Updates in Heart Failure: Ivabradine and Sacubitril/Valsartan

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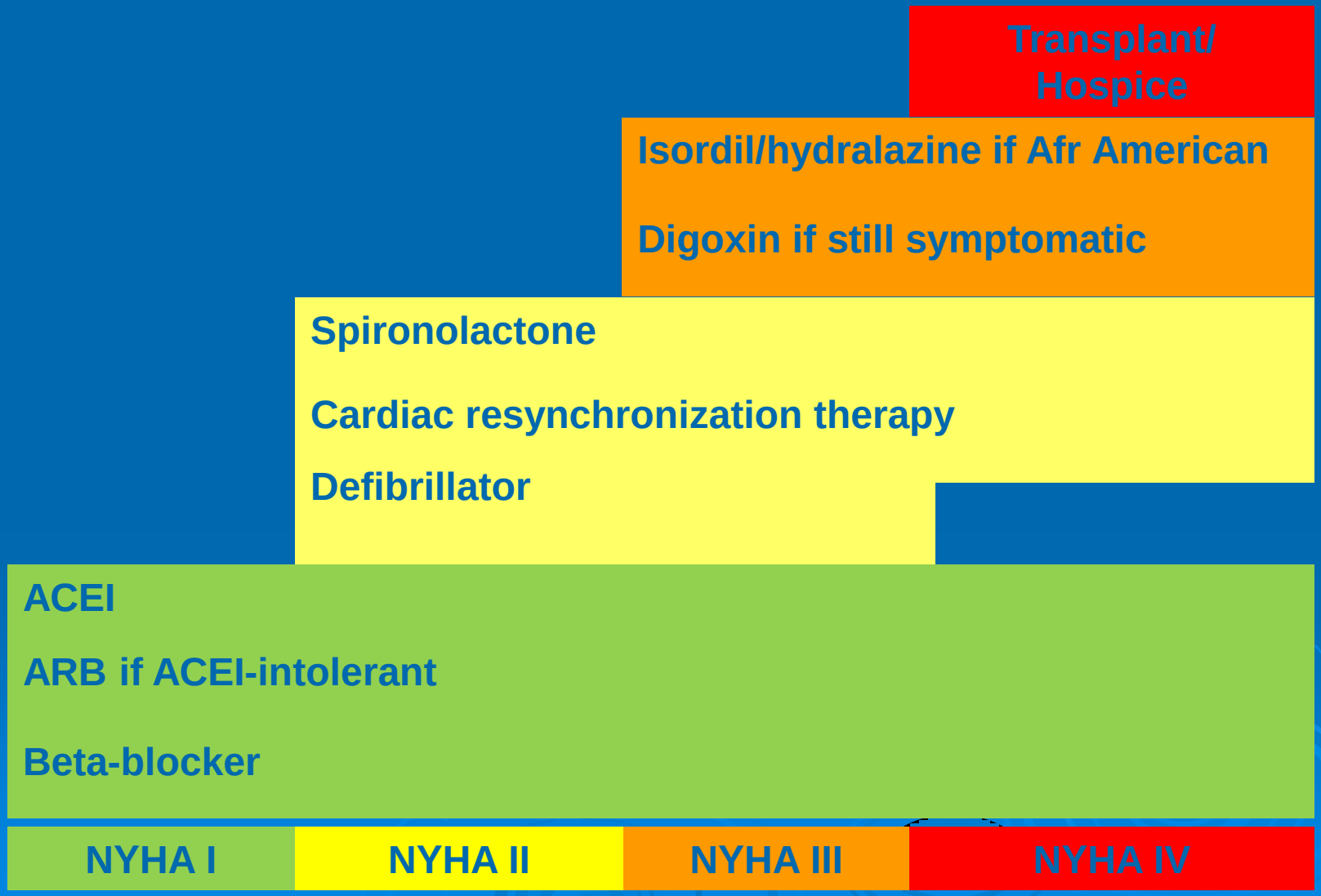
Disclosure Information

I will not discuss off label use or investigational use of drugs or devices in my presentation.

I have no financial relationships to disclose.

The Old Paradigm

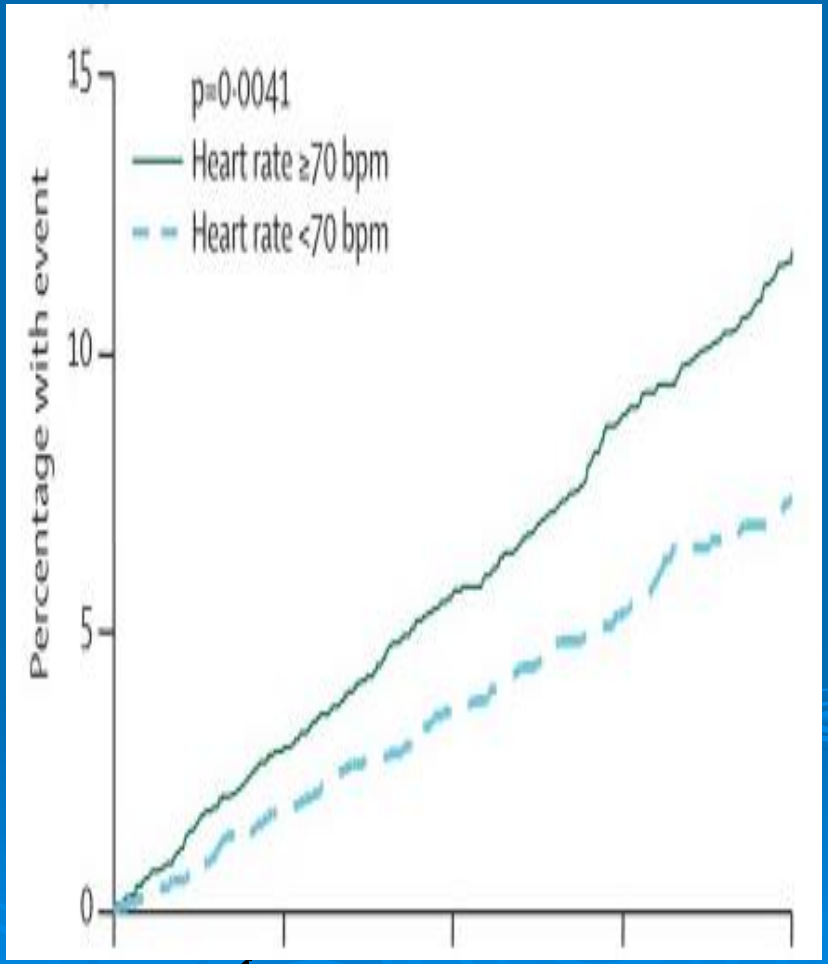


Beta-blockers

Trial	Entry criteria	Number pts/ duration/ drug	Mortality
CIBIS-II *Lancet* 1999	NYHA III-IV and EF < 35%	2647 pts/ 1.3y Bisoprolol	↓ 32%
MERIT-HF *JAMA* 2000	NYHA II-III and EF < 40%	3991 pts/ 1y Metoprolol XL	↓ 19%
COPERNICUS *NEJM* 2001	NYHA IV and EF < 25%	2289 pts/ 10.4m Carvedilol	↓ 35%
CAPRICORN *Lancet* 2001	MI 3-21d, EF < 40%, on ACEI	1959 pts/ 1.3y Carvedilol	↓ 23%
COMET *Lancet* 2003	NYHA II-IV and EF < 35%	3029 pts/ 4.8y Carved vs metop	↓ 17% in carvedilol Metop BID i/o QD XL

Lower Heart Rate = Better Outcomes

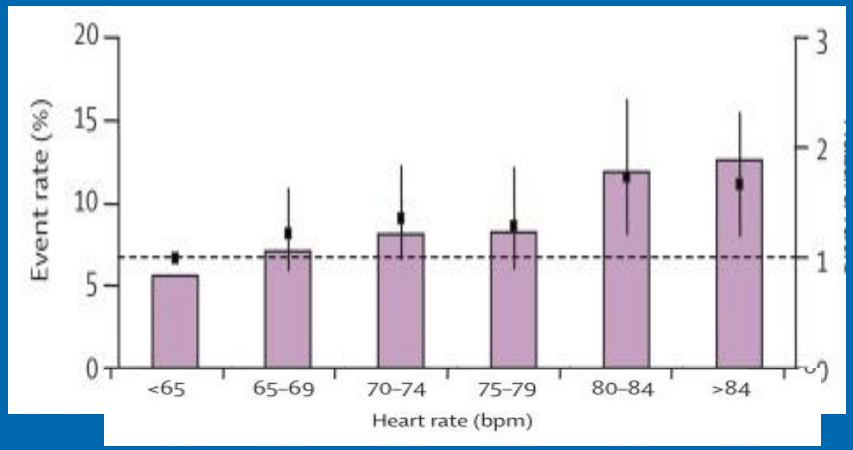
- BEAUTIFUL study subgroup analysis
- ~ 5300 pts with EF < 40% and CAD
- HR > 70:
  - ↑ 34% CV death
  - ↑ 53% HF hosp

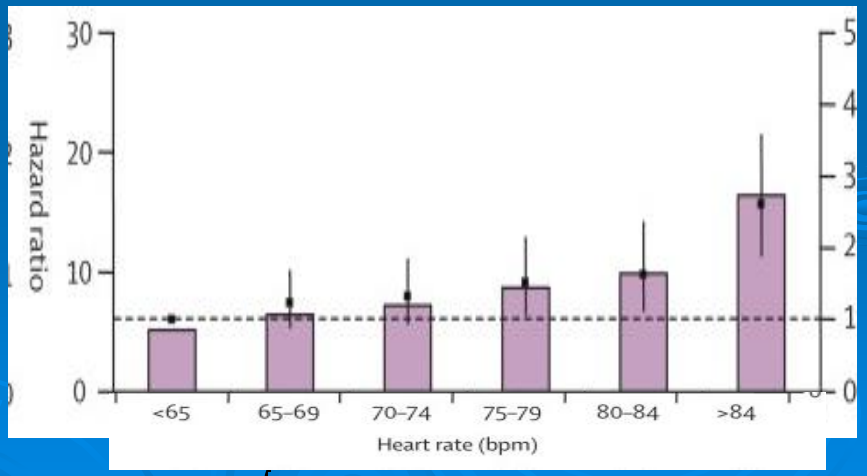


Fox K et al. Lancet 2008; 372: 817-821.

Lower Heart Rate = Better Outcomes

- BEAUTIFUL study subgroup analysis
- ~ 5300 pts with EF < 40% and CAD
- For every ↑ 5 bpm:
  - ↑ 8% CV death
  - ↑ 16% HF hosp

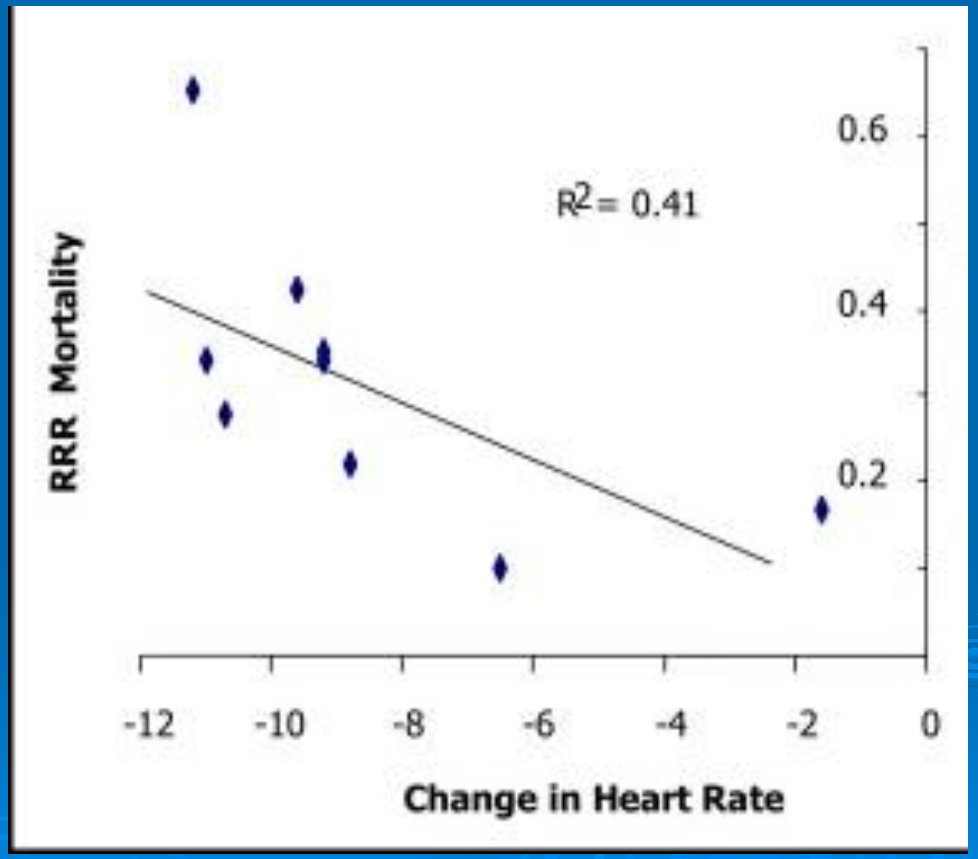




Fox K et al. Lancet 2008; 372: 817-821.

Greater Heart Rate Lowering = Better Outcomes

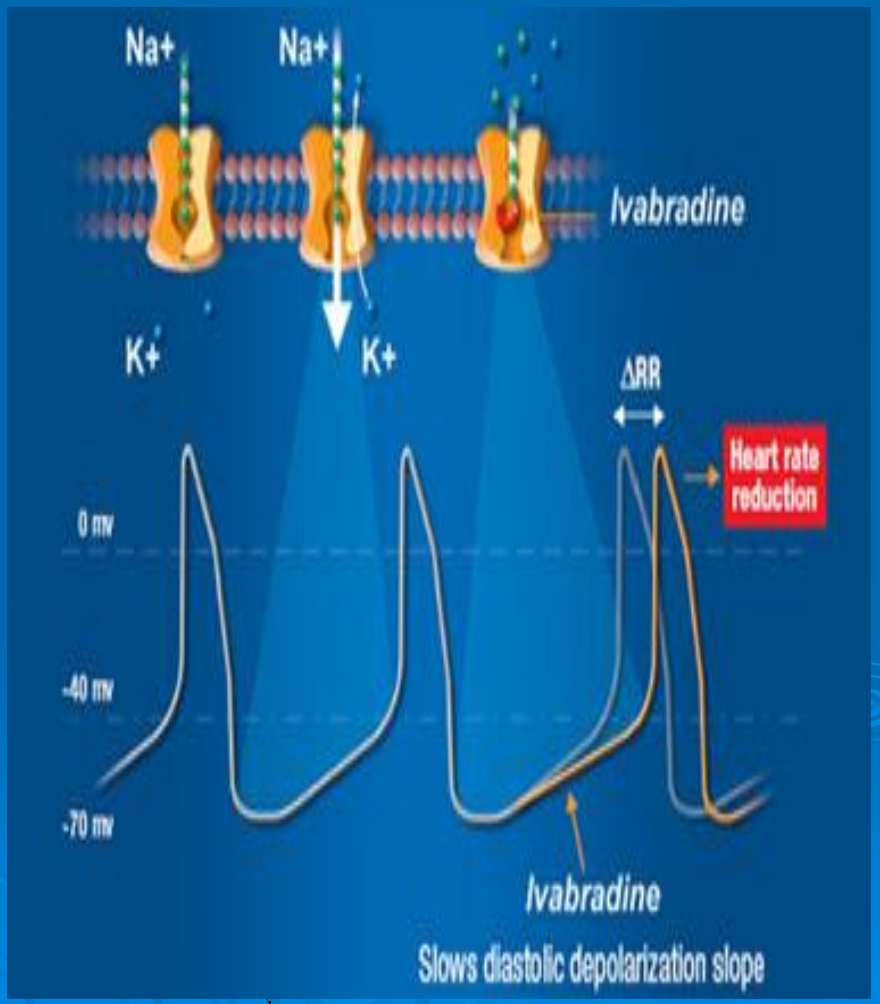
- Meta-analysis of HF BB trials
  - ~23000 pts
  - HR at start vs. end of study
- Greater decrease in HR → greater mortality benefit



Flannery G et al. Am J Cardiol 2008; 101: 865–869

Ivabradine

- Inhibits the I_f current
  - Pacemaker cells of SA node
- Decreases heart rate without decreasing contractility
- Improve outcomes in heart failure?



SHIFT study

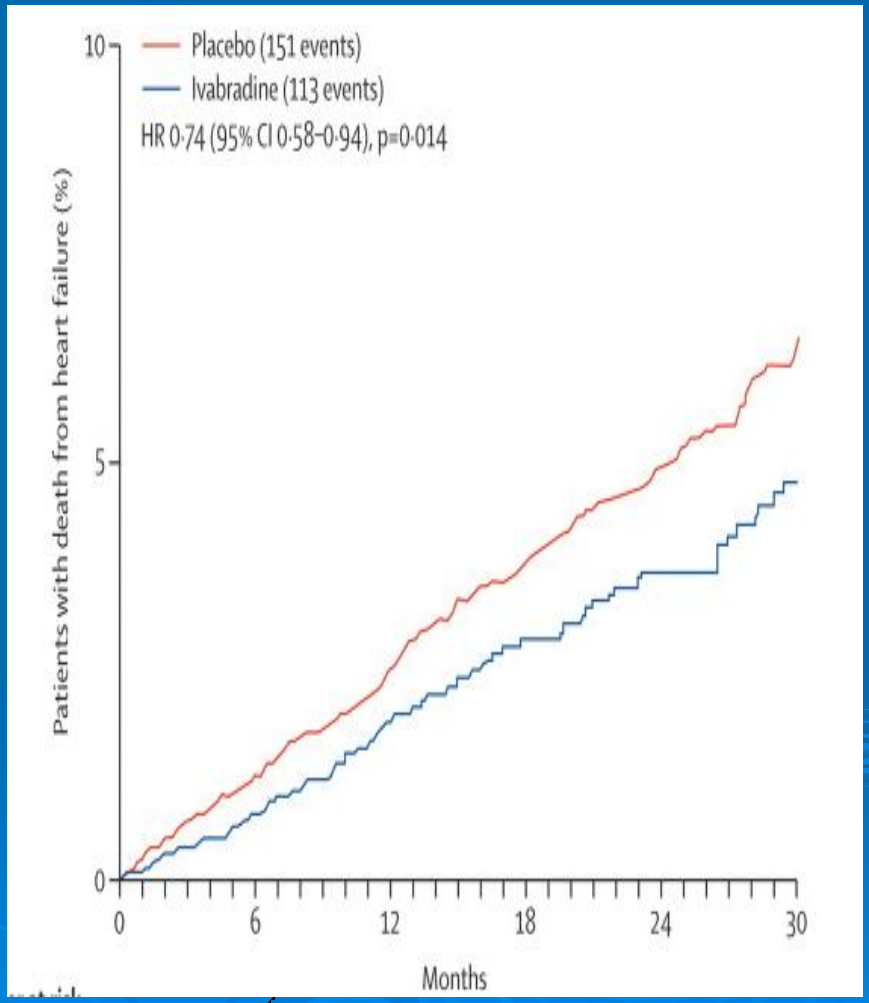
- ~6500 pts
  - EF ≤ 35%
  - HR ≥ 70
  - One HF hospitalization
  - Max tolerated BB
- Ivabradine vs placebo

	Ivabradine	Placebo
Age	61 y	60 y
Female	24%	23%
NYHA II	49%	49%
BB	89%	90%
≥50% target BB dose	56%	56%
ACEI/ARB	93%	92%
Aldo antag	61%	59%
ICD	1%	1%
CRT	3%	4%

Swedberg K et al. Lancet 2010; 376: 875-885.

SHIFT study

- ~6500 pts
  - EF ≤ 35%
  - HR ≥ 70
  - One HF hospitalization
  - Max tolerated BB
- Outcomes
  - HF deaths 5% → 3%
  - HF hosp 21% → 16%



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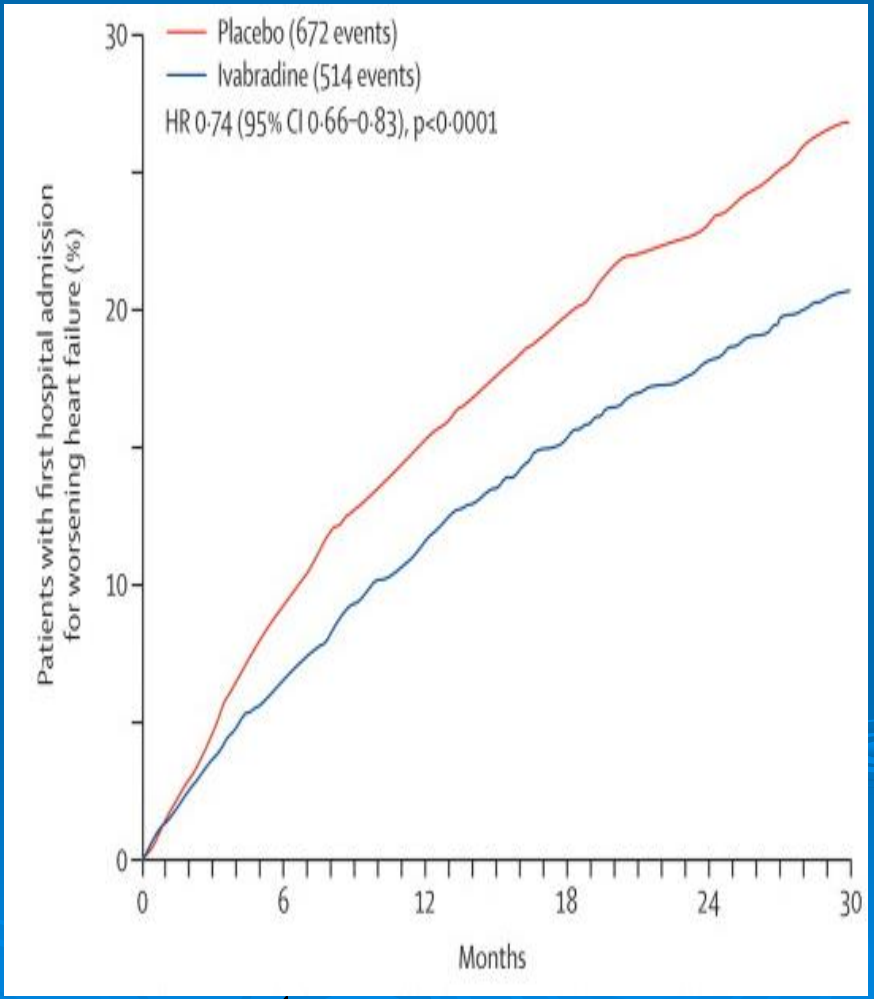


Swedberg K et al. Lancet 2010; 376: 875-885.

Ivabradine: FDA approval

- "…reduce the risk of HF hospitalization… EF ≤ 35%, in SR with resting HR ≥ 70 bpm and *either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.*"

- Dosing
  - 5 mg BID
  - Increase after 2 weeks to 7.5 BID if HR > 60

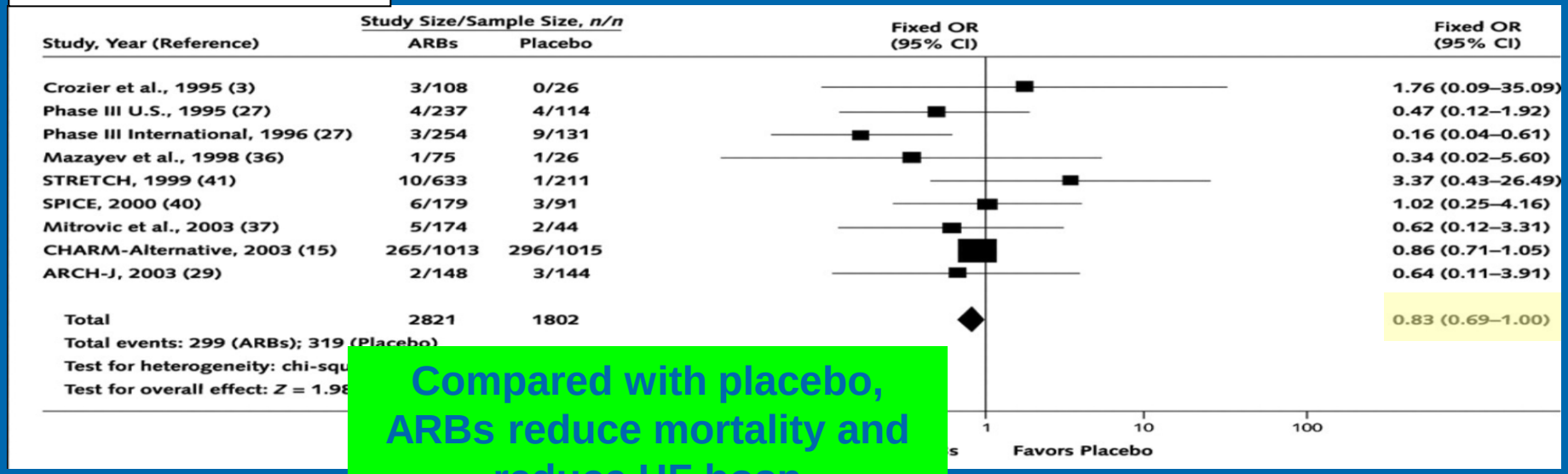
- Side effects
  - Phosphenes
  - Atrial fibrillation

ACEI save lives

Trial	Entry criteria	Number pts/ duration/ drug	Mortality
CONSENSUS *NEJM* 1987	NYHA IV	253 pts/ 6m Enalapril	↓ 31%
SOLVD-rx *NEJM* 1991	EF <35% and acute CHF (II-III)	2569 pts/ 41m Enalapril	↓ 16%
V-HeFT II *NEJM* 1991	EF <45% and NYHA II-III	804 pts/ 6m-5y Enalapril v I/H	↓ 28% vs isordil/hydral
SOLVD-prev *NEJM* 1992	EF <35% and NYHA I	4228 pts/ 37m Enalapril	↓ 8% NS ↓ 29% death/HF
SAVE *NEJM* 1992	MI w/in 3-16d and EF <40%	2231pts/ 4y Captopril	↓ 19%
AIRE *Lancet* 1993	MI w/in 2-9d and evidence of CHF	1986 pts/ 30m Ramipril	↓ 27%
TRACE *NEJM* 1995	MI w/in 2-6d and EF <35%	1749 pts/ 24m Trandolapril	↓ 24%

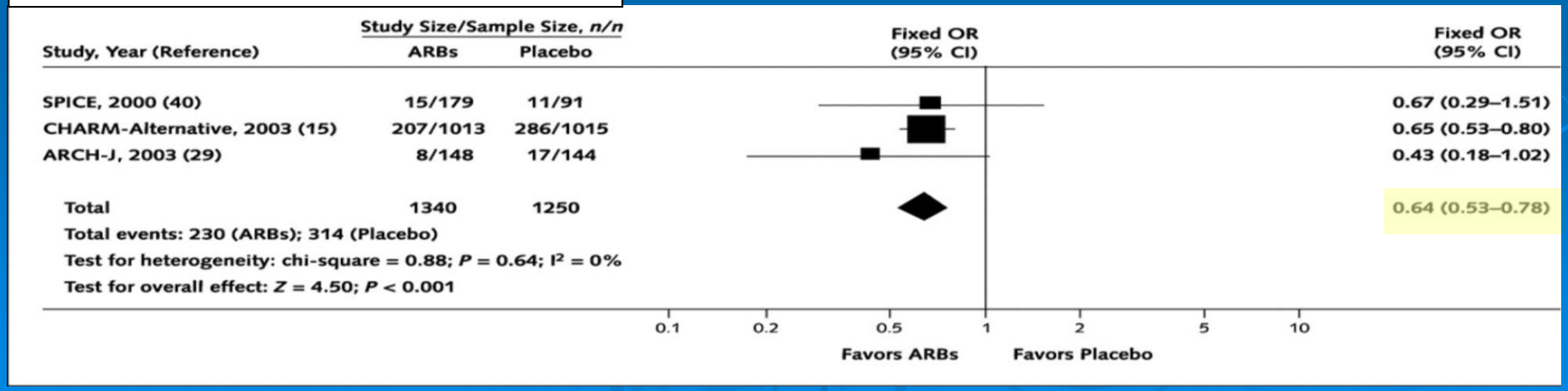
ARBs vs placebo

All-cause mortality



Compared with placebo, ARBs reduce mortality and reduce HF hosp

Heart failure hospitalizations



Lee at al. *Ann Intern Med*. 2004;141:693-704.

PARADIGM-HF study

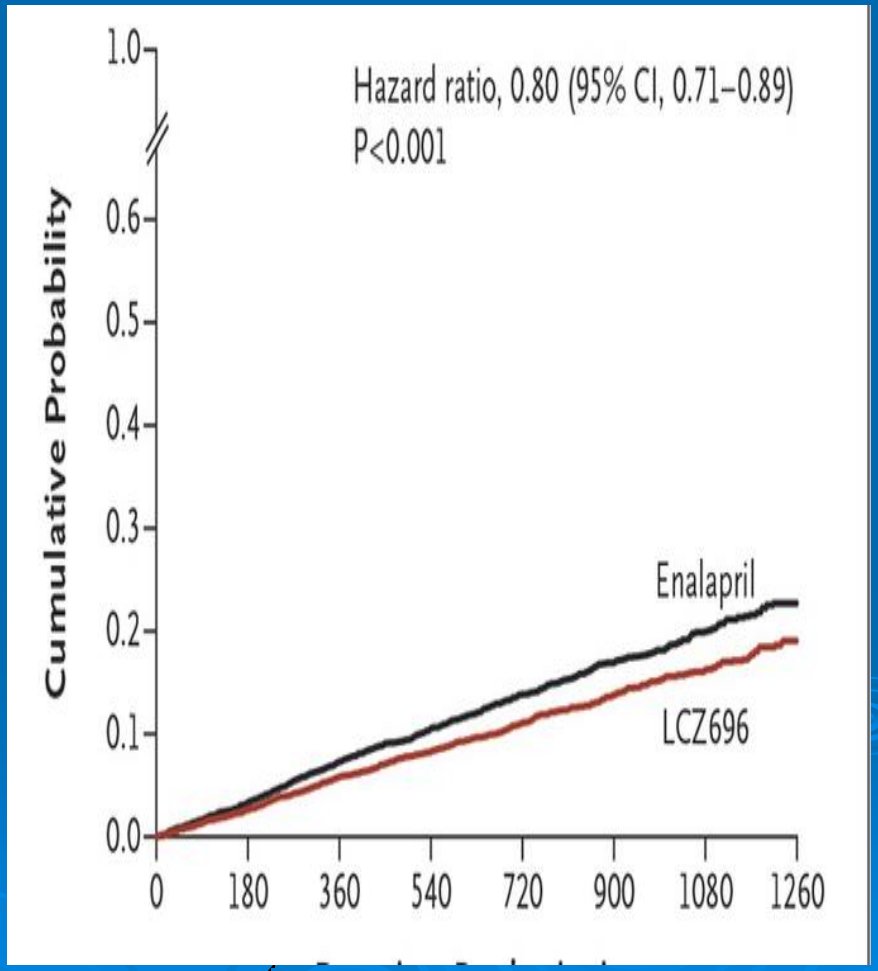
- ~8400 patients
  - EF ≤ 35%
  - One HF hosp or ↑ BNP
- Sacubitril/valsartan vs enalapril

	LCZ696	Enalapril
Age	64 y	64 y
Female	21%	23%
NYHA II	72%	69%
BB	93%	93%
Aldo antag	54%	57%
ICD	15%	15%
CRT	7%	7%

McMurray J et al. NEJM 2014; 371: 993-1004.

PARADIGM-HF study

- ~8400 patients
  - EF ≤ 35%
  - One HF hosp or ↑ BNP
- Outcomes
  - CV deaths: 17% → 13%
  - HF hosp: 16% → 13%



McMurray J et al. NEJM 2014; 371: 993-1004.

Sacubitril/Valsartan: FDA approval

- "…reduce the risk of CV death and HF hospitalization in patients with chronic heart failure and reduced ejection fraction."

- Dosing
  - 49/51 mg BID
  - Increase after 2-4 weeks to 97/103 mg BID as tolerated

- Side effects
  - Hypotension
  - Less hyperK, rise in Cr than ACEI
  - BNPs not accurate!

Practice Guideline: Focused Update | May 2016

2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America

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Paradigm, Shifted