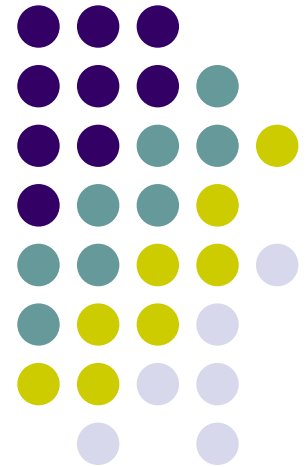


What's New in Heart Failure

14th Annual Contemporary Therapeutic Issues in Cardiovascular Disease

Kori Leblanc, BScPhm, ACPR, PharmD

May 7, 2011

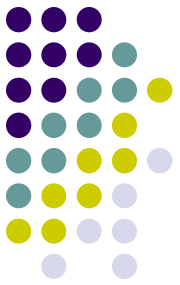


What's New in Heart Failure?



Aldosterone Antagonists

Aldosterone Antagonists: Guidelines



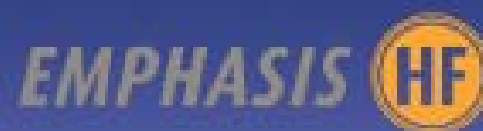
- **CCS**
 - Consider for patients with severe symptomatic chronic HF despite optimization of treatment and LVEF<30%
 - Benefit was mortality
 - Consider in AHF with LVEF less than 30% following acute MI
- **ACC/AHA/HFSA**
 - Moderately severe to severe symptoms and reduced LV dysfunction who can be carefully monitored for renal function and potassium

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

EMPHASIS-HF*

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

[ClinicalTrials.gov, NCT00232180](https://clinicaltrials.gov/ct2/show/study/NCT00232180)



* Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure

Disposition of Patients

EMPHASIS-HF Investigators (29 countries, 278 sites)

2737 Randomized

1364 Randomized
to eplerenone 25-50 mg/d

1373 Randomized
to placebo

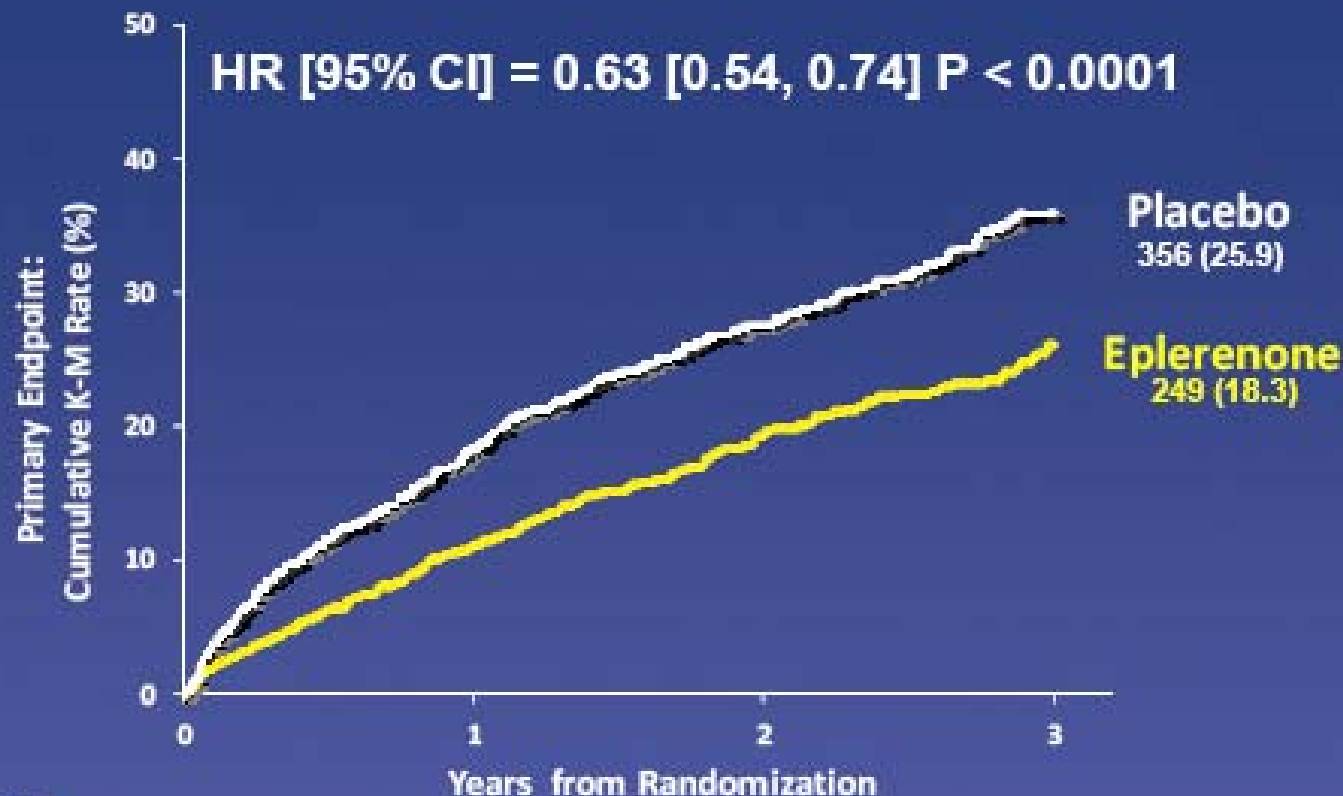
4 did not start study drug
17 lost to follow up

4 did not start study drug
15 lost to follow up

Median follow-up time 21 months,
4783 patient-years of follow-up

EMPHASIS 

Primary Endpoint Cardiovascular Death or Hospitalization for HF



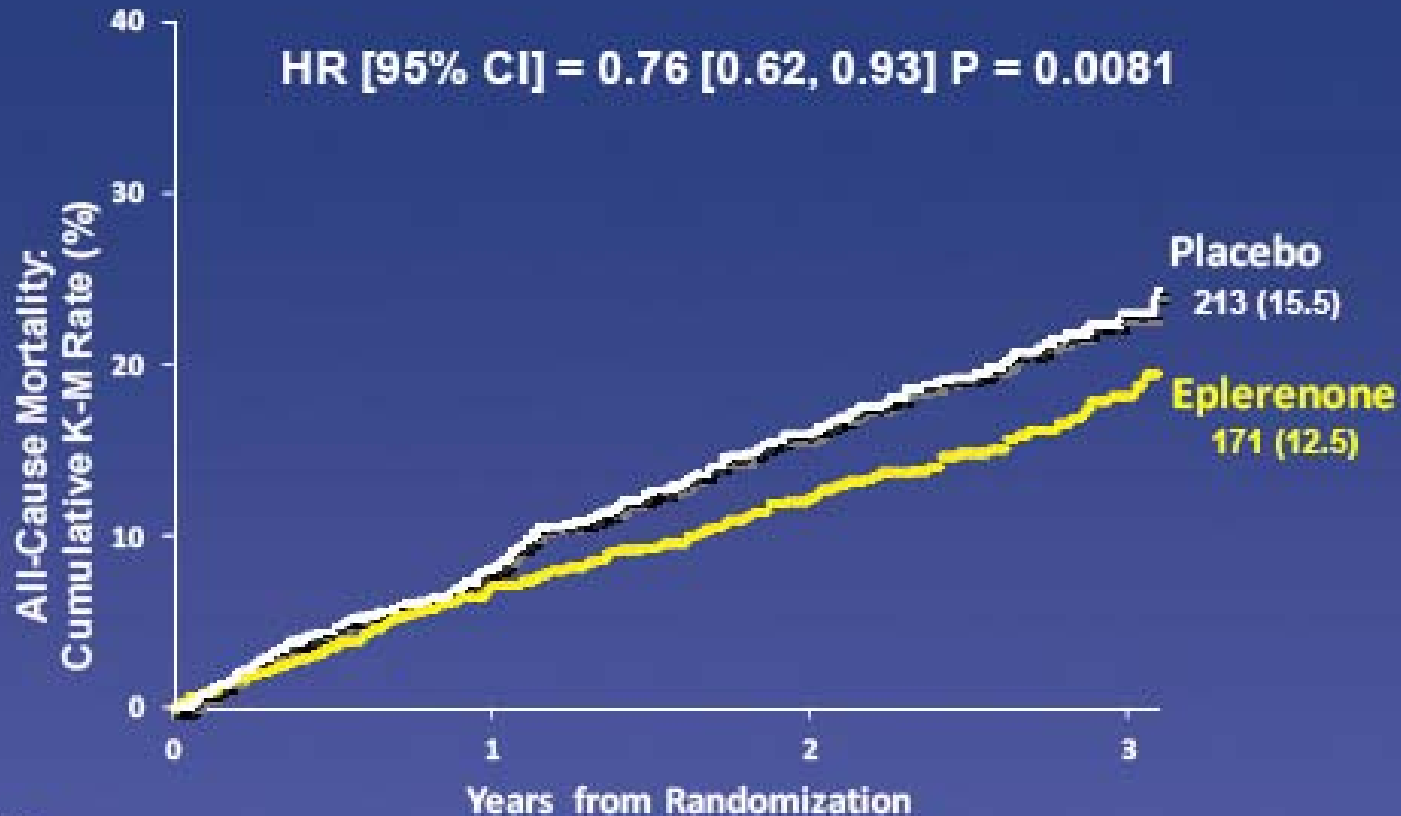
No. at Risk

Years from Randomization	0	1	2	3
Placebo	1373	848	512	199
Eplerenone	1364	925	562	232

EMPHASIS 

*Unadjusted HR 0.66; 0.56, 0.78; p<0.0001

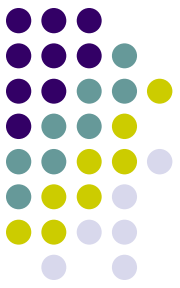
Mortality From Any Cause



No. at Risk

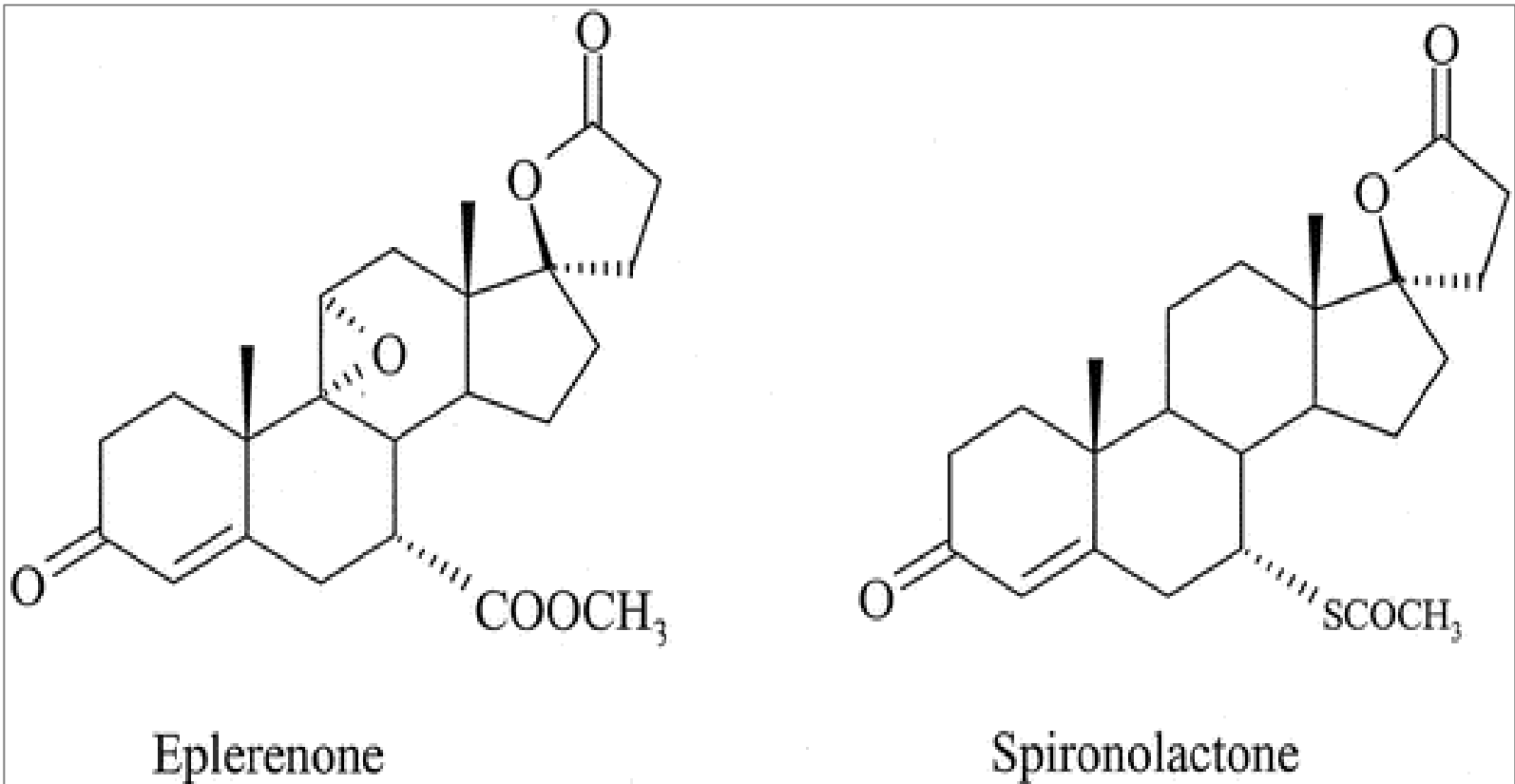
Placebo	1373	947	587	242
Eplerenone	1364	972	625	269

*Unadjusted HR, 0.78; 0.64, 0.95; p=0.01

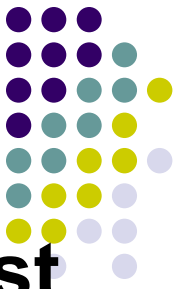


ALDOSTERONE ANTAGONISTS

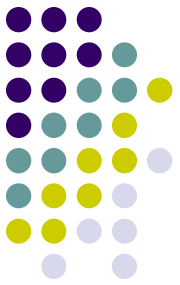
- Spironolactone
- Eplerenone (Inspra®)



Eplerenone – What is it?

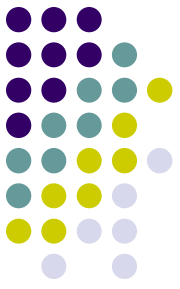


- **Selective aldosterone receptor antagonist (SARA)**
 - Minimal effects at other steroid receptors
 - Limits progestational and antiandrogenic side effects:
 - Gynecomastia
 - Impotence
 - Menstrual irregularities
 - Hirsutism



Other Important Differences

- Half Life
 - Shorter – 4-6h vs ~2-16h (active metabolites)
- Metabolism
 - Inactive metabolites
 - 3A4 involved → *drug interactions*
- Cost
 - ~\$2.60/tab
 - Exceptional Access in Ontario



Drug Interactions

- **Contraindicated:**
 - Potassium-sparing diuretics
 - K⁺ supplements
 - Strong CYP 3A4 inhibitors:
 - Ketoconazole, Itraconazole
 - Nefazodone
 - Clarithromycin, Telithromycin
 - Ritonavir, Nelfinavir

Drug Interactions



- **Mild-to-moderate inhibitors:** “dose should not exceed 25mg”
 - Amiodarone
 - Verapamil, Diltiazem
 - Erythromycin, Fluconazole
 - Saquinavir
- **Potent CYP-3A4 inducers:** “not recommended”
 - Carbamazepine, Phenytoin, Phenobarb
 - Rifampin
 - St. John’s Wort

What's New in Heart Failure?



Heart Rate Reduction?

Heart Rate Lowering Therapy

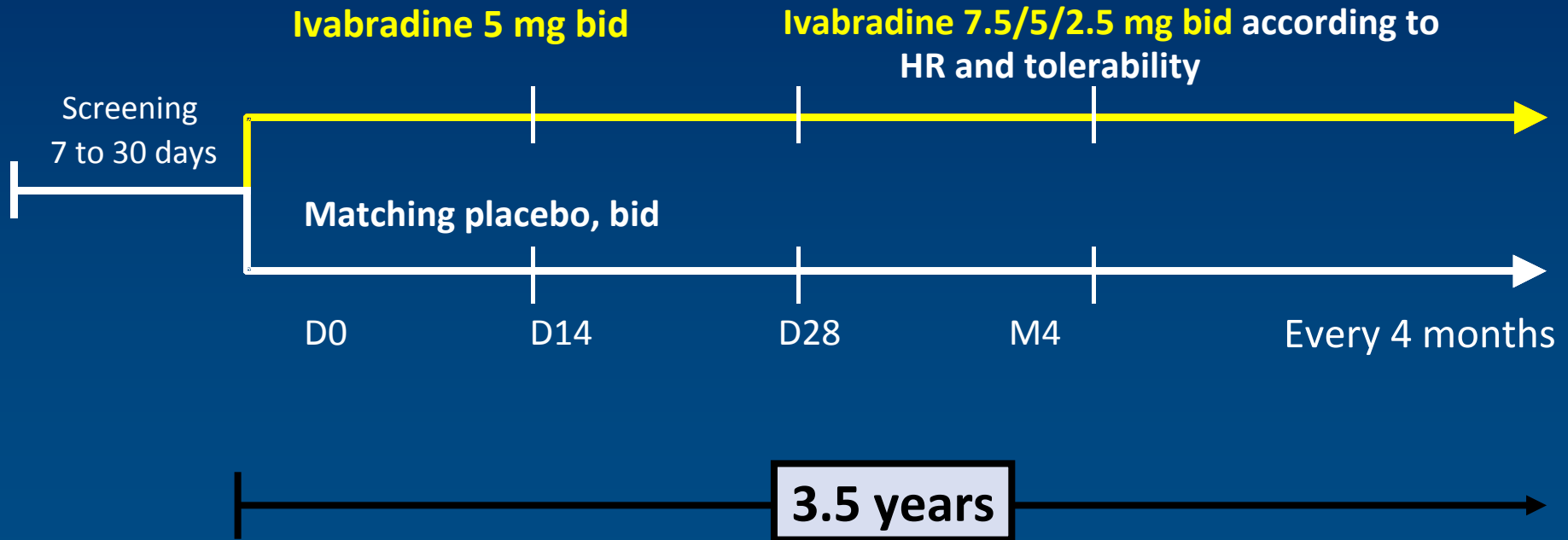


- Raised resting HR predicts CV events^{1,2}
 - HF hospitalizations
- Beta blockers continue to be underused or underdosed
 - Some patients have persistently high resting HR despite beta blocker therapy
- Other means of lowering resting HR?



Systolic **H**ear**f** failure treatment with
the **I**f inhibitor ivabradine **T**rial

Study Design



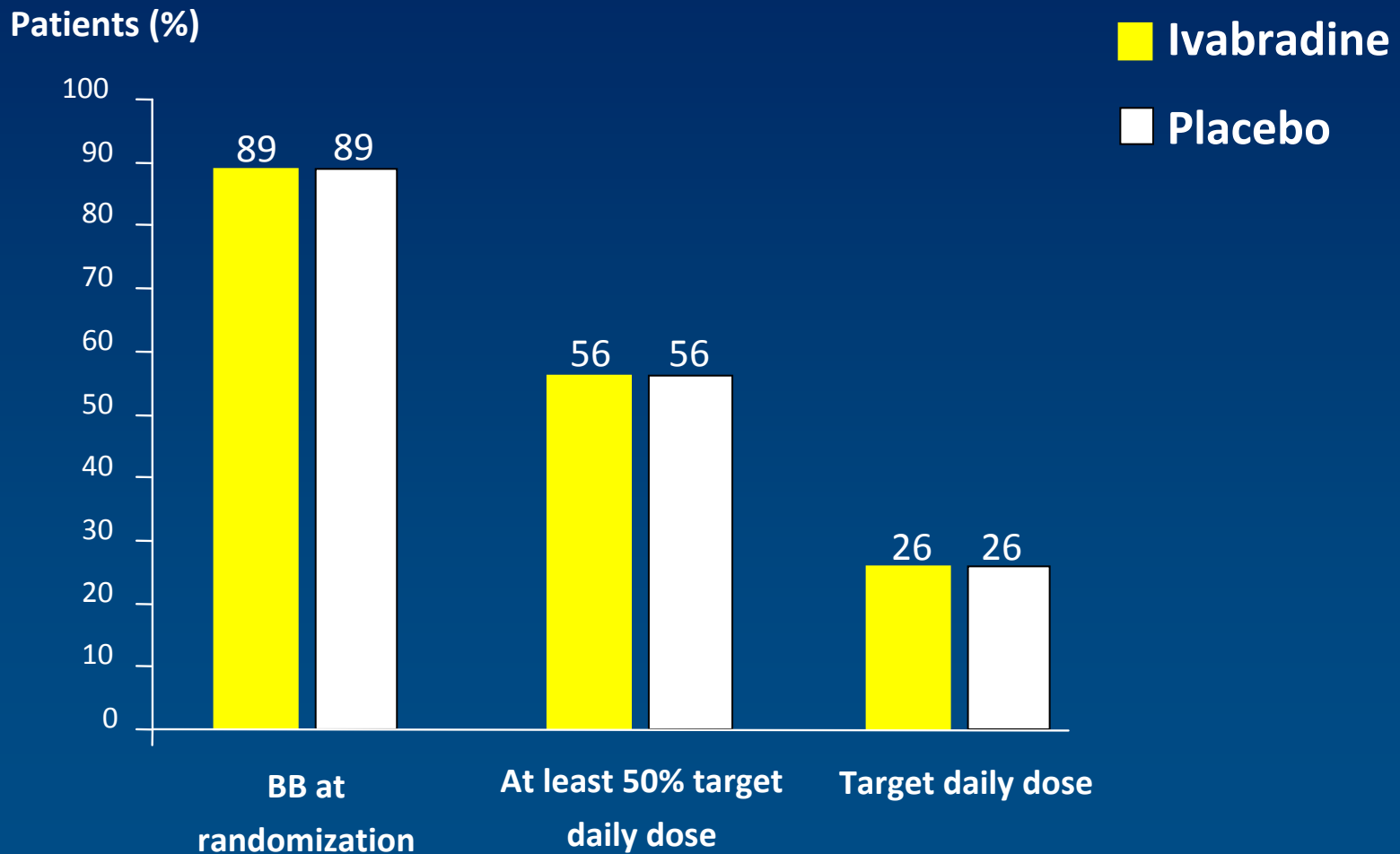
Baseline Characteristics

	Ivabradine	Placebo
	3241	3264
Mean age, y	60.7	60.1
Male, %	76	77
Ischaemic aetiology, %	68	67
NYHA II, %	49	49
NYHA III/IV, %	51	51
Previous MI, %	56	56
Diabetes, %	30	31
Hypertension, %	67	66

Baseline Characteristics

	Ivabradine 3241	Placebo 3264
Mean heart rate, bpm	80	80
Mean LVEF, %	29	29
Mean SBP, mm Hg	122	121
Mean DBP, mm Hg	76	76
eGFR, mL/min/1.73 m ²	75	75

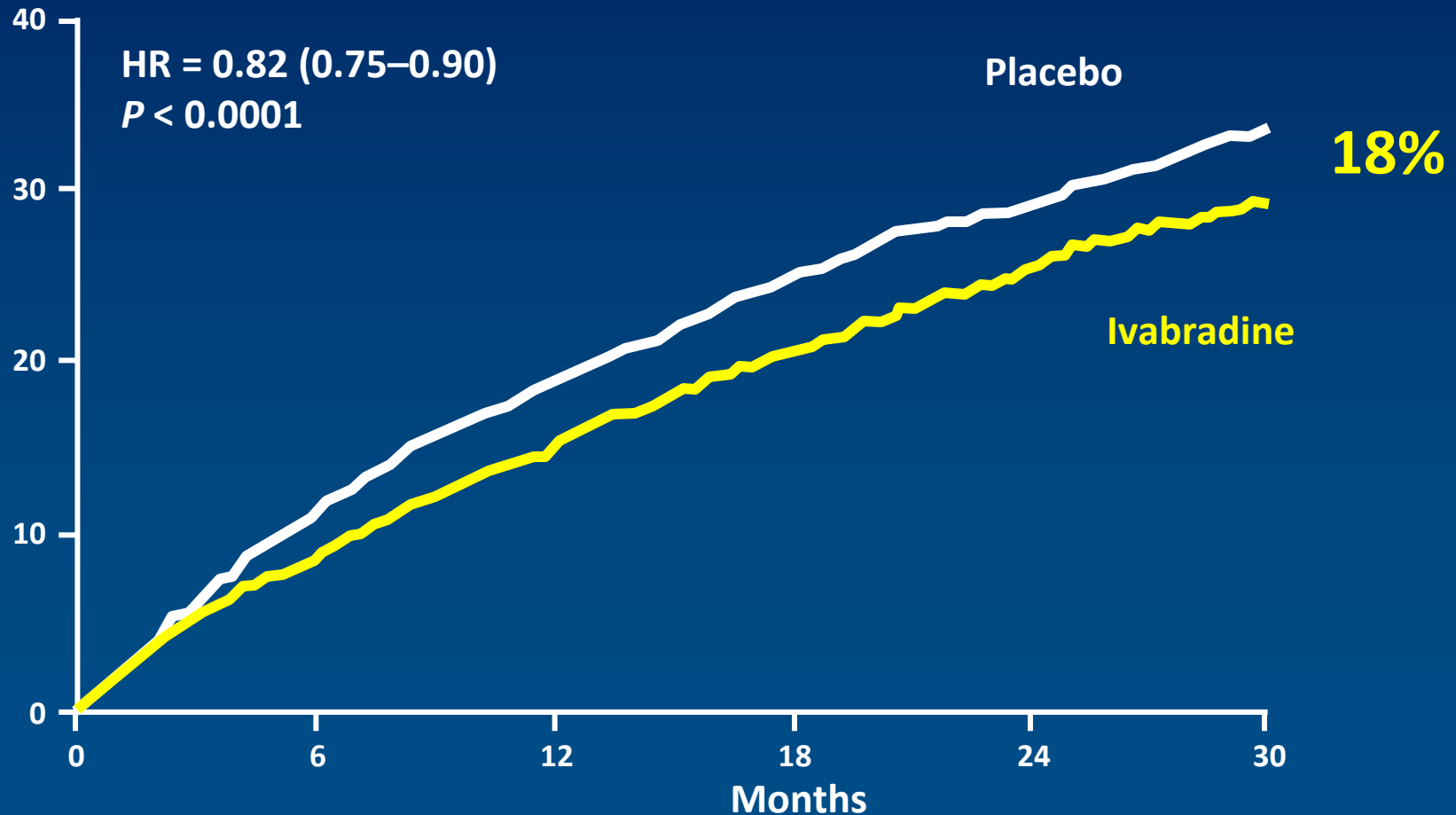
Background Beta-blocker Treatment



Primary Composite Endpoint

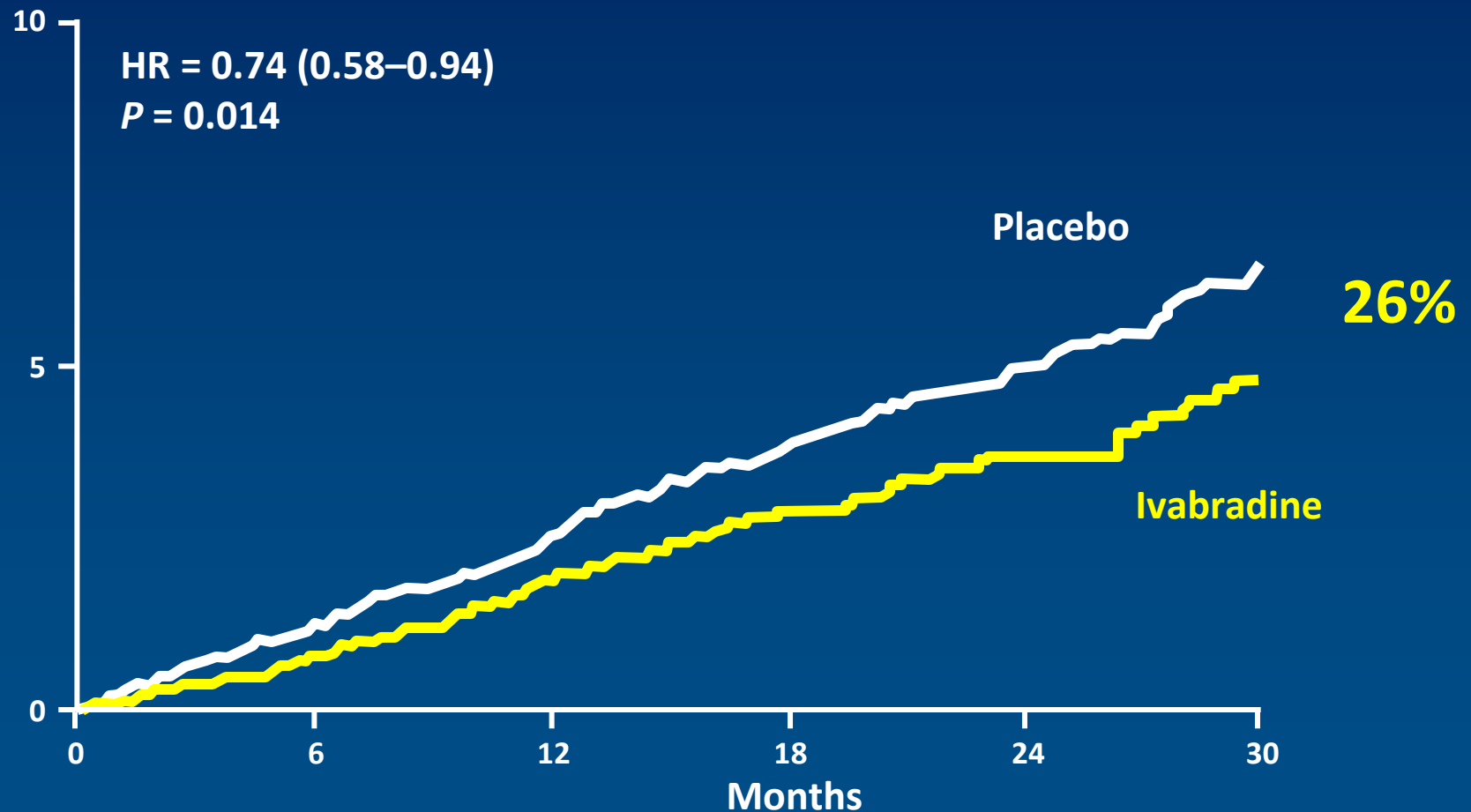
(CV death or hospital admission for worsening HF)

Cumulative frequency (%)



Death from Heart Failure

Cumulative frequency (%)



Effect of Ivabradine on Outcomes

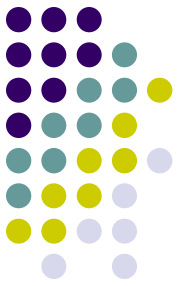
Endpoints	Hazard ratio	95% CI	<i>p</i> value
Primary composite endpoint (CV death or hospital admission for worsening HF)	0.82	[0.75;0.90]	<i>p</i> <0.0001
All-cause mortality	0.90	[0.80;1.02]	<i>p</i> =0.092
Death from heart failure	0.74	[0.58;0.94]	<i>p</i> =0.014
All-cause hospital admission	0.89	[0.82;0.96]	<i>p</i> =0.003
Any CV hospital admission	0.85	[0.78;0.92]	<i>p</i> =0.0002
CV death/hospital admission for HF or non-fatal MI	0.82	[0.74;0.89]	<i>p</i> <0.0001

Incidence of Selected Adverse Events (n = 6492)

Patients with an event

	Ivabradine N=3232, n (%)	Placebo N=3260, n (%)	<i>p</i> value
All serious adverse events	1450 (45%)	1553 (48%)	0.025
All adverse events	2439 (75%)	2423 (74%)	0.303
Symptomatic bradycardia	150 (5%)	32 (1%)	<0.0001
Asymptomatic bradycardia	184 (6%)	48 (1%)	<0.0001
Atrial fibrillation	306 (9%)	251 (8%)	0.012
Phosphenes	89 (3%)	17 (1%)	<0.0001
Blurred vision	17 (1%)	7 (<1%)	0.042

What's New in Heart Failure?



Diuretic Therapy

Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE)

G. Michael Felker, MD, MHS, FACC
Christopher M. O'Connor, MD, FACC

on behalf of the

NHLBI Heart Failure Clinical Research Network

Study Design

Acute Heart Failure (1 symptom AND 1 sign)
Home diuretics dose ≥ 80 mg and ≤ 240 mg furosemide
<24 hours after admission

2x2 factorial randomization

High Dose (2.5x oral)
Continuous infusion

High Dose (2.5x oral)
Q12 IV bolus

Low Dose (1x oral)
Continuous infusion

Low Dose (1 x oral)
Q12 IV bolus

48 hours

- 1) Change to oral
- 2) continue current dose
- 3) 50% increase in dose

72 hours

Co-Primary endpoints:

Change in creatinine from baseline to 72 hours
Patient Global Assessment VAS area under curve over 72 hours

Inclusion Criteria

- ≥ 18 years old, within 24h of admission
- Prior clinical diagnosis of heart failure with daily home use of oral loop diuretic for at least one month
- Daily oral dose of furosemide ≥ 80 mg and ≤ 240 mg (or equivalent)
- Heart failure defined by at least **1 symptom** (dyspnea, orthopnea, or edema) AND **1 sign** (rales on auscultation, peripheral edema, ascites, pulmonary vascular congestion on chest radiography)
- Anticipated need for IV loop diuretics for at least 48 hours

Exclusion Criteria

- Received or planned IV vasoactive treatment (inotropes, vasodilators) or ultra-filtration therapy for heart failure
- Systolic BP <90 mmHg
- Serum creatinine >3.0 mg/dl at baseline or renal replacement therapy
- Acute coronary syndrome within 4 weeks
- Anticipated need for coronary angiography or other procedures requiring IV contrast

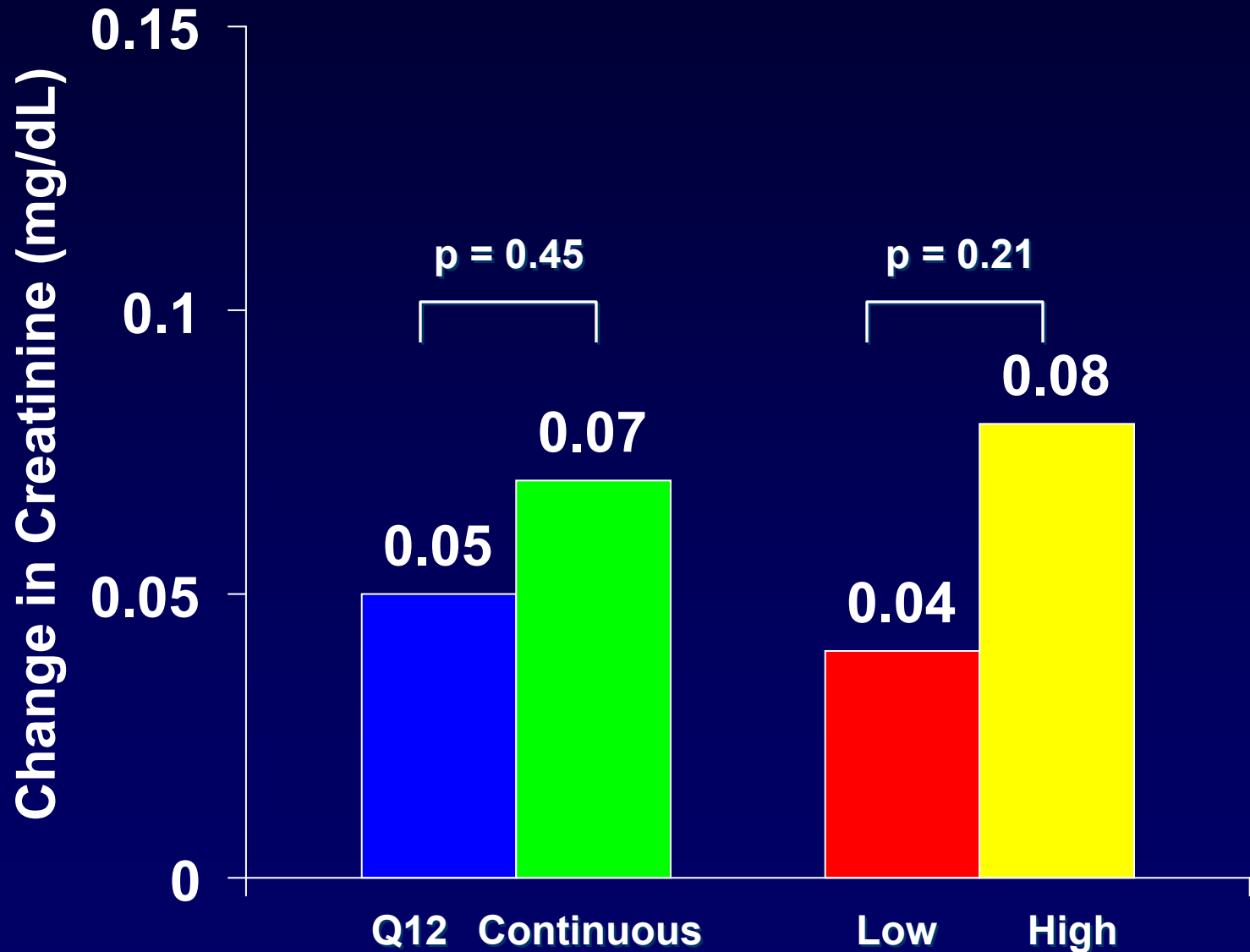
Patients

- 66y, 73% male, 72% caucasian, 50% DM
- Furosemide baseline ~130mg/day
- 74% CHF hospitalization in last 12 months
- EF~35%
- Mean SBP: 119
- Mean Cr: ~140umol/L
- Median time to randomization: 14h

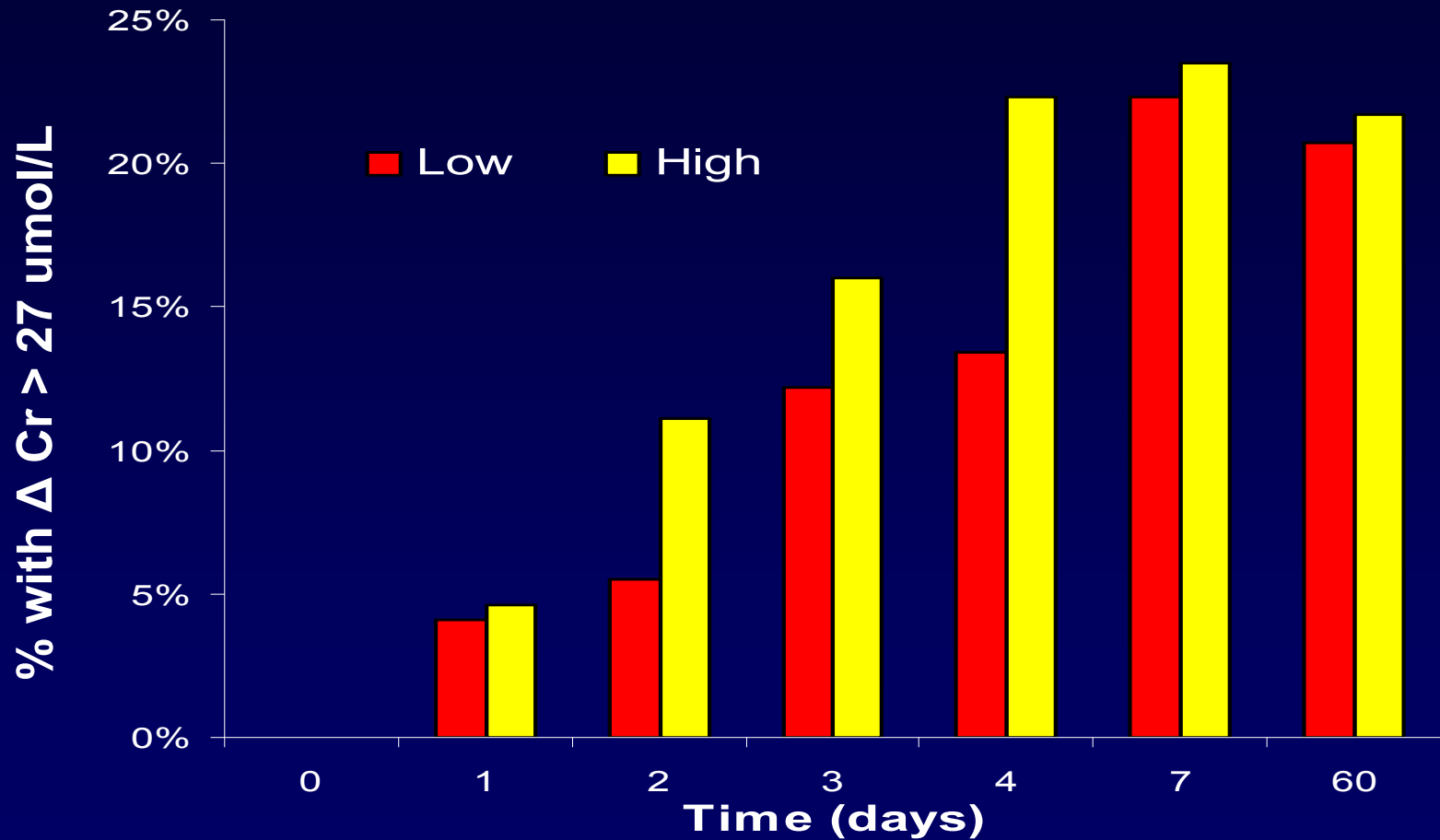
Results: Primary Endpoint

- No difference in PGA VAS
 - P=0.47 for CI vs Q12H
 - P=0.06 for HD vs LD
- Change in Creatinine?

Change in Creatinine at 72 hours

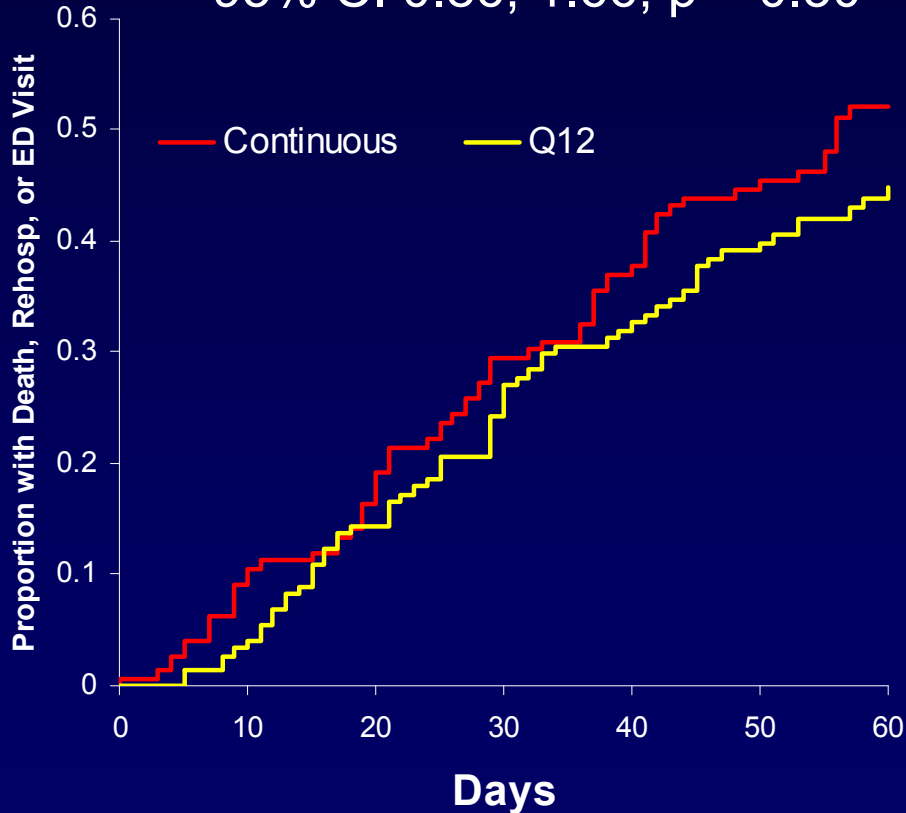


Proportion with Worsening Renal Function: High vs. Low

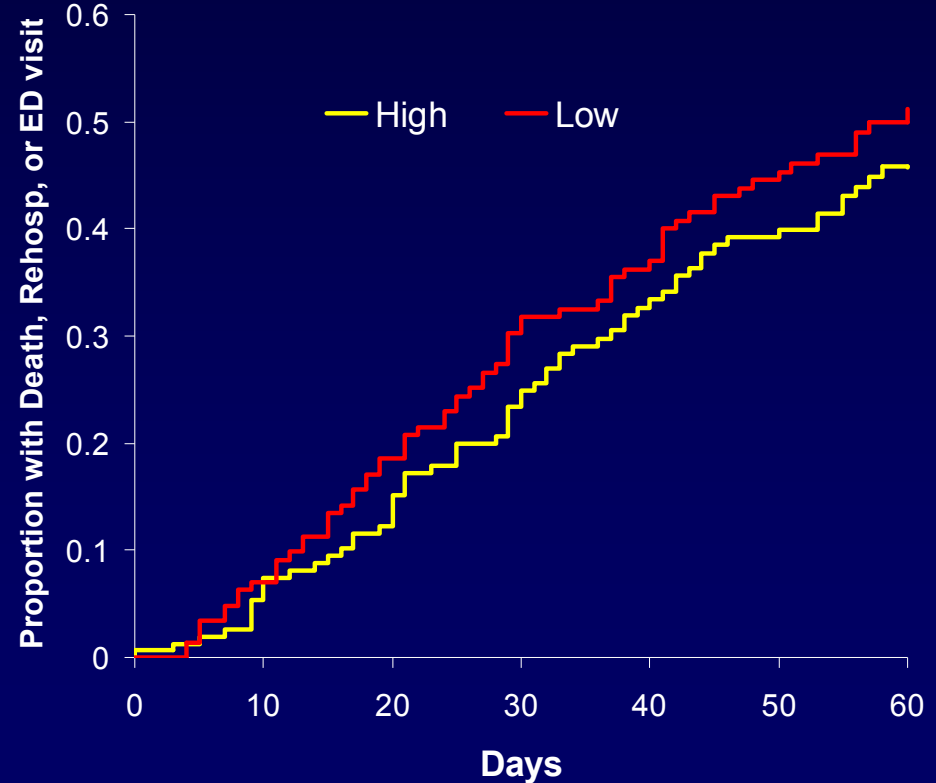


Death, Rehospitalization, or ED Visit

HR for Continuous vs. Q12 = 1.19
95% CI 0.86, 1.66, p = 0.30



HR for High vs. Low = 0.83
95% CI 0.60, 1.16, p = 0.28



Secondary Endpoints: Low vs. High Intensification

	Low	High	P value
Dyspnea VAS AUC at 72 hours	4478	4668	0.041
% free from congestion at 72 hrs	11%	18%	0.091
Change in weight at 72 hrs	-5.3 lbs	-8.2 lbs	0.011
Net volume loss at 72 hrs	3575 mL	4899 mL	<0.001
% Treatment failure	37%	40%	0.56
% with Cr increase > 25umol/L at 72 hrs	14%	23%	0.041
Length of stay, days (median)	6	5	0.55

Conclusions

- There was no statistically significant difference in global symptom relief or change in renal function at 72 hours for either:
 - Intermittent bolus vs. continuous infusion
 - Low intensification vs. high intensification