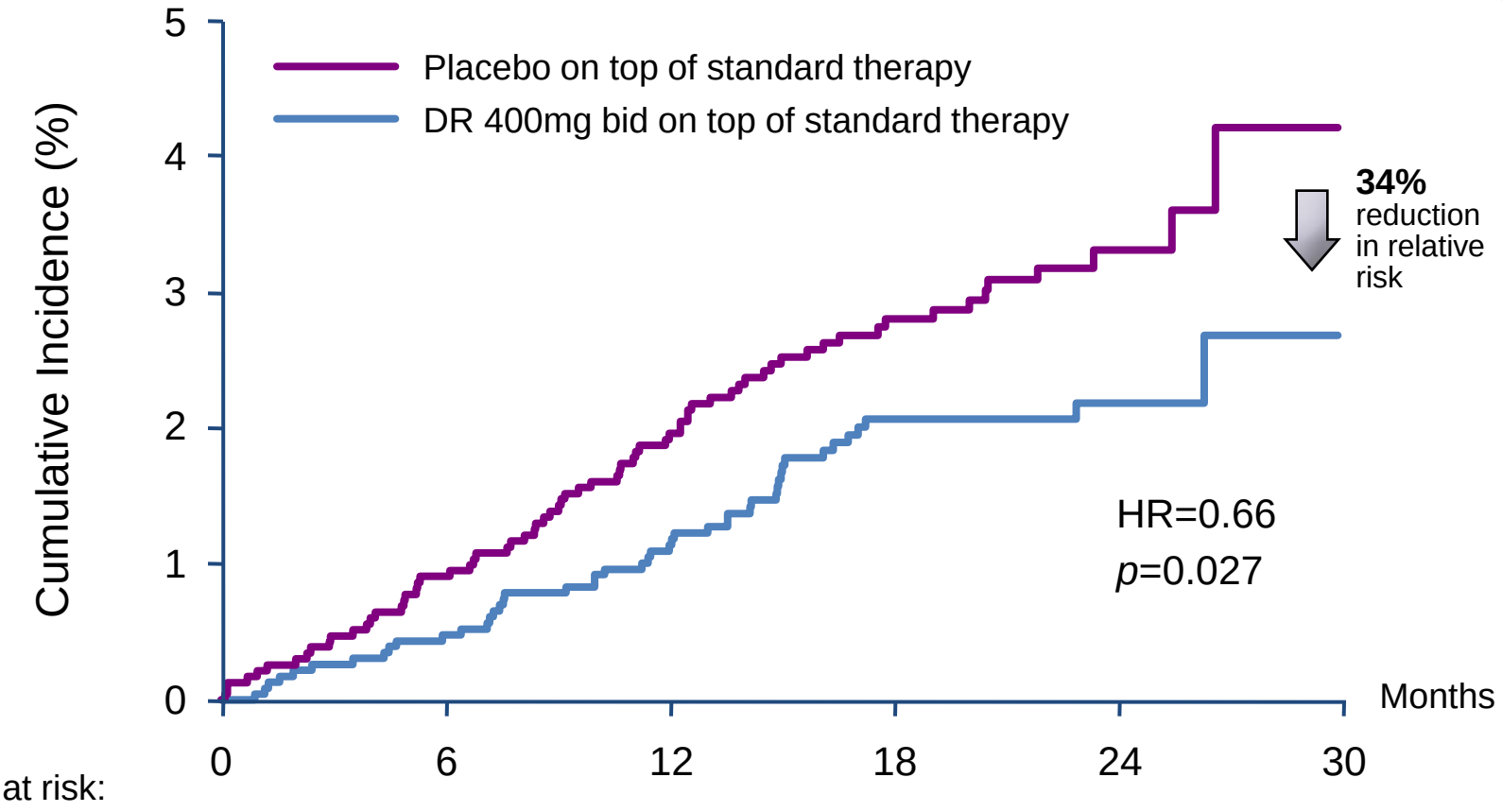
Paroxysmal/persistent AF patients



Placebo	**2313**	**1694**	**1475**	**966**	**360**	**1**
DR 400mg bid	**2291**	**1726**	**1546**	**1016**	**372**	**0**

Page R, *et al. AHA Scientific Sessions* 2008
Page R, *et al. Circulation.* 2008;118:S_827.

Dronedarone significantly reduced the relative risk of stroke by 34%



Patients at risk:

Placebo	**2327**	**2275**	**2220**	**1598**	**618**	**6**
DR 400mg bid	**2301**	**2266**	**2223**	**1572**	**608**	**4**

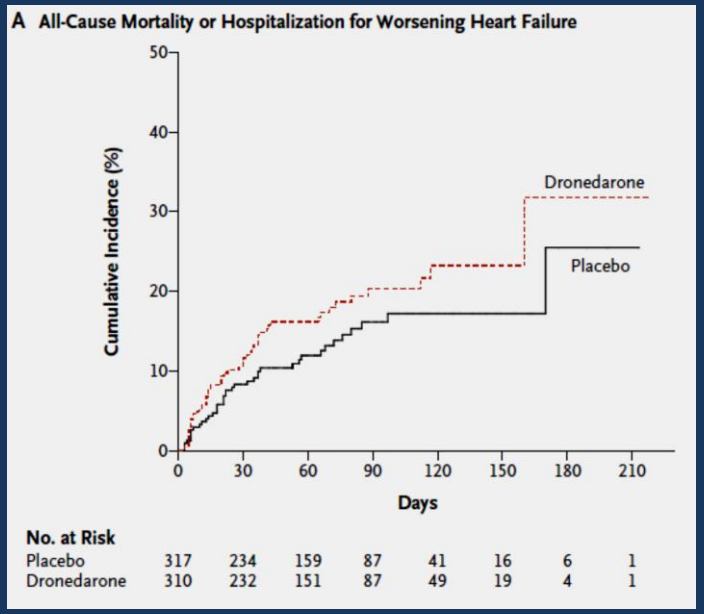
Mean follow-up 21 ±5 months.
Connolly *et al; Circulation.* 2009;120:1174-1180.

Increased Mortality after Dronedarone Therapy for Severe Heart Failure

Characteristic	Dronedarone Group (N=310)	Placebo Group (N=317)
Atrial fibrillation at randomization — no. (%)	72 (23.2)	85 (26.8)
NYHA functional class — no. (%)		
I	0	0
II	131 (42.3)	121 (38.2)
III	173 (55.8)	183 (57.7)
IV	6 (1.9)	13 (4.1)

Table 2. Cause of Death.

Cause	Dronedarone Group (N=310)	Placebo Group (N=317)
	no. (%)	
Cardiovascular	24 (7.7)	9 (2.8)
Myocardial infarction	0	2 (0.6)
Progressive heart failure	10 (3.2)	2 (0.6)
Documented arrhythmia	6 (1.9)	2 (0.6)
Other cardiovascular cause	3 (1.0)	0
Presumed cardiovascular cause	5 (1.6)	3 (0.9)
Arrhythmia or sudden death*	10 (3.2)	6 (1.9)
Noncardiovascular	1 (0.3)	3 (0.9)
Total	25 (8.1)	12 (3.8)



Kober et al, NEJM 2008

Permanent Atrial fibriLLAtion Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS)

This study is ongoing, but not recruiting participants.

- Primary Outcome Measures: Time from randomization to first occurrence among stroke, systemic arterial embolism, myocardial infarction or cardiovascular death

- Time from randomization to first occurrence of unscheduled cardiovascular hospitalization or death from any cause.
-

Secondary Outcome Measures: Time from randomization to cardiovascular death.

Inclusion criteria:

- Permanent AF defined by the presence of all of the following criteria:
  - Availability of one 12-lead ECG not more than 14 days prior to randomization showing that the patient is in AF or atrial flutter
  - Availability of documentation (including either rhythm strips or medical report of the rhythm) showing that the patient was in AF or atrial flutter at least 6 months prior to randomization
  - No evidence of sinus rhythm in the period between these two documentations of AF
  - Patient and physician decision to allow AF to continue without further efforts to restore sinus rhythm
- At least one of the following risk criteria:
  - Coronary artery disease
  - Prior stroke or Transient Ischemic Attack (TIA)
  - Symptomatic heart failure
  - Left ventricular ejection fraction $\leqq 0.40$
  - Peripheral arterial occlusive disease
  - Aged 75 years or older with both hypertension and diabetes mellitus

Exclusion criteria:

- Paroxysmal AF
- Persistent AF without a decision to allow AF to continue without further efforts to restore sinus rhythm
- Heart failure of New-York Heart Association (NYHA) class IV or recent unstable NYHA class III

Events during the PALLAS study as of June 30, 2011.

	Multaq N=1572 n (%)	*Placebo N=1577 n (%)*	*Hazard Ratio*	p-value
CV Death, Myocardial Infarction, Stroke, Systemic Embolism*	32 (2)	14 (0.9)	2.3	0.009
Death, Unplanned CV Hospitalization*	118 (7.5)	81 (5.1)	1.5	0.006
Death	16 (1)	7 (0.4)	2.3	0.065
Myocardial Infarction	3 (0.2)	3 (0.2)	1.0	1
Stroke	17 (1.1)	7 (0.4)	2.4	0.047
Heart Failure Hospitalization	34 (2.2)	15 (1)	2.3	0.008

European Medicines Agency recommends restricting use of Multaq

•Treatment with Multaq should be restricted to patients with paroxysmal or persistent atrial fibrillation when sinus rhythm has been obtained. It is no longer indicated for use in patients when atrial fibrillation is still present.

•Treatment with Multaq should only be started and monitored by a specialist after other anti-arrhythmic medicines have been considered.

•Multaq must not be used in patients with permanent atrial fibrillation, heart failure or left ventricular systolic dysfunction (impairment of the left side of the heart).

•Doctors should consider discontinuation of treatment if atrial fibrillation reoccurs.

•Multaq must not be used in patients who have had previous liver or lung injury following treatment with amiodarone, another anti-arrhythmic medicine.

•Patients on Multaq should have their lung and liver function as well as their heart rhythm regularly monitored. Especially the liver function should be closely monitored during the first few weeks of treatment.

Safety first, efficay second…..

Probably, **safety and efficacy** must go hand to hand.

Facts about Multaq

- Used to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors, who are in sinus rhythm or who will be cardioverted [Refer to Multaq label]
- From approval in July 2009 through June 2011, approximately 1 million Multaq prescriptions were dispensed and approximately 241,000 patients received Multaq prescriptions from U.S. outpatient retail pharmacies.[2]

Table 4: Net clinical benefit (95% confidence interval) of antithrombotic treatment vs. no treatment.

	Stroke				VKA		ASA		VKA+ASA	
	Ischaemic		Haemorrhagic		HAS-BLED score		HAS-BLED score		HAS-BLED score	
	N (%)	Person to years at risk	N (%)	Person to years at risk	Score ≤2	Score ≥3	Score ≤2	Score ≥3	Score ≤2	Score ≥3
$CHADS_2$										
Score 0	323 (1.0)	157,279	184 (0.6)	157,511	–0.02 (-0.09 to 0.06)	0.19 (-1.39 to 1.77)	–0.10 (-0.20 to –0.00)	0.37 (-0.74 to 1.48)	–0.25 (-0.48 to –0.03)	-
Score 1	1,853 (3.9)	169,755	436 (0.9)	170,606	0.84 (0.70 to 0.99)	0.56 (0.16 to 0.95)	–0.26 (-0.44 to –0.07)	0.21 (-0.18 to 0.60)	0.46 (0.17 to 0.75)	0.60 (0.14 to 1.07)
Score 2–6	5,034 (7.9)	180,237	761 (1.2)	182,250	1.95 (1.70 to 2.20)	2.68 (2.33 to 3.04)	0.21 (-0.14 to 0.55)	0.30 (-0.08 to 0.68)	1.67 (1.20 to 2.13)	2.31 (1.86 to 2.76)
CHA_2DS_2-VASc										
Score 0	46 (0.4)	66,020	32 (0.3)	66,076	–0.11 (-0.20 to –0.03)	-	–0.00 (-0.09 to 0.08)	-	–0.03 (-0.21 to 0.15)	-
Score 1	170 (0.9)	86,370	108 (0.6)	86,474	–0.02 (-0.15 to 0.11)	0.25 (-0.86 to 1.36)	–0.02 (-0.15 to 0.11)	0.14 (-0.89 to 1.17)	–0.20 (-0.46 to 0.06)	-
Score 2–9	6,994 (6.2)	354,881	1,241 (1.1)	357,817	1.19 (1.07 to 1.32)	2.21 (1.93 to 2.50)	–0.04 (-0.22 to 0.14)	0.23 (-0.06 to 0.53)	0.81 (0.56 to 1.07)	1.97 (1.62 to 2.32)

Values >0 favours treatment. If less than 200 person-years in treatment in a cell the net clinical benefit was not calculated. ASA: acetylsalicylic acid; $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED: see text; VKA: vitamin K antagonist.

Olesen et al Tromb Haemost 2011