Antiarrhythmic Drugs

Antonis S. Manolis, MD

Heart Failure & Atrial Fibrillation: Vicious Twins

Antiarrhythmic Drugs

- Antonis S. Manolis, MD
- Athens University School of Medicine

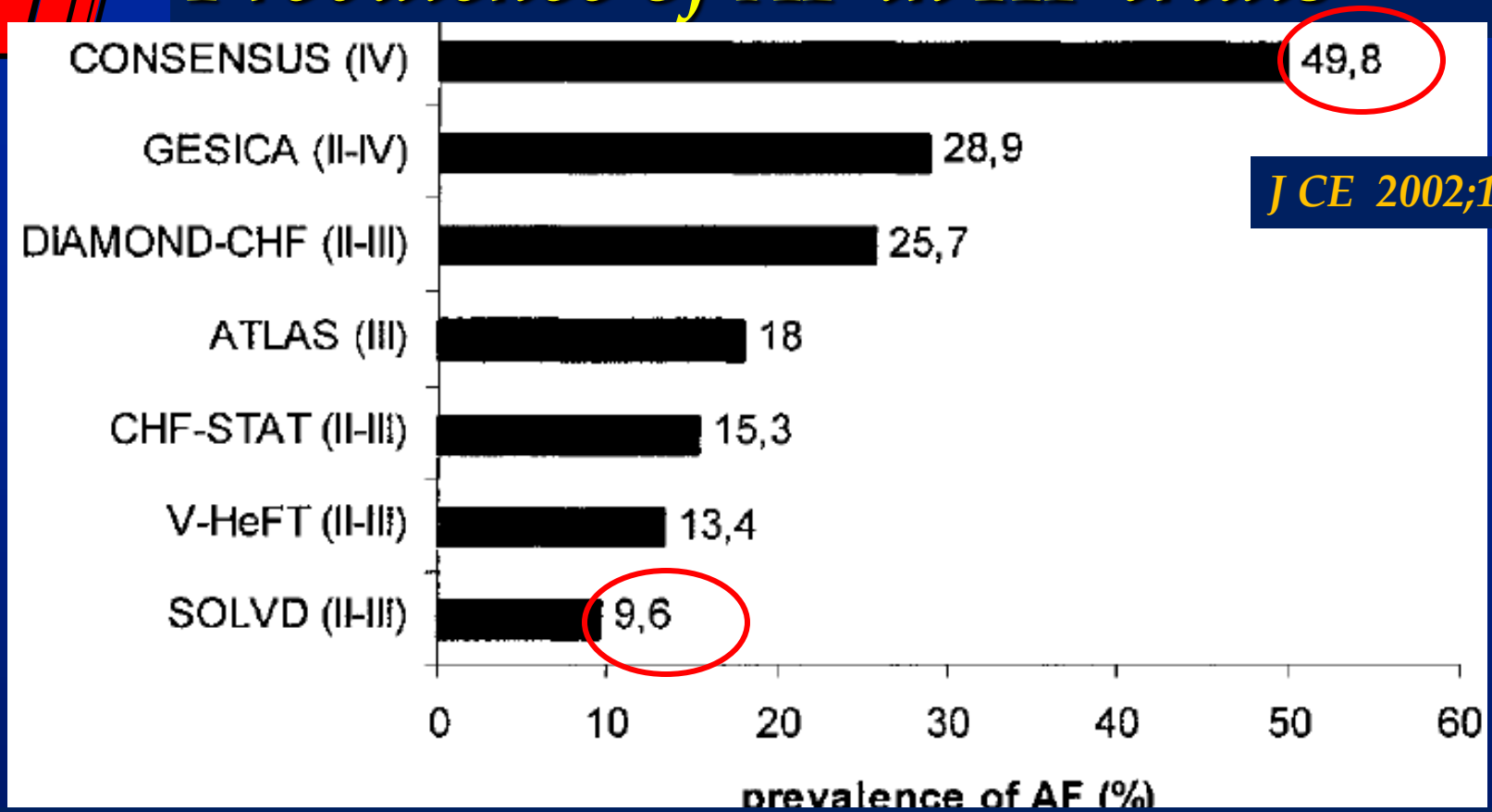
Conflict of Interest: none

ΕΚΠΑ

AF in Heart Failure

- AF is the most common arrhythmia in HF
- Its onset may lead to worsening of Sx, an ↑ risk of thrombo-embolic complications, & poorer long-term outcomes
- Potential precipitating factors & co-morbidity should be identified &, if possible, corrected, e.g.
- • electrolyte abnormalities, • hyperthyroidism, • alcohol consumption, • MV disease, • acute ischemia, • cardiac surgery, • acute pulm. disease, • infection, • uncontrolled HTN
- Background HF Rx should be carefully re-evaluated & optimized

Prevalence of AF in HF trials



J CE 2002;13:399-405

↑ AF prevalence in pts with more advanced CHF

AF in 40%-50% of pts in NYHA IV c/w 10% of pts with class II

CHF predisposes to AF, & AF may worsen prognosis of CHF

Precautions for specific CHF-related SE (TdP) when treating AF

CHF: 1 of most powerful independent predictors of AF (6-fold↑)

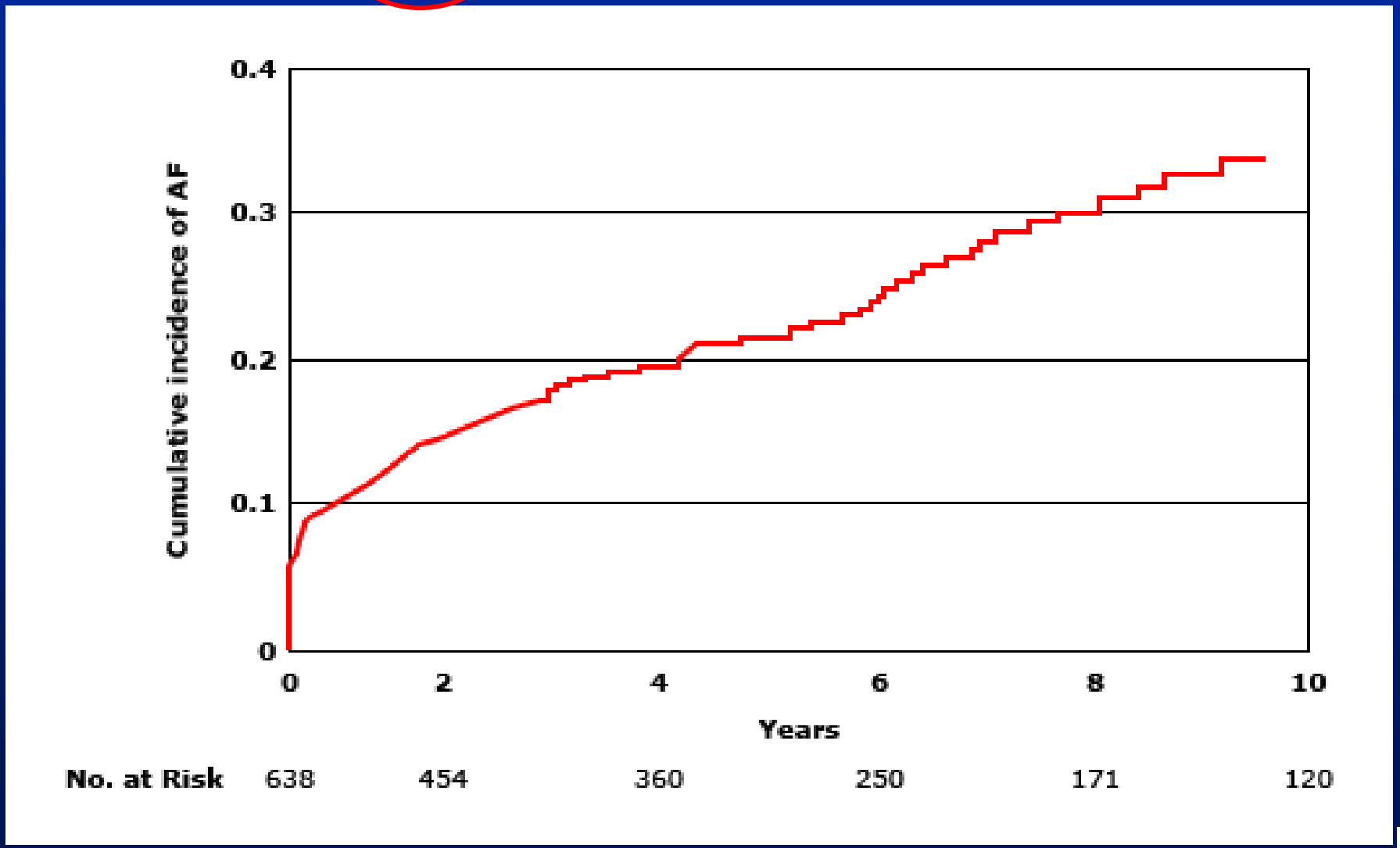
Overall, AF affects ~15% - 30% of pts with clinically overt CHF

Incidence & Prevalence

- AF & HF may co-exist/Presence of one ↑likelihood of the other
- Incidence of AF in pts HF in the Framingham Heart Study in which 1470 pts developed AF, HF, or both over a 47-y interval
- Among 708 who developed HF c no prior AF, 159 (22%) subsequently developed AF over 4.2 y (incidence 5.4%/y)
- Pts who developed AF first, incidence of HF: 3.3% /y
- Association between LV diastolic dysfunction & AF: among 840 pts ≥65 y: 80 (17%) developed AF over 4 y
- Pts c abn. (vs nl) diastolic function had an ↑ risk of AF

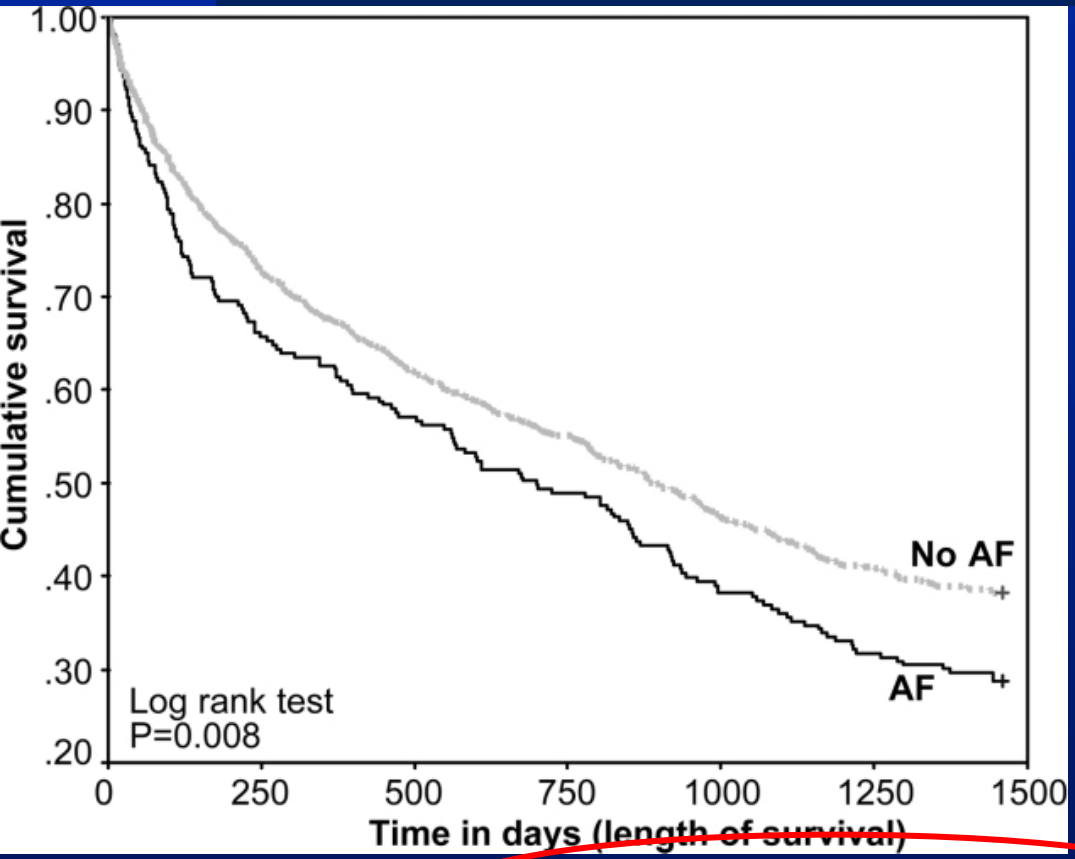
Cumulative incidence of AF in individuals with HF

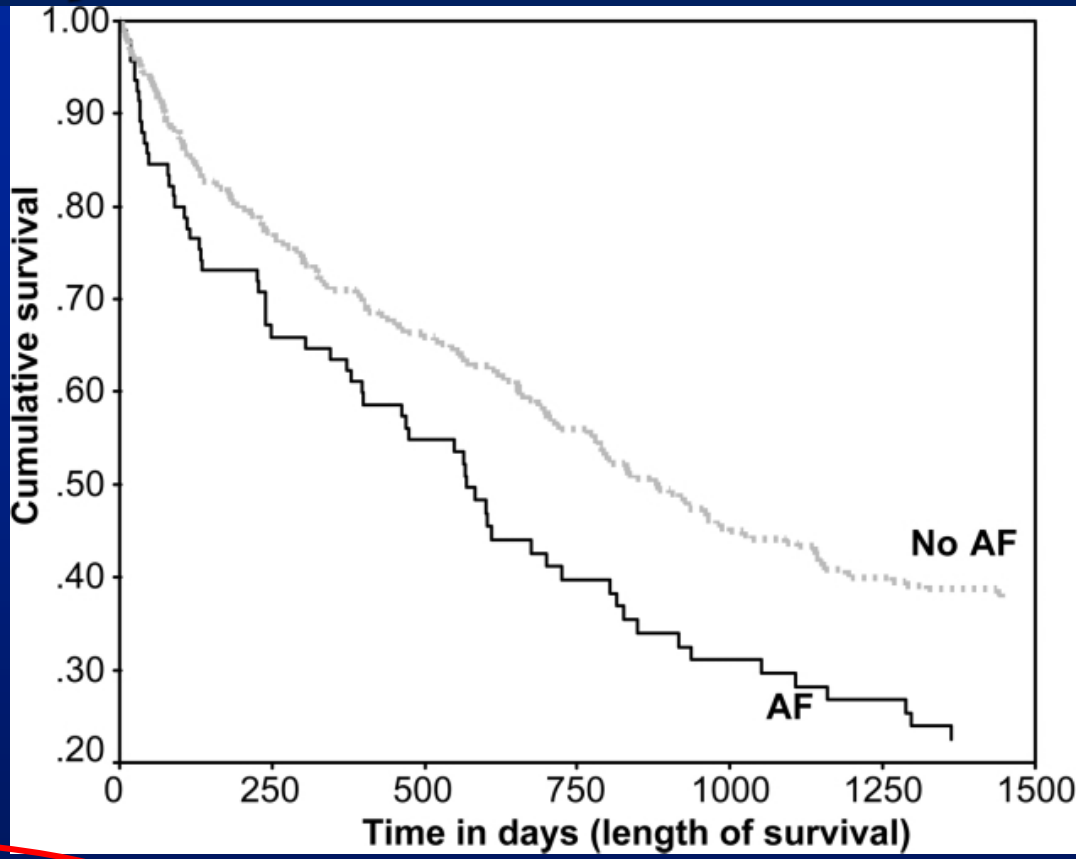
In an analysis from the Framingham Heart Study of 708 pts with HF who were in SR, 159 (22 %) developed AF at an average of 4.2 y of follow-up



Wang TJ et al. Framingham Heart Study. Circulation 2003; 107:2920.

Impact of AF on mortality & readmission in older adults hospitalized with HF





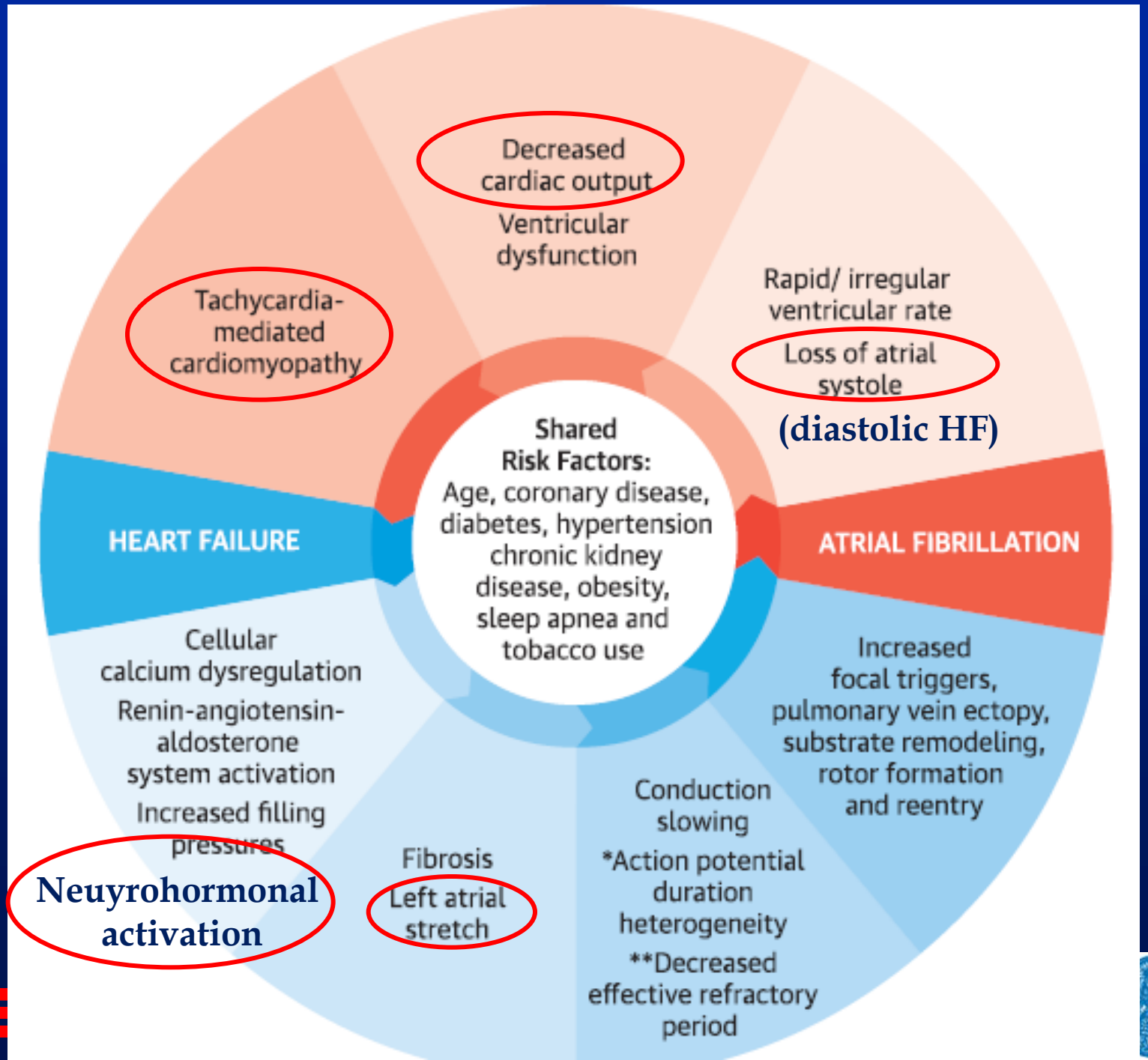
Pts with AF had a 52% ↑ risk of 4-year mortality (adjusted HRs1.52). AF was also a/w higher risk of readmission (unadjusted HRs1.64). However, the association lost its statistical significance after adjustment for various pt & care variables (adjusted HR2.09)

Eur J Heart Failure 2004; 6 : 421–426

ΕΚΠΑ

ASM

The Physiological Relationship Between AF and HF



Trulock et al,
J Am Coll Cardiol 2014;64:710–21

Prognosis

- A 2009 meta-analysis of 16 studies involving 53,969 pts concluded that AF was independently a/w all-cause mortality (odds ratio of 1.15-1.4)

Correction of Reversible Causes of AF and HF

- AF may worsen HF and uncontrolled HF can accelerate VR of AF or precipitate AF in pts in SR
- Thus, all reversible causes of AF and HF should be identified and corrected when possible

Antiarrhythmic Drug (AAD) Therapy

Antiarrhythmic drug therapy is indicated as first-line therapy for AF that remains symptomatic despite adequate rate control

AF in Pts with Heart Failure

- For pts with AF, also appropriate for the relatively large subset of AF pts with HF, the main goals of therapy are
  - control of symptoms,
  - prevention of cardiac dysfunction, &
  - prevention of arterial thromboembolism, particularly stroke
- In HF pts,
- symptoms are frequent and potentially disabling due to the interaction between the two processes (vicious twins!)
- There are few differences in management between those with systolic (HFrEF) or diastolic HF (HFpEF)

Acute Management

- Management of pts with acutely worsening HF & uncontrolled rates AF is a clinical challenge
- Initial strategy: treat the HF with diuretics, vasodilators, & other agents while also slowing the VR of the AF
- In systolic HF pts with congestion or hypotension, IV digoxin or IV amiodarone are recommended to acutely control the heart rate
- Beta blocker therapy should be instituted only following stabilization of pts with decompensated HF
- Generally, nondihydropyridine calcium channel antagonists should be avoided due to their negative inotropic effects.
- Once the acutely decompensated HF has been adequately treated, amiodarone as an agent for chronic control of VR should be reserved for pts who do not respond to or are intolerant of digoxin or beta blockers

Acute Management

- Rx of the HF pt with agents to slow the VR in AF is usually successful as the initial strategy to improve clinical status
- Occ. necessary: perform DCCV for acutely decompensated HF
- CV in the setting of acutely decompensated HF is commonly accompanied by early recurrence of AF
- In some pts, persistent rapid VRs in AF may contribute to myocardial dysfunction despite optimal medical Rx
- In these pts, a strategy of rhythm control should be attempted.
- If unsuccessful, AVN ablation may be considered when rate cannot be controlled & tachycardia-mediated CM is suspected, but, should not be performed without a pharmacologic trial to control VR
- **Anticoagulation** — Most AF pts with HF meet criteria for long-term anticoagulation
- In addition, anticoagulation is required prior to, during, and after CV, whether it be pharmacological or electrical

Systolic or Diastolic HF

- While clinical presentation & prognosis of AF pts with systolic & diastolic HF are similar, some differences in management exist

- For diastolic heart failure, calcium channel blockers may be more appropriate but
- for systolic heart failure, beta blockers and/or digoxin may be first choice therapy

Rhythm vs Rate Control

- While rhythm & rate control strategies are reasonable for AF pts with HF, irrespective of systolic or diastolic dysfunction,
- a rhythm control strategy may be preferred, particularly in younger pts, for several reasons:
- The presence of an atrial contraction may provide better long-term symptom and HF control at rest
- Due to presence of generally higher levels of physical activity in younger people, rate response is better controlled and hemodynamic response improves further in sinus rhythm

- Although no difference in outcomes of mortality and serious morbidity between rhythm & rate control strategies in AF pts with HF.
- However, some evidence that quality of life is improved & for some pts, a dramatic improvement with SR
- Thus, we have a lower threshold for rhythm control in pts with HF, due to more Sx

Rhythm vs Rate Control

- The **AF-CHF** trial was the first large, randomized trial to test the hypothesis that long-term rhythm control with drug therapy is better than rate control in pts with HF and PAF

- In this trial, 1376 pts with LVEF <35%, HF Sx, & a history of PAF or pers AF were assigned to a strategy of either rhythm control (amiodarone, sotalol, or dofetilide) or rate control (with beta blockers)

- At a mean FU of 37 mos, there was no signif. difference in primary outcome of death from CV causes between rhythm- & rate-control gps (27% s 25%, respectively) or the outcome of the event-free survival

- Improvements in QOL & functional capacity were similar in treatment arms, as were assessments of the 6-min walk distance & NYHA class

AAD / RFA for Rhythm Control

- If rhythm control (either using AADs or catheter ablation) is not possible,
- then rate control may be preferred through more definitive means, including AVN ablation with pacing support.
- However, for these pts, unopposed RV pacing can have a deleterious effect & even CRT may not emulate electrical activation via the HPS
- Presence of an atrial contraction may provide better long-term symptom & HF control at rest
- Due to the presence of generally higher levels of physical activity in younger people, rate response is better controlled & hemodynamic response improves more substantially in SR

RFA for Rhythm Control

- In the ARC-HF open label trial, 52 pts with symptomatic HF (NYHA class II - IV Sx & LVEF ≤35%) were randomly assigned to undergo catheter ablation or rate control
- Primary end point, MVO2, significantly increased in the ablation arm compared with rate control (difference 3.07 mL/kg/min)
- QOL & BNP were improved significantly with catheter ablation.
- PABA-CHF trial: 81 pts c symptomatic, drug-resistant AF, & EF ≤40%, were assigned to either CRT (rate control) or RFA (rhythm control)
- At 6 mos, the group of catheter ablation reported a better quality of life, had a longer 6-min walk distance, & a higher EF (35% vs 28%, P<0.001)
- In the CAMTAF trial, 50 pts with persistent AF, symptomatic HF, & EF <50% were randomly assigned to RFA or medical rate control
- Freedom from AF (off AADs) was achieved in 81% of the RFA group.
- LVEF was significantly higher in the RFA group (40 vs 31%), as was peak oxygen consumption & "Minnesota living with HF questionnaire" score

Rate Control vs Rhythm Control

- Control VR / Treat HF
- Consider possible benefit of a CV
- Once the acute HF exacerbation has been corrected, a continued rate-control or scheduled CV strategy may be appropriate
- In pts with new- or recent-onset AF, an attempt at CV & drug Rx is reasonable, with final decision on a long-term strategy based on symptoms, drug tolerance, & frequency of recurrent episodes
- at least 1 attempt to maintain SR in any pt with > mild Sx a/w AF
- In selected pts, RFA may prove effective

Initial approach to rhythm control

- Sequential steps to achieve rhythm control in AF pts with HF:
- Decide whether anticoagulation is necessary
- Decide on whether electrical CV is appropriate
- Choose an AAD (eg, amio, sotalol, or dofetilide) for maintenance control
- One may generally start with dofetilide, if available, based on its relatively good side effect profile & efficacy; however, its use is limited by stringent guidelines for administration and the fact that it should not be used in pts with CKD
- Sotalol is a reasonable choice for individuals with mild renal dysfunction It should not be used in pts with more advanced HF symptoms
- Amiodarone can be started as an outpatient and can be used in renal failure. However, side effects are potentially serious. It is preferred for older individuals.

Initial approach to rhythm control

- **Electrical CV** — For the first episode of AF, electrical CV may be performed without initiation of AAD
- For those pts who have recurrent episodes of AF or who convert back to AF rapidly after CV, amio or dofetilide make sense as first line AAD
- In most cases, pts with persis. AF do not return to SR with med Rx alone
- DCCV in pts in whom it is not clear that AF is specifically responsible for the Sx / CV can be useful to determine if AF is of importance in restoring functional capabilities, QOL, & improving Sx, such as dyspnea
- CV makes no sense in those who have paroxysmal AF
- Most AF pts with HF will have recurrent AF unless it was due to an acute precipitant (acute PEd, MI, PE, cardiac surgery, etc).
- CV has a limited role in a pt with acute HF decompensation
- Stabilize pt as best possible and try HF management
- If the patient does not improve, CV (with or without a TEE) is performed.

AAD Rx

- Concerns have been raised re: ↑ mortality with AADs
- AAD selection is important: some AADs (dron, flec,etc) have clearly been shown to worsen outcomes in HF, while other drugs (dofetilide) may not
- One may use amiodarone, sotalol, or dofetilide as the first AAD in pts with persistent AF & HF or for those with symptomatic PAF
- Dofetilide is usu. tried first, esp. in younger pts c preserved renal function
- Given the β-blocker effects of sotalol,many pts do not tolerate doses often necessary for rhythm control, esp. in those c poor LV function & highly symptomatic HF/may be preferred in younger healthy pts & those with renal dysfunction
- The 2014 AHA/ACC/HRS AF guideline recommends either amiodarone or dofetilide to maintain SR in pts with AF & HF

Dofetilide

- a class III AAD, is effective for preventing recurrent AF in pts with HF
- DIAMOND-CHF or DIA-MOND-MI trials : 506 pts enrolled who had LV dysfunction & were initially in AF/AFlu
- Over the course of the study, pts treated with dofetilide were signific. more likely to convert to SR (59 vs 34% with placebo).
- Among these 234 pts, the probability of maintaining SR at one year was greater with dofetilide (79 vs 42%)
- Dofetilide is relatively safe in pts with HF: established by DIAMOND-CHF trial, which enrolled 1518 pts with symptomatic HF, including 391 with AF at baseline; randomly assigned to dofetilide or placebo Dofetilide was more likely to be a/w reversion to SR at 1 month (12 vs 1%) & 1 yr (44 vs 13%), but at a mean FU of 18 mos, there was no overall difference in mortality between dofetilide & placebo gps (41 vs 42%)
- The most important side effect of dofetilide was torsades de pointes, which was seen in 25 cases (3.3%); 3/4 of episodes occurred within the first 3 days while the patient was in the hospital

Dofetilide

- Recommended dose of dofetilide: 500 mcg bid in the absence of renal insufficiency but it is adjusted based on renal function
- Because of the risk of torsades de pointes, the FDA approval for dofetilide was contingent upon the following restrictions:
- • Dofetilide is available only to hospitals and subscribers that have received dosing & treatment initiation education and certification
- • Pts must be **hospitalized** for a min of 3 days for dofetilide initiation (to give 6 pills, one every 12 h) at a facility that can provide measurement of creatinine clearance, cardiac monitoring, & cardiac resuscitation. The majority of episodes of TdP occur within this 3-day period, time of peak ↑ in the QT interval. A QT of >500 ms may be an indication for D/C
- • Most are more comfortable using dofetilide for HF pts with an ICD in place or in younger pts with less severe impairment of LV systolic function

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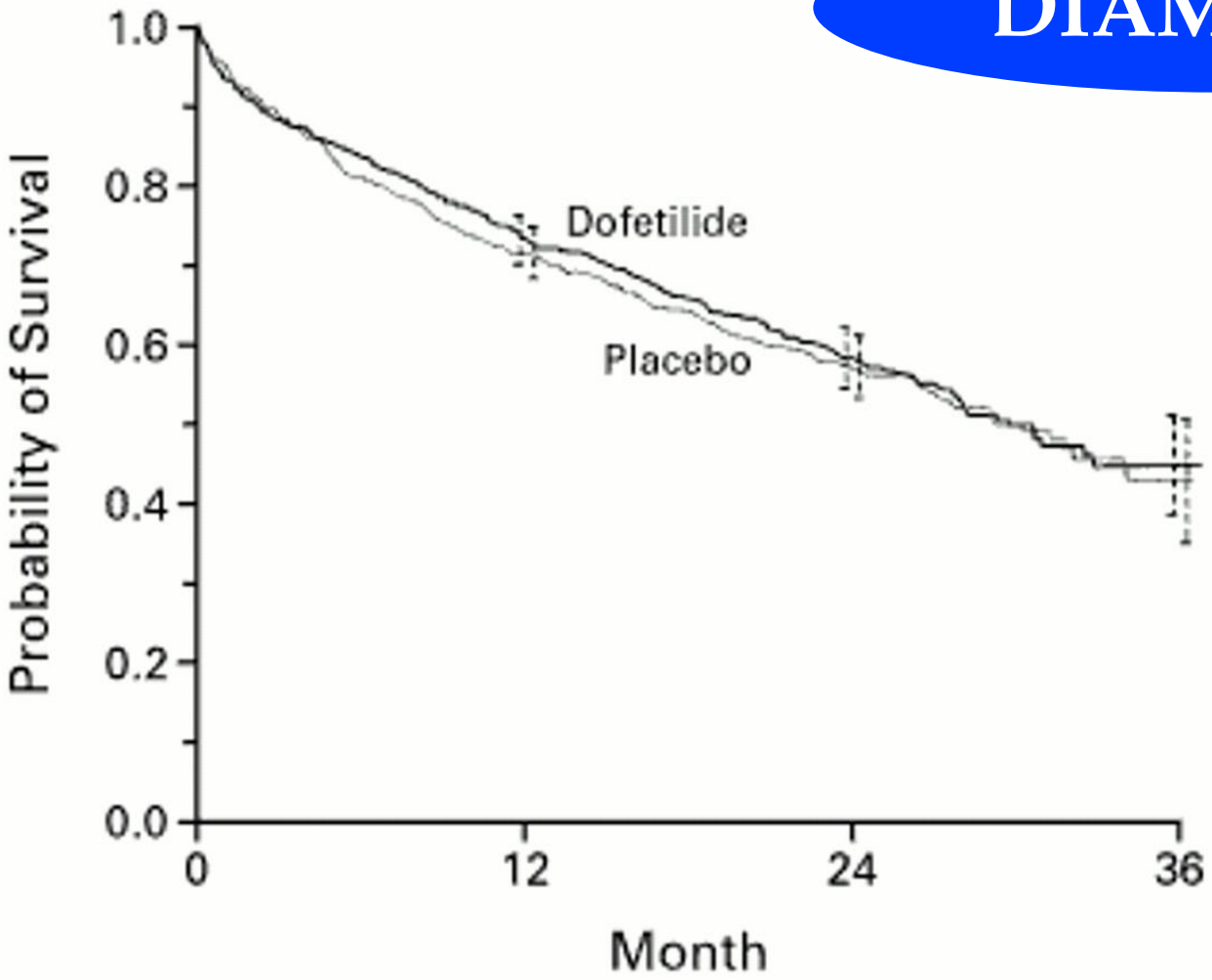
VOLUME 341 SEPTEMBER 16, 1999 NUMBER 12

DOFETILIDE IN PATIENTS WITH CONGESTIVE HEART FAILURE AND LEFT VENTRICULAR DYSFUNCTION

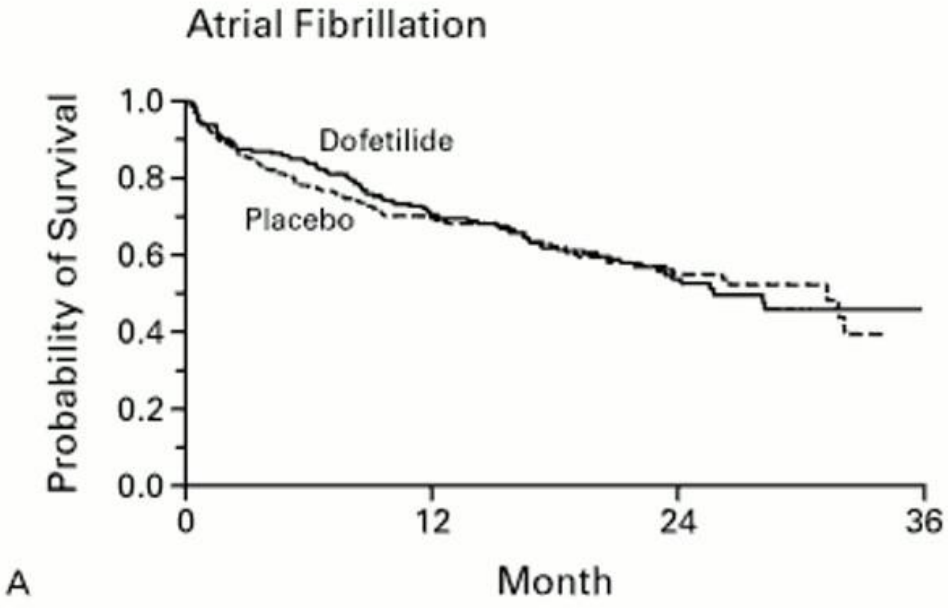
CHRISTIAN TORP-PEDERSEN, M.D., MOGENS MØLLER, M.D., POUL ERIK BLOCH-THOMSEN, M.D., LARS KØBER, M.D., ERIK SANDØE, M.D., KENNETH EGSTRUP, M.D., ERIK AGNER, M.D., JAN CARLSEN, M.D., JØRGEN VIDEBÆK, M.D., BRADLEY MARCHANT, M.D., AND A. JOHN CAMM, M.D.,
FOR THE DANISH INVESTIGATIONS OF ARRHYTHMIA AND MORTALITY ON DOFETILIDE STUDY GROUP*

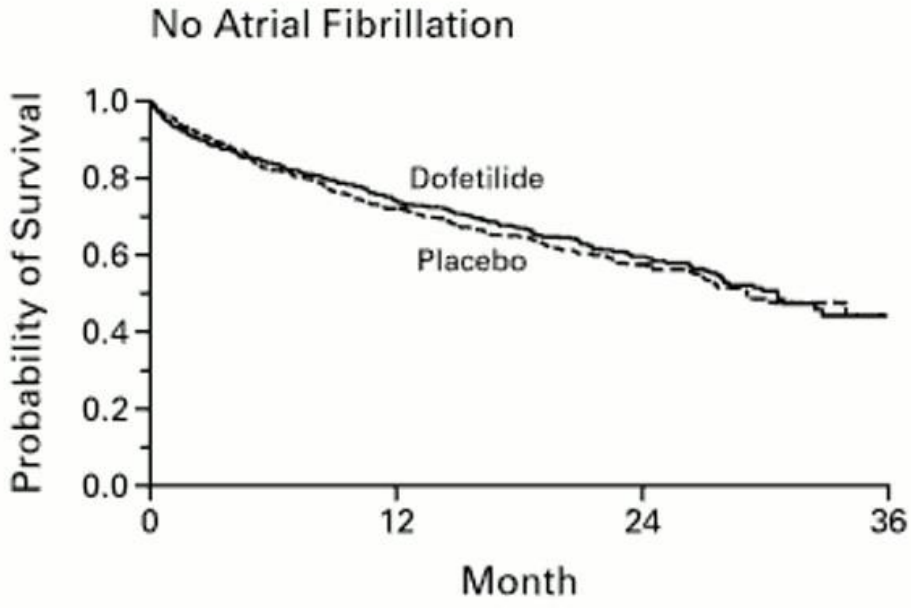
DIAMOND

DIAMOND



No. at Risk				
Dofetilide	762	554	214	5
Placebo	756	536	199	1


Atrial Fibrillation
Probability of Survival
1.0
0.8
0.6
0.4
0.2
0.0
Dofetilide
Placebo
0
12
24
36
Month
A


No Atrial Fibrillation
Probability of Survival
1.0
0.8
0.6
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Dofetilide
Placebo
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24
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Month
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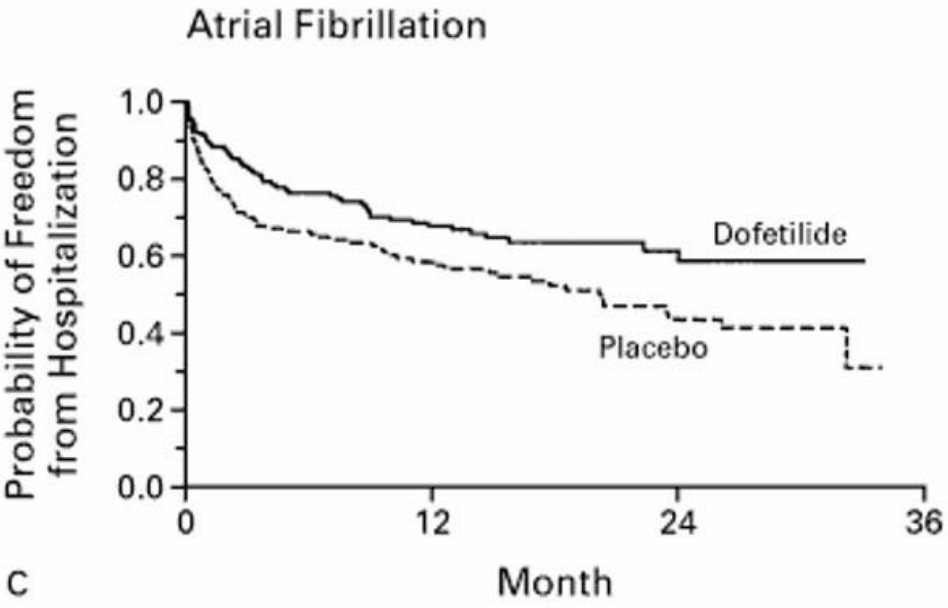
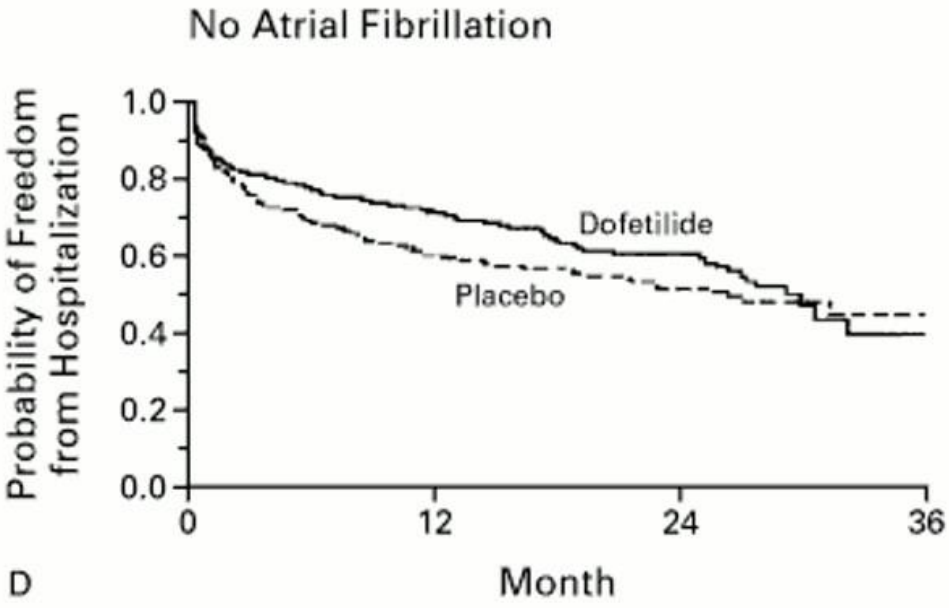

Atrial Fibrillation
Probability of Freedom from Hospitalization
1.0
0.8
0.6
0.4
0.2
0.0
Dofetilide
Placebo
0
12
24
36
Month
C


No Atrial Fibrillation
Probability of Freedom from Hospitalization
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Dofetilide
Placebo
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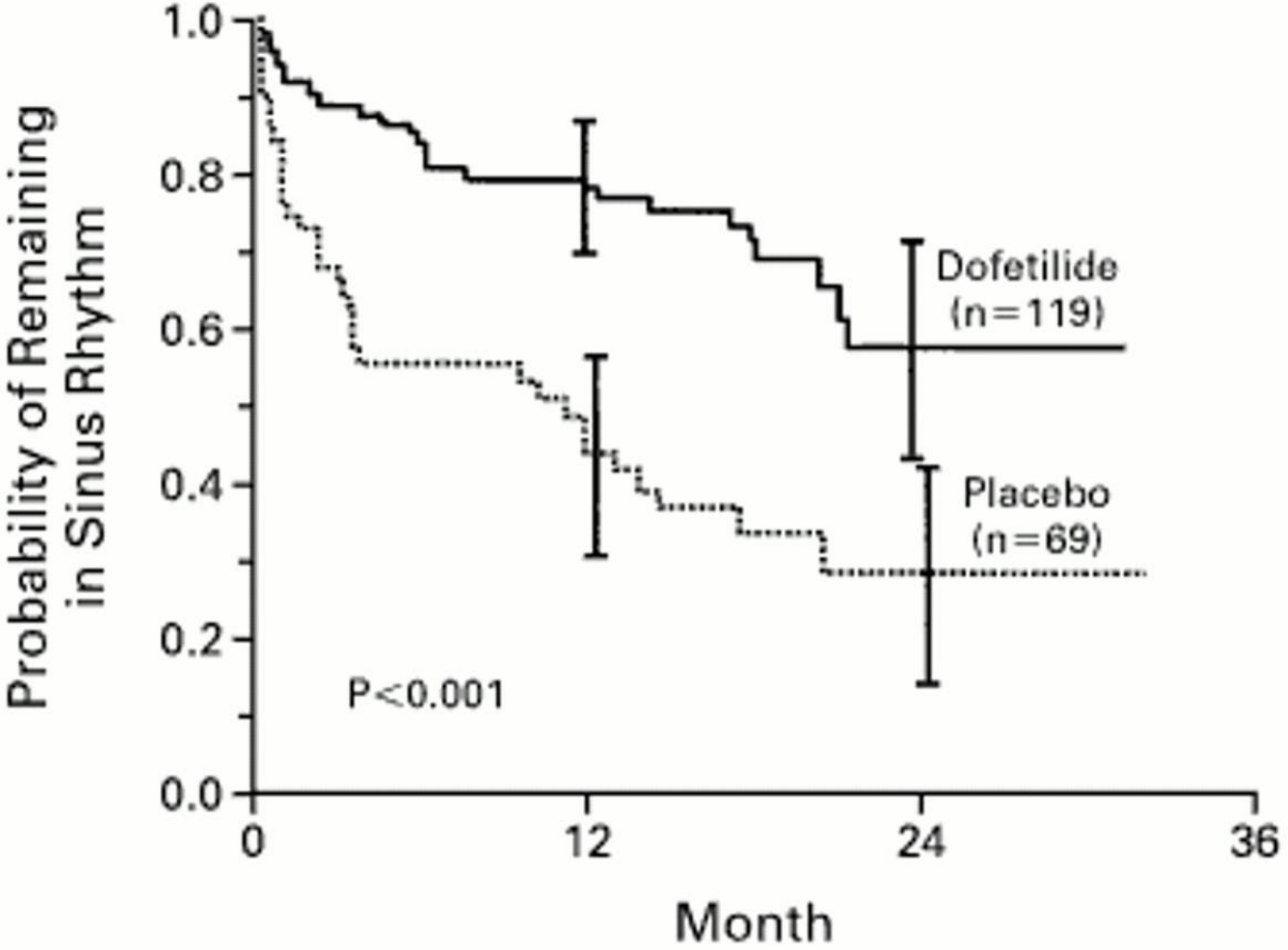

Probability of Remaining in Sinus Rhythm
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Month
Dofetilide (n=119)
Placebo (n=69)
P<0.001

Pause-Dependent Polymorphic Ventricular Tachycardia During Long-Term Treatment With Dofetilide

A Placebo-Controlled, Implantable Cardioverter-Defibrillator-Based Evaluation

Alexander Mazur, MD,* Mark E. Anderson, MD, PHD,* Sharon Bonney, MD,† Dan M. Roden, MD, FACC*

Nashville, Tennessee and Groton, Connecticut

JACC
March 15, 2001

Table 2. Incidence of Polymorphic Ventricular Tachycardia by Patient

	Pause-Dependent PVT*	TdP	Pause-Dependent PVT + TdP†	Nonpause-Dependent PVT
Placebo (n = 87)	5 (6%)	1 (1%)	5 (6%)	4 (5%)
Dofetilide (n = 87)	9 (10%)	7 (8%)	15 (17%)	5 (6%)
p	NS	NS	< 0.05	NS
Total (n = 174)	14 (8%)	8 (5%)	20 (13%)	9 (5%)

The data are presented as actual number of patients (% of total number of patients in the corresponding group). *Not including TdP; †one patient in each group had both TdP and PVT on separate occasions.

n = number; PVT = polymorphic ventricular tachycardia; TdP = torsades de pointes.

ASM

EDITORIAL COMMENT

Dofetilide: Is the Treatment Worse Than the Disease?*

Michael R. Lauer, MD, PhD
San Jose and *Stanford, California*

- The pharmaceutical industry may seek to employ even greater numbers of pts with implantable ICD systems in clinical trials of AADs,
- both to evaluate the effectiveness of these agents to suppress ventricular arrhythmias, &
- also to investigate the antiarrhythmic efficacy and proarrhythmic potential of these agents in the case of non-life-threatening, but difficult-to-treat, atrial tachyarrhythmias

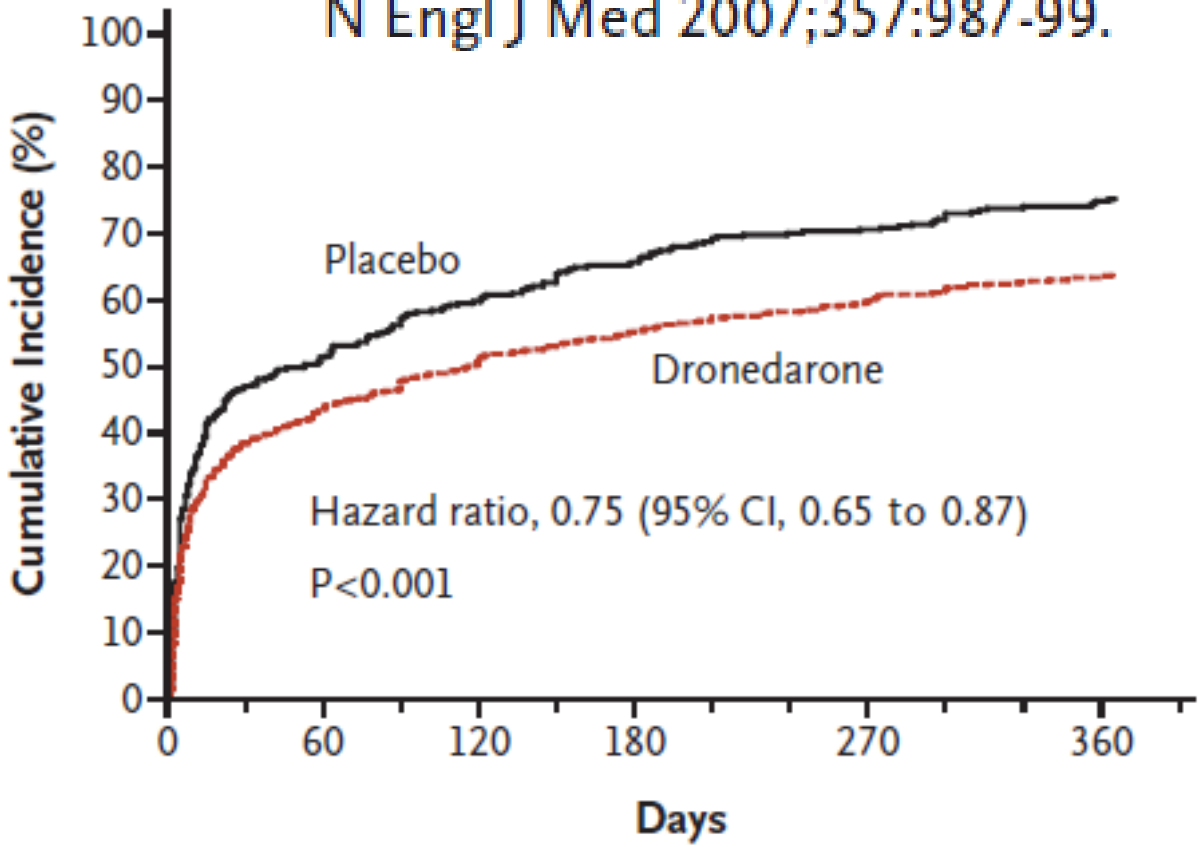
Dronedarone for Maintenance of Sinus Rhythm in Atrial Fibrillation or Flutter

Bramah N. Singh, M.D., D.Sc., Stuart J. Connolly, M.D., Harry J.G.M. Crijns, M.D., Denis Roy, M.D., Peter R. Kowey, M.D., Alessandro Capucci, M.D., Ph.D., David Radzik, M.D., Etienne M. Aliot, M.D., and Stefan H. Hohnloser, M.D., for the EURIDIS and ADONIS Investigators*

N Engl J Med 2007;357:987-99.

Dronedarone

C



No. at Risk

Placebo	409	192	156	133	112	90
Dronedarone	828	450	389	347	307	262

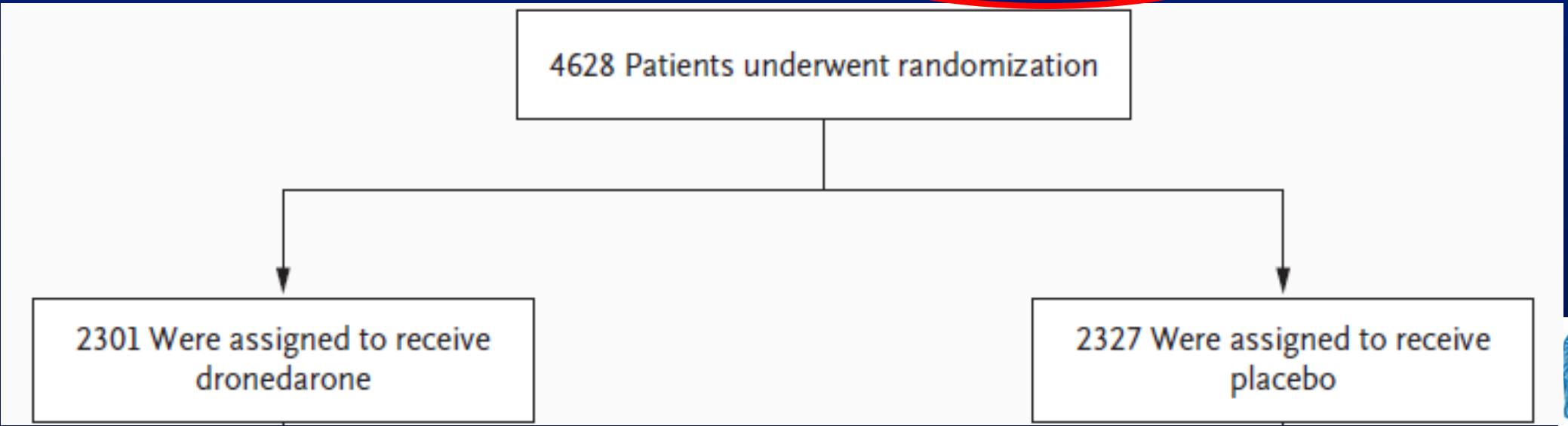
Dronedarone

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation

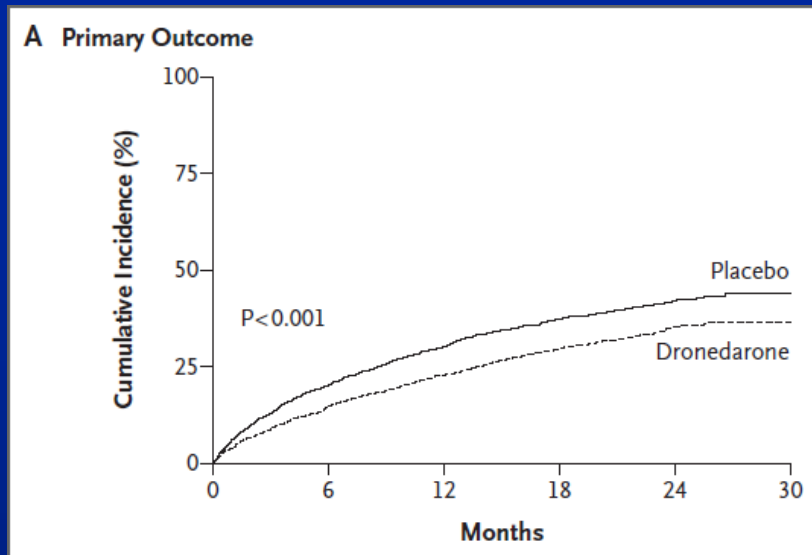
Stefan H. Hohnloser, M.D., Harry J.G.M. Crijns, M.D., Martin van Eickels, M.D., Christophe Gaudin, M.D., Richard L. Page, M.D., Christian Torp-Pedersen, M.D., and Stuart J. Connolly, M.D., for the ATHENA Investigators*



ATHENA Trial

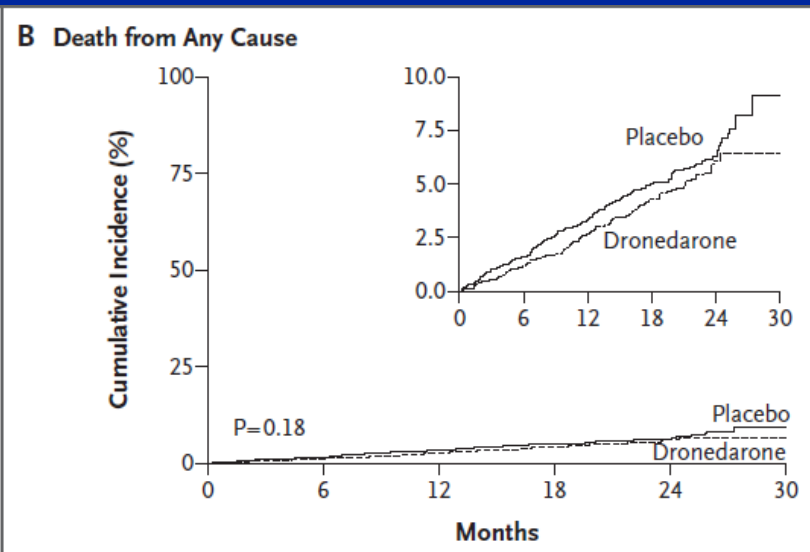
ASM

Dronedarone reduced the incidence of hospitalization due to CV events or death in pts with AF



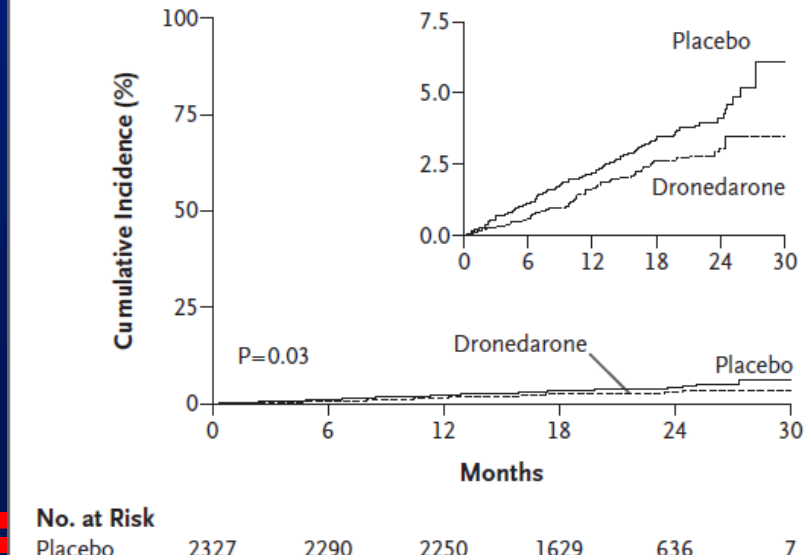
No. at Risk

Placebo	2327	1858	1625	1072	385	3
Dronedarone	2301	1963	1776	1177	403	2



No. at Risk

Placebo	2327	2290	2250	1629	636	7
Dronedarone	2301	2274	2240	1593	615	4



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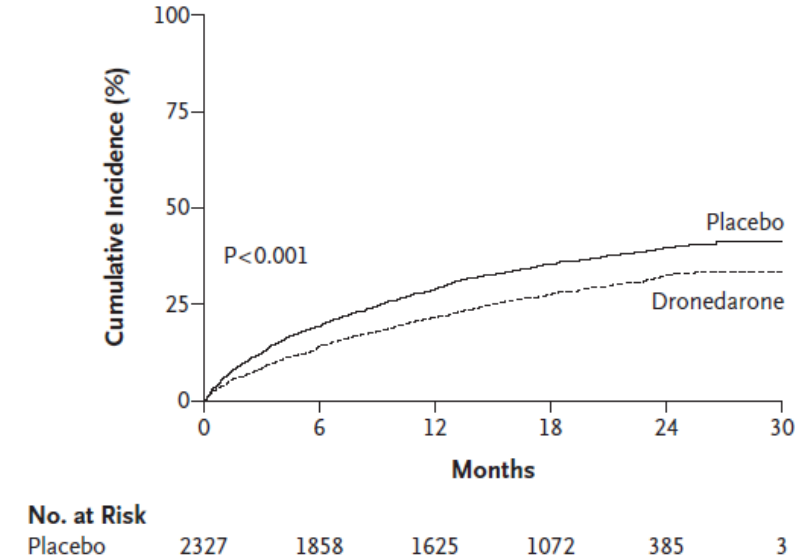

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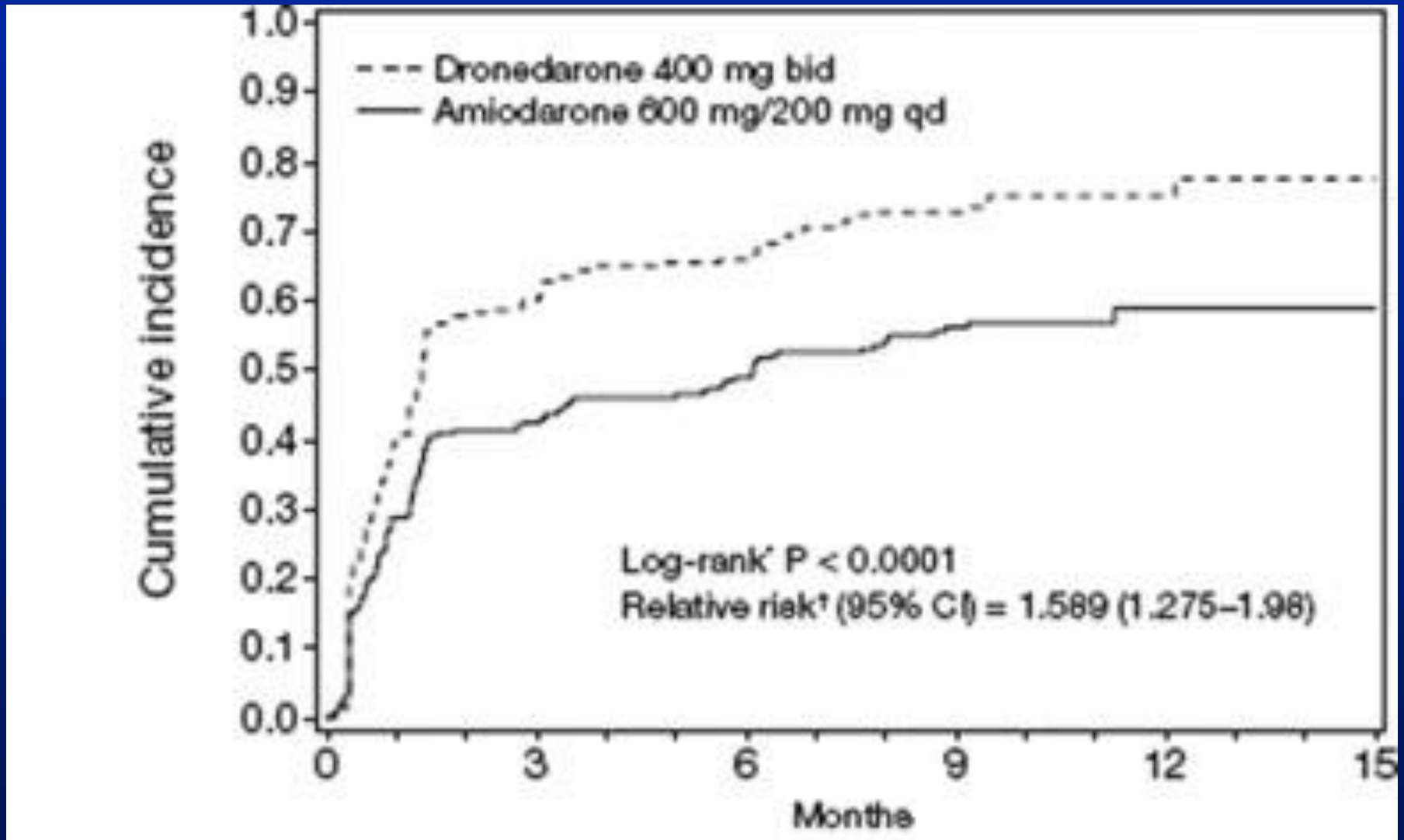
DIONYSOS Study



Patients at risk:						
Dronedarone	249	99	84	40	12	0
Amiodarone	255	146	126	61	13	0

ASM

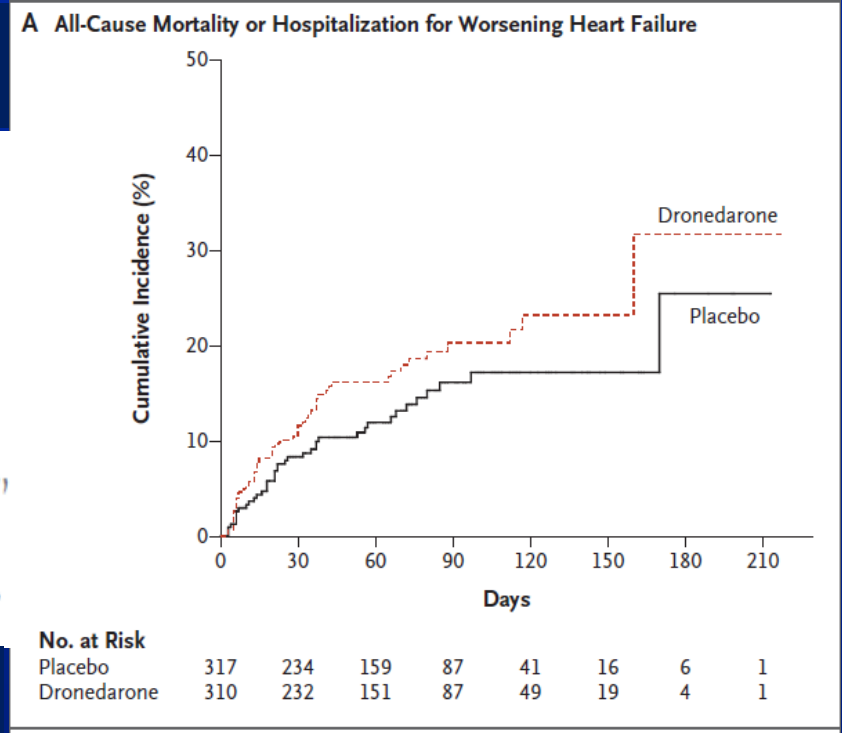
ANDROMEDA

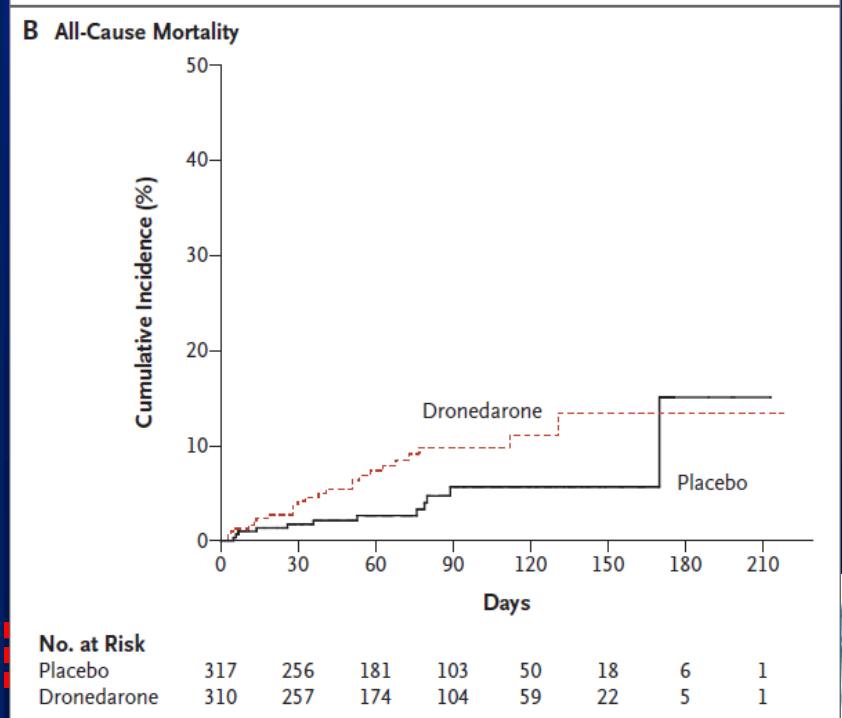
Increased Mortality after Dronedarone Therapy for Severe Heart Failure

Lars Køber, M.D., Christian Torp-Pedersen, M.D., John J.V. McMurray, M.D., Ole Gøtzsche, M.D., Samuel Lévy, M.D., Harry Crijns, M.D., Jan Amlie, M.D., and Jan Carlsen, M.D., for the Dronedarone Study Group*

After inclusion of 627 pts (310 in the dronedarone gp & 317 in the placebo gp), the trial was prematurely terminated for safety reasons

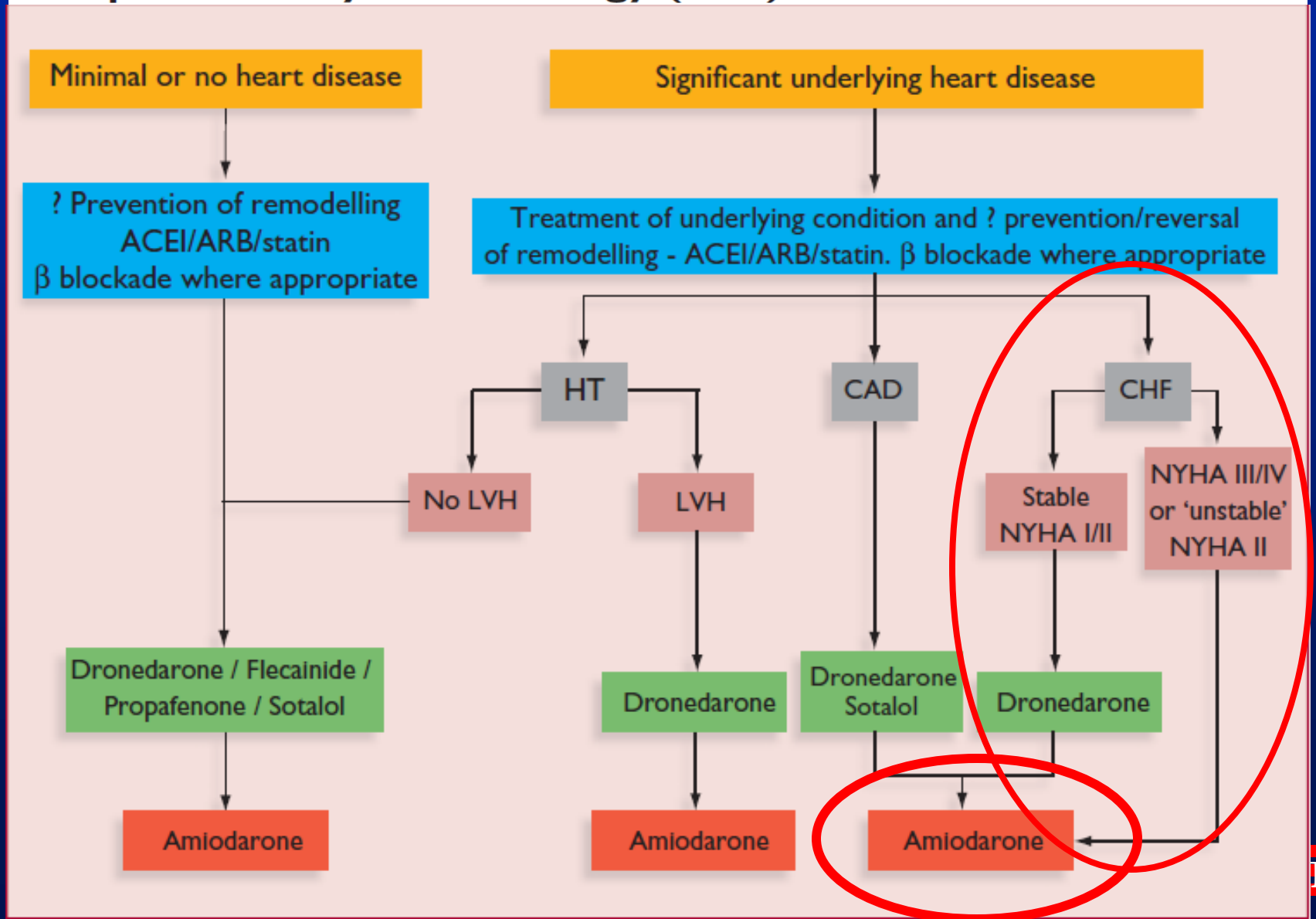
During a median FU of 2 mos, 25 pts in the dronedarone gp (8.1%) & 12 pts in the placebo gp (3.8%) died (hazard ratio, 2.13; P = 0.03). The excess mortality was related to worsening of HF — 10 deaths in the dronedarone gp and 2 in the placebo gp





Guidelines for the management of atrial fibrillation

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



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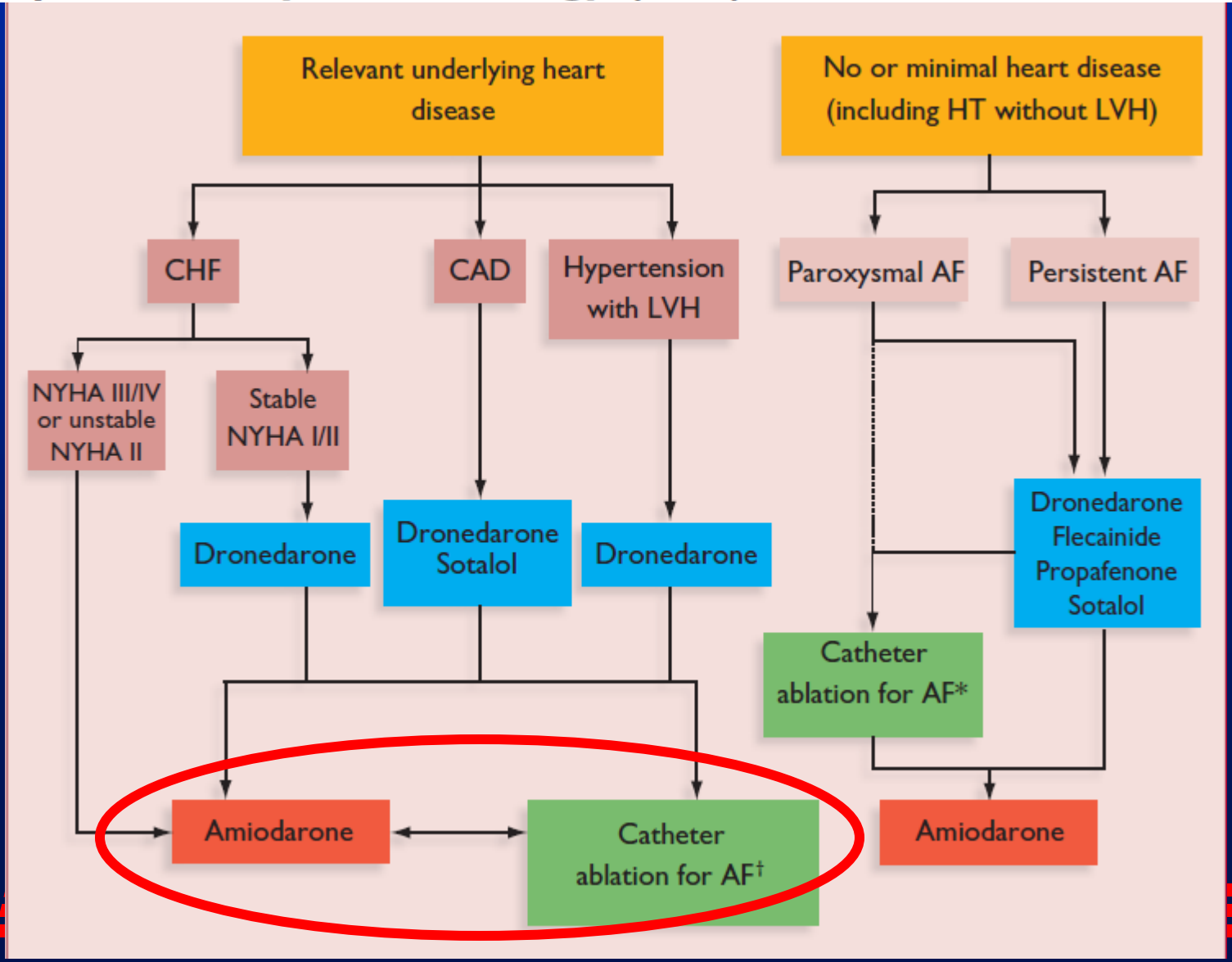
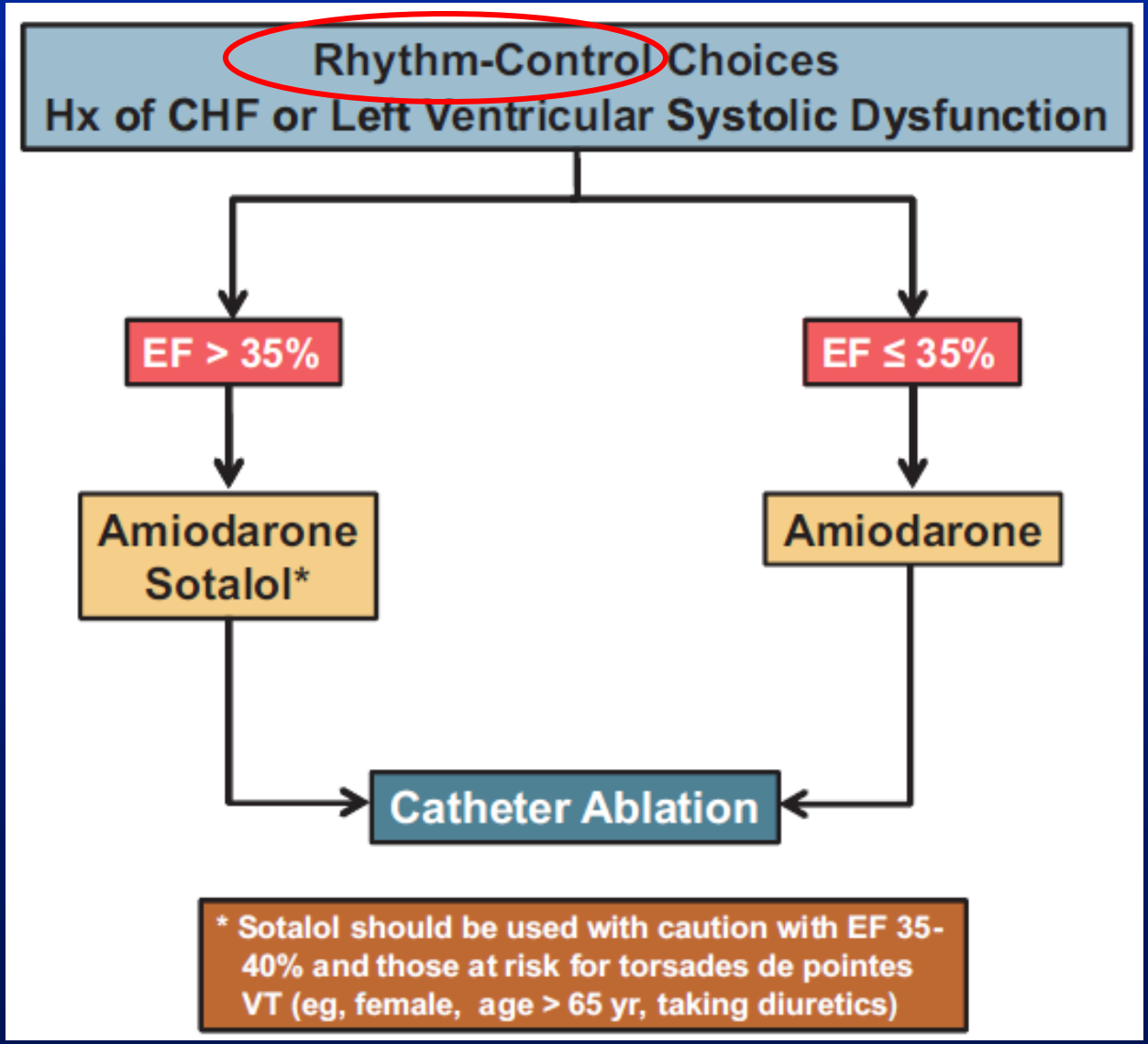


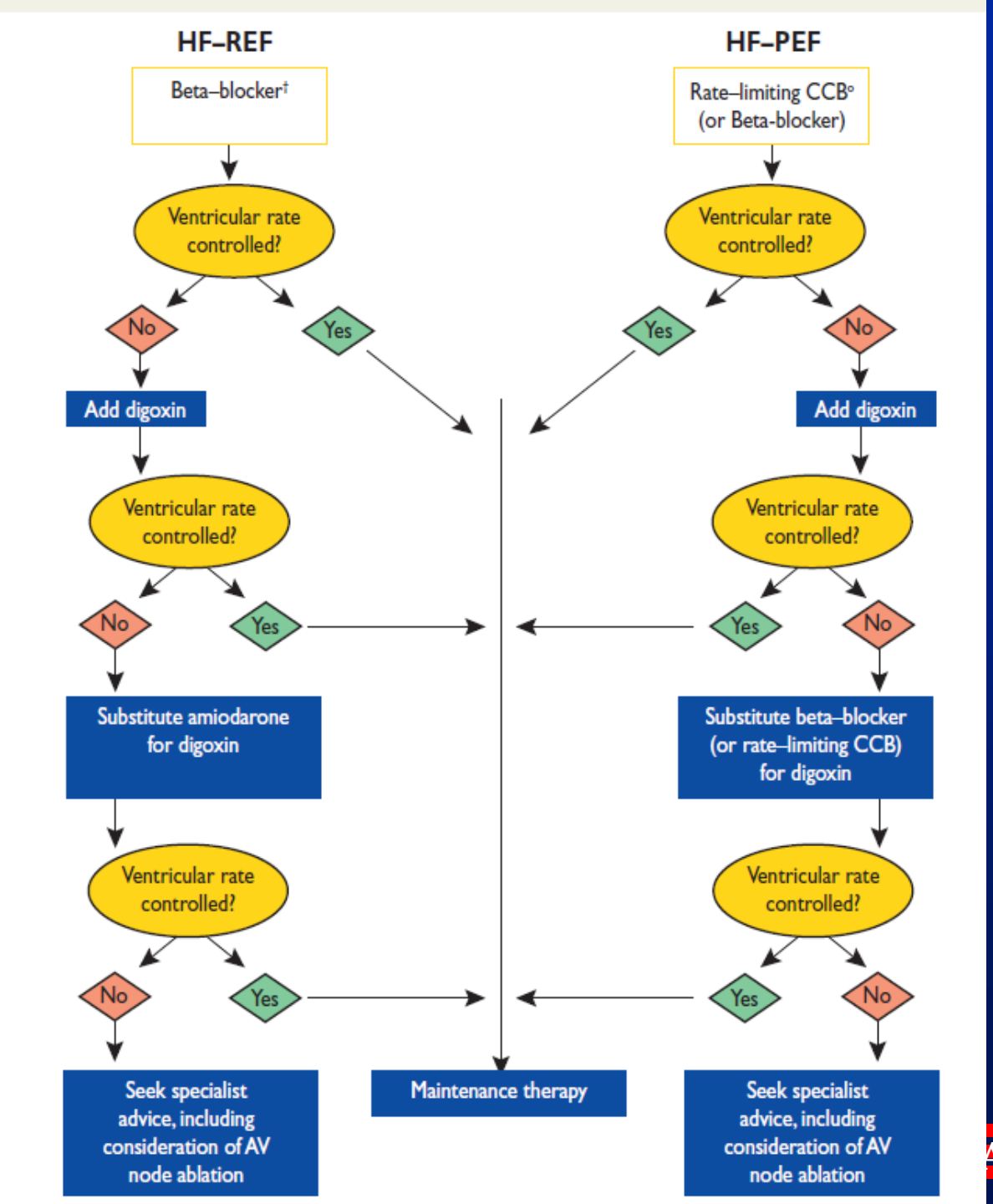
CCS AF Guidelines 2012



ASM

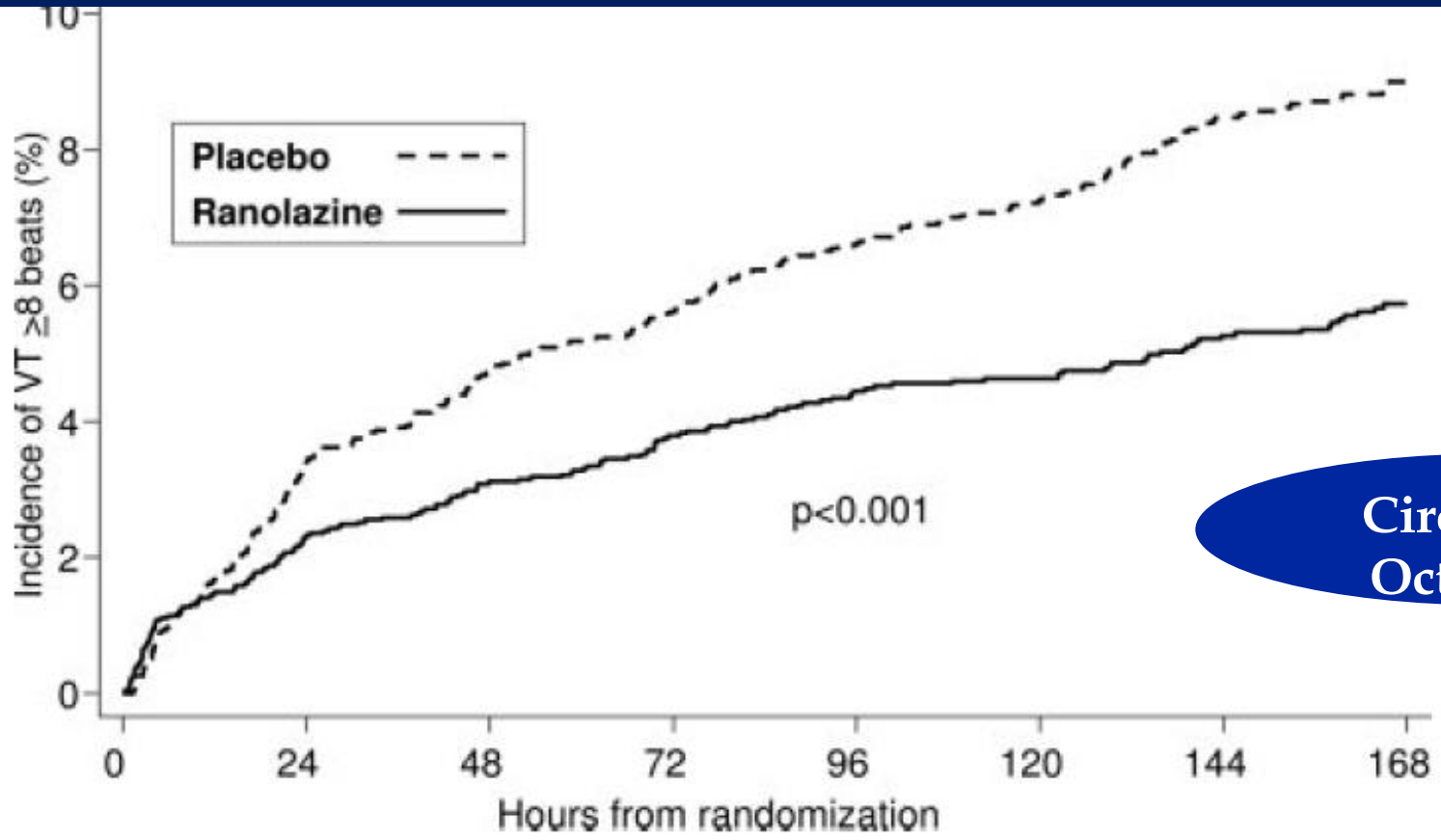
ESC (2012) HF Guideliness

Rate control during AF with HF



Effect of Ranolazine, an Antianginal Agent With Novel Electrophysiological Properties, on the Incidence of Arrhythmias in Patients With Non–ST-Segment–Elevation MERLIN-TIMI 36 Acute Coronary Syndrome

Estimated rates of the first occurrence of an episode of VT lasting at least 8 beats. The incidence of VT was significantly lower in pts treated with ranolazine vs placebo at 24 h after randomization (2.3% vs 3.4%; RR, 0.67; *P0.008) & 48 h (3.1% vs 4.7%; RR, 0.65; P0.001)*



Circulation
Oct 9, 2007

Ranolazine

- Despite modest ↑ in QTc, ranolazine appears to lack the proarrhythmic activity typically a/w drugs that inhibit Ikr
- Ranolazine ameliorated arrhythmia triggers in preclinical studies, suppressing EADs & ↓beat-to-beat variability &/or dispersion of APDs
- did not induce arrhythmias (VT or TdP) & hadd antiarrhythmic activity
- Ranolazine prevented TdP & VF in an intact canine model of LQTS & both terminated and prevented TdP in an intact rabbit model of TdP
- In addition, ranolazine suppressed arrhythmic activity induced by other drugs that block Ikr (e.g. cisapride, moxifloxacin, sot / quin)
- A proposed explanation: the inhibition of IKr by ranolazine (which ↑APD) is offset by its inhibition of late INa (which ↓APD)
- Thus, the net effect of inhibition of both IKr & late INa is a modest increase in the QTc , but without deleterious EP consequences

Experimental data suggest that ranolazine may be safe and effective for rhythm control Rx of AF in pts with HF

Burashnikov et al, ***Circ Heart Fail*** 2014;7:627-633

Amiodarone

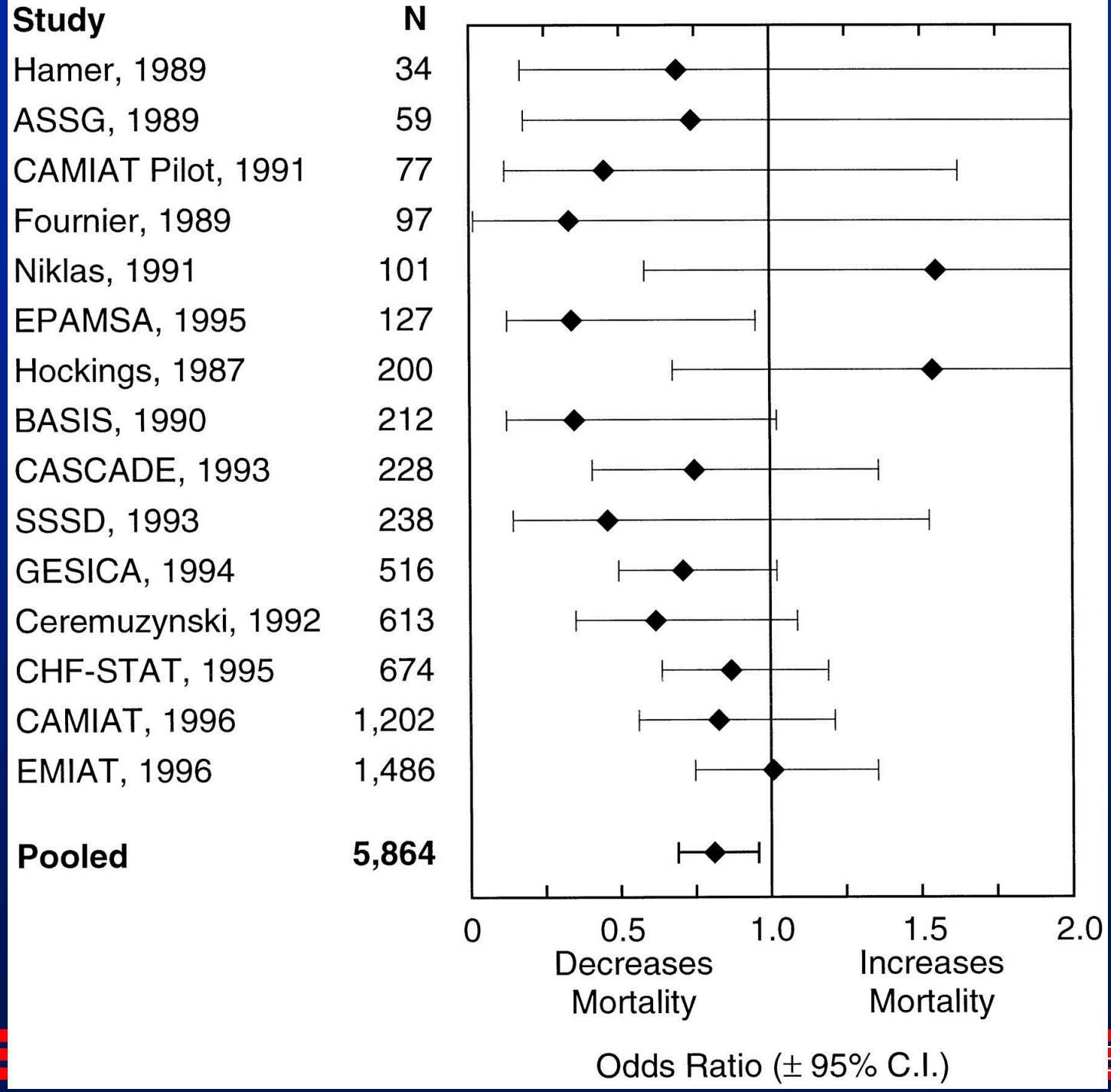
- When used for preventing recurrence of AF, amiodarone, particularly in lower doses (<400 mg/day and occasionally <200 mg/day), has the advantages of lack of a negative inotropic effect and little or no proarrhythmia, despite QT prolongation
- The near absence of proarrhythmia was illustrated in a meta-analysis of 4 trials of low-dose amiodarone therapy for a minimum of one year in pts with underlying HF or MI; there were no cases of torsades de pointes in the 738 pts treated with amiodarone
- In addition, since amiodarone has beta blocking and calcium channel blocking activity, the ventricular rate is usually slow and well tolerated if AF does recur.
- Its use in HF pts does not necessarily require hospitalization, but careful monitoring of the INR is necessary, as amiodarone can potentiate the effects of warfarin

Amio: Subset analysis fm CHF-STAT (15% had AF at baseline)

- Among these 103 pts, 51 were randomly assigned to amiodarone & 52 to placebo. The following significant benefits were noted with amio:

- A greater likelihood of reverting to SR (31 vs 8%). Pts treated with amio who converted to SR had a lower total mortality / not clear if ↓ mortality was because pts who converted were less sick to begin with or if due to SR
- During AF, a 16-20% ↓ in the mean VR & a 14-22% ↓ in the max VR
- Also, in 531 pts initially in SR, amio was a/w a ↓ AF (4.1 vs 8.3%)

- There are, however,potential complications, esp.during the loading phase / illustrated in a report of 37 pts c AF/Aflu with HF & mean LVEF 24%
- During the period of loading with amio (1.2 g/day), 32% developed a bradycardia requiring D/C of digoxin & 19% required a PPM
- After 9.5 mos, 57% of pts remained in SR & 14% had complications, incl. hypothyroidism & neurotoxicity / SE with maintenance Rx are less likely with lower doses but still occur. Advantages to amio c/w dofetilide include the ability to start Rx as an outpt, once-a-day dosing, & lower risk of TdP


Study
N
Hamer, 1989
34
ASSG, 1989
59
CAMIAT Pilot, 1991
77
Fournier, 1989
97
Niklas, 1991
101
EPAMSA, 1995
127
Hockings, 1987
200
BASIS, 1990
212
CASCADE, 1993
228
SSSD, 1993
238
GESICA, 1994
516
Ceremuzynski, 1992
613
CHF-STAT, 1995
674
CAMIAT, 1996
1,202
EMIAT, 1996
1,486
Pooled
5,864
0
0.5
1.0
1.5
2.0
Decreases Mortality
Increases Mortality
Odds Ratio (± 95% C.I.)

Lancet 1997 Nov 15;350(9089):1417-24

Effect of prophylactic amiodarone on mortality after AMI and in CHF: meta-analysis of individual data from 6500 patients in randomised trials. Amiodarone Trials Meta-Analysis Investigators

♦ 13 randomised controlled trials of prophylactic amiodarone in pts with recent MI or CHF. None of these was powered to detect a mortality reduction of ~ 20%.

♦ There were 8 post-MI and 5 CHF trials; 9 were double-blind & placebo-controlled, & 4 compared amiodarone with usual care

♦ 6553 pts, 78% were in post-MI trials and 22% in CHF trials. 89% had had previous MI. The mean LVEF was 31%, and median frequency of VPCs 18 per h.

♦ Total mortality was reduced by 13% (p = 0.030) based on classic fixed-effects meta-analysis and by 15% (p = 0.081) with the more conservative random-effects approach.

♦ Arrhythmic/sudden death was reduced by 29% (p = 0.0003). There was no effect on non-arrhythmic deaths (1.02 [0.87-1.19], p = 0.84). No difference in treatment effect between post-MI and CHF studies.

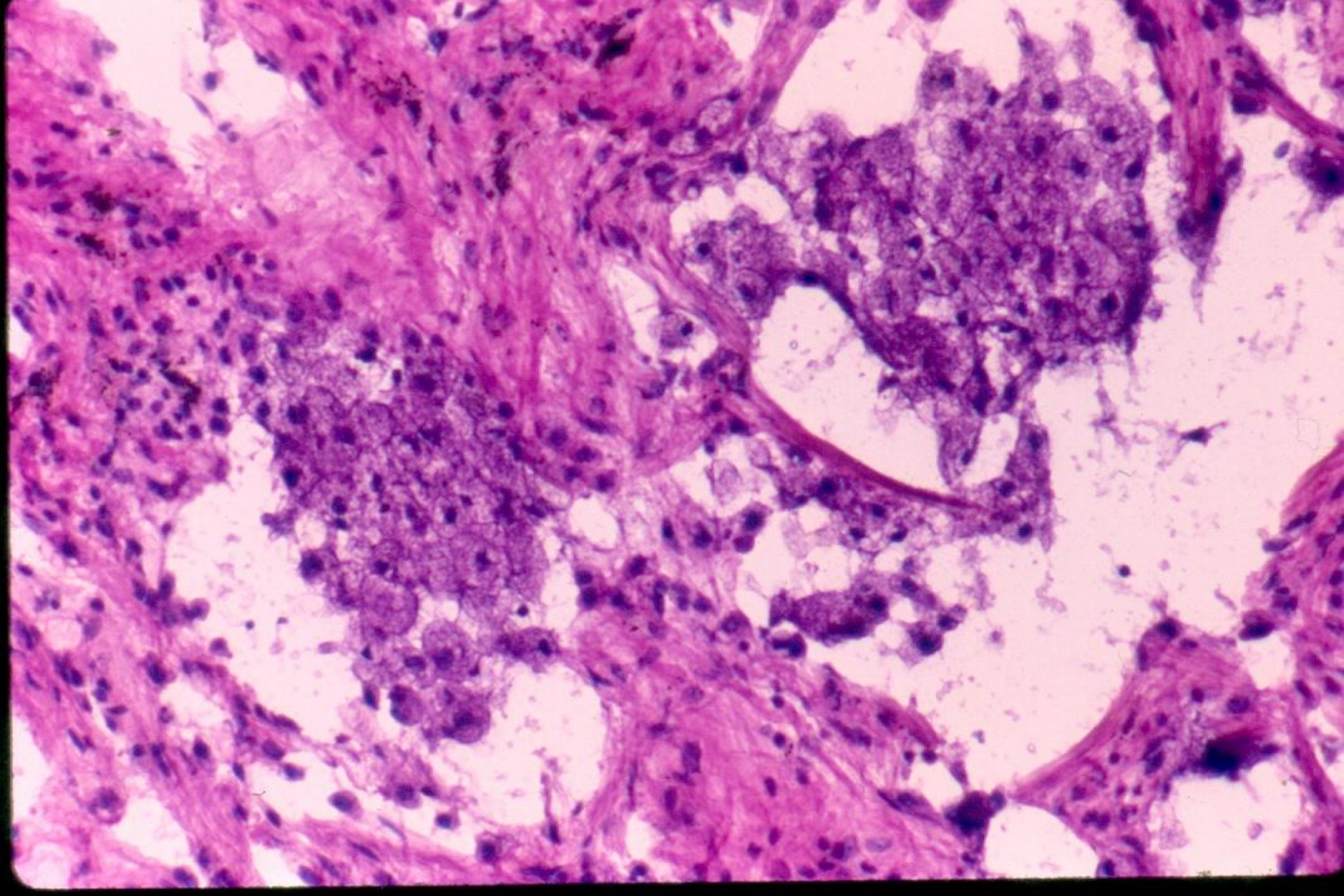
♦ The risk of arrhythmic/sudden death in control-group pts was higher in CHF than in post-MI studies (10.7 vs 4.1%), and the best single predictor of risk of arrhythmic/sudden death among all patients was symptomatic CHF. The excess (amiodarone minus control) risk of pulmonary toxicity was 1% per year.

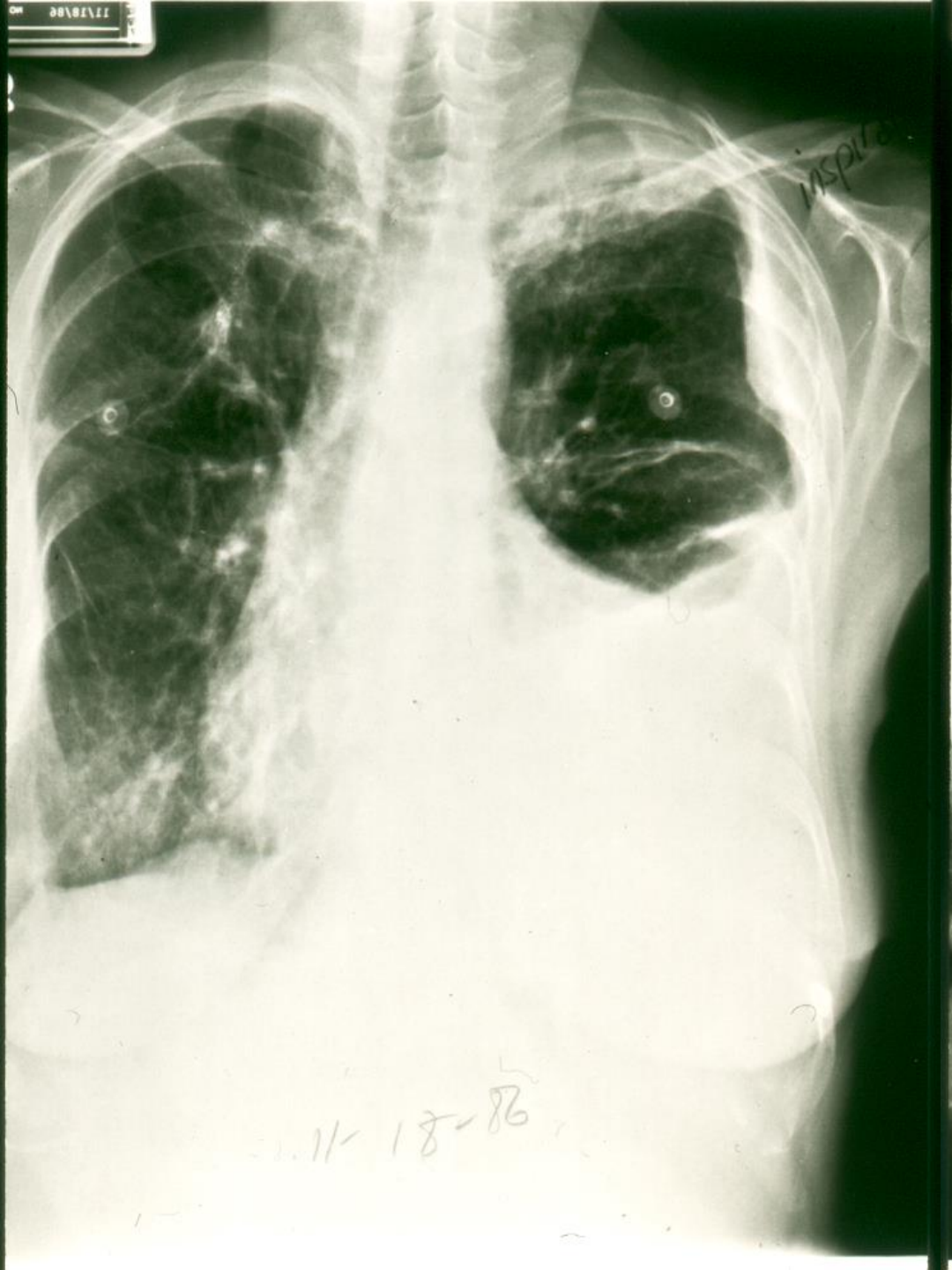
Amiodarone

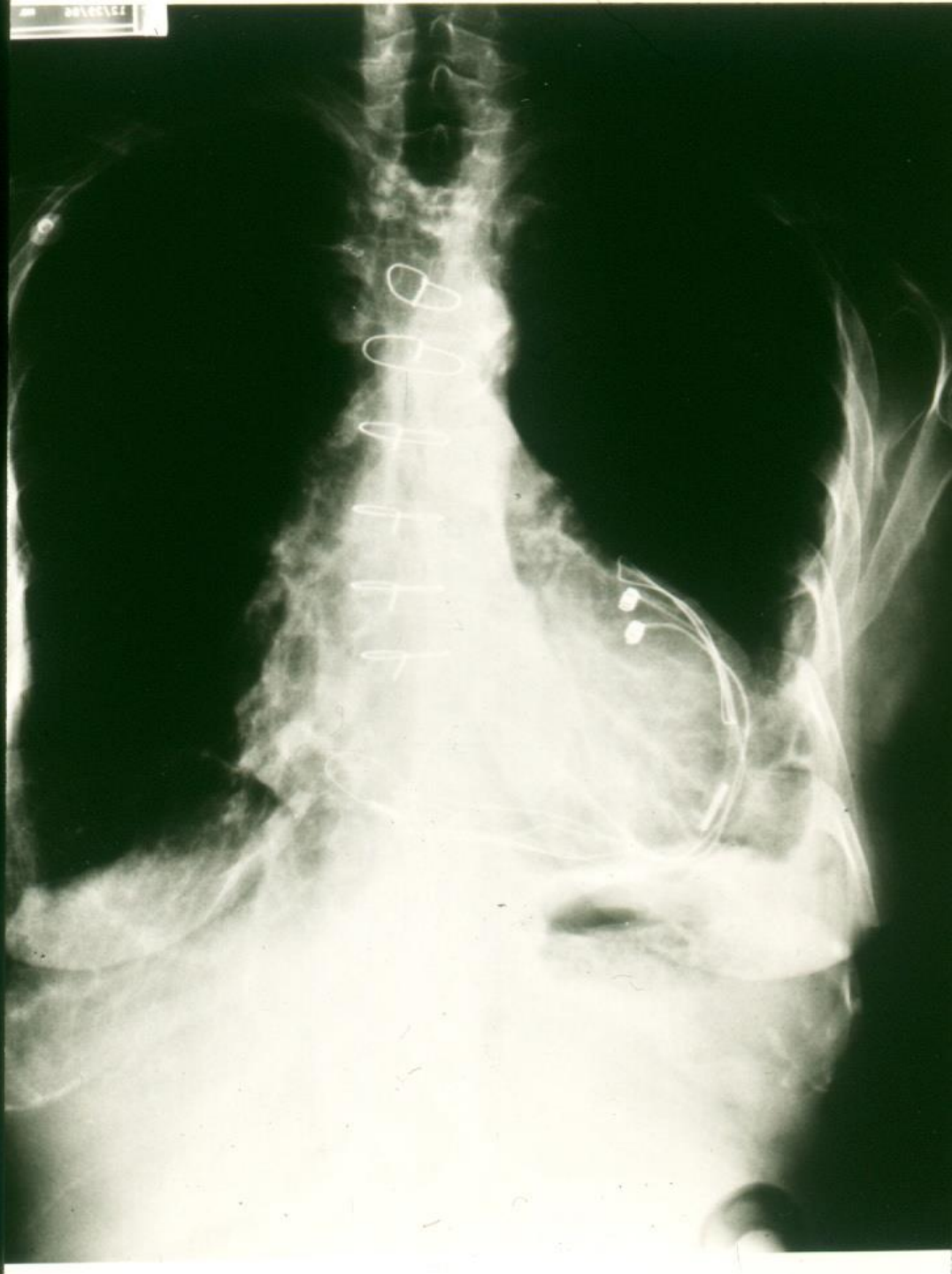
- **Toxicity**
  - Pulmonary fibrosis
  - Hypo- or hyper-thyroidism
  - Liver failure
  - Bone marrow suppression
  - Renal failure
  - Photosensitivity
  - Corneal deposits
- **Side effects**
  - Myalgias
  - Gait disturbance
  - Insomnia
  - Prolongation of coagulation time (PT)
    (need to reduce coumadin dosage)
  - Digoxin toxicity (need to reduce digoxin dosage)

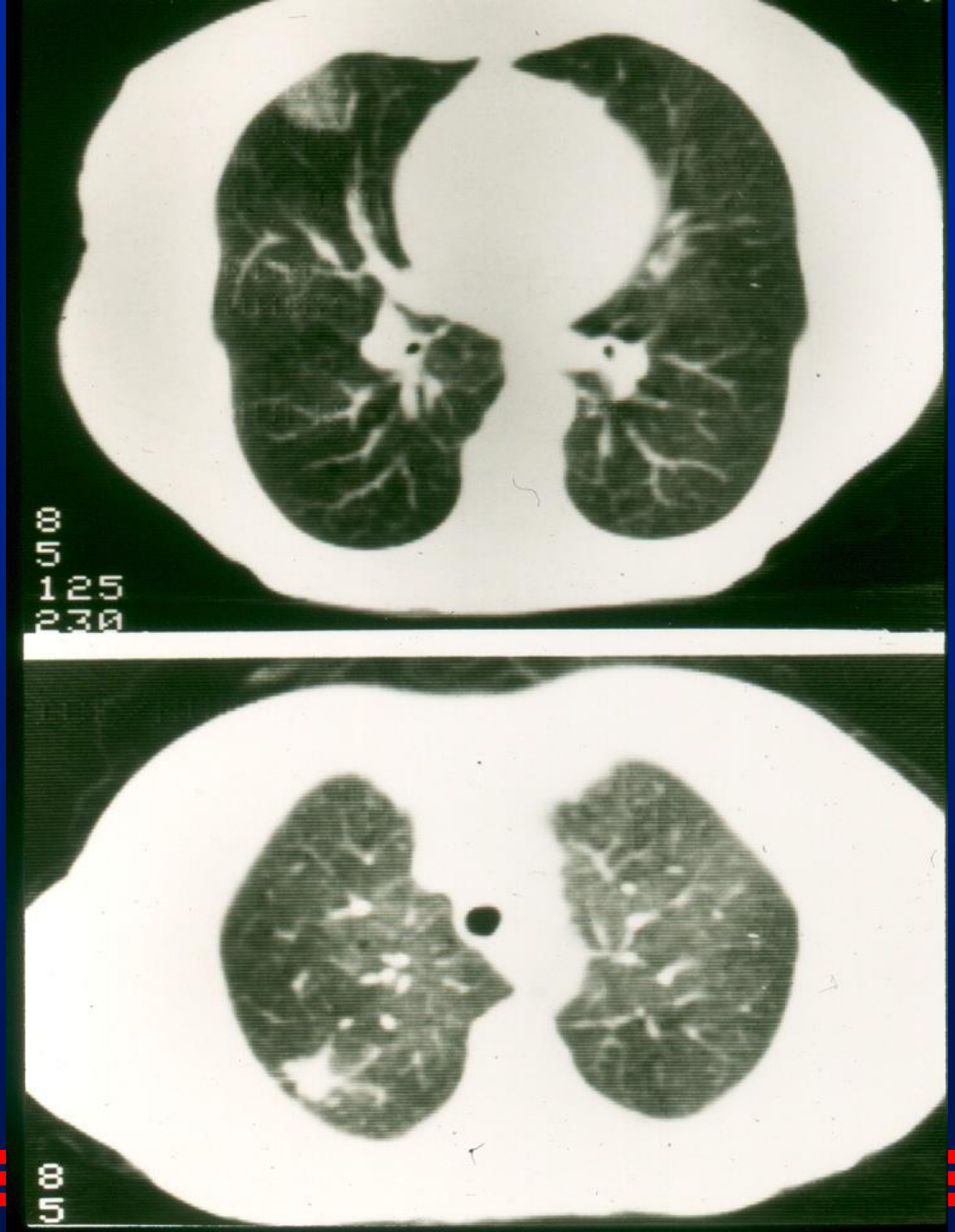
Amiodarone: Tests for Follow-up

- CXR
- CBC
- Liver function tests
- Renal panel
- Thyroid function tests
- Opthalmologic exam
- Pulmonary function tests

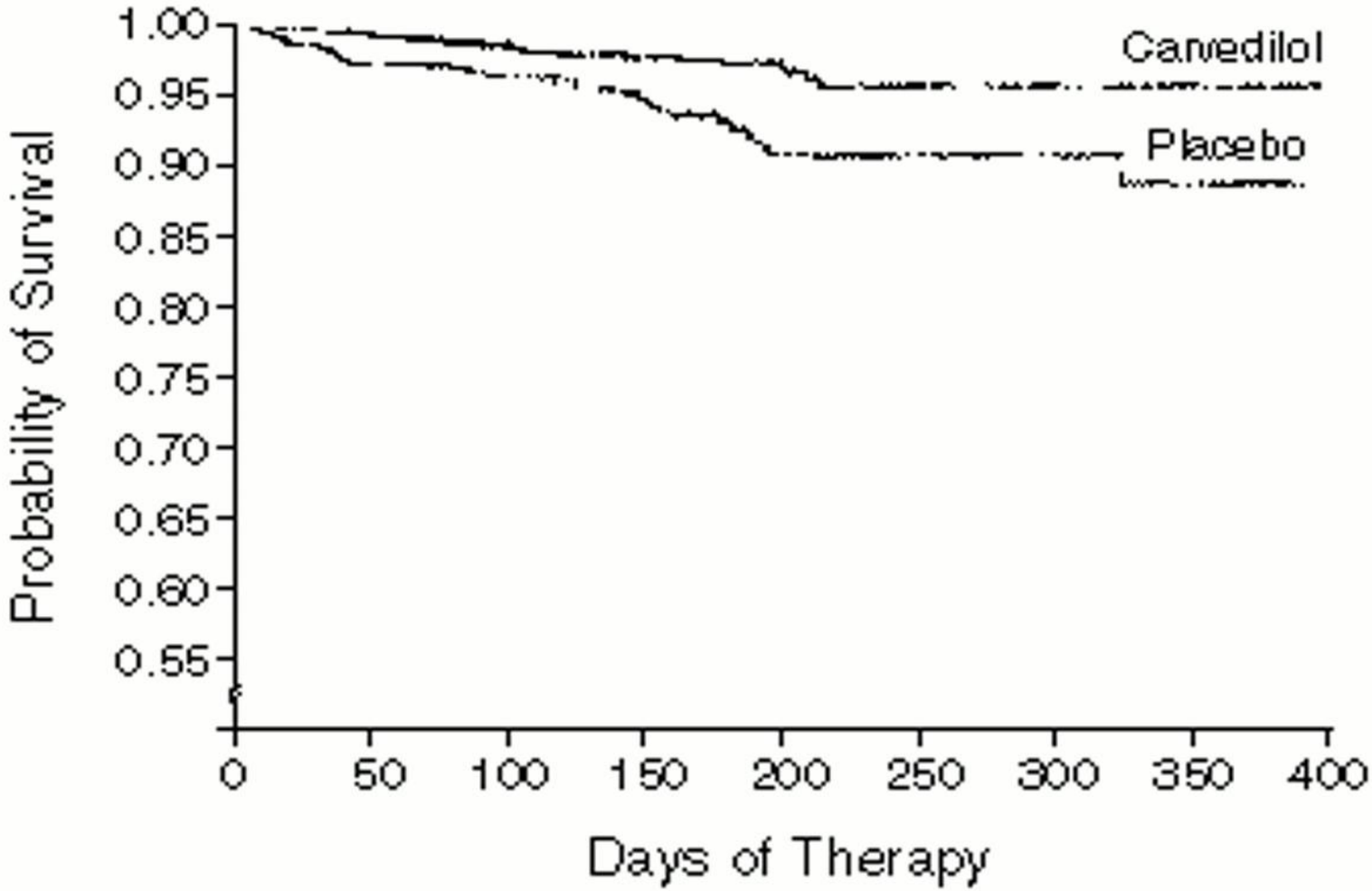



11-18-86




8
5
125
230
8
5

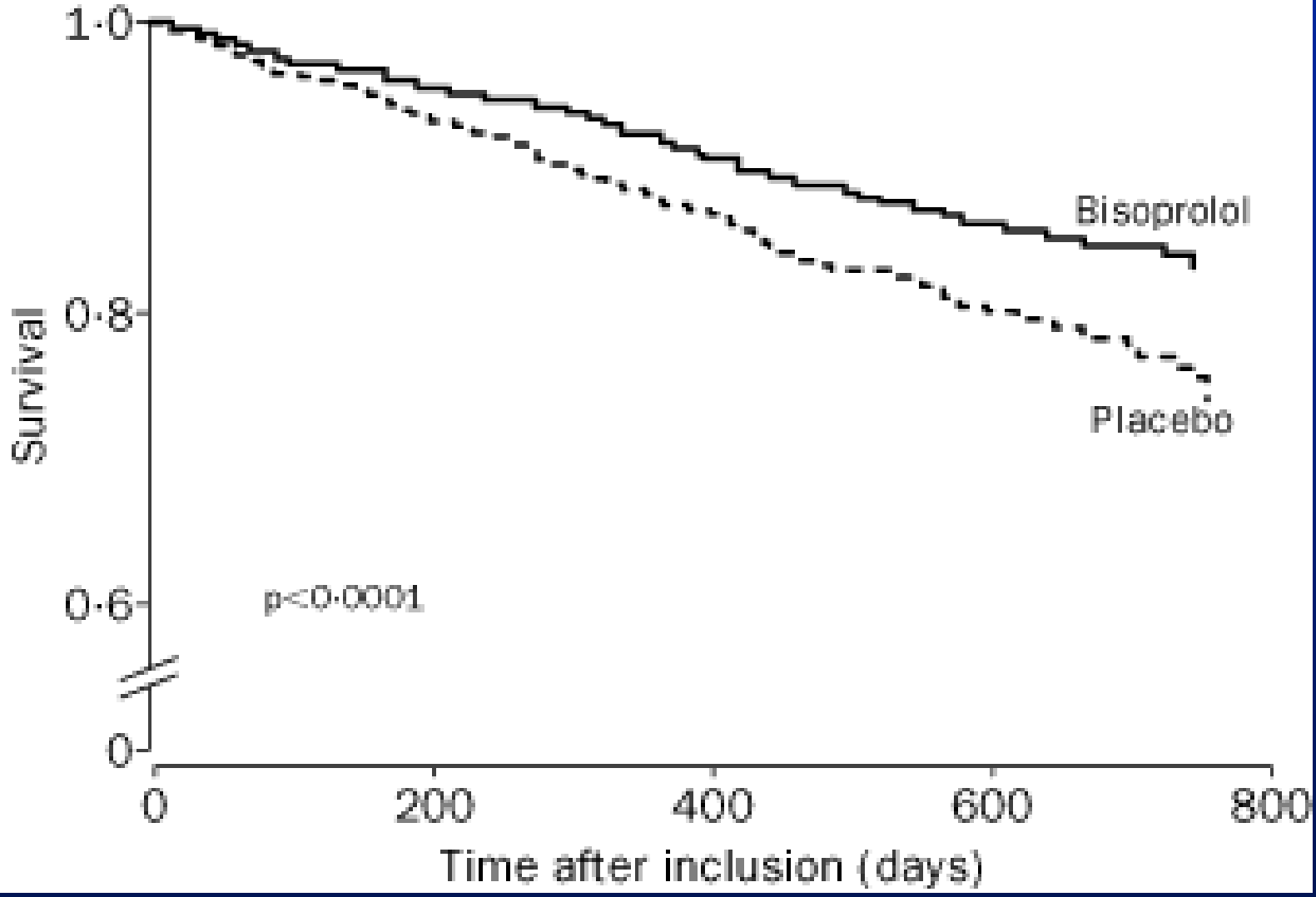
CHF patients in the carvedilol group had a 65% lower risk of death than pts in the placebo group (P<0.001)



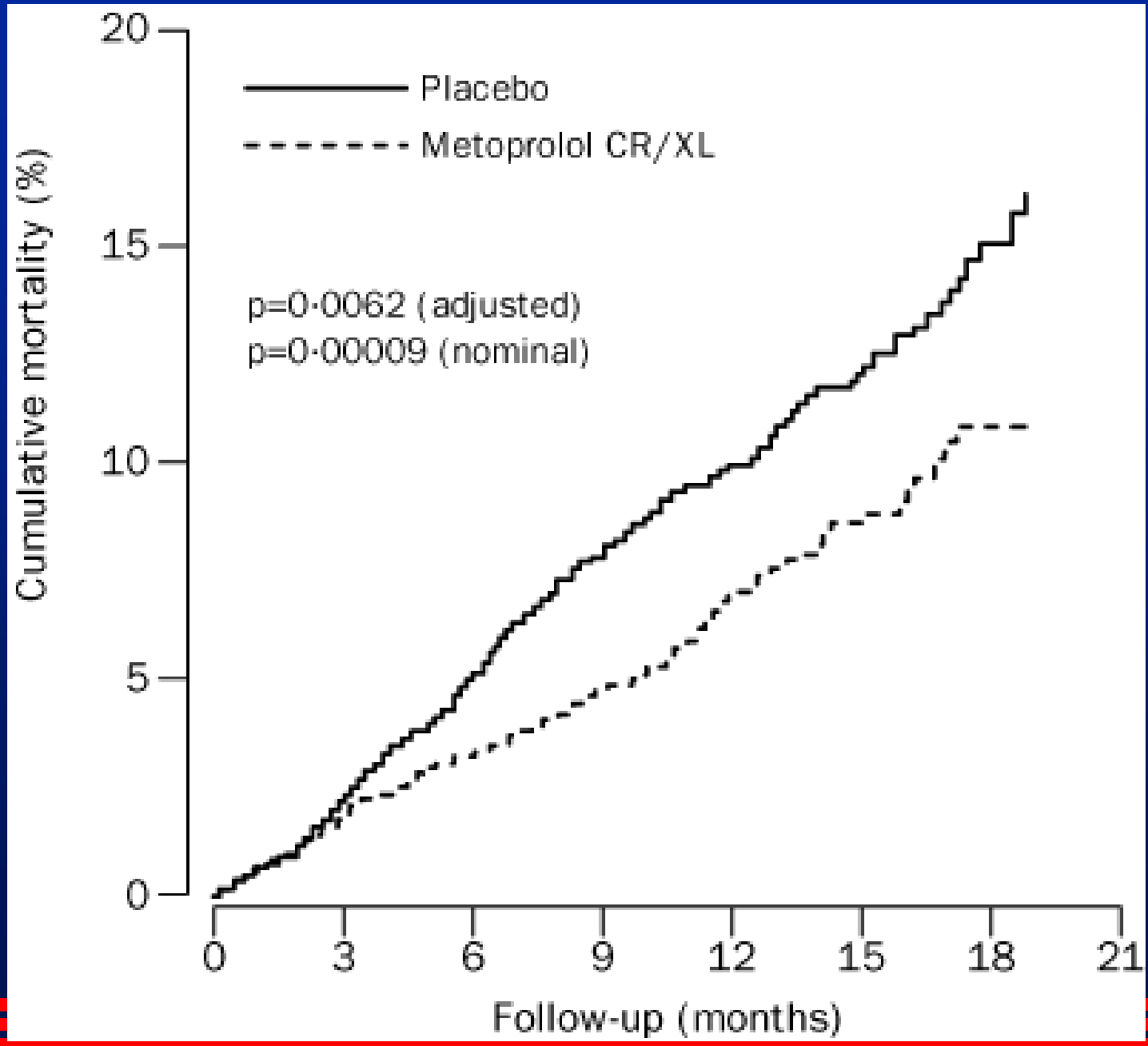
No. at Risk									
Placebo	398	353	329	305	163	71	55	43	3
Carvedilol	696	637	581	546	314	131	106	83	11

Packer et al
NEJM 1996

CIBIS II
Lancet 1999



MERIT-HF
Lancet 1999

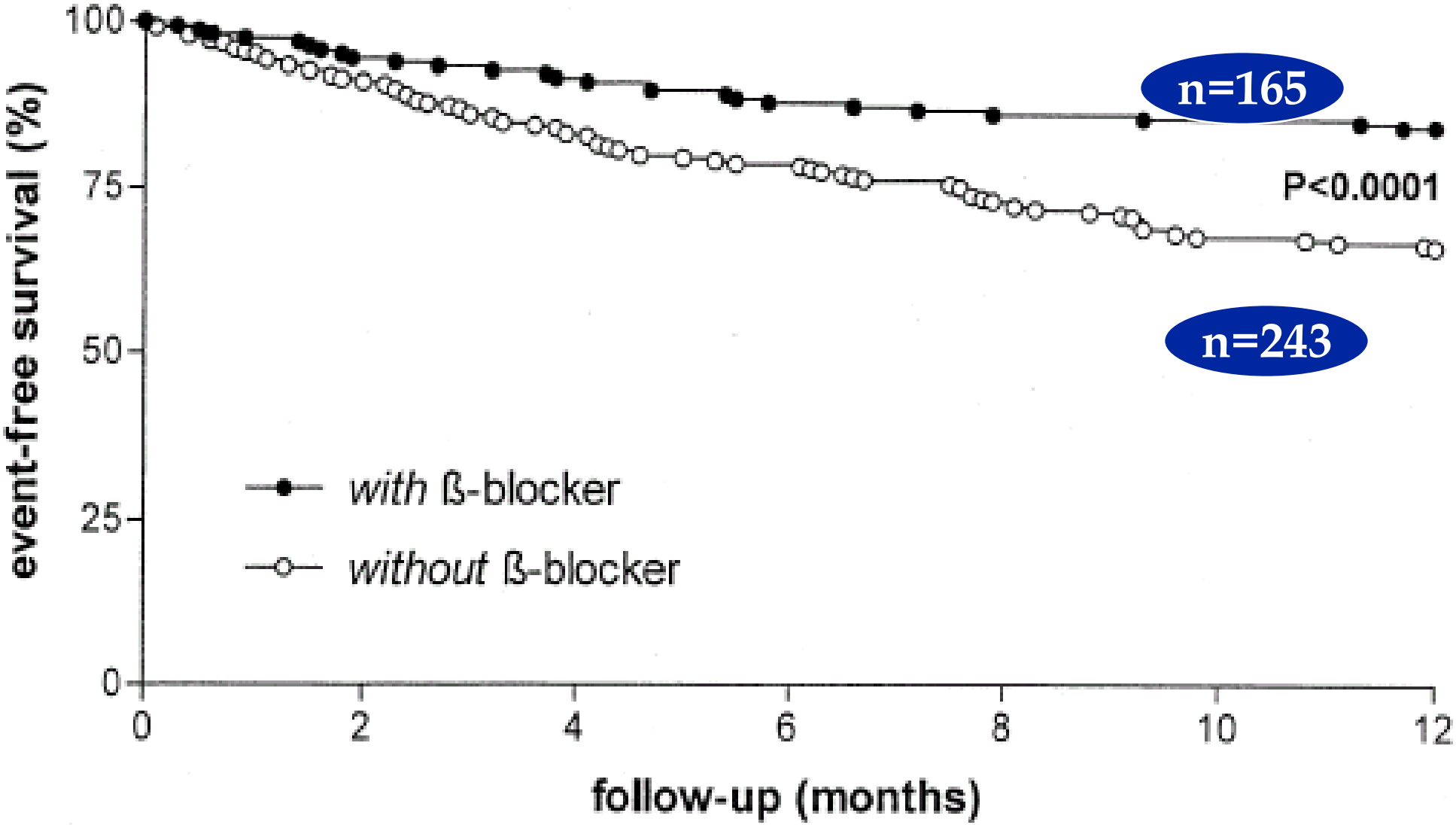


ASM

CHF

N=408, EF<45%, all on ACEI

Zugck et al, JACC May 15, 2002



Sotalol/Dronedarone

- Sotalol should be used with caution in HF pts who have very poor LV function (LVEF <30%) based on a report of possible increased risk for TdP, esp. true if there are marked fluctuations electrolyte levels, if there is a low LVEF (≤30%), if there is acute onset of HF, if there is decompensated HF, or if there is evidence of renal dysfunction
- Dronedarone should not be used in pts with NYHA class III to IV HF or LV dysfunction (LVEF <0.40), as efficacy is poor and safety is a concern (EMA Sep 2011 & FDA Dec 2011
- While the available data do not do not allow for firm recommendations regarding the use of dronedarone in pts with NYHA class I to II HF or mild LV systolic dysfunction, we suggest that the drug be used with caution in these pts if at all.
- In the general population of pts with AF, a 2009 meta-analysis found a significantly lower rate of recurrent AF with amiodarone compared to dronedarone (odds ratio 0.49)
- ● Strong evidence for an adverse effect from its use in pts with HF comes from results of the ANDROMEDA trial, which evaluated safety & efficacy of dronedarone compared to placebo in pts with symptomatic HF and LV systolic dysfunction (LVEF ≤35%)
- The trial was discontinued early due to a signif. ↑ in the incidence of death in the pts assigned to dronedarone (8.1 vs 3.8%) during a median follow-up of 2 mos
- It should be noted that in the ATHENA trial, in which ~20% of pts with NYHA class I or II HF, dronedarone appeared safe, but not necessarily effective. The rationale to use dronedarone in symptomatic HF pts is extremely weak

Beta blockers for rhythm control / Possible role of angiotensin inhibition

- There is evidence that chronic beta blocker therapy may reduce the likelihood of the development of AF in pts with HF due to systolic dysfunction

- Although ACE inhibitors and ARBs have not previously been considered a specific therapy in pts with AF, an increasing number of observations suggest that they may prevent both new onset AF and recurrent AF
- Although the data are not definitive, these drugs might be given empirically in pts with recurrent AF, particularly if there are other indications for their use such as hypertension, HF, or DM

Rate Control

- Rate control to prevent rapid AF acutely and/or chronically usually leads to an improvement in symptoms in pts with HF
- In addition, slowing of the VR often leads to a moderate or, in some cases, marked improvement in LV function
- While the use of one rate slowing drug is preferred, a combination of drugs may be required to achieve adequate heart rate control.
- It is important to measure heart rate during moderate exercise and not to base heart rate control solely on values obtained in the resting state.
- Potential benefit of rate control: demonstrated in a post-hoc analysis fm the US Carvedilol HF Trials in which 136 of 1094 pts with HFrEF had AF
- Pts treated with carvedilol had a signif. ↑ in LVEF (from 23 to 33% c/w 24 to 27% with placebo); there was also an almost signif. trend toward a ↓ in the combined end point of death & HF hospitalization (7 vs 19%). This study does not prove that the improved outcomes are due to rate control, but rather a beneficial effect of the use of one beta blocker in this setting

Approach to Rate Control

- For those whose VR varies markedly with minimal changes in activity, esp. if associated with Sx, a rhythm control strategy may be necessary
- For pts with compensated HF due to systolic dysfunction & AF requiring rate control:
- ● Choose a rate control goal
- ● Choose a beta blocker as first therapy. The rationale for doing so stems from the fact that, although they do not appear to improve mortality in this setting, there is no evidence of harm with their use. In addition, the alternatives of Ca++ channel blockers (greater mortality), digoxin (lesser efficacy), and amiodarone (more side effects) have significant limitations.
- Can start c carvedilol, extended release metoprolol succinate, or bisoprolol. The doses should be optimized before considering a 2nd agent
- The nondihydropyridine calcium channel blockers (verapamil & diltiazem) should be avoided in pts with decompensated HF or those with reduced LV function. They may be considered in pts with preserved LV systolic function and compensated HF

Approach to Rate Control

- In pts who cannot receive either a β-blocker or a Ca++ channel blocker, and in whom rhythm control will not be attempted,
- digoxin may be considered
- If 2 drugs are needed, one may add digoxin to a β-blocker
- For pts with decompensated HF, initiation or ↑ of β-blockers is contraindicated / If such a pt also has rapid AF requiring rate control, use of digoxin is suggested
- However, dig is often ineffective when used alone, esp. in pts c ↑ sympathetic tone
- Adequacy of rate control in AF should be assessed both at rest and with typical exertion
- In the event that rate control with either beta blockers or a combination of beta blockers & digoxin has not been achieved, amiodarone may be useful either alone or in combination with other rate-slowing agents.
- Amiodarone is not recommended as a chronic rate-control medication, but in the acute setting can assist with rate control as it is being loaded or can be used as a temporary rate-control agent in a patient who is unable to tolerate other therapies. Use of amiodarone may prove helpful for rate control in this setting, but care must be exercised when using these agents, especially in those without adequate anticoagulation since there is the possibility of pharmacologically restoring sinus rhythm. If amiodarone is used for rate control, an attempt to load the drug and cardiovert should be considered for those with recent onset AF

Rate Control Goal

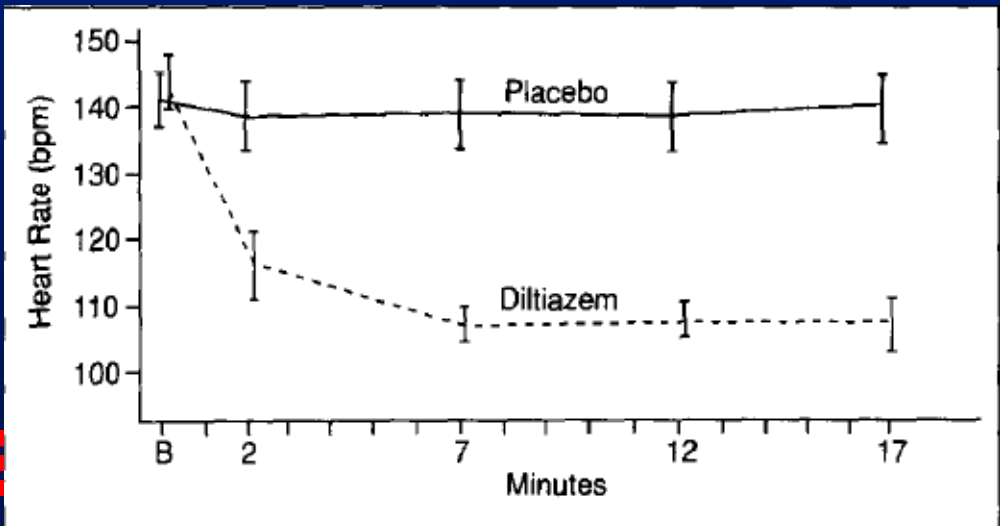
- Similar to AF pts without HF, optimal HR in pts with HF is not known
- There are no well-performed studies that have addressed this issue
- Broad goal of rate control is to minimize symptoms with exercise & rest
- Thus, the adequacy of rate control should be assessed in both circumstances
- Approaches differ on the rate control goal, with some aiming for a resting heart rate <110 bpm (the lenient approach) and
- most preferring a heart rate <85 bpm at rest & <110 bpm during moderate exercise (the strict approach).

AV node ablation with pacing — Rate control can also be achieved with RF ablation of the AV node & permanent pacemaker placement. This strategy may be useful in pts (usually c permanent AF) in whom rate control with AAD or catheter ablation has failed or been contraindicated

In HF pts with AF who undergo AVN ablation, if the LVEF is <40% and there is an expectation that ventricular pacing will occur >50%, strong consideration for a biventricular pacing system should be made as opposed to a standard RV pacing system

IV diltiazem is rapid, safe, & effective in acutely lowering a rapid VR in pts with AF or flutter & moderate to severe CHF

- 37 pts c rapid (VR, 142 ± 17 bpm) AF or flutter & moderate to severe CHF (EF, 36 ± 14%; NYHA class III [23 pts], class IV [14 pts])
- IV diltiazem, 0.25 mg/kg over 2 min, or placebo followed 15 min later by diltiazem or placebo, 0.35 mg/kg over 2 min
- Placebo nonresponders: open-label IV diltiazem (all 15 responded)
- 21 pts (95%) responded to diltiazem, & 0 of 15 pts (0%) to placebo ($p < 0.001$) / Overall, 36 of 37 pts (97%) / median time to response ~ 5 min.
- Hypotension was the most common adverse event occurring in 4 of 37 pts (11%). No patient had an exacerbation of CHF due to diltiazem



Goldenberg et al, AJC 1994; 74 (9) : 884–889

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

- **Class I**
- **1. Control of resting heart rate using either a beta blocker or a nondihydropyridine calcium channel antagonist is recommended for pts with pers or perm AF & compensated HF with HF*p*EF *(LoE: B)***
- **2. In absence of pre-excitation, IV beta blocker administration (or a nondihydropyridine calcium channel antagonist in pts with HF*p*EF) is recommended to slow the VR to AF in the acute setting, with caution needed in pts with overt congestion, hypotension, or HFrEF *(LoE: B)***
- **3. In absence of pre-excitation, IV dig or amio is recommended to control heart rate acutely in pts with HF. *(Level of Evidence: B)***

- Nondihydropyridine Ca++ antagonists, such as diltiazem, should be used with caution in HFrEF because of their negative inotropic effect
- For those with HFpEF, nondihydropyridine calcium antagonists can be effective at achieving rate control but may be more effective when used in combination with digoxin

Rate Control

- For pts who can potentially benefit from CRT but have AF, it may be necessary to ablate the AV node so that a high percentage of ventricular pacing can be insured since pts with AF may "override" the pacing and reduce the efficacy of the CRT device.
- Compelling data would suggest that AVJ ablation in pts who are not pacing at rates of >95% with CRT pacing may benefit from RFA

Patients with Diastolic HF

- Approach to pts with diastolic HF is nearly identical to that for those with systolic HF. Rhythm control is preferred to rate control for most pts
- Approach to rate control is also similar. Rate control goal may be more lenient in some pts with diastolic HF
- One can typically start with a beta blocker; for pts who cannot receive a beta blocker due to issues such as bronchospasm, a nondihydropyridine calcium channel blocker may be used. More caution with use of digoxin in this group.

A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry.

- a registry of consecutive in- and outpts with AF presenting to cardiologists in 9 participating ESC countries
- enroled a total of 3119 pts from Feb 2012 to Mar 2013, with full data on clinical subtype available for 3049 pts (40.4% female; mean age 68.8 y)
- Common comorbidities were hypertension, coronary disease, & HF
- Amiodarone was the most common antiarrhythmic agent used (~20%), while beta-blockers & digoxin were the most used rate control drugs

Lip et al, Europace 2014 Mar;16:308-19

Enalapril Decreases the Incidence of Atrial Fibrillation in Patients With Left Ventricular Dysfunction

Insight From the Studies Of Left Ventricular Dysfunction (SOLVD) Trials

Emmanuelle Vermes, MD; Jean-Claude Tardif, MD; Martial G. Bourassa, MD; Normand Racine, MD;

2930 *Circulation* June 17, 2003

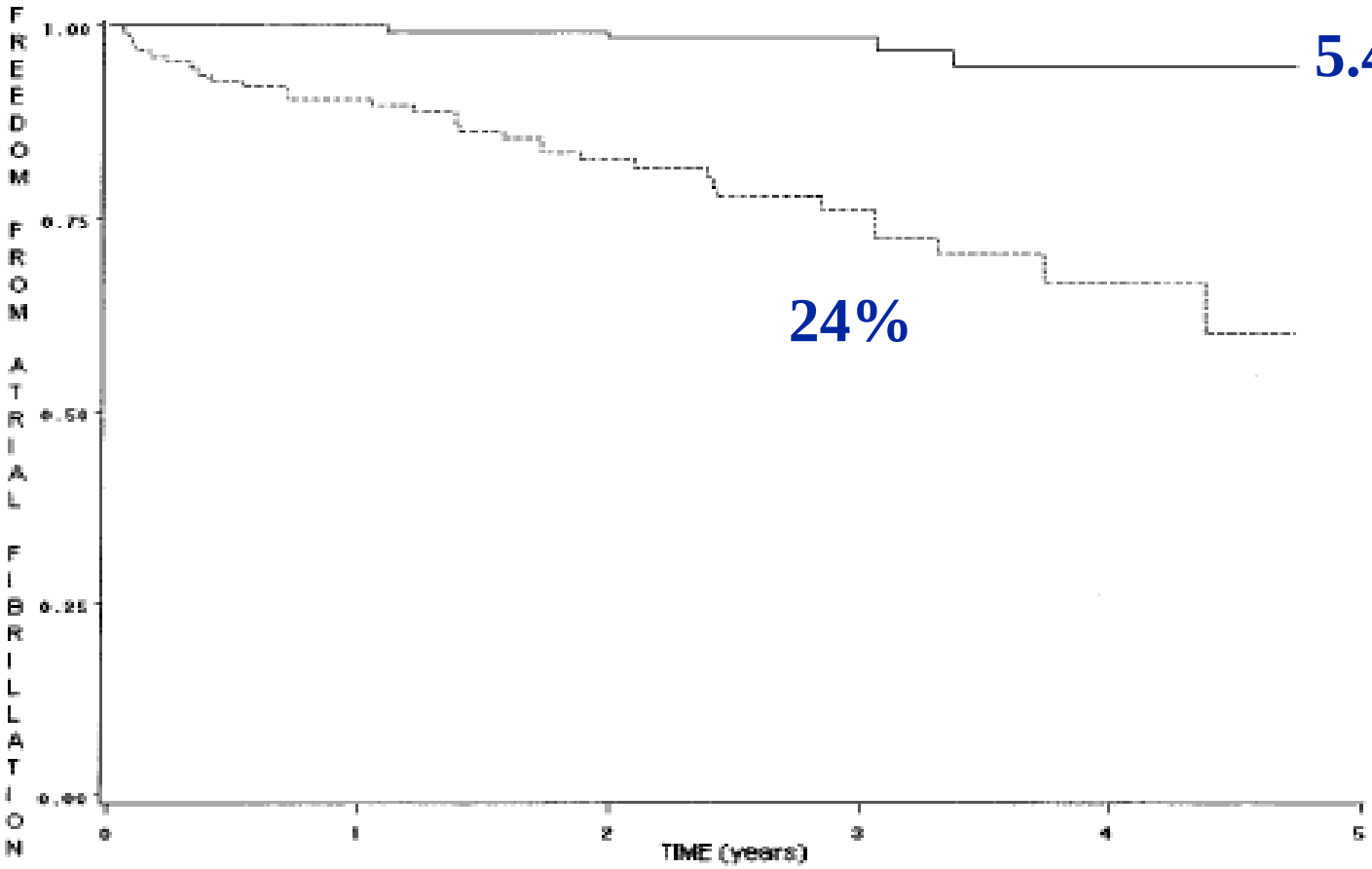
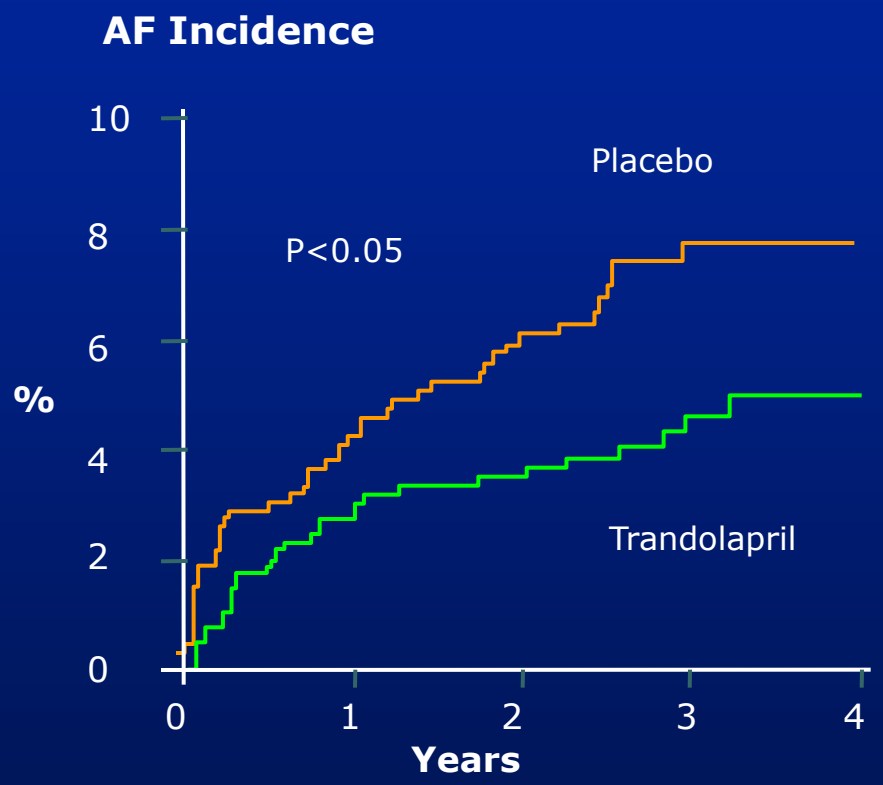


Figure 2. Kaplan-Meier curves for time to first occurrence of AF in subgroup of 251 patients of prevention arm randomly assigned to enalapril (solid line) or placebo (dotted line) ($P<0.0001$), including patients with LVEF ≤0.35 and no history of overt HF requiring treatment at entry in the trial.

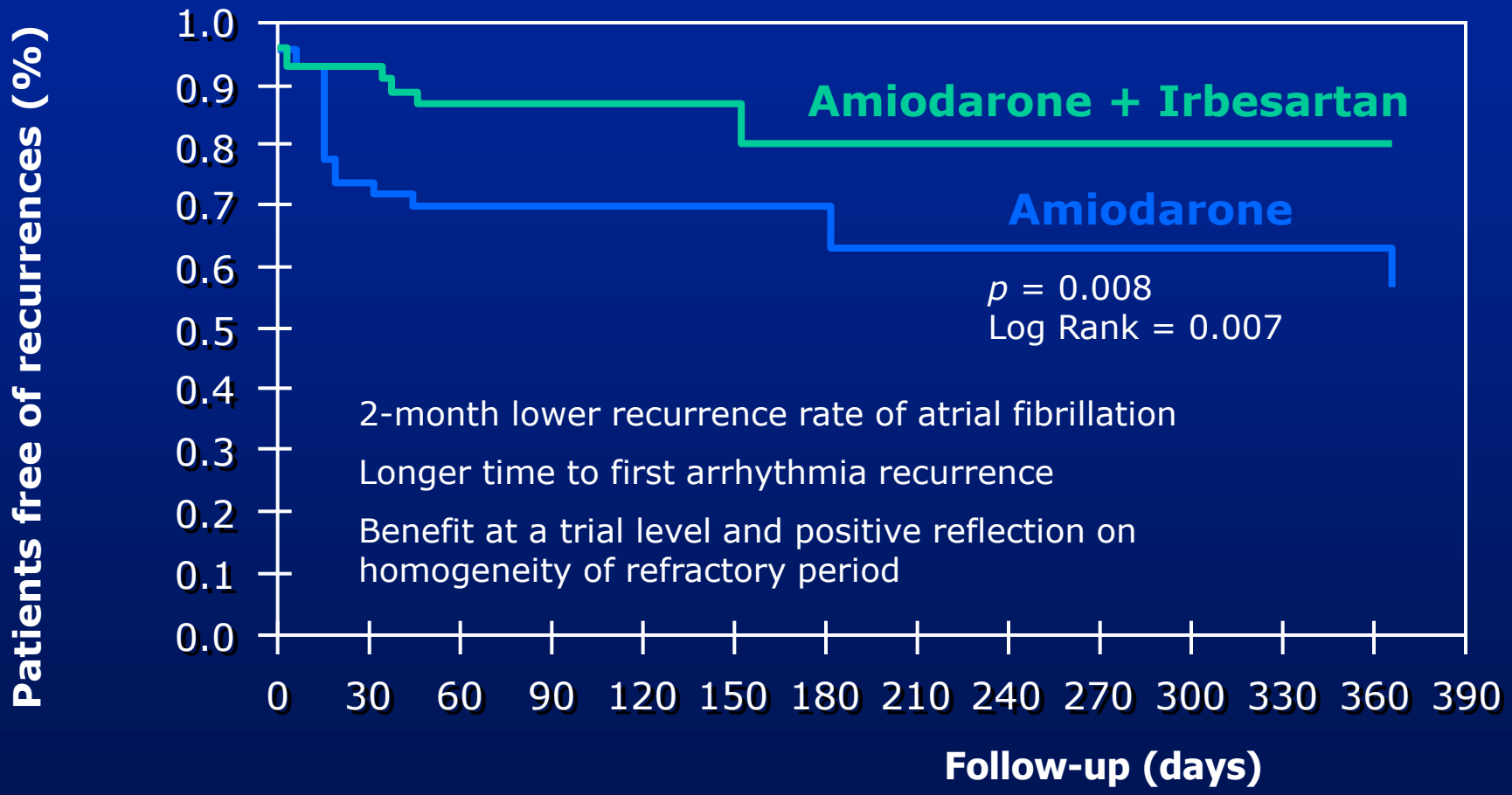
Effect of ACE-I on AF in CHF Patients



- **TRACE (1570 low EF patients post MI)**
- **Trandolapril vs Placebo**
- **LVF 33%, HBP 22%**
- **Reduced risk of AF**
- **RR: 0.45 (0.26-0.76)**

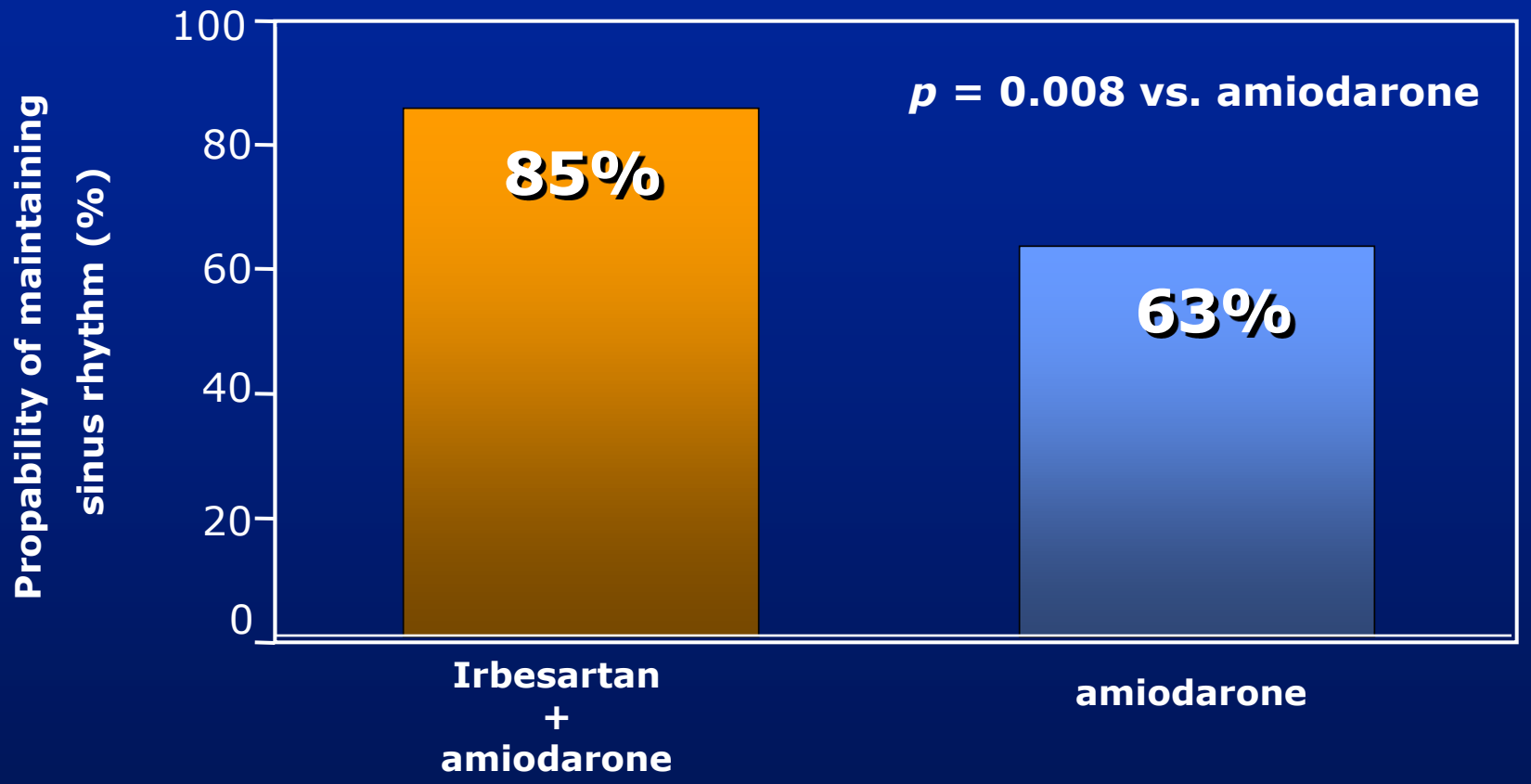
Pedersen OD, *et al. Circulation* 1999; 100: 376.

Maintenance of sinus rhythm after conversion from persistent AF



Madrid AH, Moro C et al. Circulation 2002;106:331–6.

Irbesartan significantly increased probability of maintaining sinus rhythm



159 patients with persistent atrial fibrillation were randomized to either amiodarone or amiodarone + irbesartan
Results are taken at 2-month follow-up visit

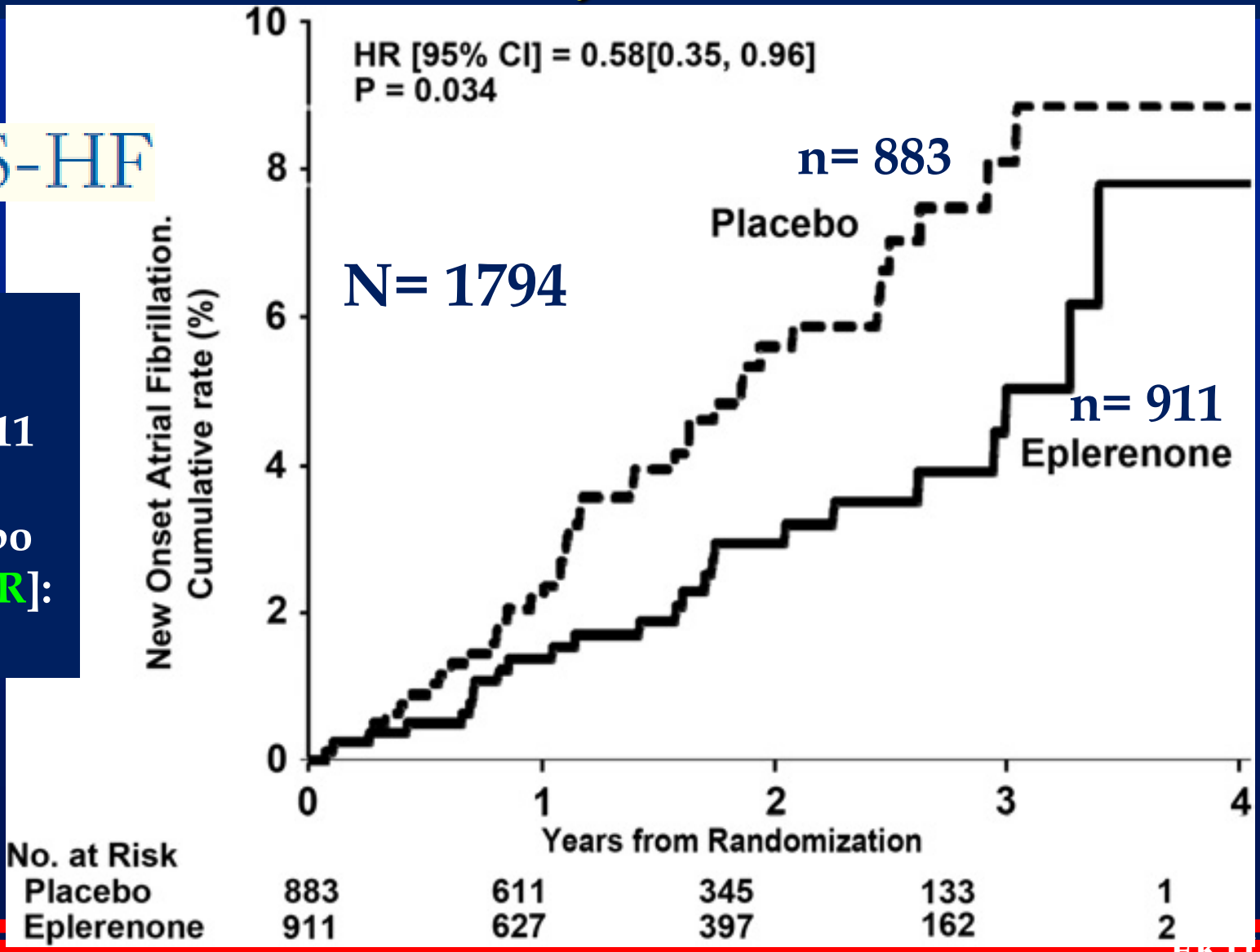
Madrid A et al. *Circulation* 2002;106:331–6.

New onset of AF or flutter in pts without AF or flutter at baseline

JACC 2012;59:1598

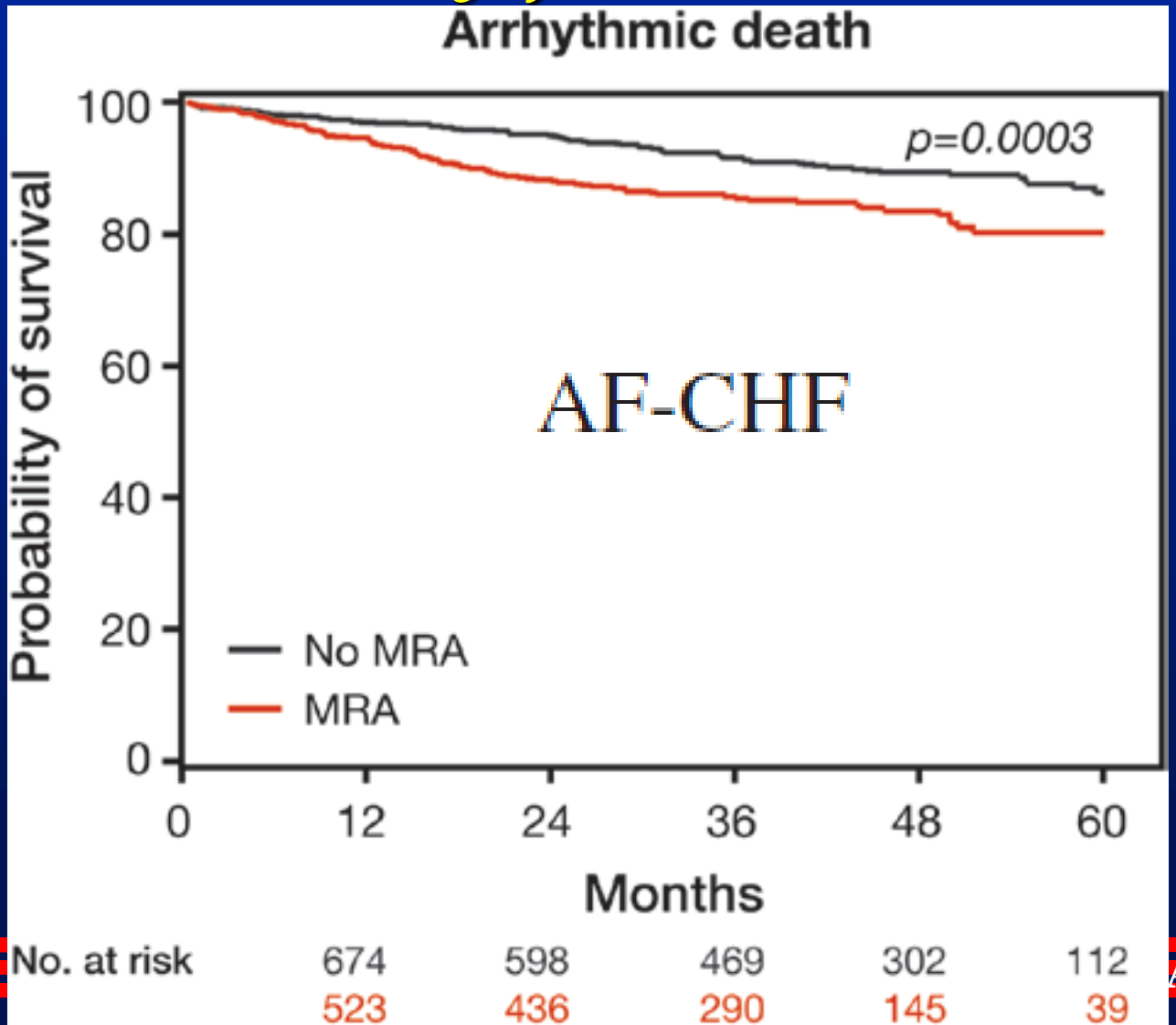
EMPHASIS-HF

New onset AF was significantly ↓ by eplerenone: 25 of 911 (2.7%) vs 40 of 883 (4.5%) in the placebo gp (hazard ratio [HR]: 0.58; p = 0.034)



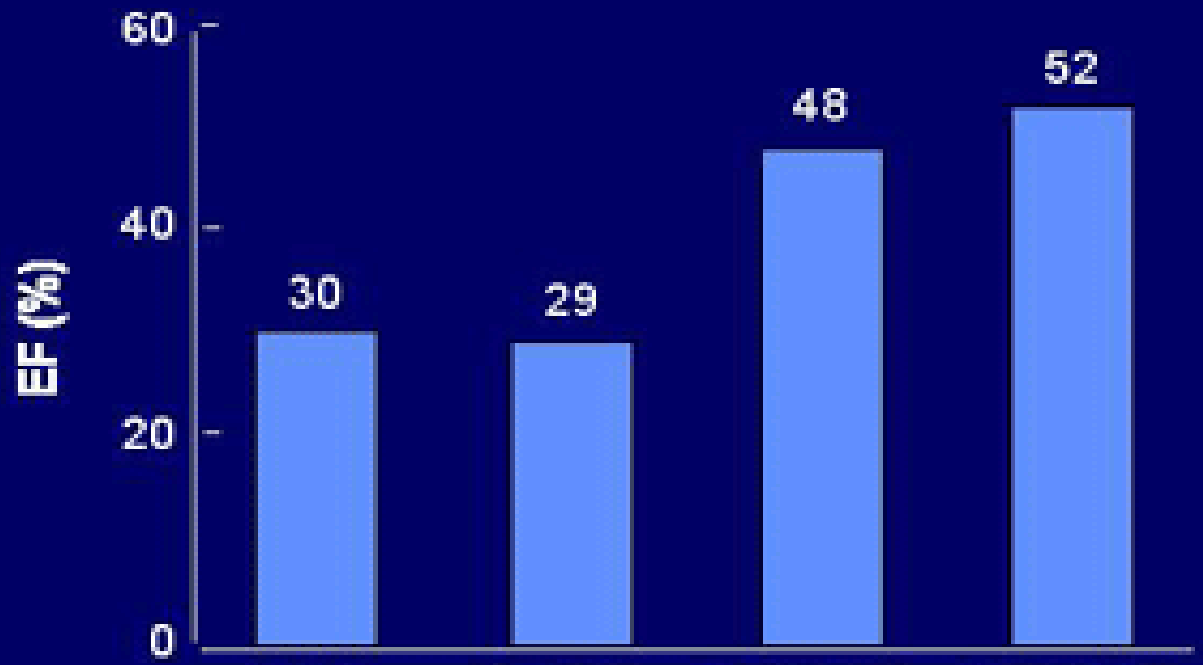
Mineralocorticoid Receptor Antagonists & CV Mortality in Pts With AF and Left Ventricular Dysfunction

N.B. c Spironolactone !



Circ Heart Fail. 2012;5:586-593

Case Study



Improved EF of 36-year-old male who presented with AF (HR 140 bpm) 1 week prior to initial echo

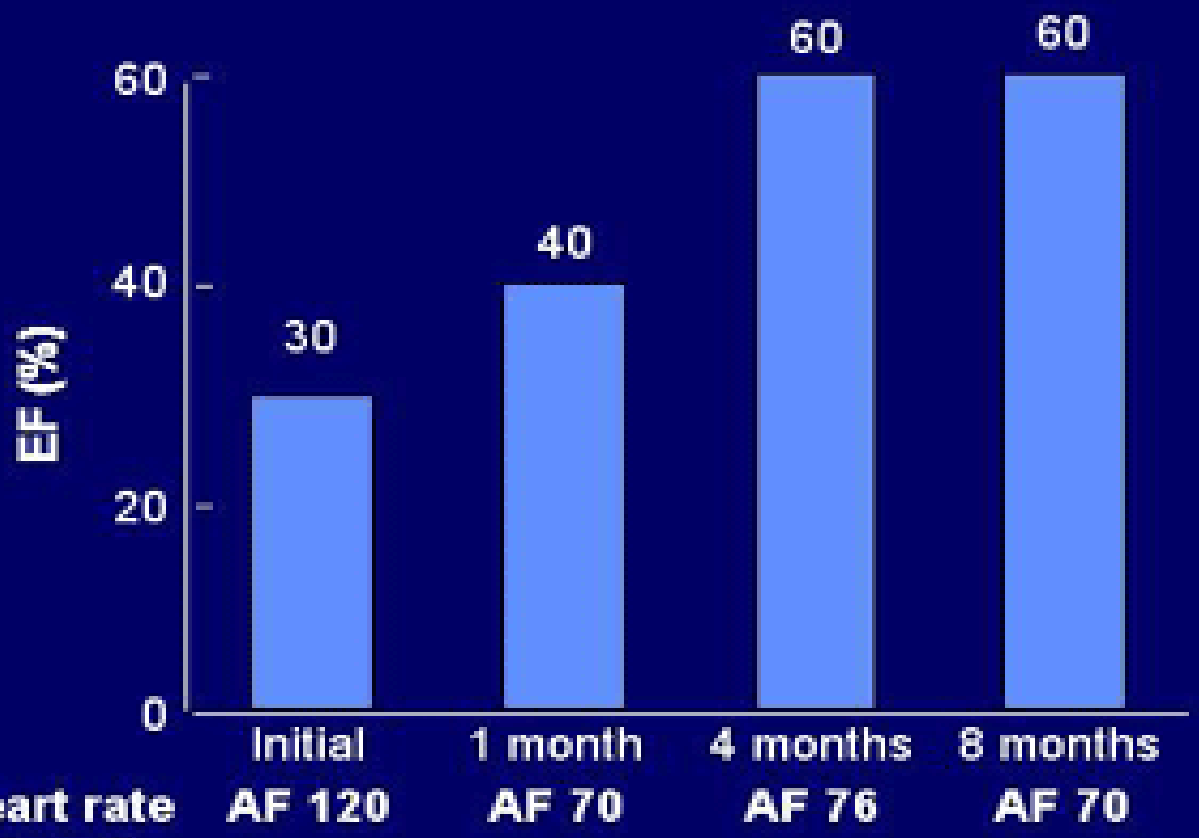
* Heart rate 140 one week earlier

Primary Rx: DC cardioversion

Other Rx: digoxin and quinidine

Grogan M. Am J Cardiol. 1992;69:1570-1573.

Case Study

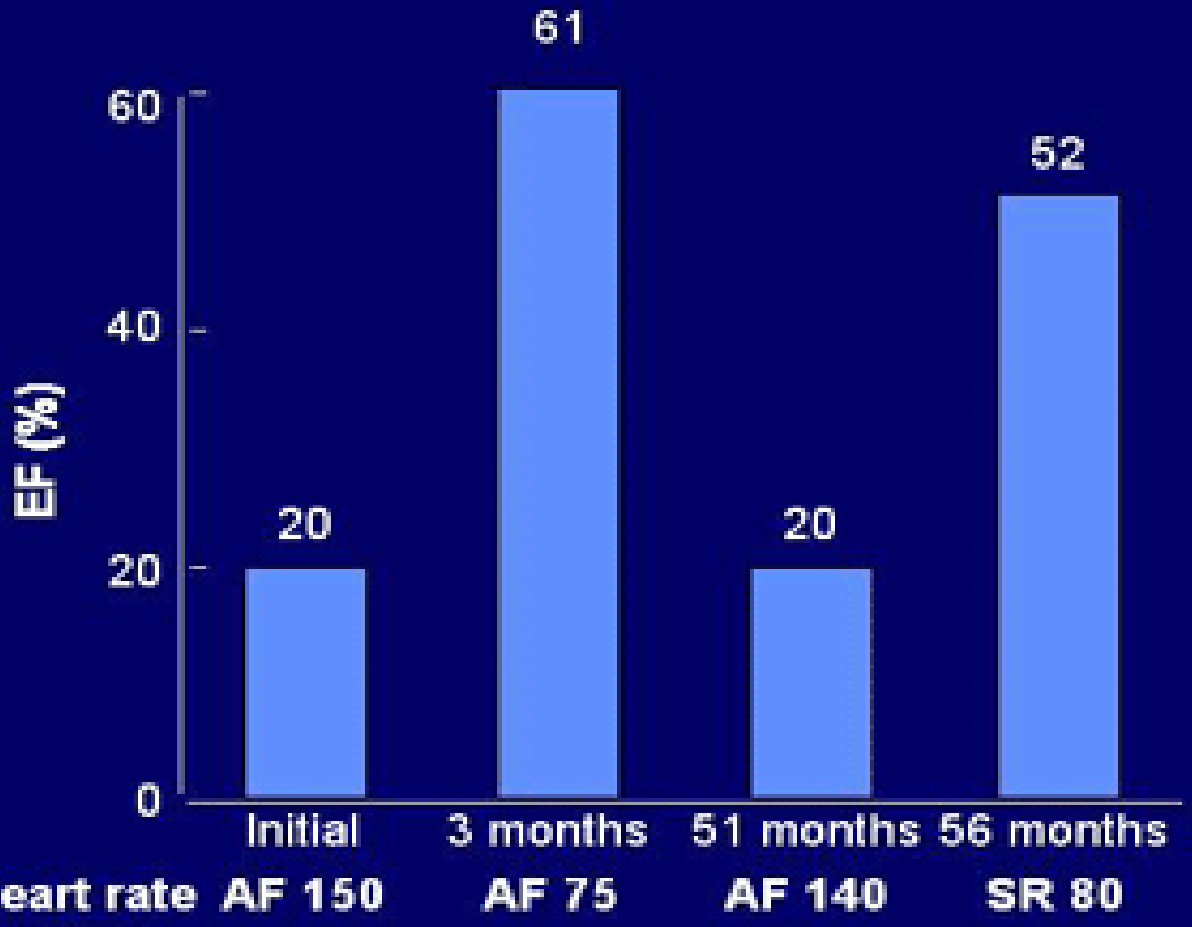


Improved EF in 80-year-old female with chronic AF but with improved rate control

Primary Rx: digoxin and propranolol

Grogan M. Am J Cardiol. 1992;69:1570-1573.

Case Study



Markedly improved EF in 55-year-old female with both rate control & NSR, with reversion to AF (HR 140 bpm) and subsequent decrease in EF

Primary Rx: amiodarone

Other Rx: digoxin and lisinopril

Grogan M. Am J Cardiol. 1992;69:1570-1573.

Future Developments

- Pts with HF who are b_1 adrenergic receptor 389 Arg homozygotes exhibit a signif. reduction in new-onset AF when treated with bucindolol (vs. placebo) when c/w $b_1$389 Gly carriers (hazard ratio: 0.26 vs 1.01; p for interaction = 0.008)

- Ongoing GENETIC-AF (Genetically Targeted Therapy for the Prevention of Symptomatic AF in Pts With HF) clinical trial will test the hypothesis that genotype-directed bucindolol therapy is superior to metoprolol for prevention of Sxic AF in pts with HF

Aleong et al, J Am Coll Cardiol Heart Fail 2013;1:338–44.

- Landiolol: ultra-short-acting β-adrenergic blocking agent
- F 16915(docosahexaenoic acid derivative):promising new drug as upstream therapy for Rx of AF in pts with HF

Le Grand et al, Naunyn Schmiedebergs Arch Pharmacol 2014;387:66

- Emerging ablation technologies / Hybrid approaches

ASM

Summary and Recommendations

- AF is common in pts c HF, can worsen Sx,a/w poorer prognosis
- Both rate- & rhythm-control strategies effective in controlling Sx / have comparable survival rates
- [Most AF pts c HF meet criteria for long-term anticoagulation]
- For pts with AF & compensated HF, rhythm control rather than rate-control may be preferable as an initial treatment strategy
- A rate control strategy is a reasonable approach in older pts who prefer to avoid the potential burdens of rhythm control
- For pts who are chosen for a rhythm control strategy using an AAD, dofetilide may be used, where available
- Amiodarone is otherwise chosen, esp. for older individuals, while sotalol may be a reasonable choice for pts with mild renal dysfunction

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Summary and Recommendations II

- For pts who fail rhythm control with AAD Rx & in whom a rhythm-control strategy continues to be preferred over a rate-control strategy, catheter ablation is a therapeutic option

- For pts in whom a rate-control strategy is chosen, we recommend beta blockers rather than calcium channel blockers or digoxin as initial therapy

- For pts who fail a rate-control strategy using AAD and are either not candidates for or have failed a rhythm-control strategy, AV nodal ablation with pacing is a reasonable therapeutic option

ASM

Management of HF in AF patients

Prevention of thromboembolic events

Risk stratification
- CHA_2DS_2-VASc
- HASBLED

- VKAs
- NOACs
- LAA occluders

Rate or rhythm control

- Persistent symptoms

Rate control

- Digoxin
- Amiodarone
- Beta blockers (e.g., Carvedilol, Bisoprolol, etc.)

Rhythm control

- Cardioversion
  - Amiodarone
  - AV node ablation + Pacemaker
- AF ablation

as recommeded by current guidelines

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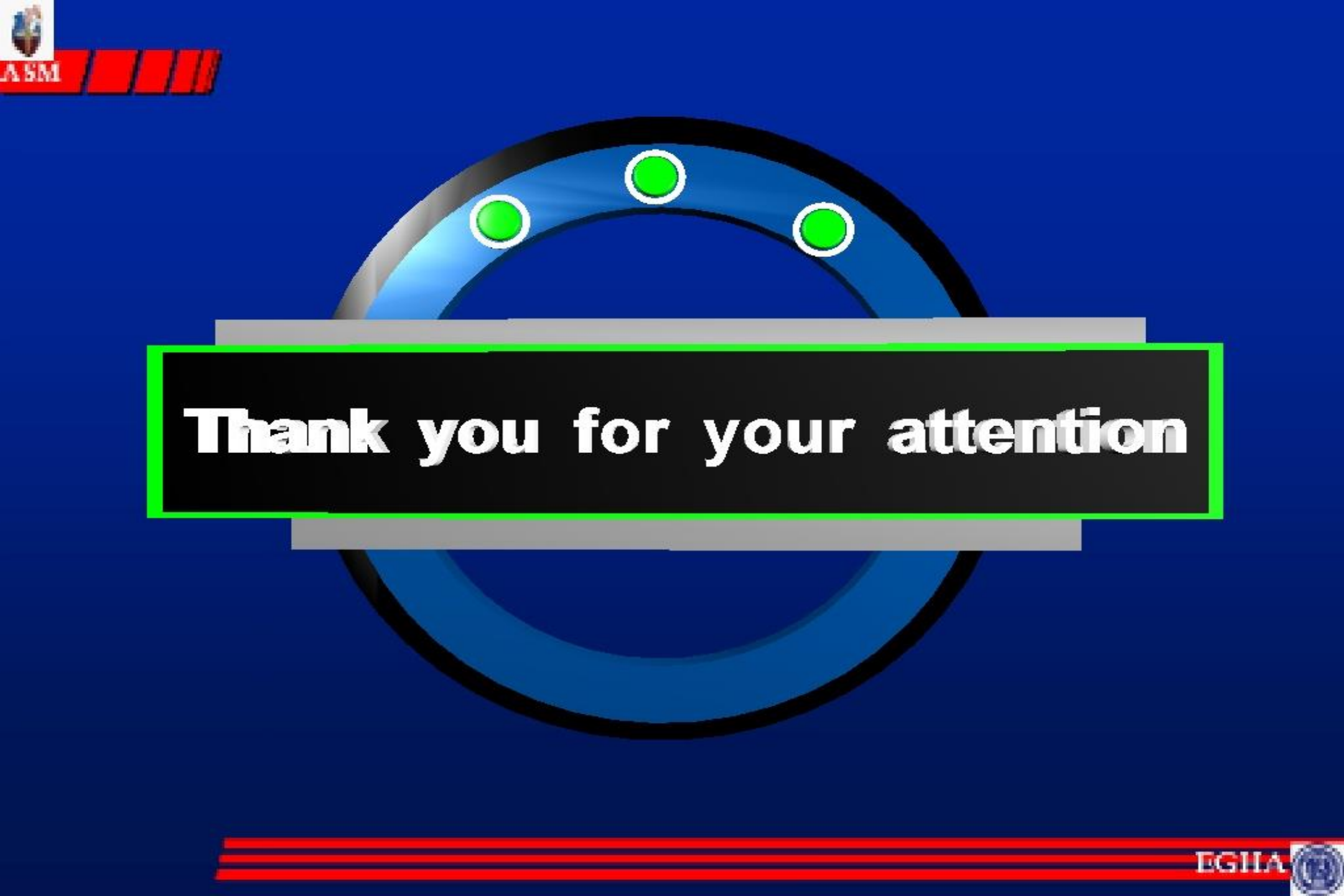
Thank you for your attention