

Heart Failure Update 2011

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Canadian Heart Failure Statistics

- Heart failure affects approximately 500,000 Canadians
 - 50,000 new cases diagnosed each year
- In hospital mortality
 - 10% within a month
 - 17% within 3 months
 - 23% within 6 months
 - other studies have shown mortality rates 15-50% within 1 year
- Readmission rates
 - 15% patients readmitted within 30 days
 - 48% patients readmitted within 1 year

CCS Heart Failure Treatment

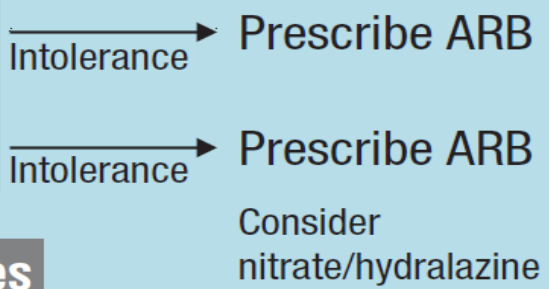
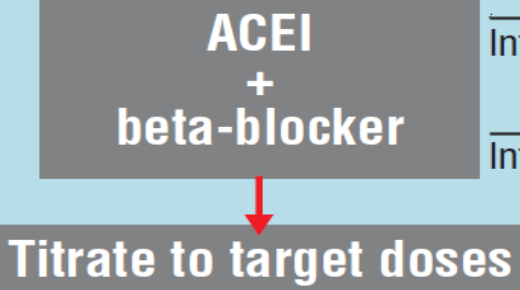
Algorithm

Treatment of heart failure (HF)

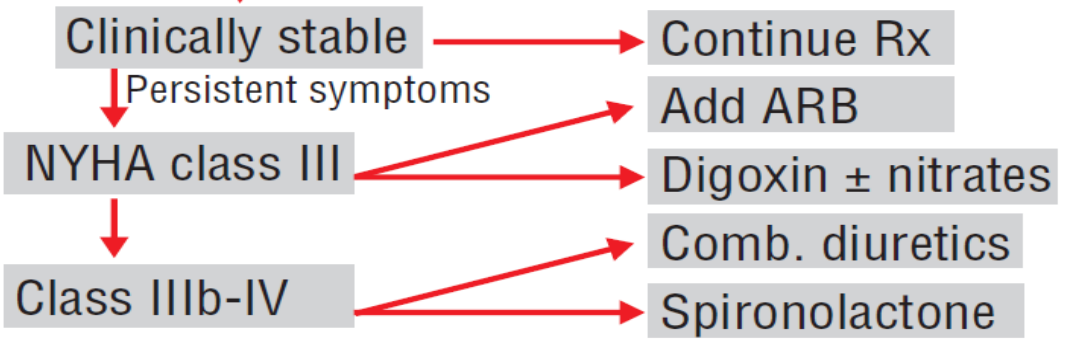
If symptoms severe, refer to specialist: acute to ER, chronic to HF clinic
If HF symptoms but LVEF >40%, treat cause (eg, hypertension, ischemia)
If systolic HF LVEF <40%

For all symptomatic patients with systolic HF:

- Education
- Aggressive risk factor reduction
- Lifestyle modifications
- Salt/fluid vigilance
- Tailored diuretic Rx



- If LVEF <30%, consider ICD referral
- If QRS >120 ms, consider CRT referral
- If refractory, consider transplant





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Society Guidelines

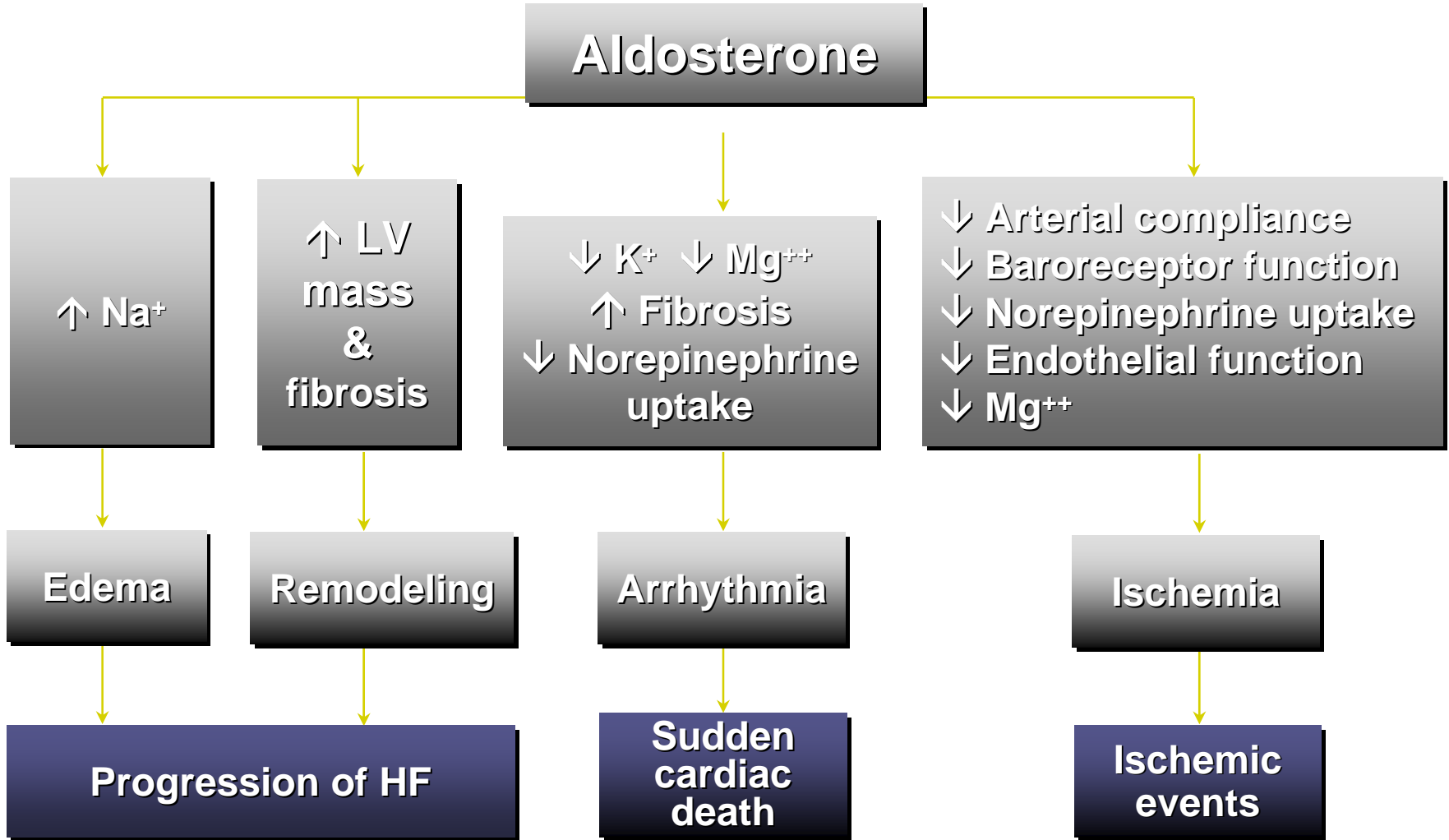
The 2011 Canadian Cardiovascular Society Heart Failure Management Guidelines Update: Focus on Sleep Apnea, Renal Dysfunction, Mechanical Circulatory Support, and Palliative Care

Old and New Targets

Aldosterone Antagonists

Heart Rate Reduction

Why is excess aldosterone harmful?



Aldosterone Antagonists in HF



- **RALES (1999)**
 - 1663 patients with NYHA III-IV heart failure and EF \leq 35%
 - spironolactone added to standard HF medications

Results	Spironolactone N=822 (%)	Placebo N=841 (%)	ARR (%)	NNT
All cause death	34.5	45.9	11.4	9
Death due to HF	15.5	22.5	7.0	14
Sudden death	10.0	13.1	3.1	32
Hospitalization for HF	26.2	35.6	9.4	11

Eplerenone



- **aldosterone receptor antagonist**
 - similar in structure to spironolactone
 - selectively blocks the mineralocorticoid receptor not glucocorticoid, progesterone, or androgen receptors
- **well absorbed**
 - peak effect occurs 1-2 hours post dose
- **half life**
 - 4-6 hours
 - excreted 67% in the urine
- **substrate of cyp3A4**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

APRIL 3, 2003

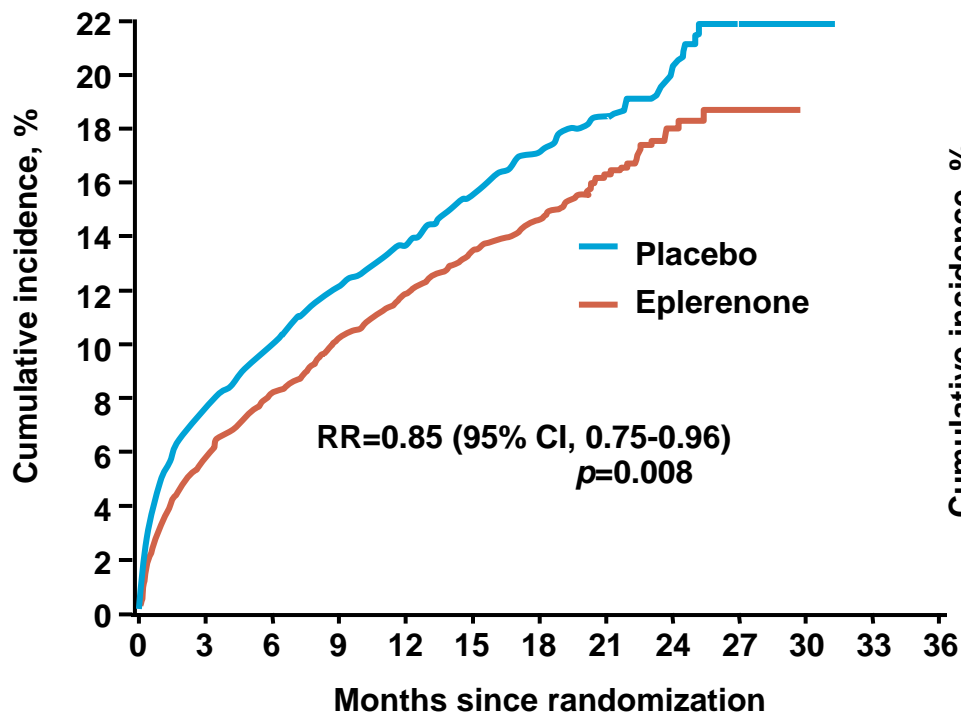
VOL. 348 NO. 14

Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction

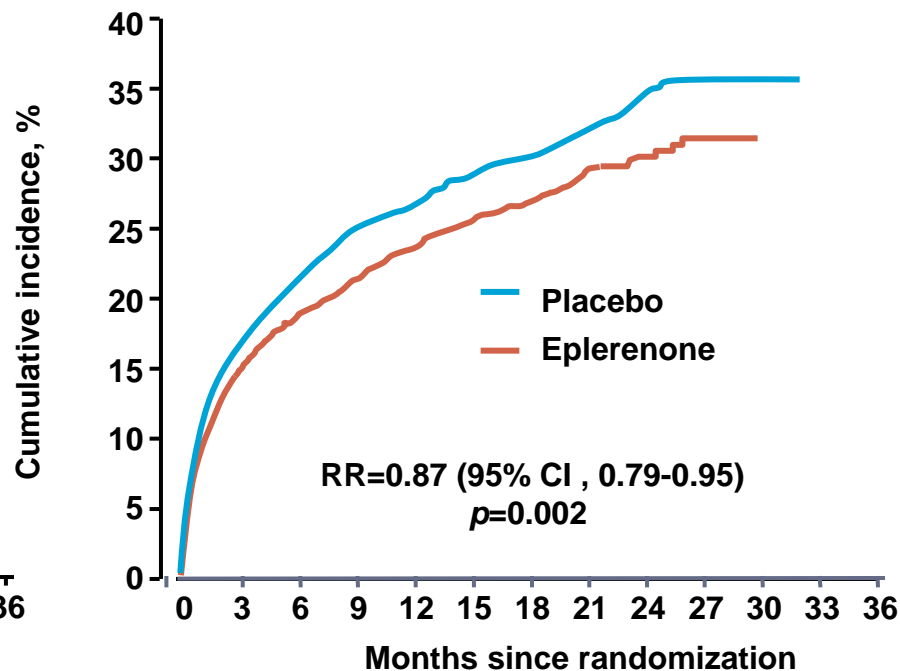
- P: 6642 patients post MI with documented EF \leq 40% and heart failure symptoms
- I: eplerenone 25 mg titrated to 50 mg/d with standard therapy
- C: placebo with standard therapy
- O: death from any cause

EPHESUS: Co-Primary Endpoints

All-Cause Mortality



CV Mortality/CV Hospitalization



EPHESUS Results



Results	Eplerenone n=3319 (%)	Placebo N=3313 (%)	Relative Risk	ARR (%)	NNT	P value
All cause death	14.4	16.7	0.85 (0.75-0.96)	2.3	44	0.008
Death due to CV cause or hospitalization	26.6	30.0	0.87 (0.79-0.95)	3.4	29	0.002
Sudden death	4.9	6.1	0.79 (0.64-0.97)	1.2	83	0.03
Hospitalization for HF	10.4	11.8	0.85 (0.74-0.99)	1.4	71	0.03

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

Faiez Zannad, M.D., Ph.D., John J.V. McMurray, M.D., Henry Krum, M.B., Ph.D., Dirk J. van Veldhuisen, M.D., Ph.D., Karl Swedberg, M.D., Ph.D., Harry Shi, M.S., John Vincent, M.B., Ph.D., Stuart J. Pocock, Ph.D., and Bertram Pitt, M.D.,
for the EMPHASIS-HF Study Group*

- 2737 patients NYHA II heart failure and an ejection fraction of no more than 35%
- eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy
- primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure

EMPHASIS-HF

- Inclusion criteria

- ≥ 55 years old
- NYHA II heart failure
- $EF \leq 30\%$
- Maximum tolerated doses of usual background therapies
- Could also enrol depending on BNP level

- Exclusion criteria

- Acute MI
- NYHA III-IV heart failure
- $K^+ > 5.0$ mmol/L
- $GFR < 30$ ml/min
- Potassium sparing diuretics

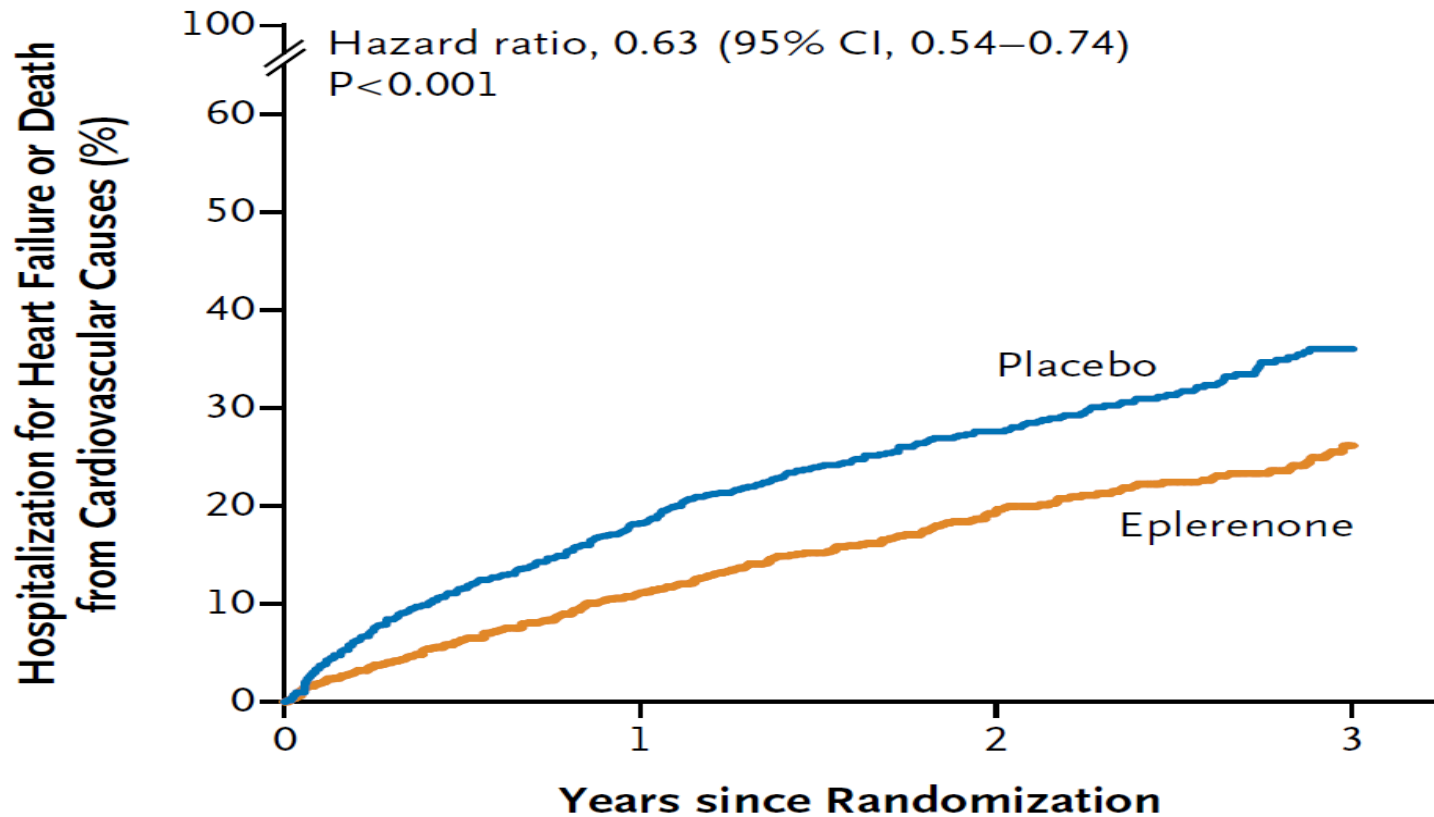
EMPHASIS-HF: Baseline Characteristics



	Eplerenone (n=1364)	Placebo (n=1373)
Mean age (years)	68.7±7.7	68.6±7.6
Female sex (%)	22.7	21.9
Race/ethnicity (%)		
White	82.6	83.1
Black	2.7	2.2
Asia	11.6	11.5
Other	3.1	3.2
Left ventricular ejection fraction (%)	26.2±4.6	26.1±4.7
Principle cause of HF (%)		
Ischemic heart disease	69.7	68.1
Nonischemic heart disease	30.1	31.8
Duration of HF (years)	4.8±5.9	4.6±5.5
Previous hospitalization for HF (%)	52.3	52.9
Estimated GFR rate <60 ml/min/1.73 m ² (%)	32.2	34.5

EMPHASIS-HF

A



No. at Risk

Placebo	1373	848	512	199
Eplerenone	1364	925	562	232

EMPHASIS-HF: Results



Results	Eplerenone n=1364 (%)	Placebo N=1373 (%)	Adjusted hazard ratio	ARR (%)	NNT	Adjusted P value
Death due to CV cause or hospitalization for HF	18.3	25.9	0.63 (0.54-0.74)	7.6	13	<0.001
Death from any cause or hospitalization for HF	19.8	27.4	0.65 (0.55-0.76)	7.6	13	<0.001
Death from any cause	12.5	15.5	0.76 (0.62-0.93)	3.0	33	0.008
Hospitalization for HF	12.0	18.4	0.58 (0.47-0.70)	6.4	16	<0.001

EMPHASIS-HF: Safety



Table 3. Selected Investigator-Reported Adverse Events and Those Leading to Permanent Withdrawal of the Study Drug, According to Study Group.*

Event	Adverse Event			Adverse Event Leading to Study-Drug Withdrawal		
	Eplerenone (N= 1360)	Placebo (N= 1369)	P Value	Eplerenone (N= 1360)	Placebo (N= 1369)	P Value
	<i>no. of patients (%)</i>			<i>no. of patients (%)</i>		
All events	979 (72.0)	1007 (73.6)	0.37	188 (13.8)	222 (16.2)	0.09
Hyperkalemia	109 (8.0)	50 (3.7)	<0.001	15 (1.1)	12 (0.9)	0.57
Hypokalemia	16 (1.2)	30 (2.2)	0.05	0	3 (0.2)	0.25
Renal failure	26 (1.9)	32 (2.3)	0.51	4 (0.3)	6 (0.4)	0.75
Hypotension	46 (3.4)	37 (2.7)	0.32	0	3 (0.2)	0.25
Gynecomastia or other breast disorders	10 (0.7)	14 (1.0)	0.54	2 (0.1)	2 (0.1)	1.00

EMPHASIS-HF



- eplerenone reduced both the risk of death and the risk of hospitalization among patients with systolic heart failure and mild symptoms
- CCS Heart Failure Guidelines 2011

RECOMMENDATION

We recommend that an aldosterone receptor blocking agent such as eplerenone be considered for patients with mild to moderate (NYHA II) HF, aged > 55 years with LV systolic dysfunction (LVEF $\leq 30\%$, or if LVEF $> 30\%$ and $\leq 35\%$ with QRS duration > 130 ms), and recent hospitalization for CVD or elevated BNP/NT-pro-BNP levels, who are on standard HF therapy (Strong Recommendation, High-Quality Evidence).

Eplerenone :Dosing and Monitoring



- **start dose is 25 mg/day**
 - titrate dose to 50 mg/d as tolerated by the patient
 - dose may be reduced/withheld if patient hyperkalemic
- **monitoring**
 - baseline potassium, SCr
 - repeat above at 1 week after initiation or dose adjustment
 - watch the patients at highest risk
 - ✦ preexisting CKD
 - ✦ diabetics +/- proteinuria
 - ✦ concomitant therapies affecting potassium

Eplerenone and CYP450



- potent CYP_{3A4} inhibitors
 - significantly increase eplerenone AUC
 - concomitant use contraindicated
- mild to moderate CYP_{3A4} inhibitors eplerenone AUC increases
 - dose should not exceed 25 mg/d

Eplerenone: Place in therapy



- **indication**

- an adjunct to standard therapy, to reduce the risk of mortality following myocardial infarction, in clinically stable patients who have evidence of heart failure and left ventricular systolic dysfunction (ejection fraction $\leq 40\%$)

- **should not be administered to patients:**

- initial $K^+ > 5.0$ mmol/L
- SCr > 221 $\mu\text{mol/L}$ and/or
- CrCl < 50 mL/min

Eplerenone versus Spironolactone



- indications are different
- eplerenone does not cause gynecomastia but hyperkalemia is still a concern
- would spironolactone have the same benefit?
 - need a study !
- cost:
 - Eplerenone : \$97.35/month
 - Spironolactone: \$14.91/month

Importance of Heart Rate

- Resting heart rate is an independent predictor of poor outcomes
- Reduction of HR in heart failure
 - Prolongs diastolic filling
 - May improve ventricular filling and stroke volume
 - Potential to improve heart function

Heart Rate and Ejection Fraction

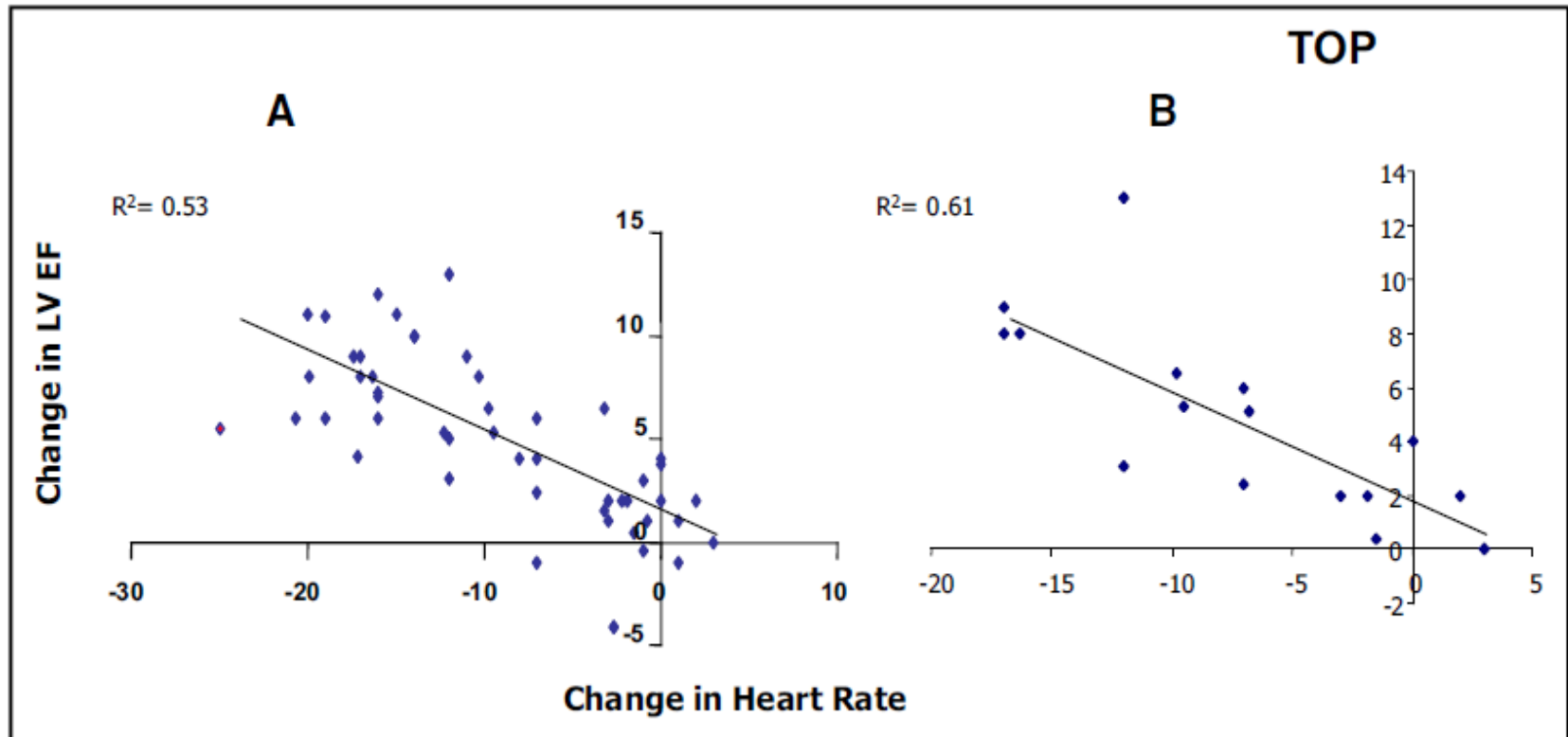


Figure 2. Correlation of change in heart rate (HR) with change in the LVEF in (A) 26 β -blocker trials of 3,389 patients and (B) 8 β -blocker trials of >100 patients (n = 2,599).

Heart Rate and Mortality

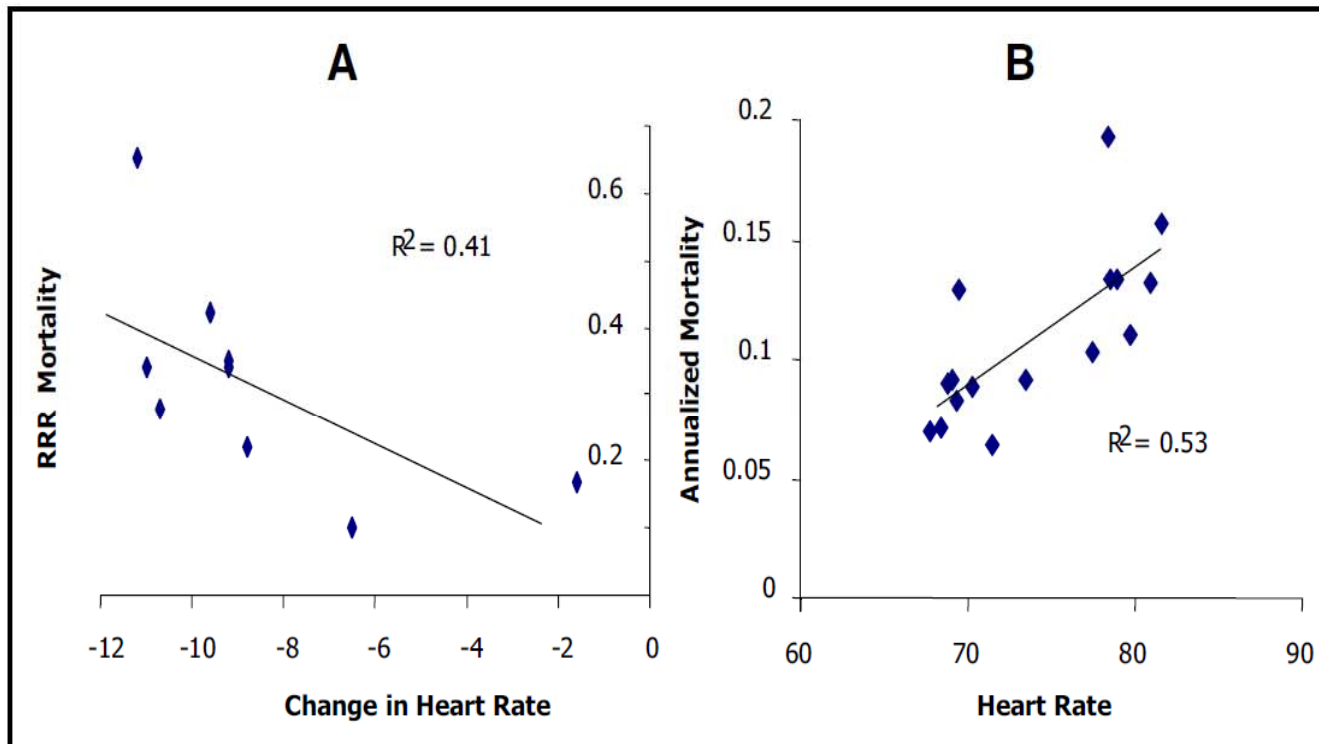
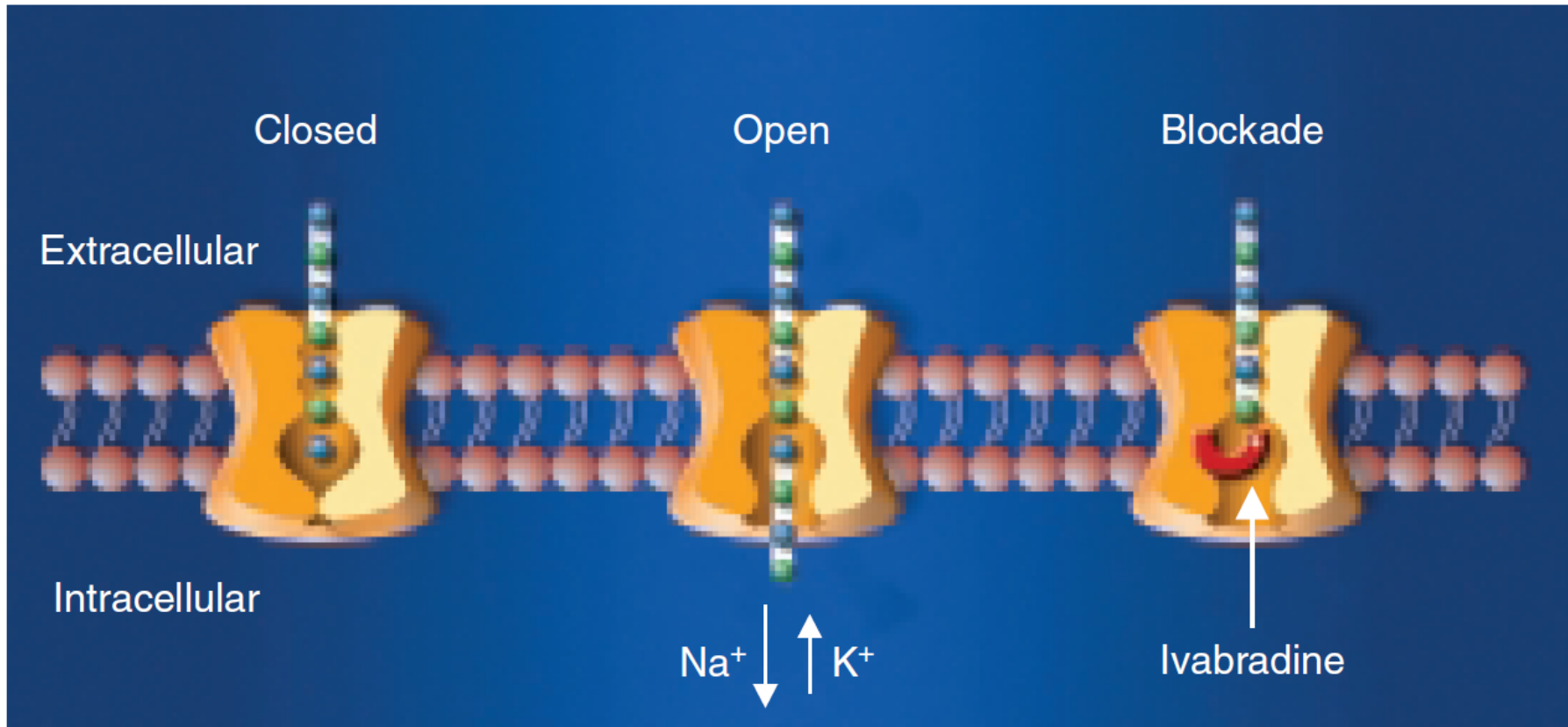


Figure 1. (A) Correlation of change in HR with relative risk reduction (RRR) in all-cause mortality and (B) correlation of final achieved HR with annualized mortality in 9 β -blocker trials of 19,537 patients.

Ivabradine



- Ivabradine is a selective sinus node If inhibitor
 - controls the time interval between successive action potentials and the heart rate



Systolic Heart failure treatment with I_f inhibitor ivabradine Trial

Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study



*Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators**

SHIFT

Systolic Heart failure treatment with I_f inhibitor ivabradine Trial

- Inclusion criteria

- 6558 patients
- Class II-IV heart failure
- EF \leq 35 %
- HR \geq 70 bpm
- Sinus rhythm

- Exclusion criteria

- recent (<2 months) MI
- ventricular or atrioventricular pacing operative for 40% or more of the day
- atrial fibrillation or flutter
- symptomatic hypotension



Systolic Heart failure treatment with I_f inhibitor ivabradine Trial

- Intervention
 - Ivabradine 5 mg bid
 - Dose titrated up/down depending on HR and tolerability
- Primary outcome
 - composite of cardiovascular death or hospital admission for worsening heart failure
- Mean duration of follow up
 - 23 months

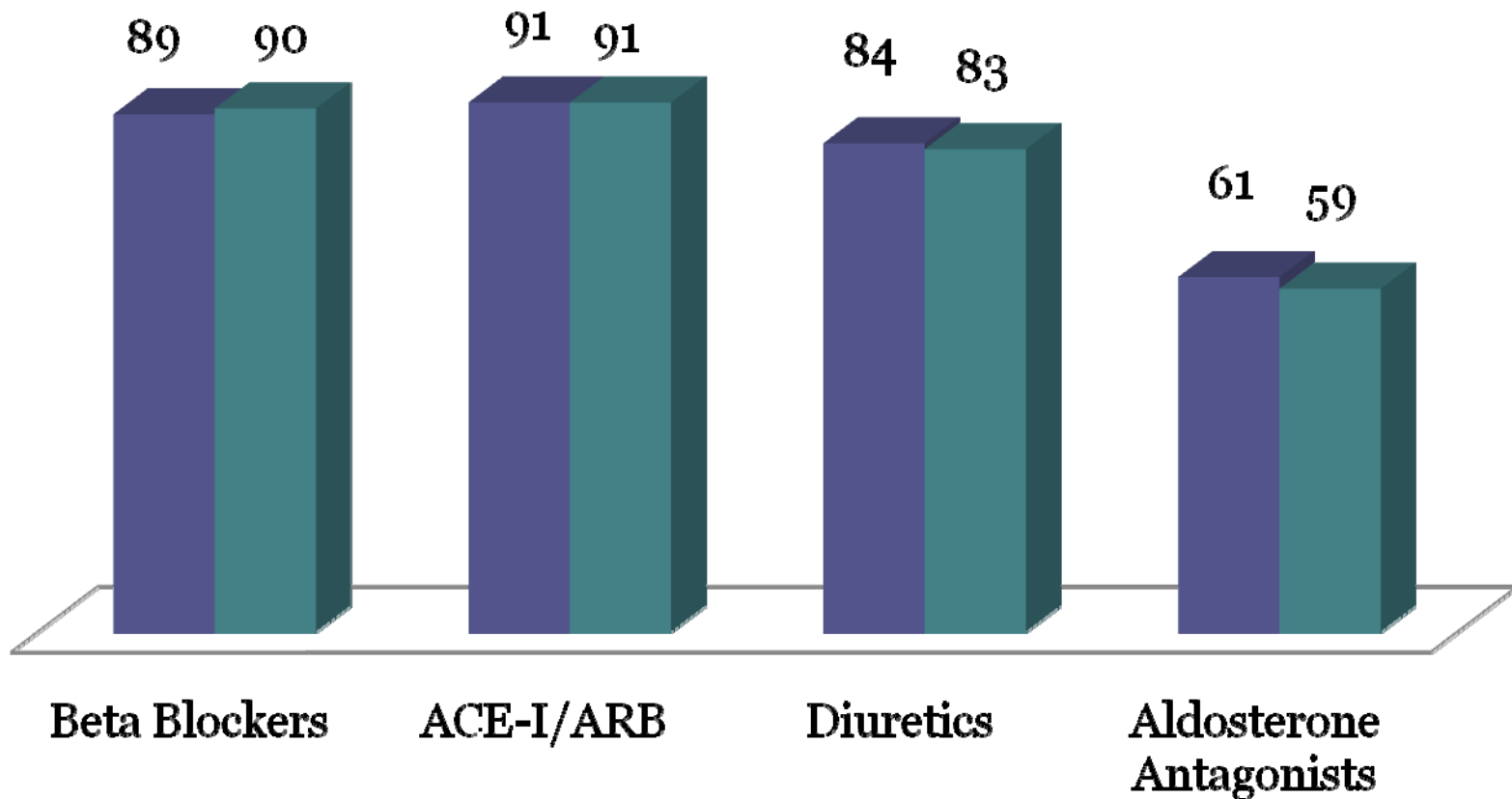


Systolic Heart failure treatment with I_f inhibitor ivabradine Trial

Baseline Demographics	Ivabradine (n=3241)	Placebo (n=3264)
Age	60.7	60.1
Gender (%)	76	77
Heart Rate (bpm)	79.7	80.1
LVEF (%)	29	29
NYHA HF Class (%)		
II	49	49
III	50	50
IV	2	2
Medical History:		
Myocardial infarction	56	56
Hypertension	66	67
Diabetes	30	31

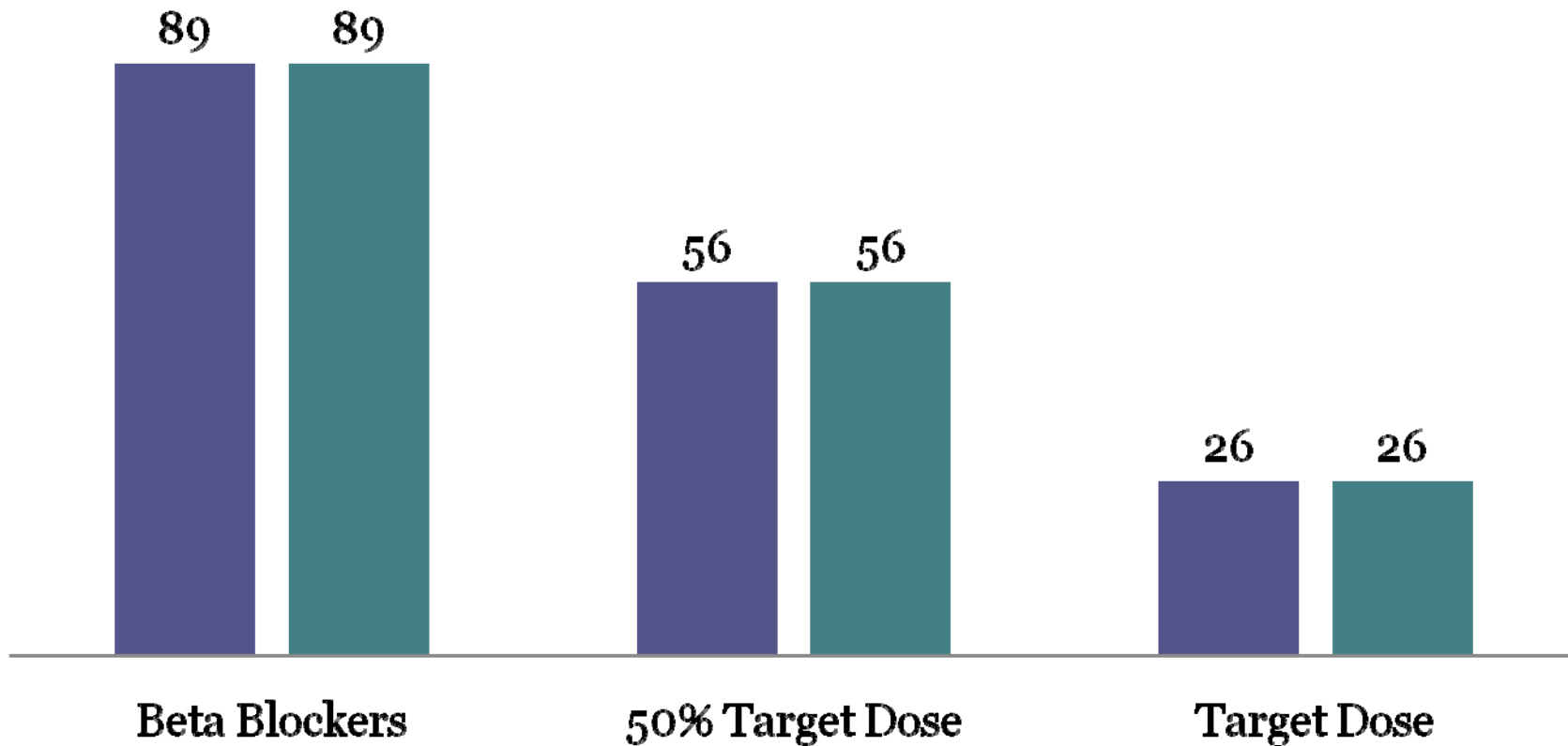
Background HF Therapy

■ Ivabradine ■ Placebo



β -blocker use at baseline

■ Ivabradine ■ Placebo



SH/fT Heart Rate

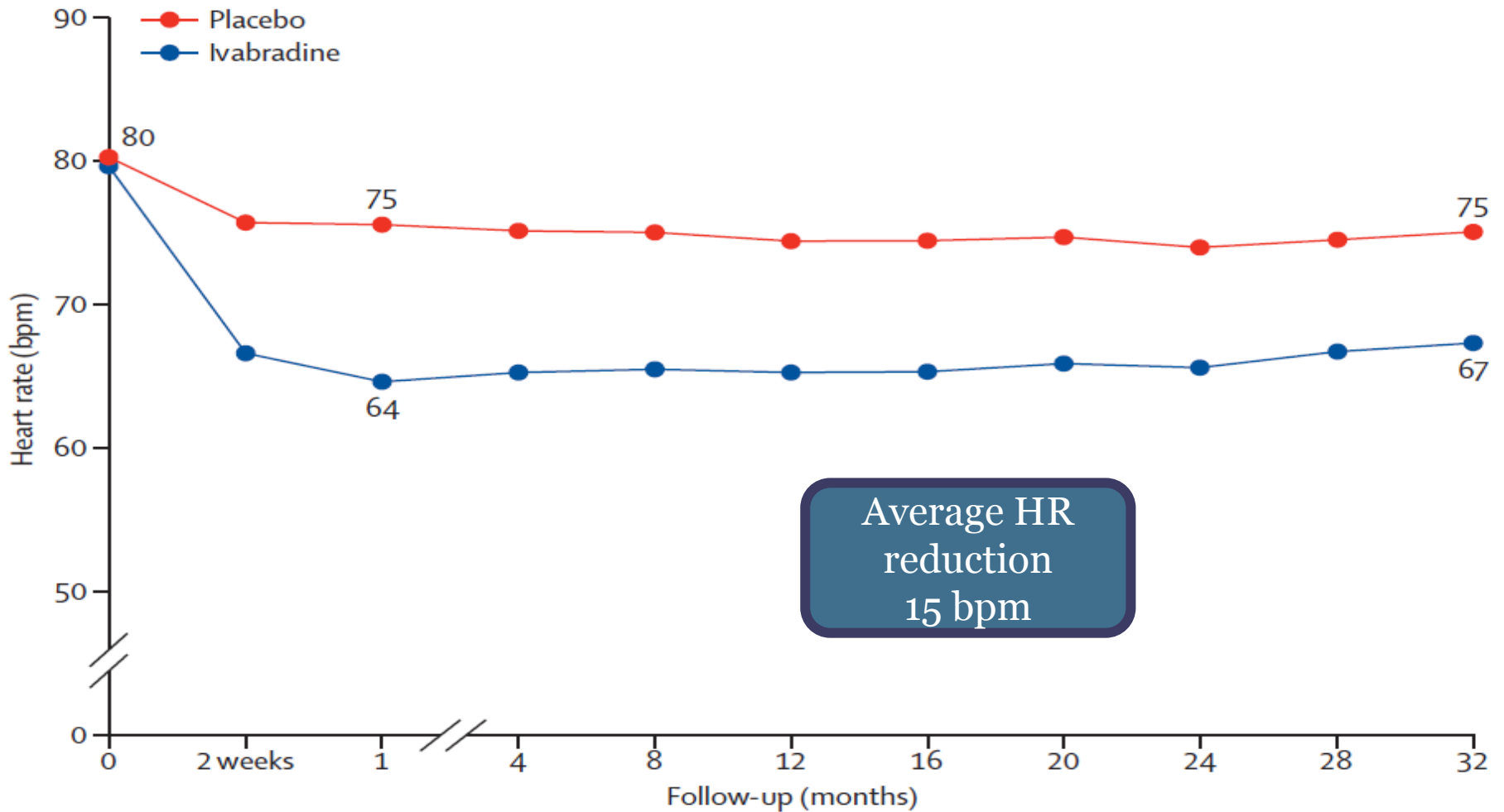
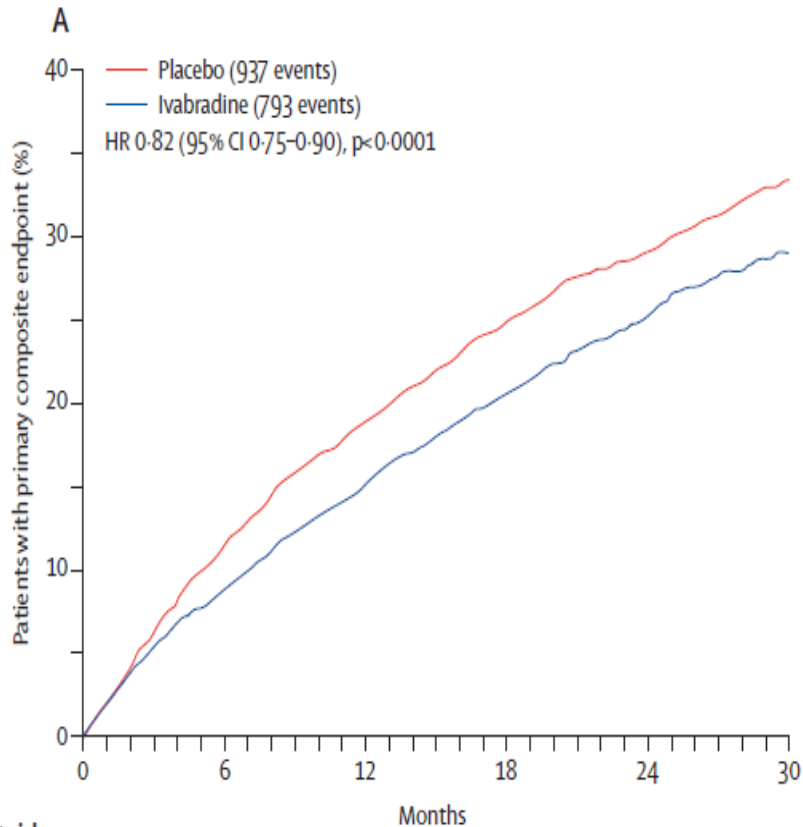


Figure 2: Mean heart rate during the study in the total study population, by allocation groups

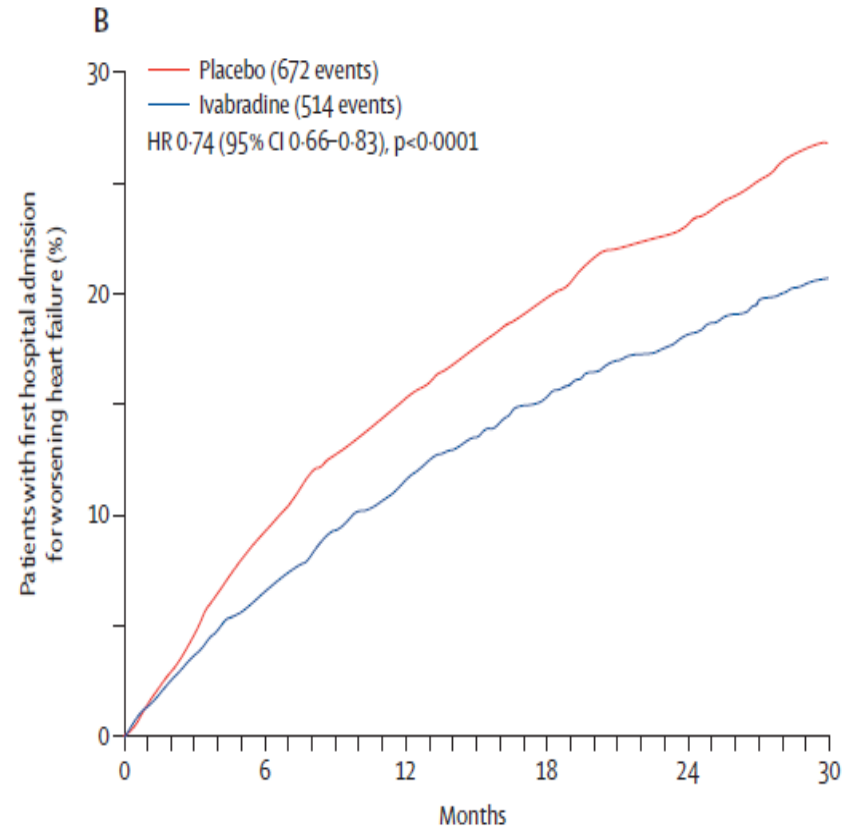
SHIFT

Systolic Heart failure treatment with I_f inhibitor ivabradine Trial



Number at risk	0	6	12	18	24	30
Placebo group	3264	2868	2489	2061	1089	439
Ivabradine group	3241	2928	2600	2173	1191	447

A. Cardiovascular death or hospital admission for worsening heart failure



Number at risk	0	6	12	18	24	30
Placebo group	3264	2868	2489	2061	1089	439
Ivabradine group	3241	2928	2600	2173	1191	447

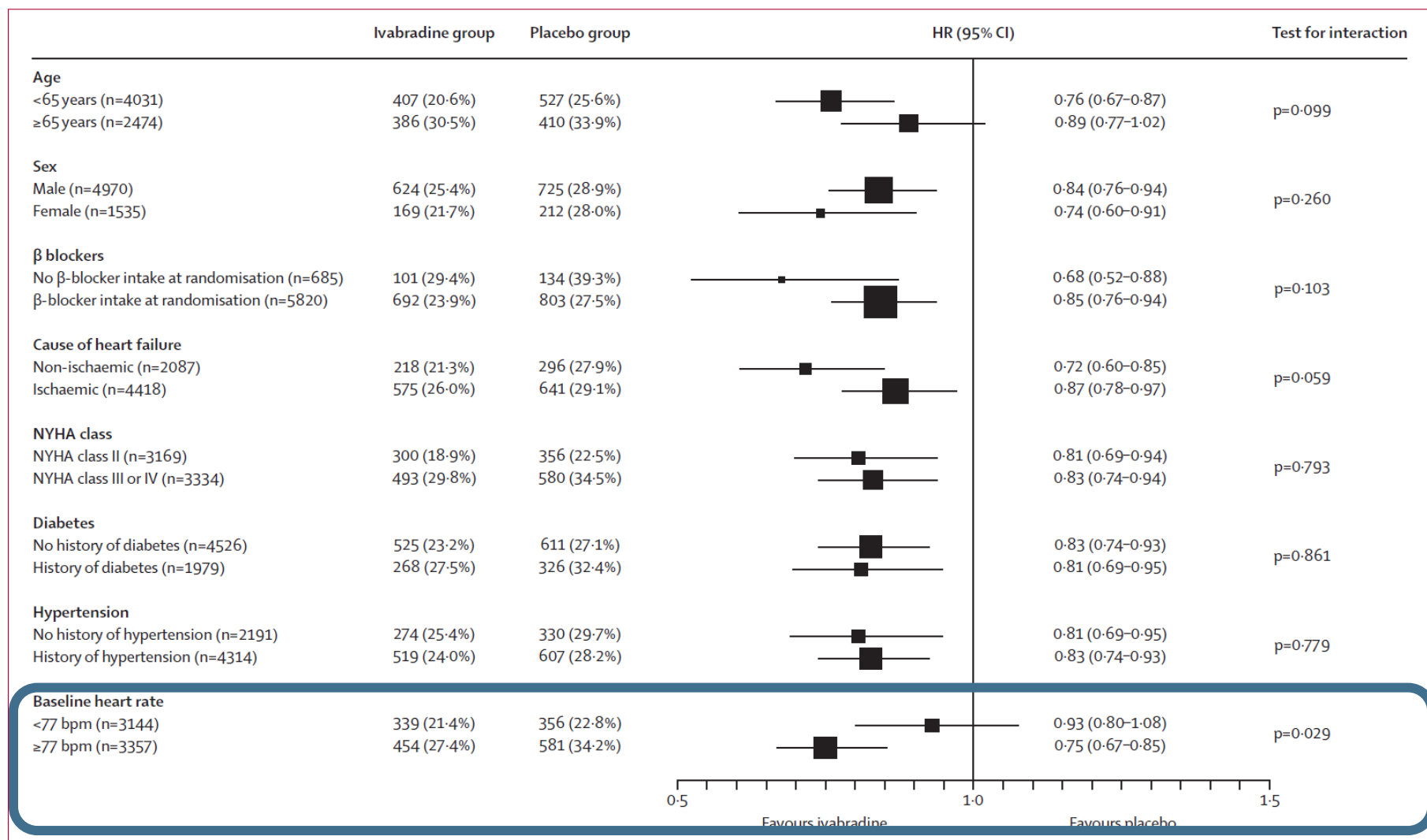
B. Hospital admission for worsening heart failure



Systolic Heart failure treatment with I_f inhibitor ivabradine Trial

Outcome	Ivabradine (%)	Placebo (%)	Hazard Ratio	ARR (%)	NNT	P value
CV death/hospital for HF	24	29	0.82 (0.75-0.90)	5	20	<0.0001
All cause mortality	16	17	0.90 (0.80–1.02)			NS
CV Mortality	14	15	0.91 (0.80-1.03)			NS
HF Mortality	3	5	0.74 (0.58-0.94)	2	50	0.014
All Cause Hospital Admission	38	42	0.89 (0.82-0.96)	4	25	0.003
HF Hospital Admission	16	21	0.74 (0.66-0.83)	5	20	< 0.0001

SH/T Sub-group Analysis





Systolic Heart failure treatment with I_f inhibitor ivabradine Trial

Outcomes in patients on 50% target β blocker dose

	Ivabradine	Placebo	Hazard Ratio	P value
Primary Outcome	11.9	13.3	0.90 (0.77-1.04)	NS
CV Death	5.9	5.9	1.00	NS
Hospitalization for HF	7.7	9.6	0.81 (0.67-0.97)	0.021



Systolic Heart failure treatment with I_f inhibitor ivabradine Trial

	Patients with an adverse event			Patients with an adverse event leading to drug withdrawal		
	Ivabradine group (n=3232)	Placebo group (n=3260)	p value	Ivabradine group (n=3232)	Placebo group (n=3260)	p value
All	2439 (75%)	2423 (74%)	0.303	467 (14%)	416 (13%)	0.051
Heart failure	804 (25%)	937 (29%)	0.0005	70 (2%)	82 (3%)	0.367
Symptomatic bradycardia	150 (5%)	32 (1%)	<0.0001	20 (1%)	5 (<1%)	0.002
Asymptomatic bradycardia	184 (6%)	48 (1%)	<0.0001	28 (1%)	5 (<1%)	<0.0001
Atrial fibrillation	306 (9%)	251 (8%)	0.012	135 (4%)	113 (3%)	0.137
Phosphenes*	89 (3%)	17 (1%)	<0.0001	7 (<1%)	3 (<1%)	0.224
Blurred vision	17 (1%)	7 (<1%)	0.042	1 (<1%)	1 (<1%)	1.000

Data are number of patients (%). Patients included in this safety analysis are those who had taken at least one dose of study drug. p values are calculated on the basis of number of patients. *Transient enhanced brightness in a restricted area of the visual field.

Table 5: Selected adverse events and those leading to definitive withdrawal of study drug

Ivabradine

- extensive metabolism in the liver and gut via the CYP_{3A4}
- elimination half-life
 - 2 hours
- most common adverse effects
 - luminous phenomena in the visual field (phosphenes)
 - blurred vision
 - bradycardia

Ivabradine: Place in therapy

- Patients with HR > 70 and unable to tolerate β -blocker at 50% target dose
 - Reduction in CV death and hospitalization for HF
- Patients on $\geq 50\%$ β -blocker dose
 - Reduction in hospitalization for HF only
- Not to be used in patients with atrial fibrillation

CCS Heart Failure Update 2011

- Ivabradine not currently available in Canada
- SH*f*T results may support use of ivabradine in the following patients
 - $EF \leq 35\%$
 - $HR \geq 70$
 - Moderate to severe HF on optimal therapy

