A Second Look at Recent Trials in Atrial Fibrillation:

What Do These Trials Really Show Us and How May They Apply to Future Therapies.

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What have recent trials such as AFFIRM and RACE and others really shown us as regards the clinical management of patients with atrial fibrillation who come to us for help?

Therapeutic Indications

- There are only 2 reasons to administer a therapy to a patient:
  - To make the patient live longer
  - To make the patient feel better
- This is as true for the drug management of AF as for any other disorder.
- In the process we need to minimize adverse risks from our therapies.

Slide courtesy of J. Reiffel, M.D.

As regards the goals on this slide, we need to know what the probability is that if we initiate a treatment approach for atrial fibrillation, the result we desire will be attained. However we would also like to know what the likely result will be if the patient actually utilizes the therapy he/she was anticipated to receive, in contrast to never starting it, discontinuing it, or combining it with another therapeutic approach.

One Caveat:

- **Therapy of AF is not required in all patients**.
- For example: infrequent, transient, minimally symptomatic episodes require no treatment.
  - [Would you be treated if you had 2 five minute episodes 3 times a year?]
  - Moreover, recurrences of this type on drug therapy should not be considered as drug failure.
- Hence, therapy (drug or otherwise) must focus on the presentation characteristics and on appropriate target goals.

Slide courtesy of J. Reiffel, M.D.

Have Our Treatment Strategies for Atrial Fibrillation Improved QOL and/or Lengthened Survival?

Or, in Other Words,

Is Sinus Rhythm Maintenance the Definitive Solution to Atrial Fibrillation?

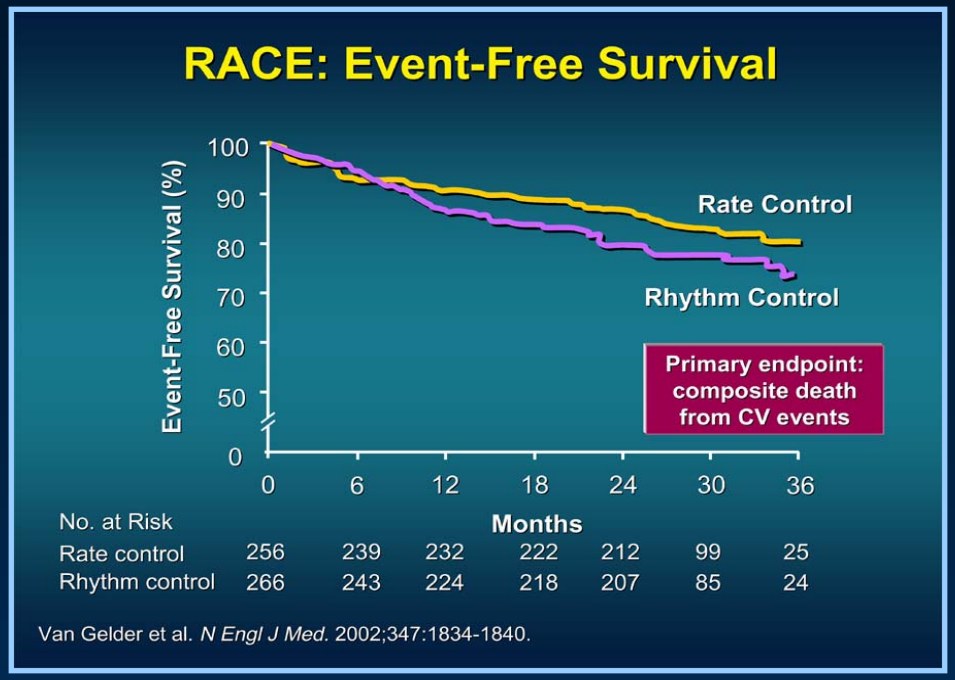
Does NSR Increase Survival?

Five prospective rate vs rhythm trials have been reported

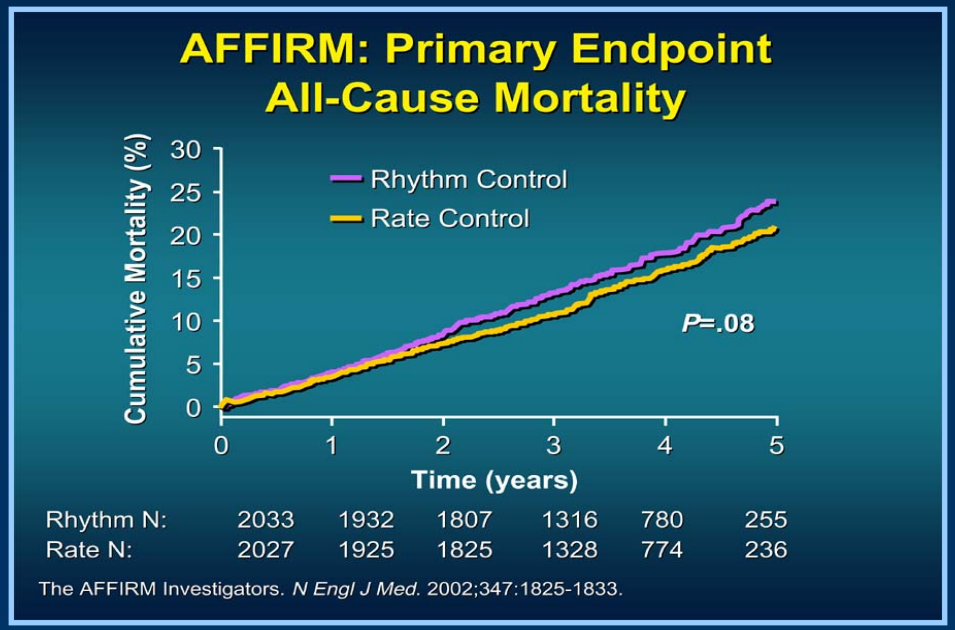
STAF (n=200), PIAF (n=252), HOT CAFÉ (n=205), RACE (n=522), AFFIRM (n=4060)

In all five, there was no survival benefit associated with a rhythm control strategy

RACE and AFFIRM demonstrated a slight risk with a rhythm control approach



By ITT Analysis



In both AFFIRM and RACE, the rhythm control strategy failed to improve survival as compared to a rate control strategy; in fact, there was a trend towards increased risk. However, this is by intention to treat analysis, and it does not tell us what the outcome was for patients who took and remained on the therapy assigned.

Rate vs Rhythm Control Trials

	Patients Reaching Primary Endpoint with:		
Trial	Rate Control, n (%)	Rhythm Control, n (%)	*P*
PIAF (2000)	76/125 (60.8%)	70/127 (55.1%)	.317
RACE (2002)	44/256 (17.2%)	60/266 (22.6%)	.11
STAF (2002)	10/100 (10.0%)	9/100 (9.0%)	.99
AFFIRM (2002)	310/2027 (25.9%)	356/2033 (26.7%)	.08
HOT CAFÉ (2004)	1/101 (1.0%)	4/104 (3.9%)	>.71

Fuster V, et al. *Circulation.* 2006;114:700-752.

There is a consistency of results across multiple trials that were similar in most respects although somewhat different in specific design.

AF Therapy

- In light of the recent trials, it appears to many that therapeutic approaches to AF *with our current drugs and procedures* should be primarily aimed at improving quality of life.
- For patients with no or minimal symptoms, rate control (plus anticoagulation) is appropriate. The morbidity/mortality profile *is not inferior* to a rhythm control strategy.
- For patients with substantial symptoms (as defined by the patient) despite rate control, sinus rhythm should be pursued to improve their QOL.
  - [Many would add young pts without SHD to this list.]

Slide courtesy of J. Reiffel, M.D.

This slide should be self-explanatory.

But also, for young patients without structural heart disease (SHD), class IC agents, which are essentially free of organ toxicity and not expectedly proarrhythmic (e.g., VT, VF, TdP) in this population can be employed. Accordingly, they may maintain NSR or reduce AF with a lesser risk than was present in the older and sicker populations of AFFIRM and RACE where more toxic agents, such as amiodarone, were used and where class I agents were at least relatively contraindicated and only infrequently used.

How many of you believe, following AFFIRM and its sister trials, that rate control is as reasonable a first-line therapy for AF as is the pursuit of sinus rhythm?

Having seen the survival curves from the AFFIRM and RACE trials, and, hopefully, having read or at least heard the reports, how would you answer this question in your practice?

Are AF and NSR Really Equal?

- I would submit to you that a close examination of trials such as AFFIRM and RACE do not prove that rate-controlled and anticoagulated AF is as good as NSR.
- They show that a rhythm control strategy, using ITT analysis, suggests equivalence.
- These trials do not disprove that if one were to actually attain and maintain sinus rhythm with safe methods, it would be better than AF re: both survival and QOL.

Slide courtesy of J. Reiffel, M.D.

This slide should be self-explanatory after you review the following portion of this presentation.

Analyses in Trials

- Intention to treat (ITT)
  - Tests outcomes on one strategy vs another
  - All pts assigned to a strategy (e.g. a treatment) are analyzed as though they received the therapy, took it, were compliant with it, continued it, and did not cross over to the other therapy [regardless of whether or not this was true].
  - Statisticians like this approach, although it may not tell you what actually happens if patients take and continue the therapy.
  - It gives information as to the likelihood of events if a particular treatment strategy is chosen.
  - If discontinuation or compliance rates are likely to be different between two strategies, this type of analysis will be biased (e.g., a drug vs a non-pharmacologic therapy would seem to favor the non-pharmacologic approach).

Slide courtesy of J. Reiffel, M.D.

This slide highlights some of the major issues in ITT analyses

Analyses in Trials

- Efficacy or On-Therapy
  - Tests outcome in pts who take and remain on the assigned therapy.
  - It gives information as to likelihood of an outcome if a patient actually takes a therapy but not on what the likelihood will be “up-front” when the therapy is chosen but not yet taken (which is provided by the ITT approach).
  - Others are excluded from analysis
  - Unequal group sizes, durations of therapy, etc. that result from such exclusions result in biases in this approach as well.

Slide courtesy of J. Reiffel, M.D.

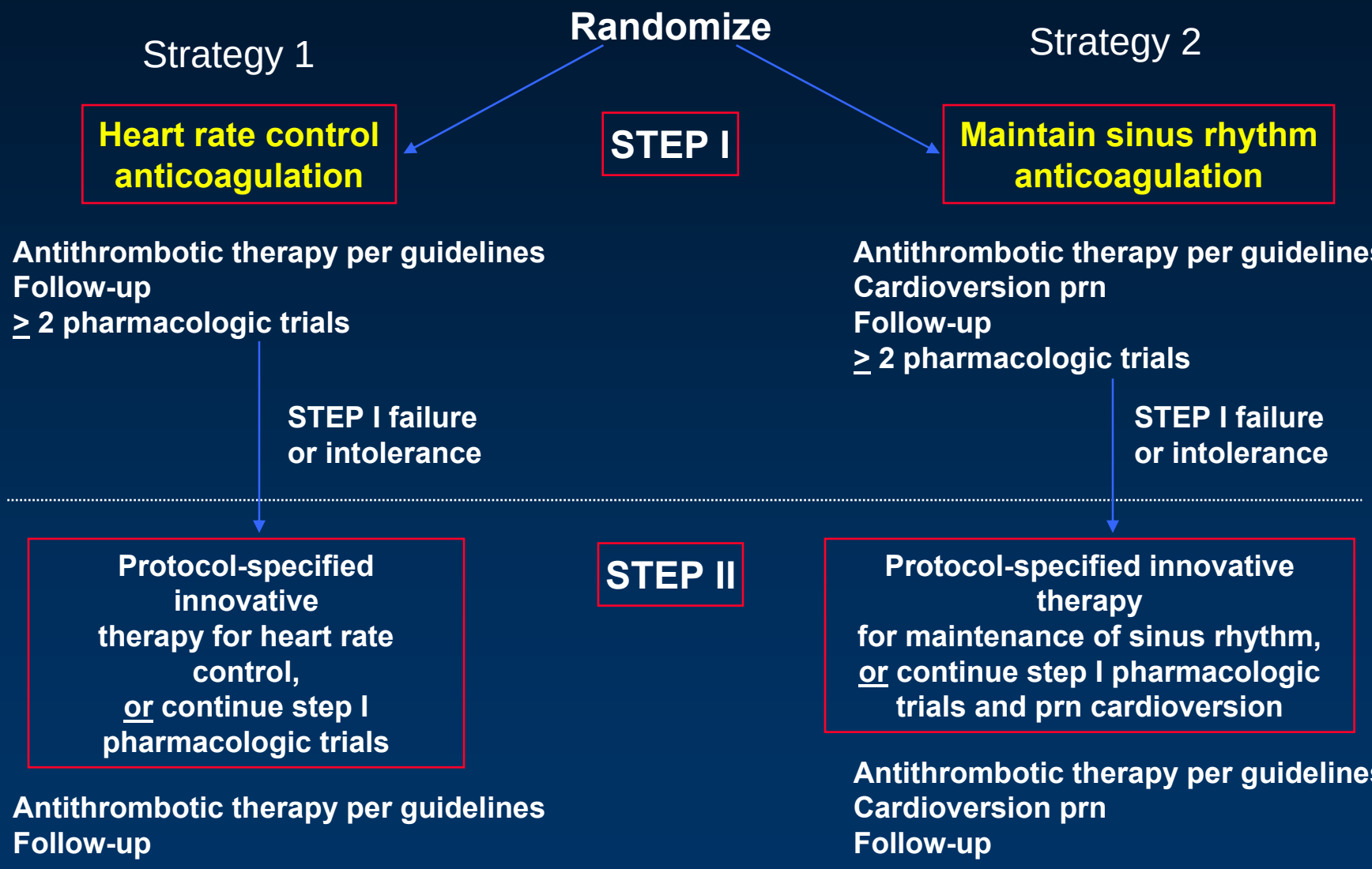
This slide highlights some of the major issues in on-therapy analyses.

Analyses in Trials

- There are also other important biases that may apply to both types of analysis.
- One, of relevance to today's symposium, is that of definition of a therapeutic failure.
- In ablation versus drug trials for AF, in general any recurrence on either limb is considered a failure, whereas in clinical practice the same may not be true.
  - If a drug changes one's pattern of AF from frequent and protracted (such as from monthly with 5 CV/yr) to rare and brief (such as 3/yr, all PAF less than 3 hrs), this would be a clinical success with drug therapy in practice but 3 recurrences in a year after ablation would usually be considered a failure by many labs.

Slide courtesy of J. Reiffel, M.D.

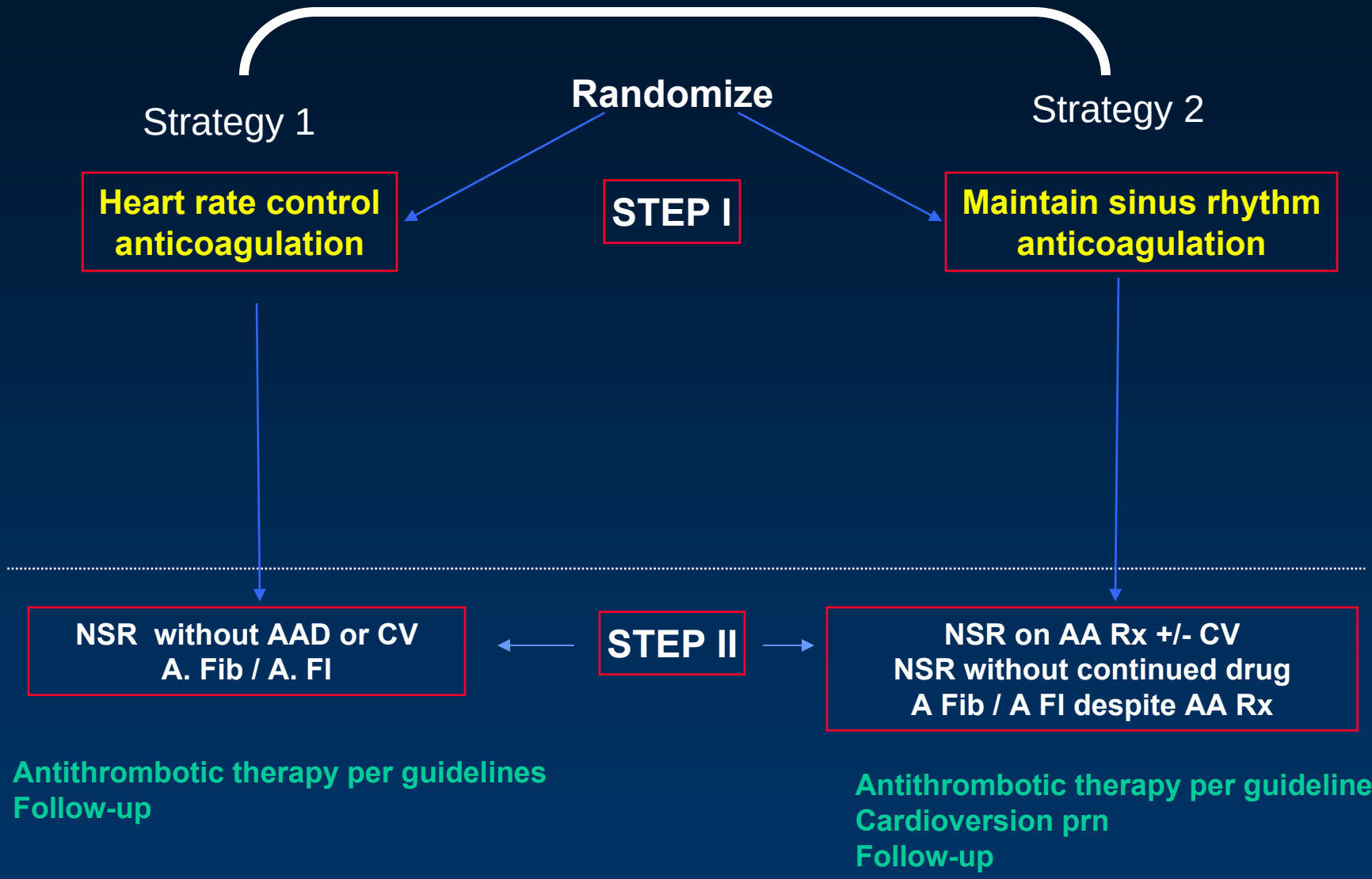
AFFIRM Study Protocol



NHLBI AFFIRM Investigators. Am J Cardiol. 1997;79:1198-1202.

Here, is an outline of the AFFIRM trial design. AFFIRM was the largest of the rate versus rhythm control trials.

Comparison by ITT analysis

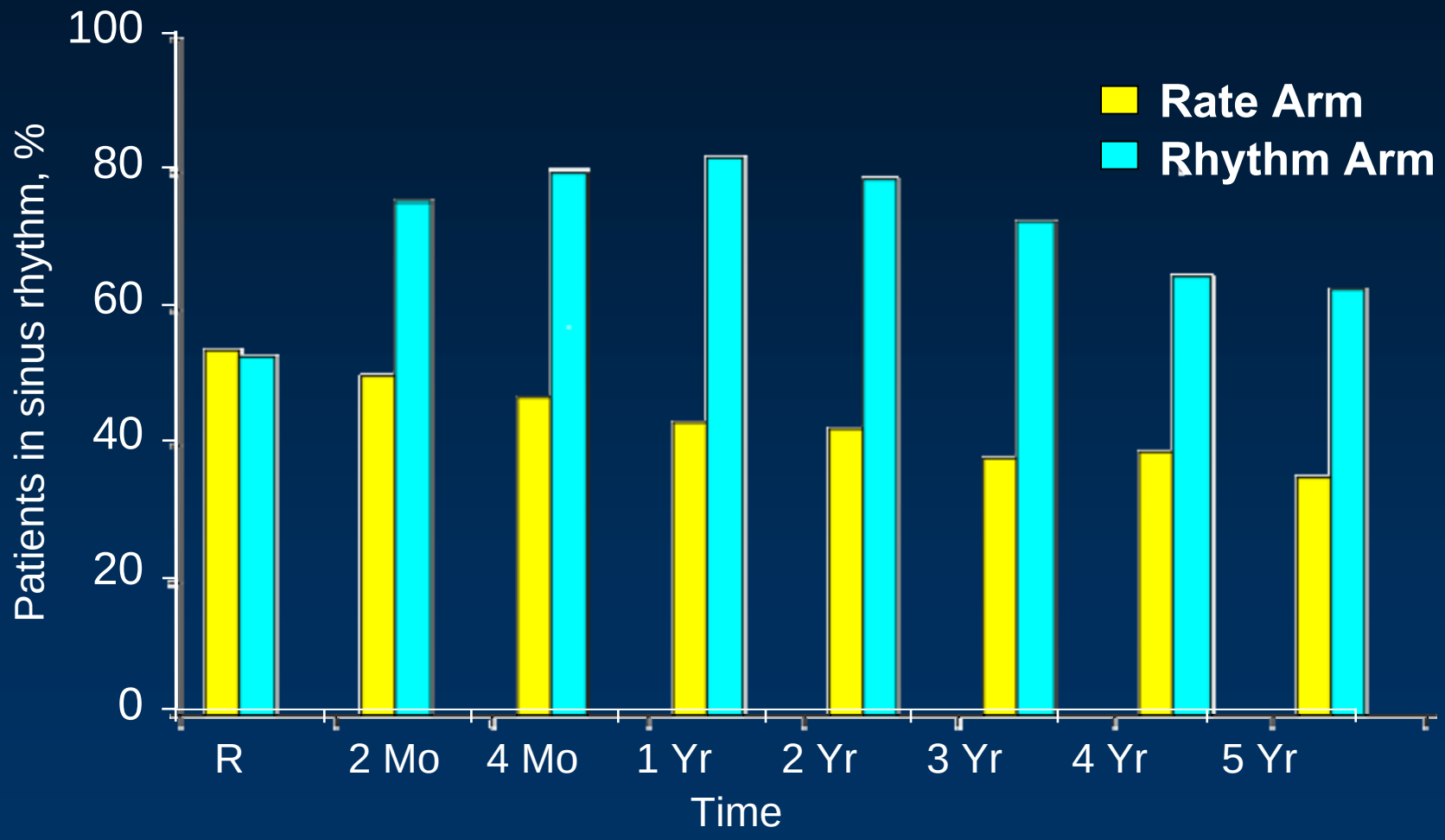


NHLBI AFFIRM Investigators. Am J Cardiol. 1997;79:1198-1202.

Slide courtesy of J. Reiffel, M.D.

Here is an outline of the ITT analysis in AFFIRM. Note that in each group, regardless of whether or not they are in sinus rhythm or in atrial fibrillation, they are analyzed according to the group assignment not according to the actual rhythm achieved or whether or not they are receiving antiarrhythmic therapy.

AFFIRM: Prevalence of Sinus Rhythm at Follow-up



Rate N:	1957	1927	1913	1831	1692	1194	710	231
Rhythm N:	1960	1945	1920	1840	1693	1213	713	262

The AFFIRM Investigators. *N Engl J Med*. 2002;347:1828-1833.

To emphasize the points in the prior slide, note that in the rate control arm a significant number of patients at each time point are in sinus rhythm rather than in rate-slowed AF. Similarly, in the rhythm control arm, a notable portion are in AF rather than in sinus rhythm.

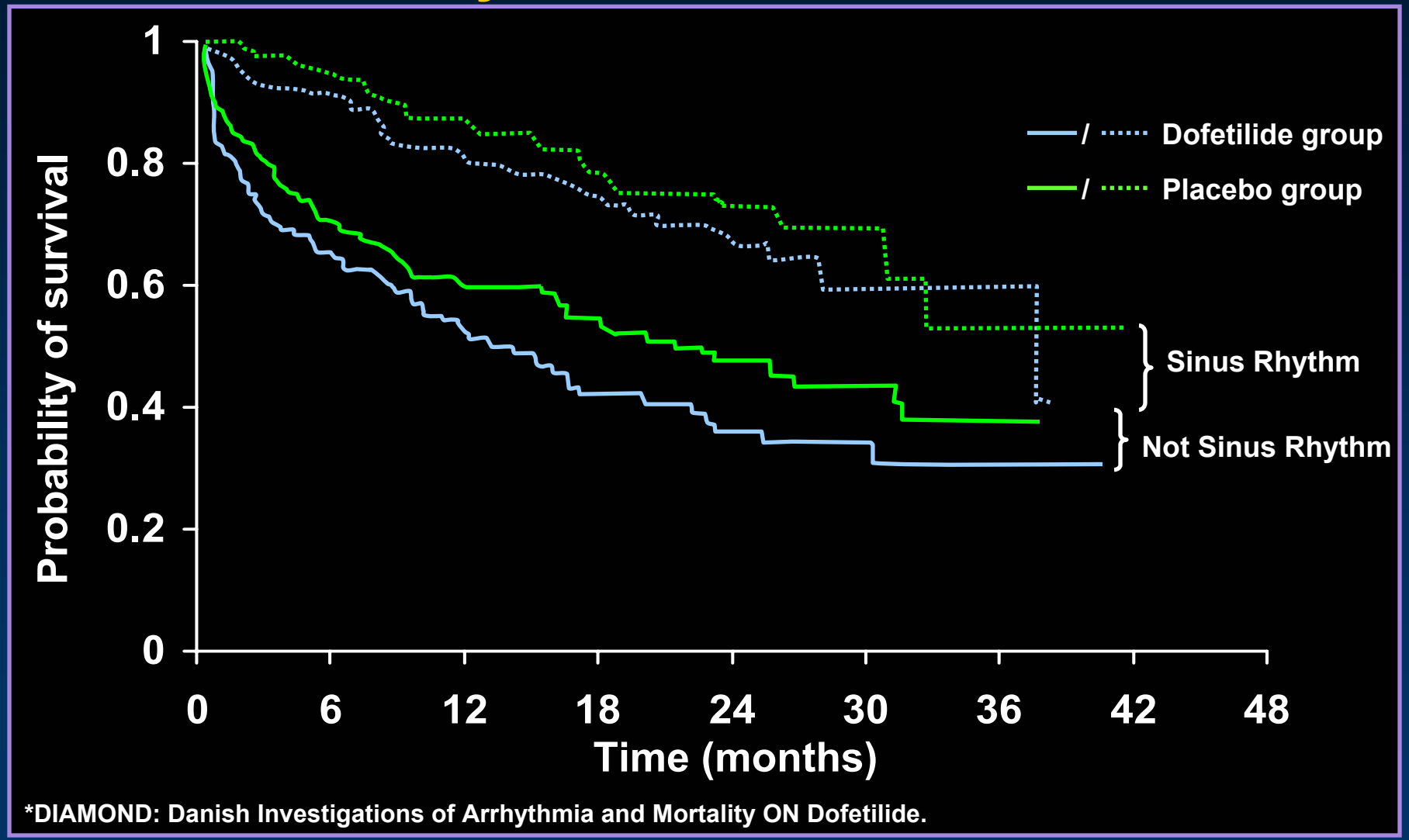
Enticing Non-ITT Observations:

- **RACE**
  - In pts successfully treated with rhythm control, the prevalence of end points was not different from those who were in AF at study end. However, the type of end point was different: *mortality*, bleeding, hospitalization for HF, and pacemaker implant *occurred less frequently with NSR. **
- **SPAF**
  - No difference in mortality, rate vs rhythm arms by ITT (10 vs 9);
  - *But, 18/19 events occurred during AF.*
- **DIAMOND AF**
  - No difference in mortality, dofetilide vs placebo by ITT;
  - But, *greater survival in pts if NSR was maintained*.
    - Relative risk 0.44 [95% CI 0.30-0.64] $P < 0.0001$
- **AFFIRM**
  - No difference in mortality, rate vs rhythm arms by ITT;
  - But, by subgroup analysis, *NSR was associated with increased survival while AADs (mostly amiodarone) were associated with off-setting increased mortality.*

* Hagens et al. Am Heart J 2005; 149:1106-11

The importance of looking at data other than just ITT analyses may be gleaned from this slide.

DIAMOND* Substudy: Survival in Patients With Reduced Left Ventricular Function in Sinus Rhythm and Atrial Fibrillation



*DIAMOND: Danish Investigations of Arrhythmia and Mortality ON Dofetilide.

Pedersen OD, et al. *Circulation.* 2001;104:292–296.

This slide depicts curves from the DIAMOND study with dofetilide; note, outcomes appear better for patients who are in sinus rhythm regardless of whether or not they are on dofetilide.

Therapeutic Indications

- There are only 2 reasons to administer a therapy to a patient:
  - To make the patient live longer
  - To make the patient feel better
- In the process we need to minimize adverse risks from our therapies.

Slide courtesy of J. Reiffel, M.D.

Therapeutic Indications

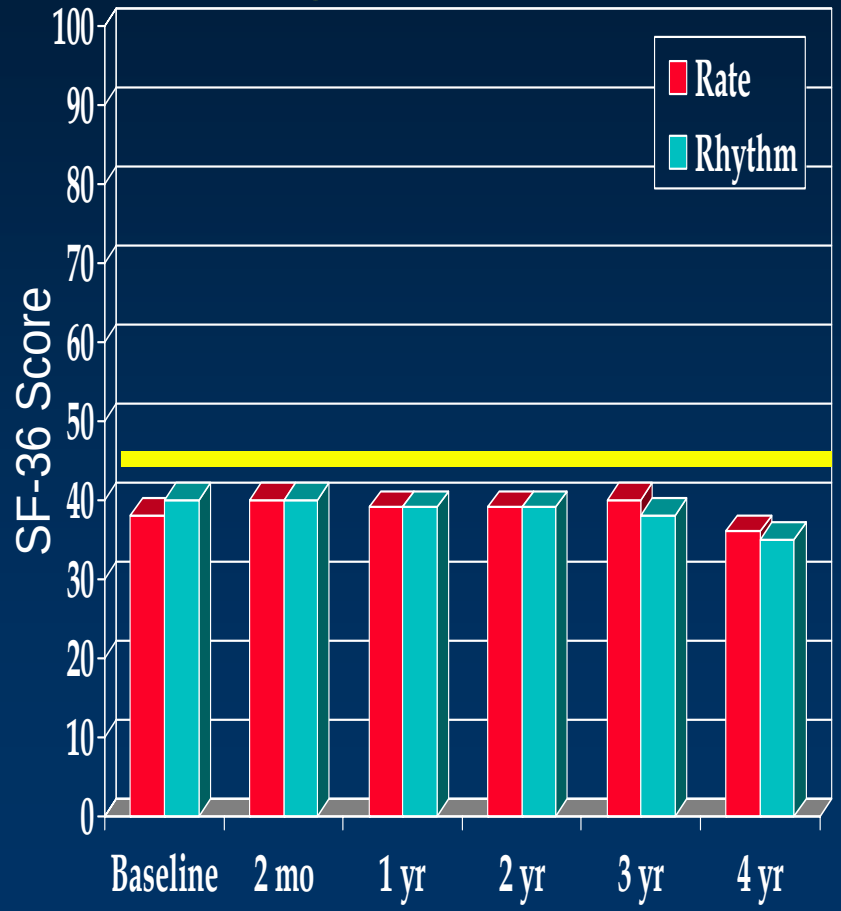
- There are only 2 reasons to administer a therapy to a patient:
  - To make the patient live longer
  - To make the patient feel better
- In the process we need to minimize adverse risks from our therapies.
- If a strategy of sinus rhythm does not increase life expectancy vs rate control in pts with AF, does it improve QOL?

Slide courtesy of J. Reiffel, M.D.

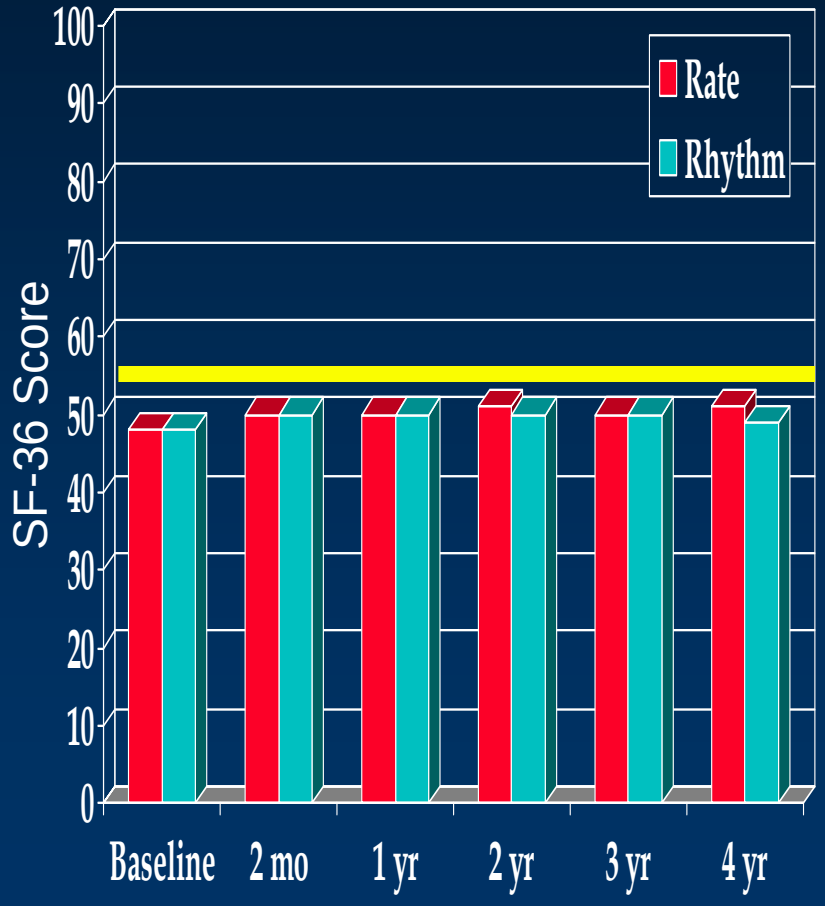
Also of importance, independent of the question as to whether pursuit of sinus rhythm will increase life expectancy in patients with AF, is how quality of life (QOL) will be affected.

AFFRIM: Quality of Life (by ITT Analysis)

Physical Function



Mental Function



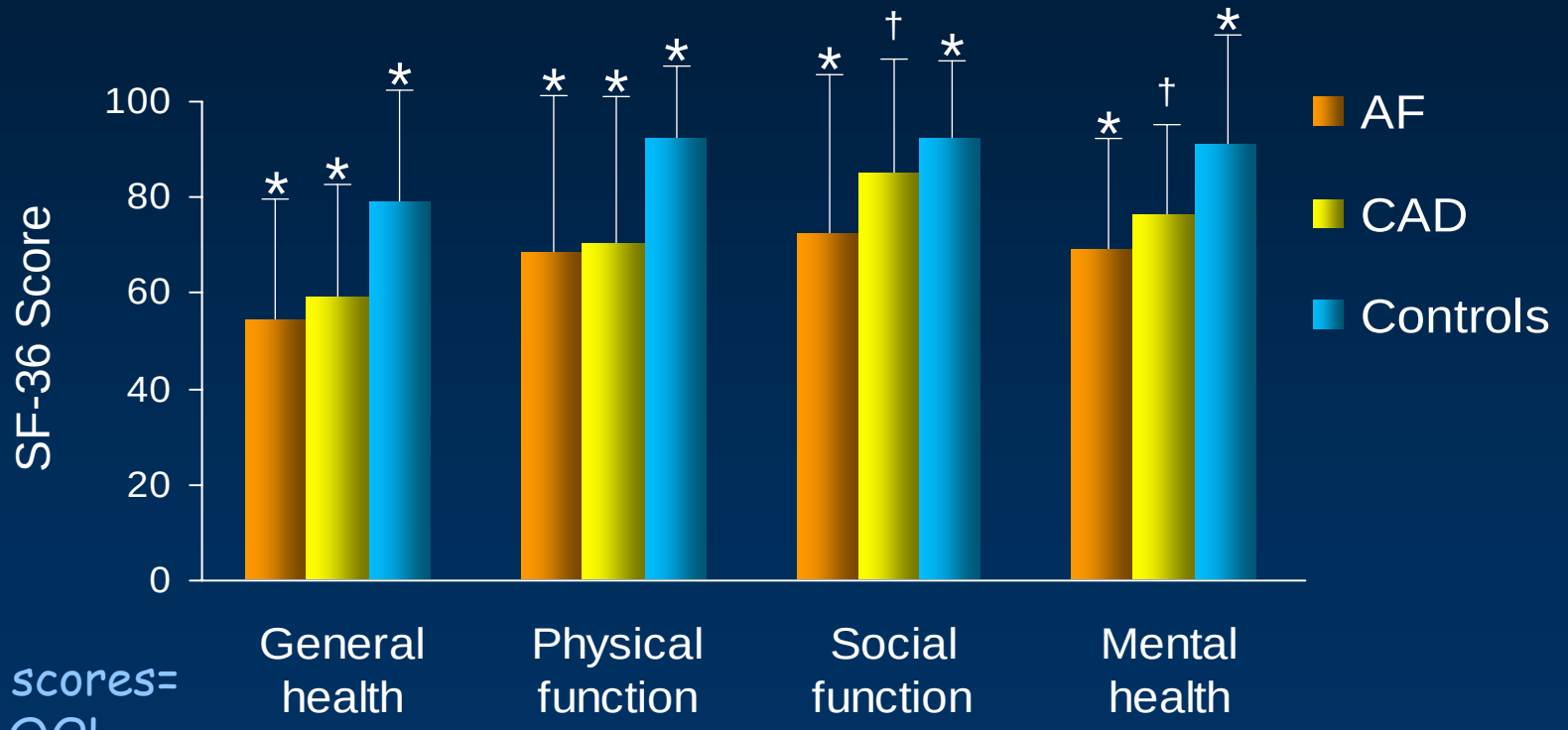
Mean general US population; no AF; Age 65-74

AFFIRM Investigators. Am Heart J 2005;149:112

Some studies, such as AFFIRM have not revealed significant differences in QOL between sinus rhythm and AF. However, this has not usually been the case. Rather, as the following slides suggest, QOL is generally poorer in AF than in NSR and it usually improves if NSR can be restored and maintained.

Atrial Fibrillation Commonly Affects QOL Adversely

AF vs CAD vs Healthy Controls



Higher scores= better QOL

*p < 0.05, patients with AF compared to healthy controls

†p < 0.05, patients with AF compared to those with CAD

Dorian et al. J Am Coll Cardiol.

This slide summarizes the results of a study comparing QOL in patients with intermittent AF and coronary artery disease (CAD) patients referred to tertiary care and healthy controls.

Patients with AF are as impaired or more impaired than CAD patients.1

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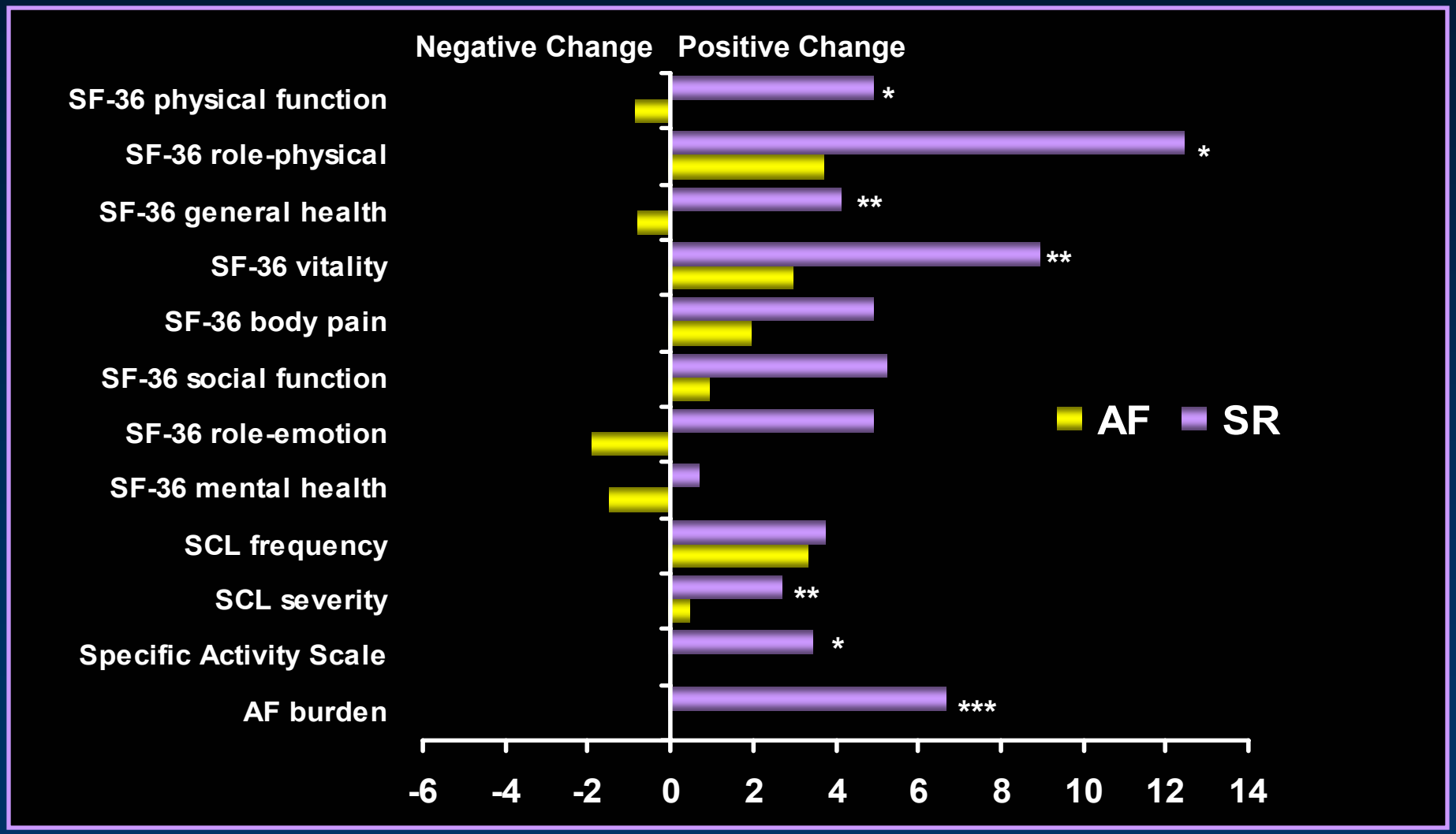
1. Dorian P, Jung W, Newman D, et al. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: Implications for the assessment of investigational therapy. J Am Coll Cardiol (in press).

Sinus Rhythm Associated Improved Quality of Life in Symptomatic AF Patients at 8 Weeks



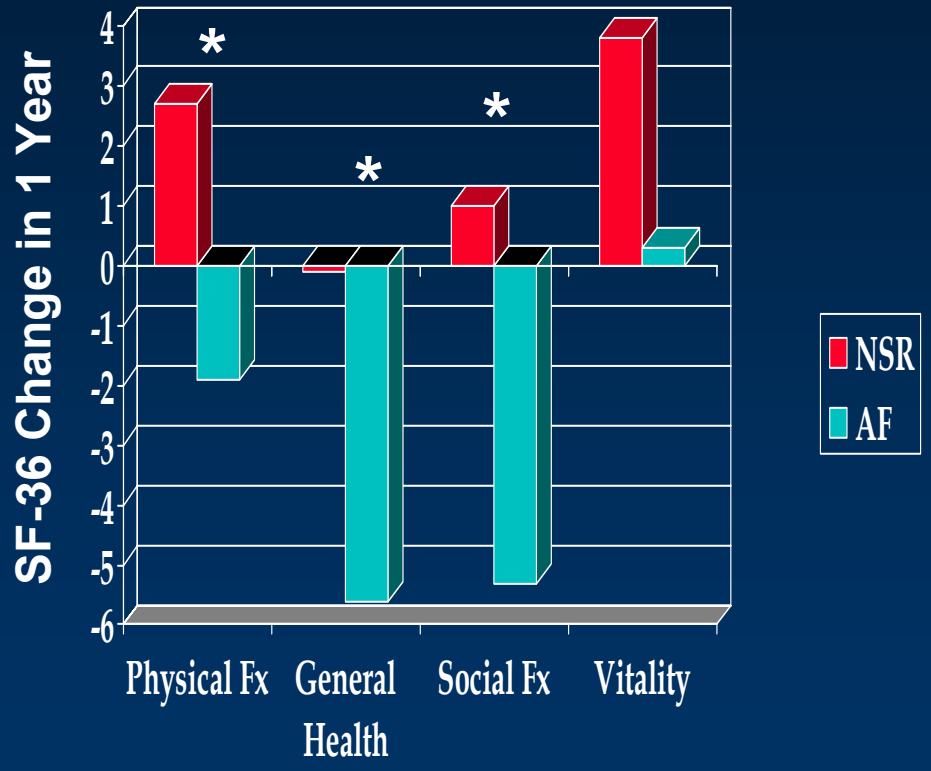
* *P* ≤ .05; ** *P* ≤ .01; *** *P* ≤ .001.

Singh SN, Tang C, Singh BN et al., *JACC*. 2006;48:721–730.

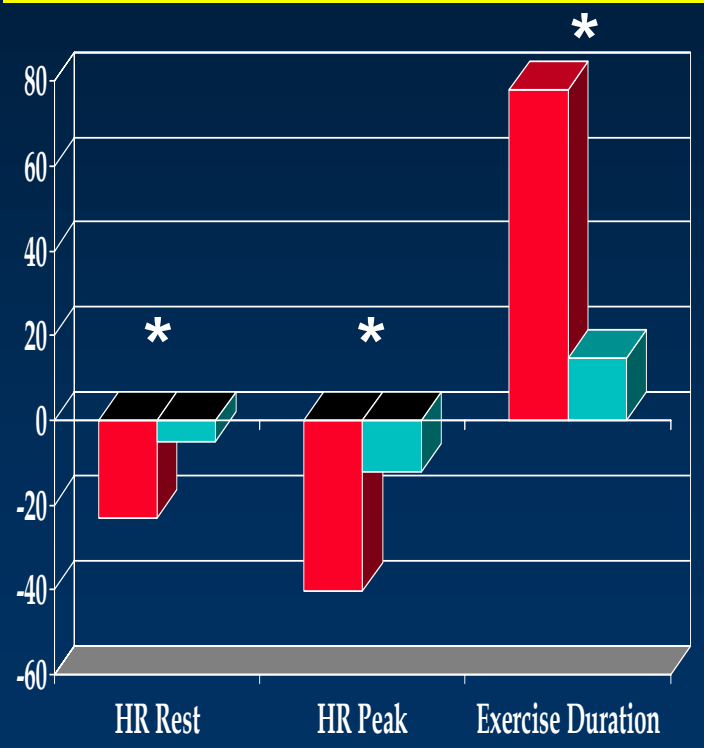
QOL in the SAFE-T study was impaired in AF as compared to NSR.

Effect of Maintaining Sinus Rhythm on Quality of Life and Exercise Capacity: SAFE-Trial

Quality of Life



Exercise Parameters

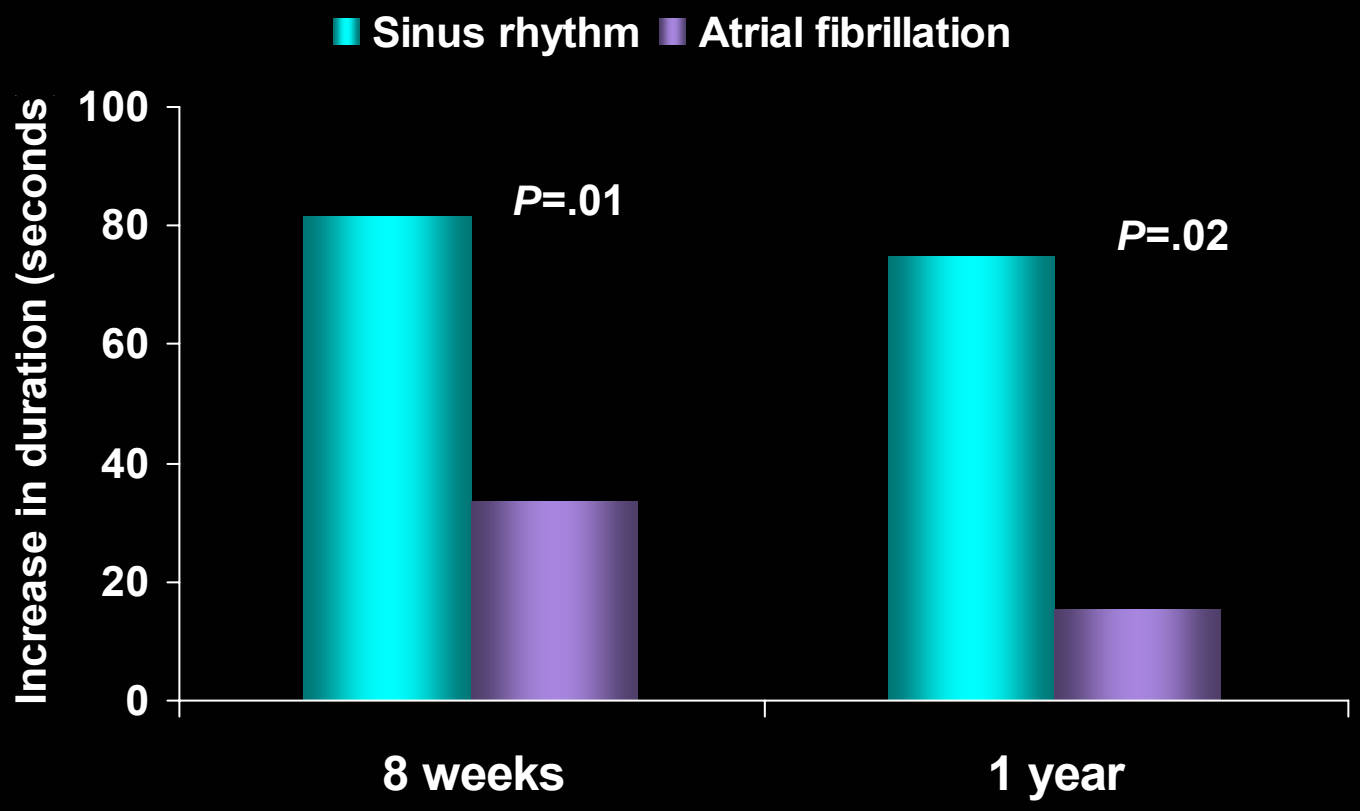


*p<0.05

Singh BN, et al. N Engl J Med 2005; 352: 1861-1872.

Additional QOL data from the SAFE-T trial.

Maximal Exercise Duration During Sinus Rhythm vs Atrial Fibrillation

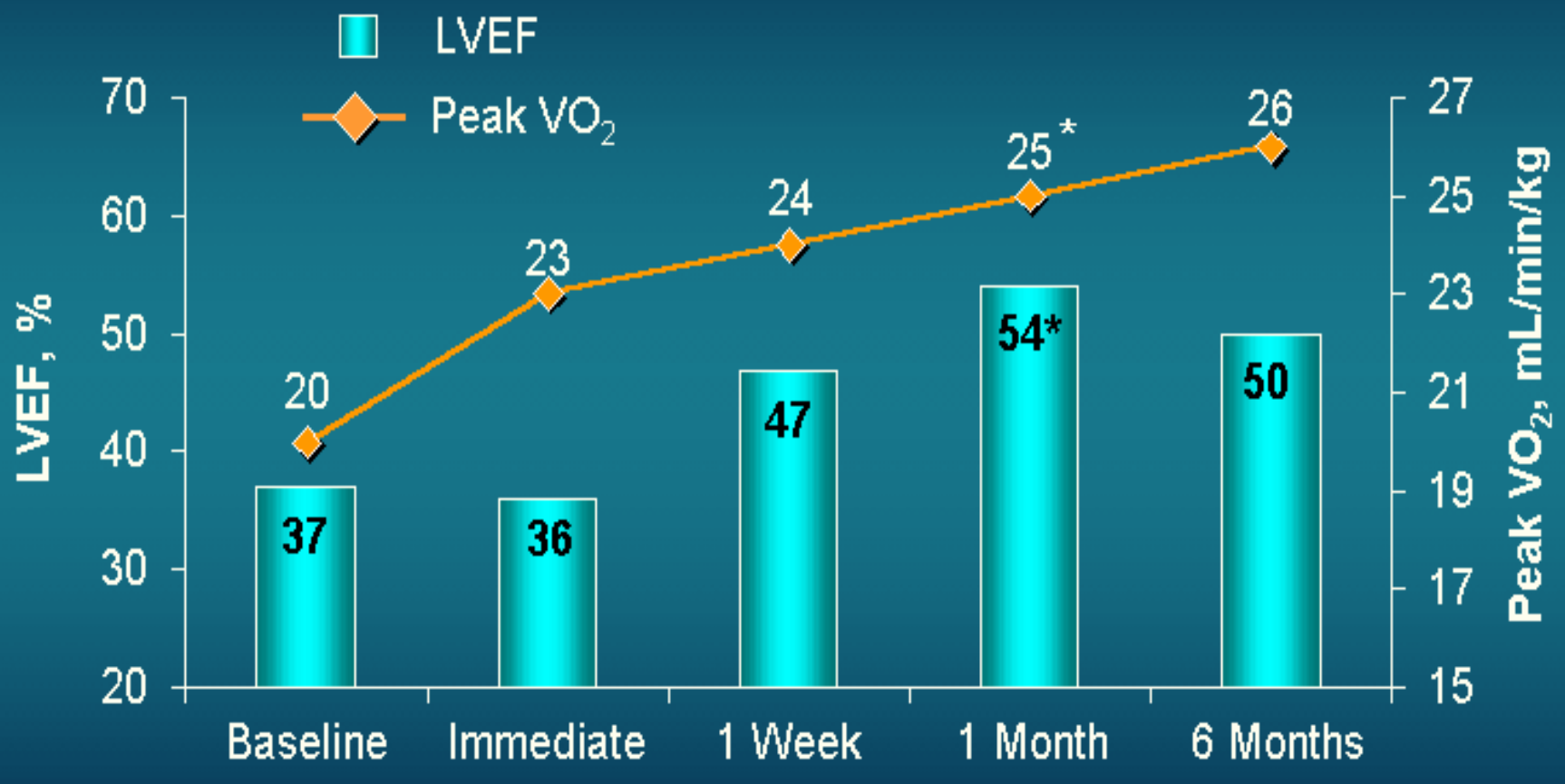


Singh SN, et al. *J Am Coll Cardiol*. 2006;48:721–730.

Exercise duration appears to be longer in NSR than in AF.

Restoration of Sinus Rhythm Can Improve it.

Hemodynamics and Functional Benefits



* *P*<.05 vs baseline.

N=8 patients.

Van Gelder et al. *Am J Cardiol*. 1993;72:560-566.

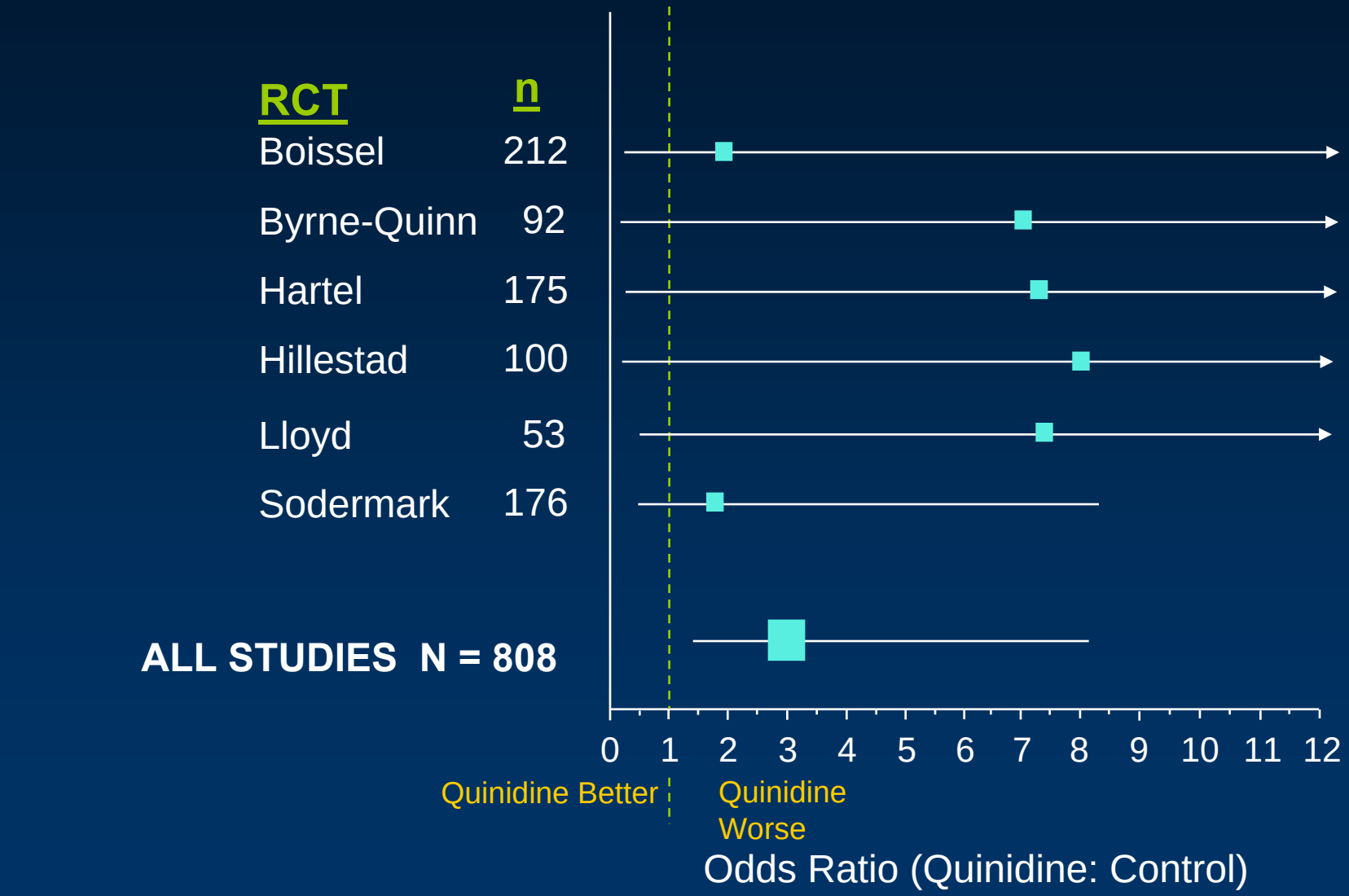
Restoration of NSR can improve hemodynamic and functional benefits in the AF patient.

Pursue NSR or Leave in AF?

- If sinus rhythm is associated with improved QOL as compared with atrial fibrillation, why not pursue sinus rhythm in everyone even if there is no survival benefit?
- Because of the competing risks, costs, etc. associated with our therapies.
- Thus, we must apply our therapies selectively !

Slide courtesy of J. Reiffel, M.D.

All Cause Mortality for Patients Treated with Quinidine Compared to Control



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

Ventricular proarrhythmic mortality risk was evident with the use of quinidine, a class IA antiarrhythmic agent.

Proarrhythmia from Antiarrhythmics Used in SPAF Study

	Number of Patients	Arrhythmic Deaths	Adjusted Risk Hazard
All patients	1,307	28	2.1
Patients with definite CHF	239	12	5.8
Patients without definite CHF	1,068	16	0.83

Adapted from Flaker GC. J Am Coll Cardiol. 1992;20:527-532.

Essentially all AADs were Class I agents.

Proarrhythmia from antiarrhythmics, esasentially all were class I agents, was increased in the SPAF study when heart disease, as manifest by CHF, was present. This is consistent with later trials of class I agents in the presence of significant structural heart disease, such as CAST.

Estimated 1-Year Mortality (Point Estimate, 95% C.I.)

	CAST Enc + Flec	CAST Placebo	Comparison SVA	Comparision Expected*	Flecainide SVA	Flecainide Expected*
Total N=	720	725	165	-	238	-
1 Year N=	272	286	144	-	93	-

Exponential Model

* Based on age, race and sex specific mortality rates in the United States in 1980

Adapted from: Pritchett E, Wilkinson W. *Am J Cardiol.* 1991;67:976-980.

Data contrasting the experience in the CAST trial with the experience of antiarrhythmic drugs for supraventricular arrhythmias in the DUKE database. Note that with flecainide, the same drug used in CAST, when it is used for SVA (almost all without significant SHD), risk was essentially absent.

Clinical Trials in SHD Patients

Increased mortality:

Class IC	**Post MI (CAST)**
Class I	**Post MI (Teo et al)**

No change or decreased mortality:

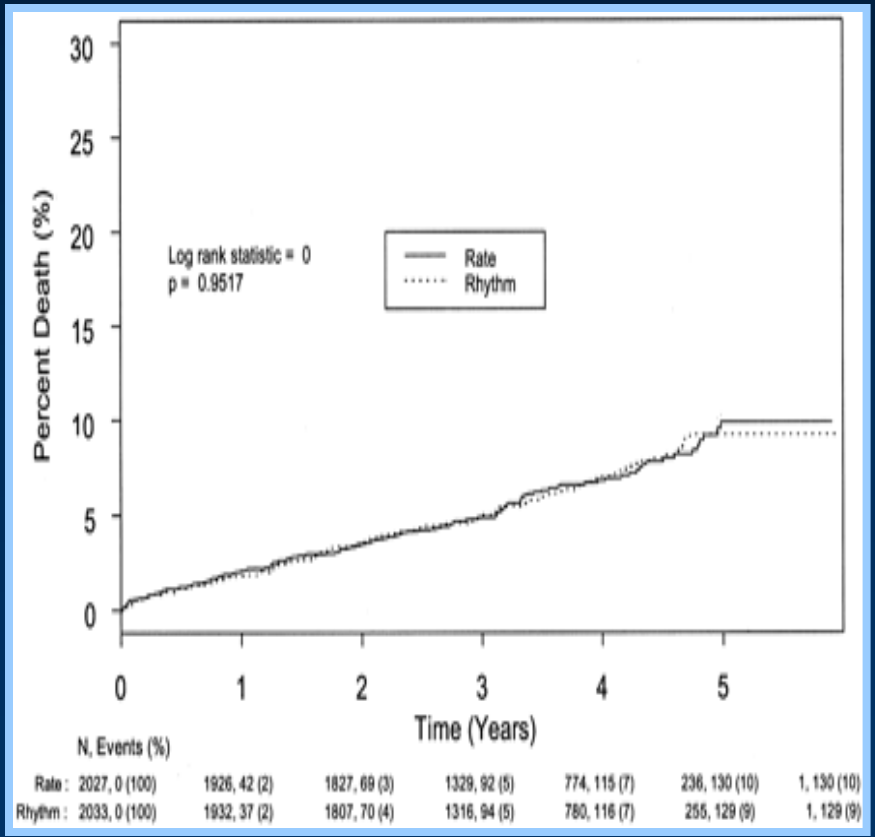
Amiodarone	**Post MI (EMIAT, CAMIAT)**
	CHF (CHF-Stat, GESICA)
Sotalol	**Post MI (Julian et al)**
Dofetilide	**CHF (DIAMOND)**
Azimilide	**Post MI (ALIVE)**

Slide courtesy of J. Reiffel, M.D.

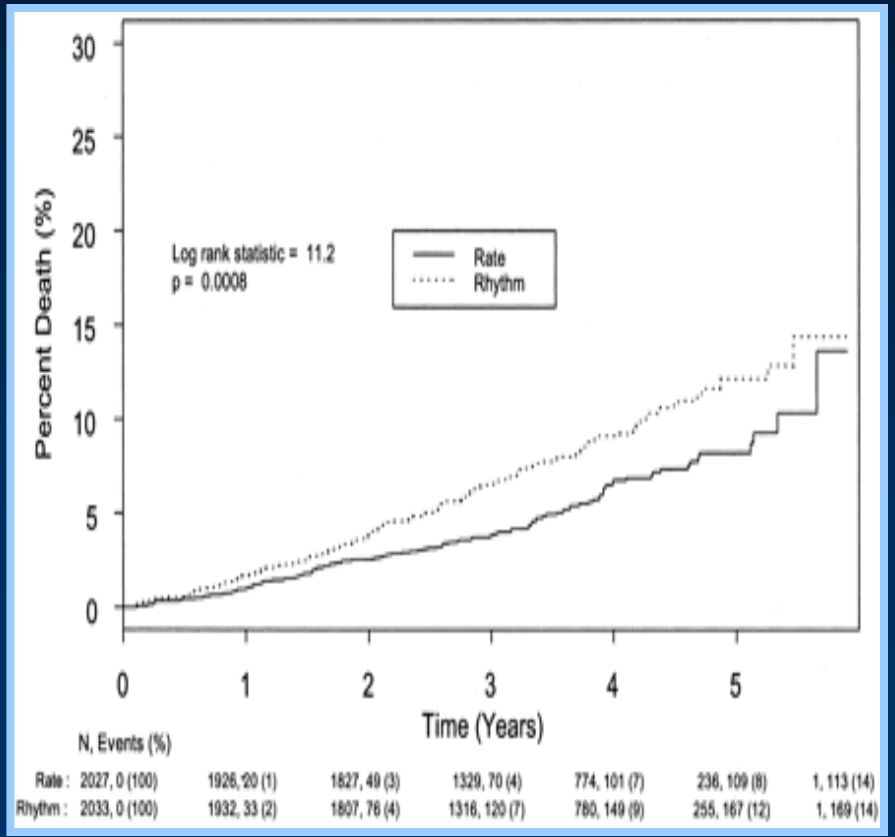
In contrast to the proarrhythmic mortality risks seen with class I antiarrhythmics in the presence of significant SHD, there appears not to be an excess risk when class III antiarrhythmics are used in such subjects (especially when appropriate precautions are taken to minimize the risk of TdP as is done in the well performed clinical trials listed in this slide).

Cause-Specific Mortality in the AFFIRM Trial

Cardiac Mortality



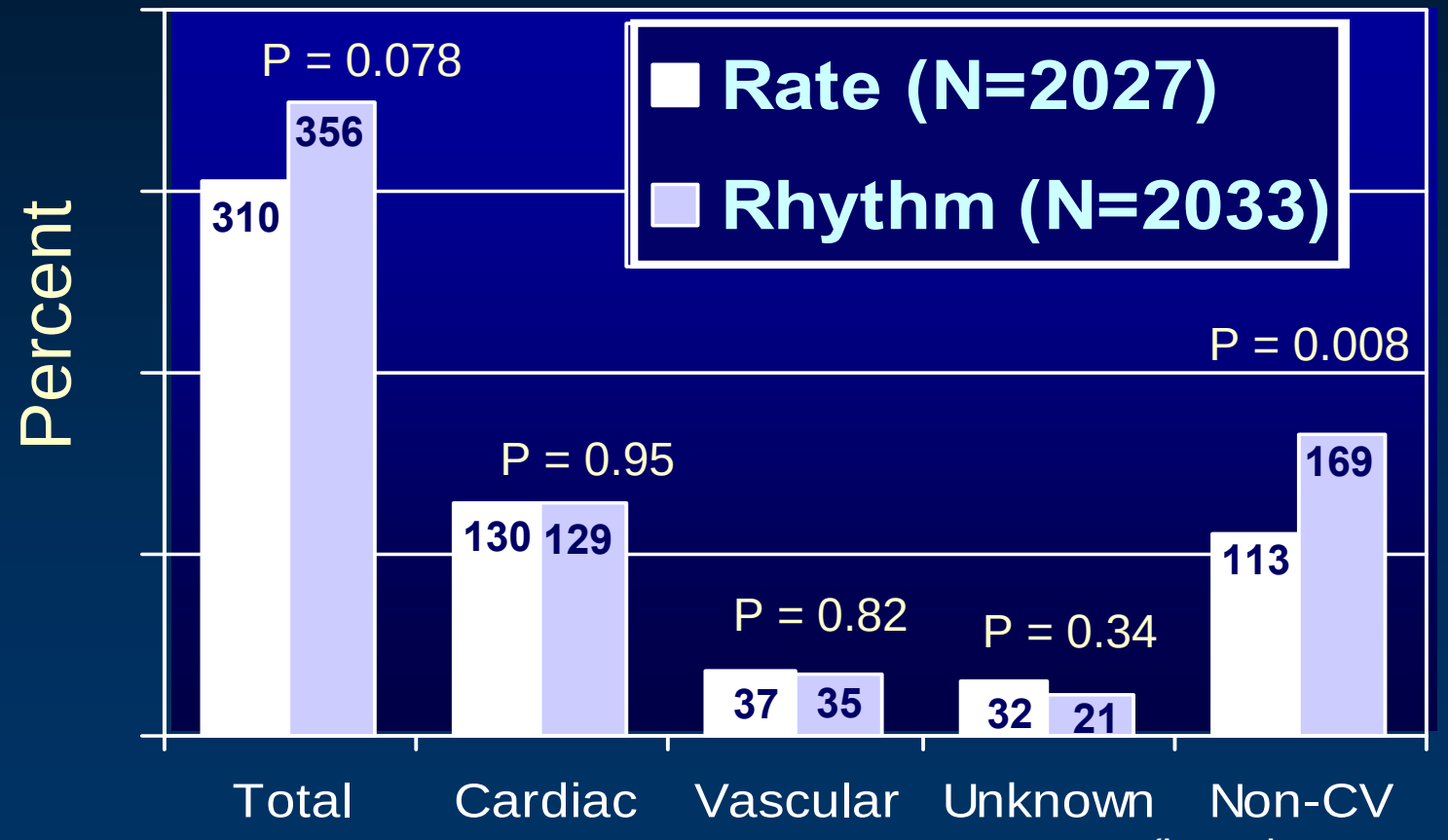
Non-Cardiovascular Mortality



Steinberg JS, et al. Circulation 2004; 109: 1973-1980.

Note, this slide demonstrates that all mortality risks associated with antiarrhythmic drugs are not the result of ventricular proarrhythmia. Rather, non-cardiac but serious toxicity can also be a fatality factor. In the AFFIRM trial, amiodarone was associated with such risks, as is further depicted on the next side.

AFFIRM – Cause-Specific Mortality



Circulation 2004;109:1973

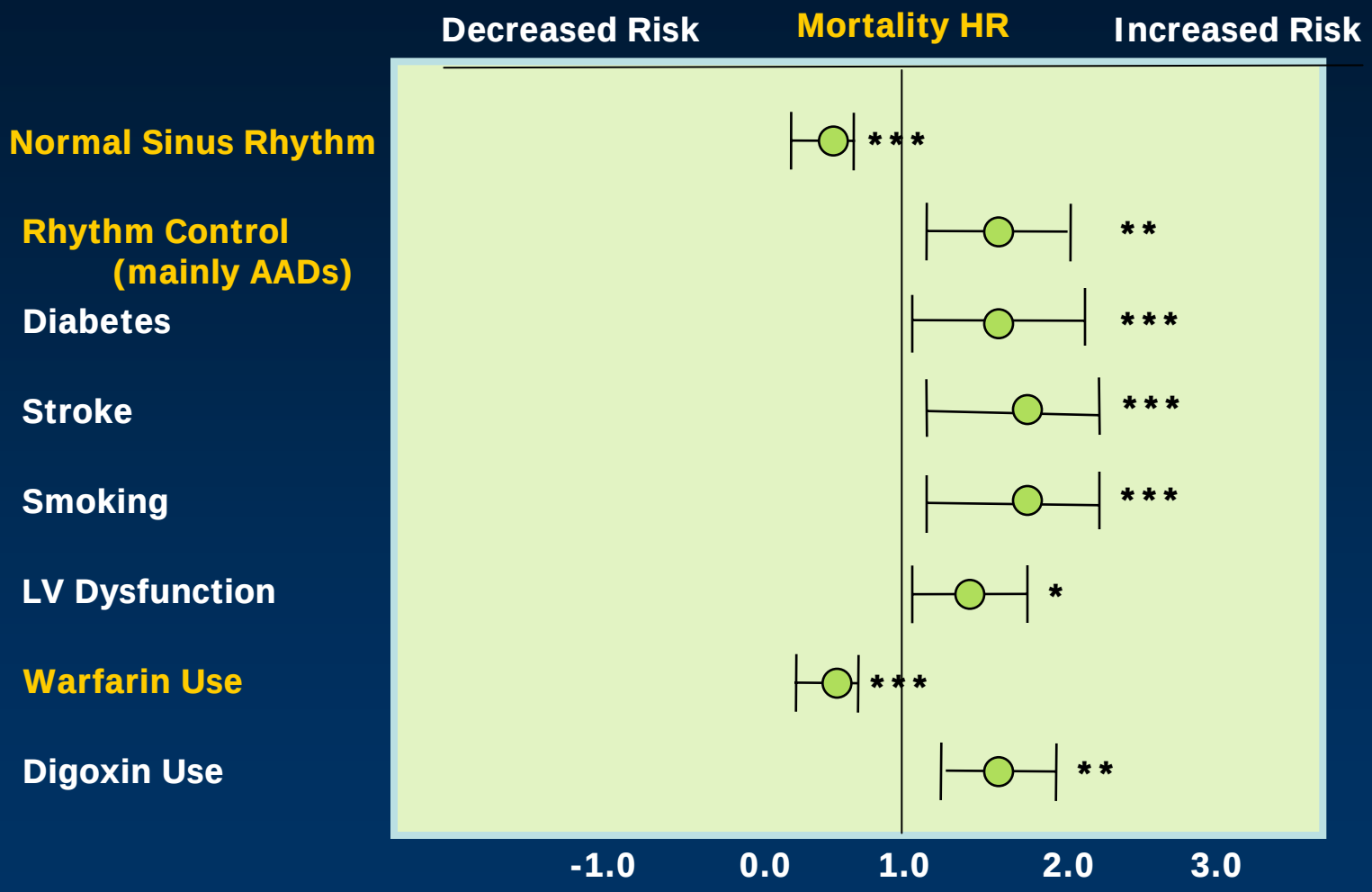
The agent used overwhelmingly in the AFFIRM trial was amiodarone, which was associated with an excess risk of non-cardiovascular mortality, including an excess risk of cancer (that, in retrospect, has now been reported in other trials as well).

“Some More Food For Thought”:

- With better/safer drugs and/or procedures, the results of clinical trials might be different.
- So, too, might be the case if we could actually maintain NSR, rather than just deal with the intention to treat approach of a strategy.

Slide courtesy of J. Reiffel, M.D.

NSR Is Associated With Better Survival – AADs are not!

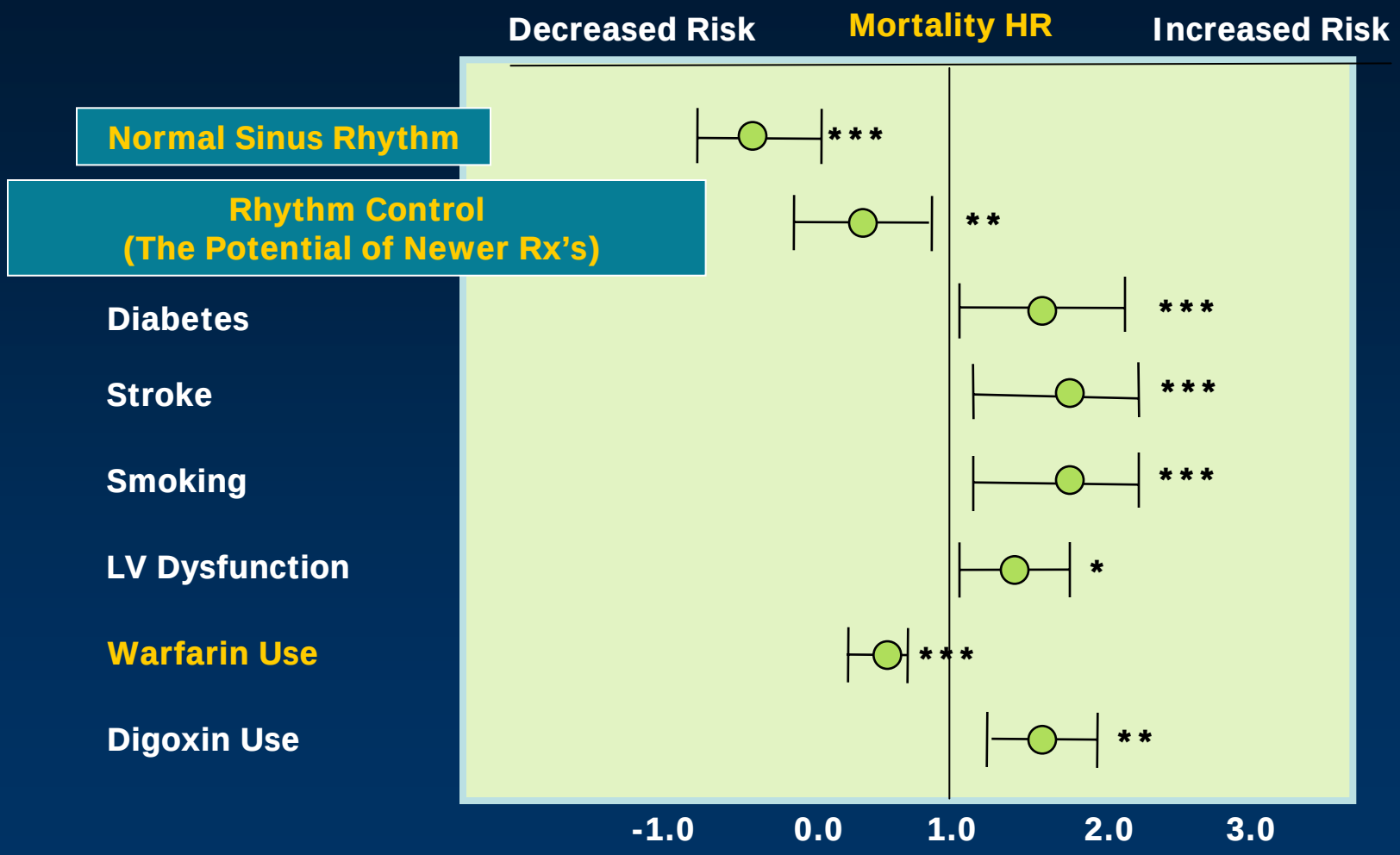


**P*<.01; ***P*<.001; ****P*<.0001

AFFIRM Study Epstein et al. *Circulation.* 2004;109:1509-1513.

In AFFIRM, sinus rhythm was associated with improved survival. However, the use of antiarrhythmic therapy to achieve it was associated with an off-setting mortality risk. If safer drugs and procedures were to become available, the results might look like the hypothetical ones depicted in the next slide.

The Hope of Newer AADs



*P<.01; **P<.001; ***P<.0001
AFFIRM Study
Epstein et al. *Circulation.* 2004;109:1509-1513.

Slide courtesy of J. Reiffel, M.D.

Future Therapies

- **Currently under development are:**
  - **New multichannel-blocking derivatives of amiodarone, such as dronedarone, which appear in trials to date not to carry the toxicity profile of amiodarone,**
  - **“Atrial specific” drugs that block channels important in atrial electophysiology, especially in the “remodeled” atria present after a period of atrial fibrillation, such as vernakalant,**
  - **And agents with other novel mechanisms of action.**
- **Also under development are:**
  - **Evolving approaches to ablation, such as using pathophysiologic or autonomic targets in addition to anatomic markers, that may increase procedure efficacy,**
  - **And new imaging methods and energy sources that may reduce procedure lengths and/or duration.**

If new drugs and/or procedures are as effective yet safer and better tolerated than current approaches, the enthusiasm for and benefits of pursuing sinus rhythm in the patient with AF will likely increase.

The Bottom Line

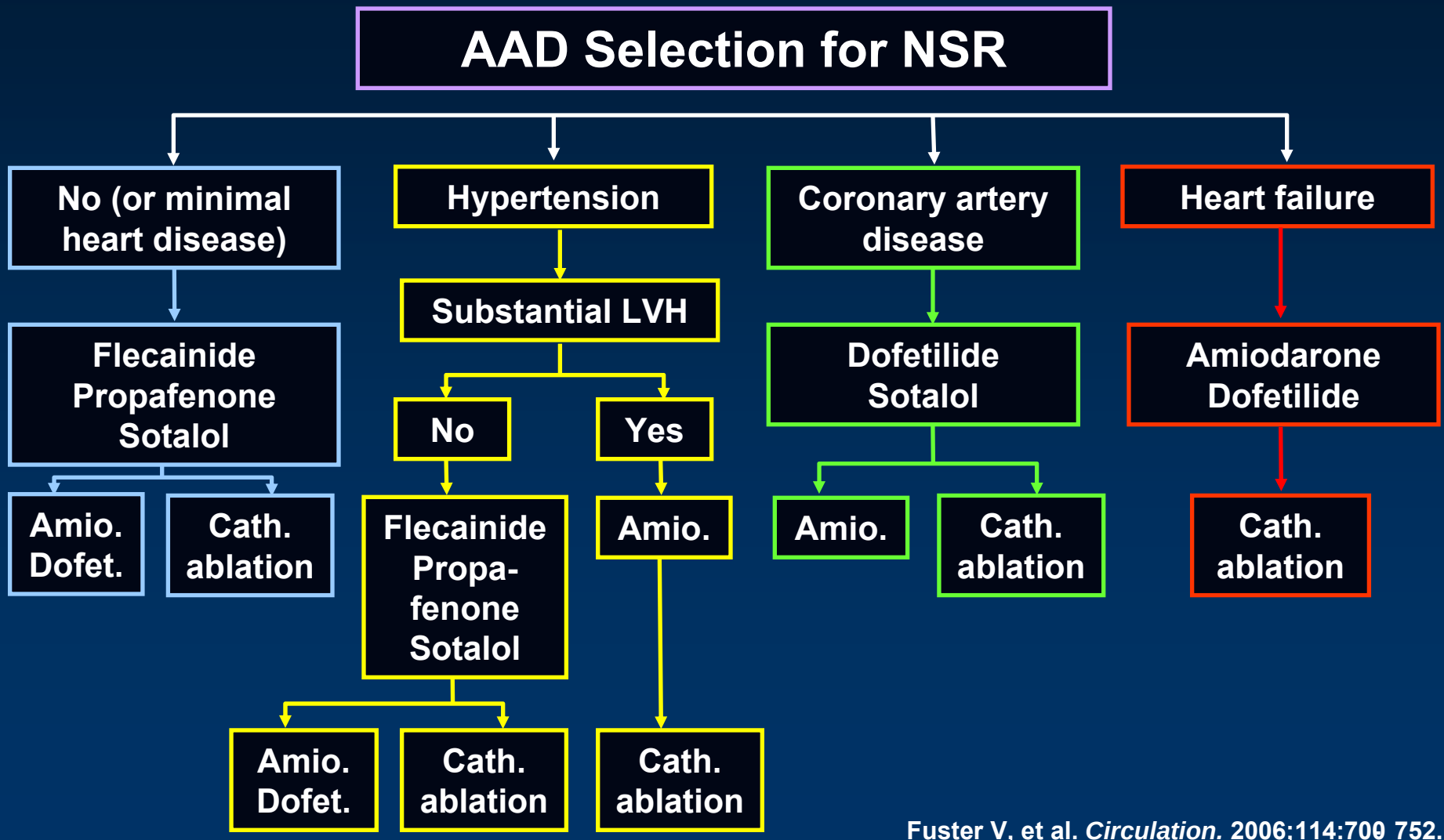
- We need to properly identify pts who require NSR
  - Such as:
    - First episode
    - Infrequent episodes with PRN therapy
    - Symptomatic AF despite rate control
    - Younger pts without SHD where drug-selection is wider
- We need to dissuade physicians from administering proarrhythmic and/or toxic agents as opposed to achieving sinus rhythm.
  - Our therapies may have risks that exceed the potential benefits of sinus rhythm in some patients.
- We do not need to pursue sinus rhythm just for its own sake.
- We need to consider the risk/efficacy balance of each new therapy as they become available.

Slide courtesy of J. Reiffel, M.D.

The “bottom line” with our current therapies is depicted in this slide.

ACC/AHA/ESC Practice Guidelines 2006

Maintenance of Sinus Rhythm

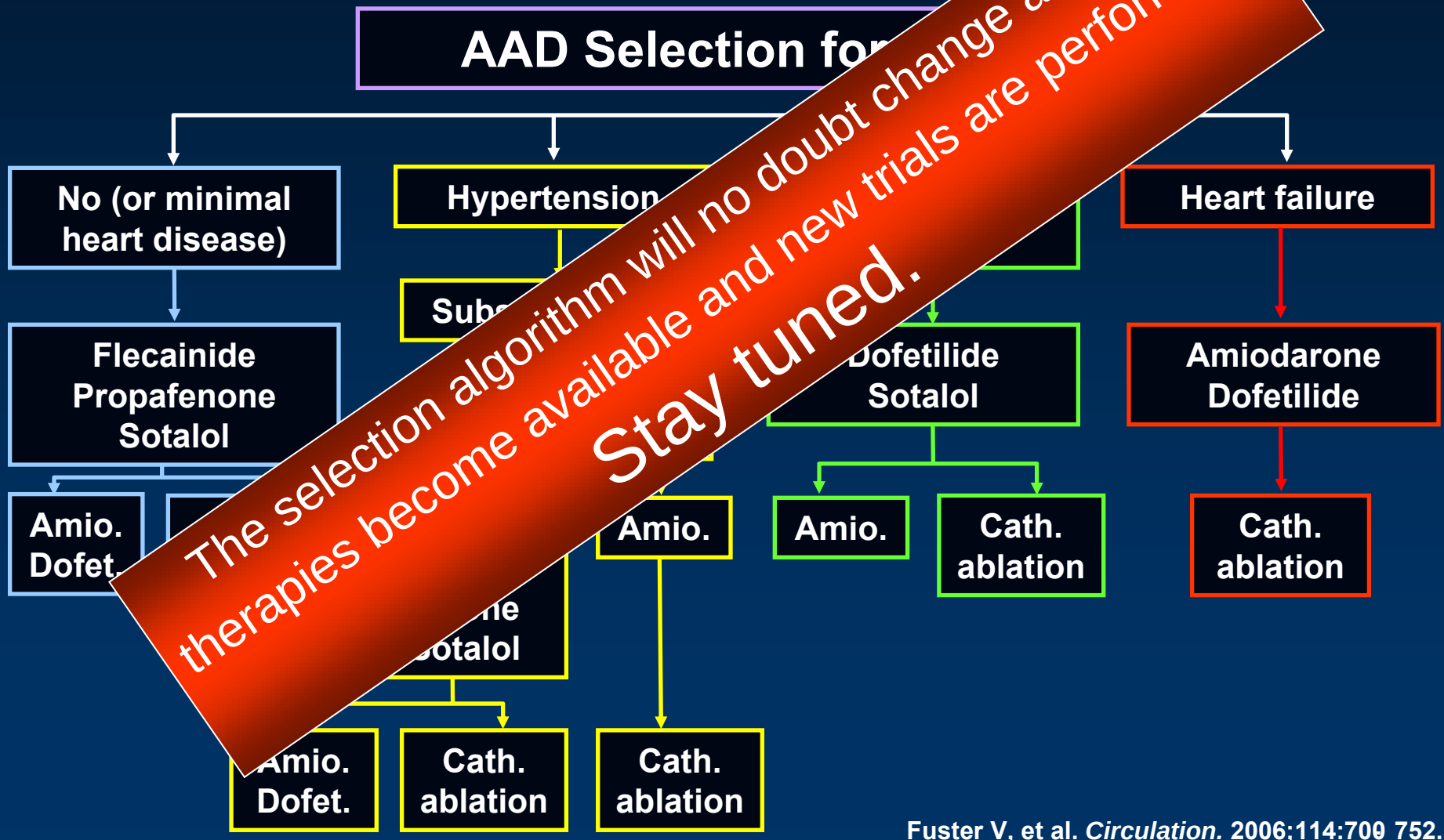


Fuster V, et al. *Circulation.* 2006;114:709 752.

Here is the current approach to antiarrhythmic drug (AAD) selection for the maintenance of NSR in patients with AF. It is stratified so that risk is minimized, by selecting an AAD and/or procedure sequence according to the type of heart disease present.

ACC/AHA/ESC Practice Guidelines 2006

Maintenance of Sinus Rhy



Fuster V, et al. *Circulation.* 2006;114:709 752.

As new drugs and procedures become available, if their risks are lower than those associated with our current therapies, this algorithm has the potential to change significantly, as does the benefit/risk profile of pursuing sinus rhythm.