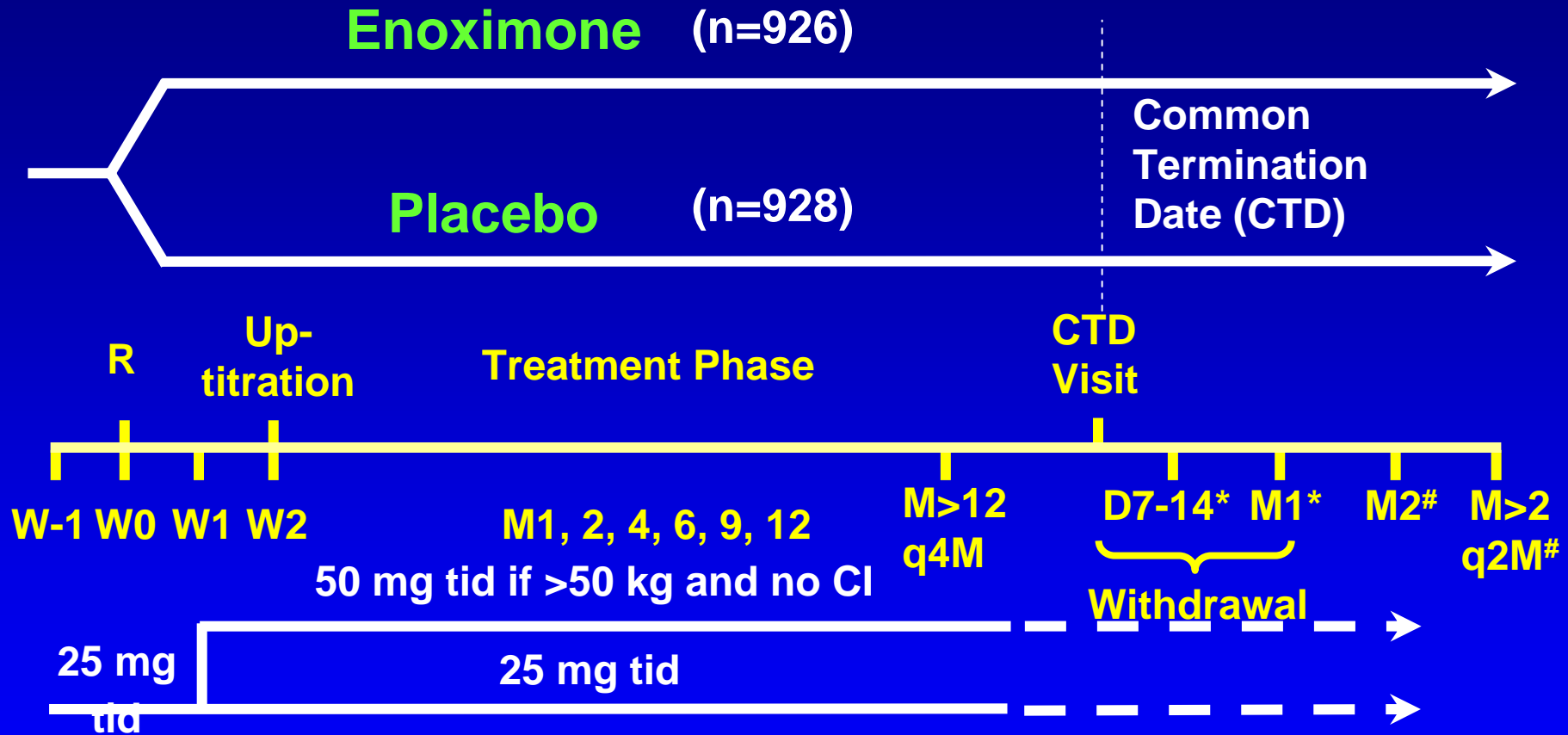


COMMENTARY on the ESSENTIAL trial

M S Nieminen, Helsinki

**Disclosures: Lecturing and grants -
MSD, Pfizer, GSK, Orionpharma, Abbott,
Sanofi, Medtronic**

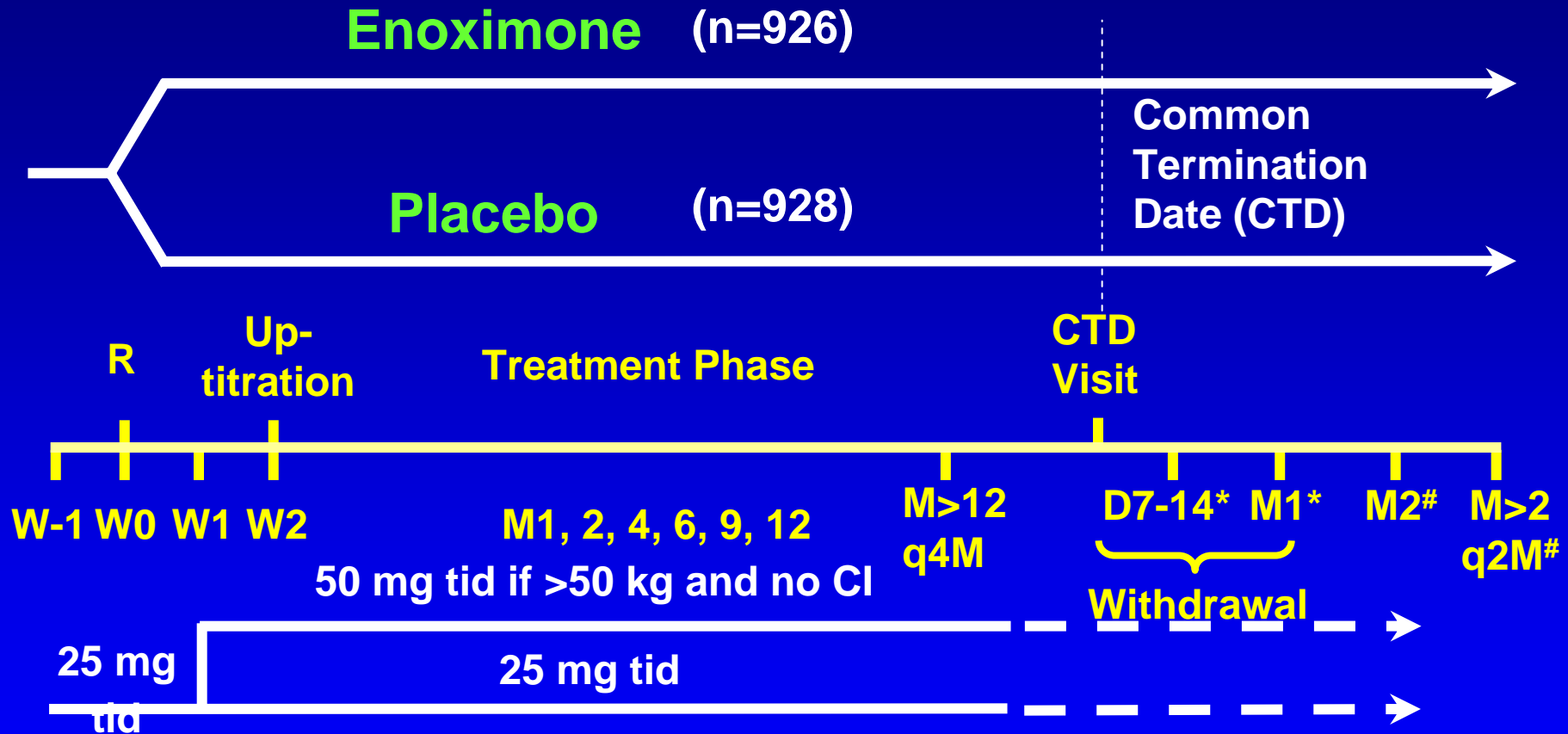
ESSENTIAL Study Design



*Patients resume blinded study drug if clinical deterioration occurs

#For patients that resumed blinded study drug only

ESSENTIAL Study Design

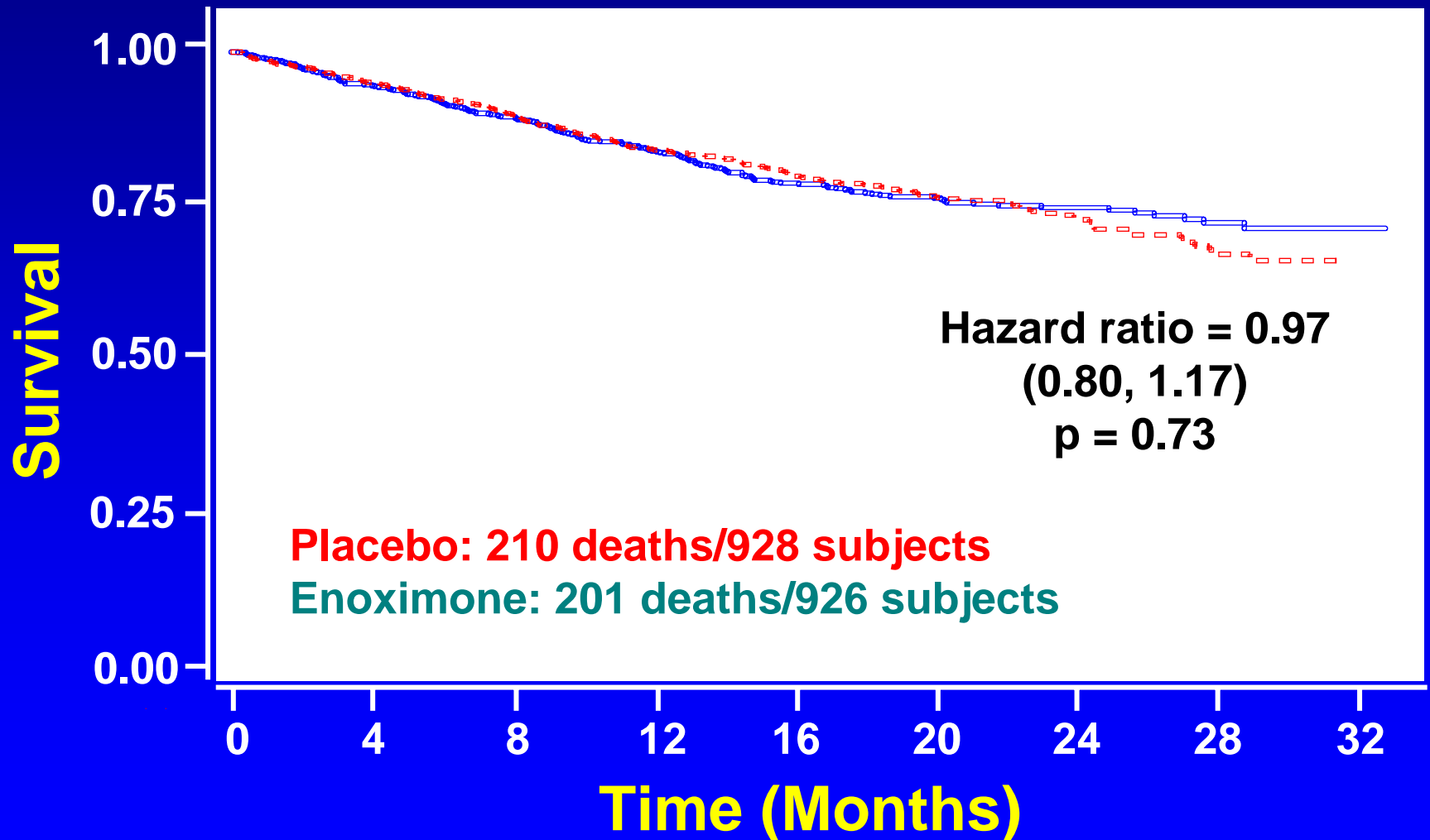


This dose is half or less than normally used to substitute iv inotropic therapy, EHJ 1994

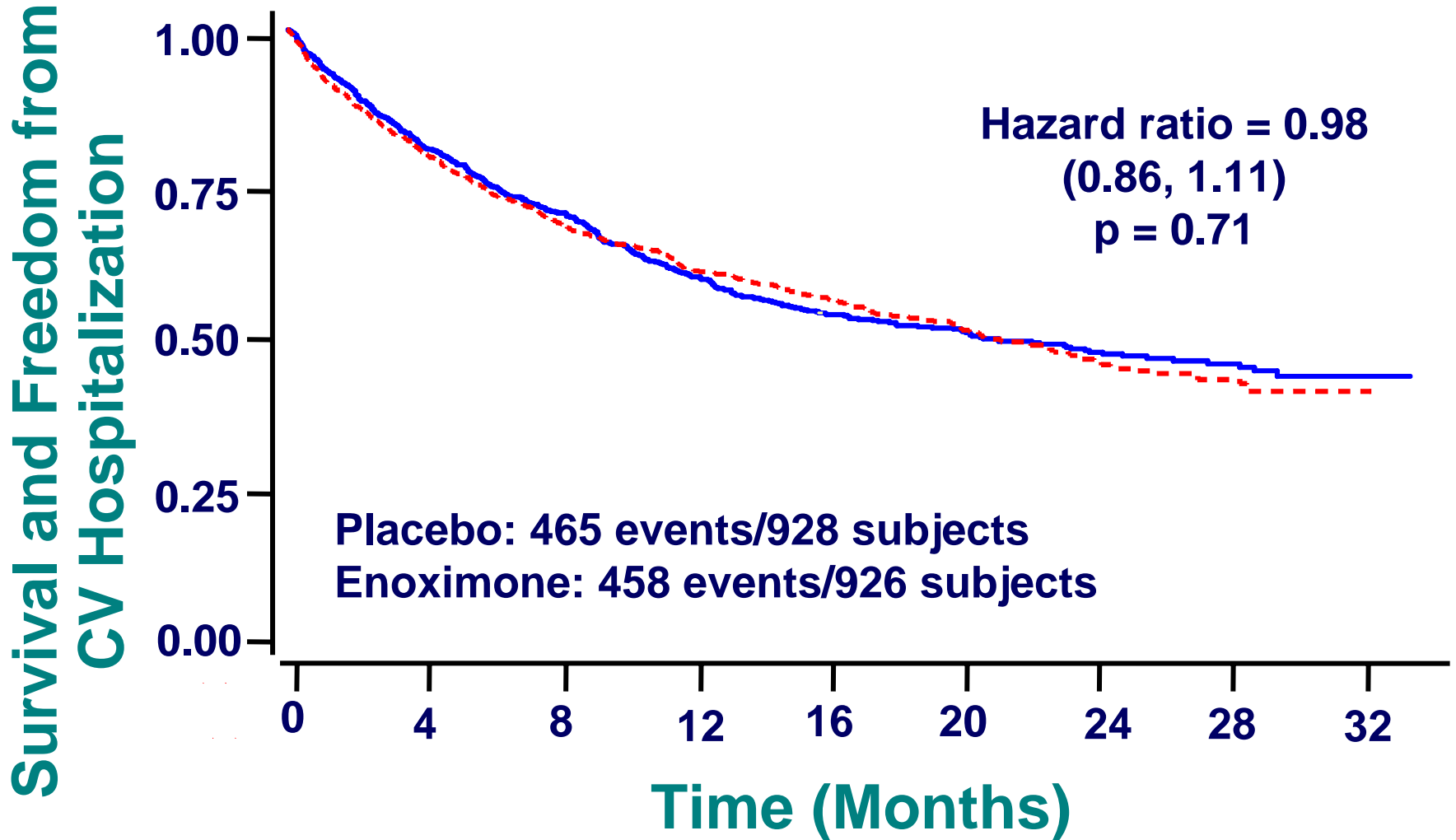
*Patients resume blinded study drug if clinical deterioration occurs

#For patients that resumed blinded study drug only

Time to All-Cause Mortality (MY-021/MY-026 Combined)



Time to All-Cause Mortality or CV Hospitalization (MY-021/MY-026 Combined)

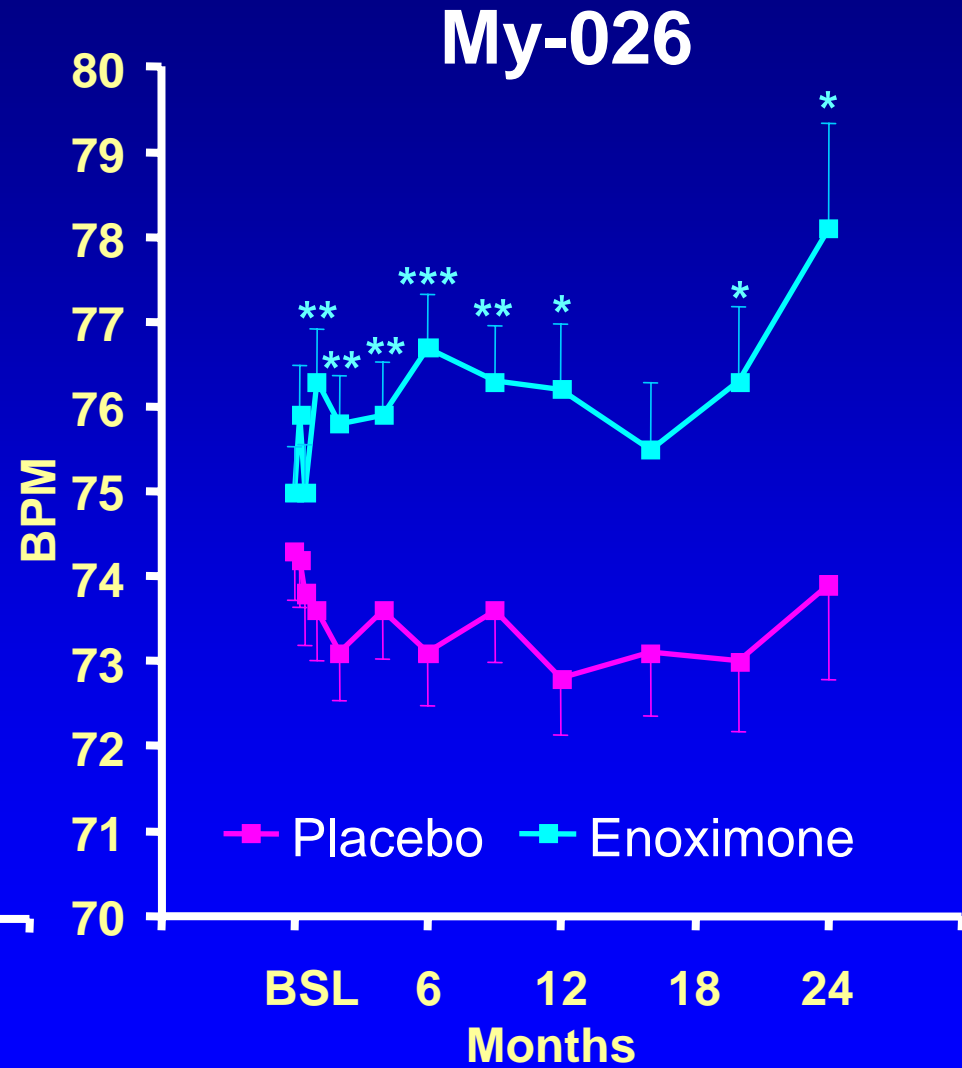
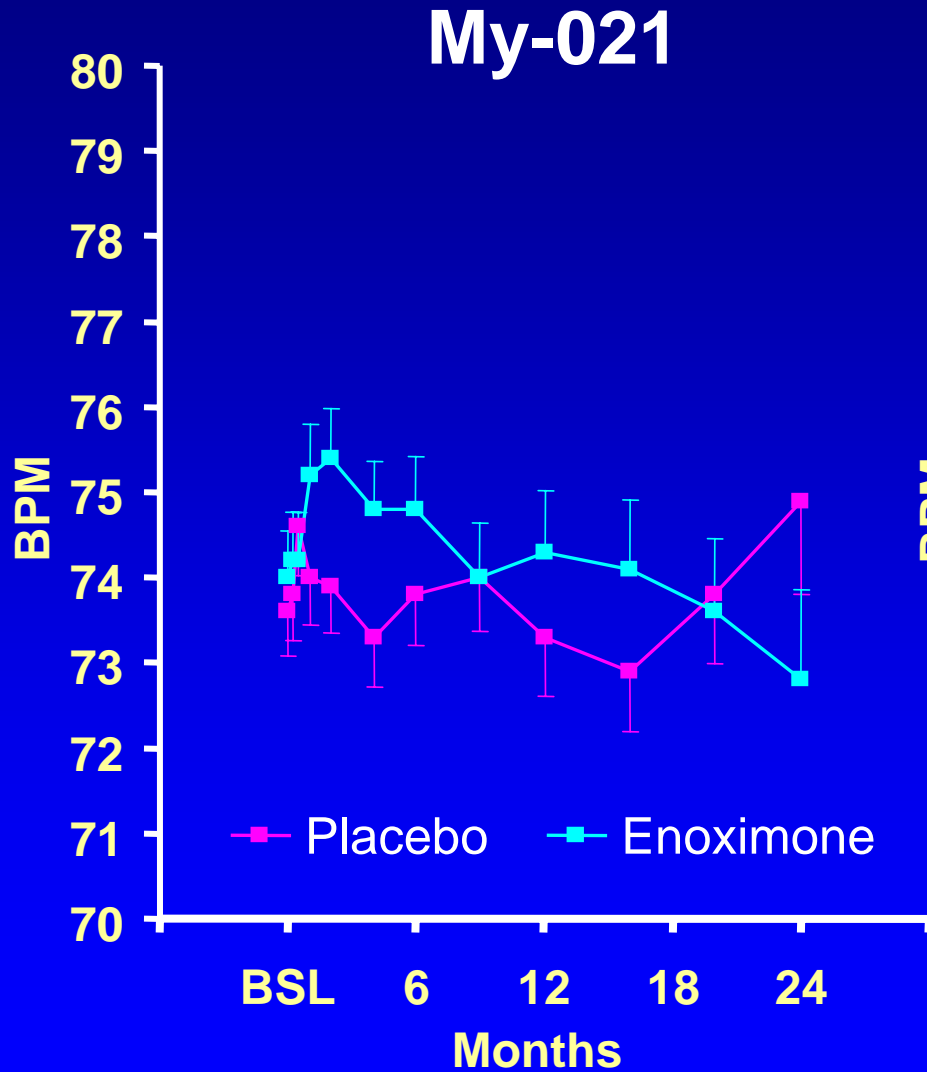


Most Frequently Reported Adverse Events

Event Term	Placebo (n=928) n (%)	Enoximone (n=926) n (%)	Total (n=1854) n (%)
Cardiac Failure Aggravated	364 (39)	360 (39)	724 (39)
Dizziness	102 (11)	115 (12)	217 (12)
Hypotension	94 (10)	113 (12)	207 (11)
Diarrhea NOS	62 (7)	110 (12)	172 (9)
Chest pain	90 (10)	82 (9)	172 (9)
Nausea	64 (7)	77 (8)	141 (8)
Palpitations	47 (5)	74 (8)	121 (7)
Hyperkalemia	64 (7)	57 (6)	121 (7)
Hypokalemia	65 (7)	69 (7)	134 (7)
Blood creatinine increased	62 (7)	61 (7)	125 (7)
Cough	64 (7)	61 (7)	125 (7)
Headache NOS	54 (6)	59 (6)	113 (6)
Sudden death unexplained	54 (6)	57 (6)	111 (6)
Atrial fibrillation	48 (5)	43 (5)	91 (5)

$p \leq 0.01$

Mean Heart Rate (SE) Over Time



*p<0.02

**p<0.01

***p<0.001

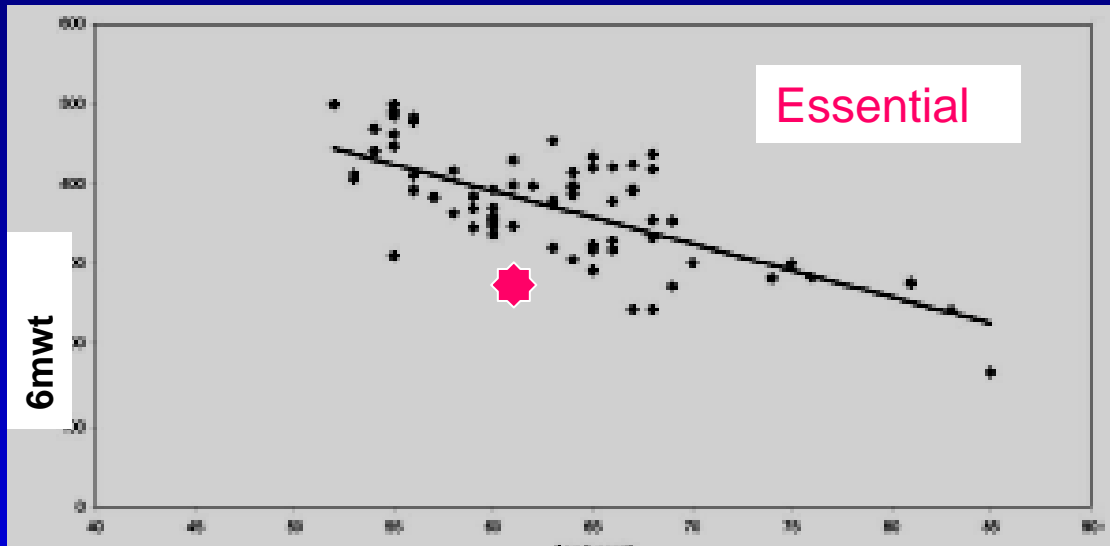
(MY-021) N/S America / (MY-026) E/W Europe

- American pts, had more carvedilol, digitalis,
 - were more often DCMP pts,
 - had lower EF, lower 6mwt, lower SBP
 - in general worse *
 - It was reported that the median 6mwt improved in MY-021
 - the median change of benefit presented, is difficult to understand, mean change could be more appropriate!
 - They experienced less HR increase and in those with lower EF ” 6mwt” improved
 - (posthoc analysis)
- * compare with the Optime study

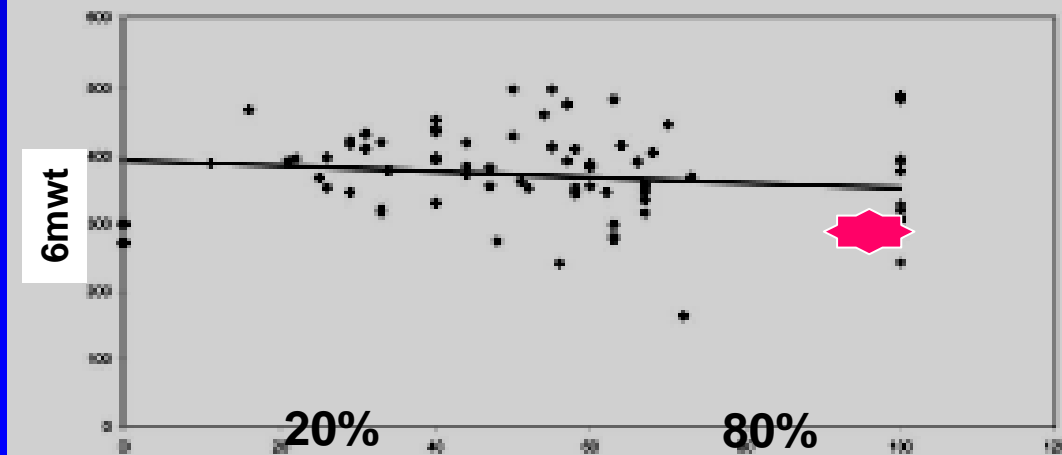
ESSENTIAL

- **There was no benefit.**
- **Enoximone patients experienced more GI symptoms 7 / 12 % and palpitation 5 / 8 %**
- **The HR (incr in EU pts) is difficult to interpret, or SBP in US at later phase**

Six minute corridor walk test as an outcome measure for the assessment of treatment in randomized, blinded intervention trials of chronic heart failure: a systematic review



Baseline 6MWT distance by age(years) in 37 trials.



Baseline 6MWT distance by severity of NYHA class (% NYHA III/IV) in 37 trials. (scale 20,40,60,80,100%)

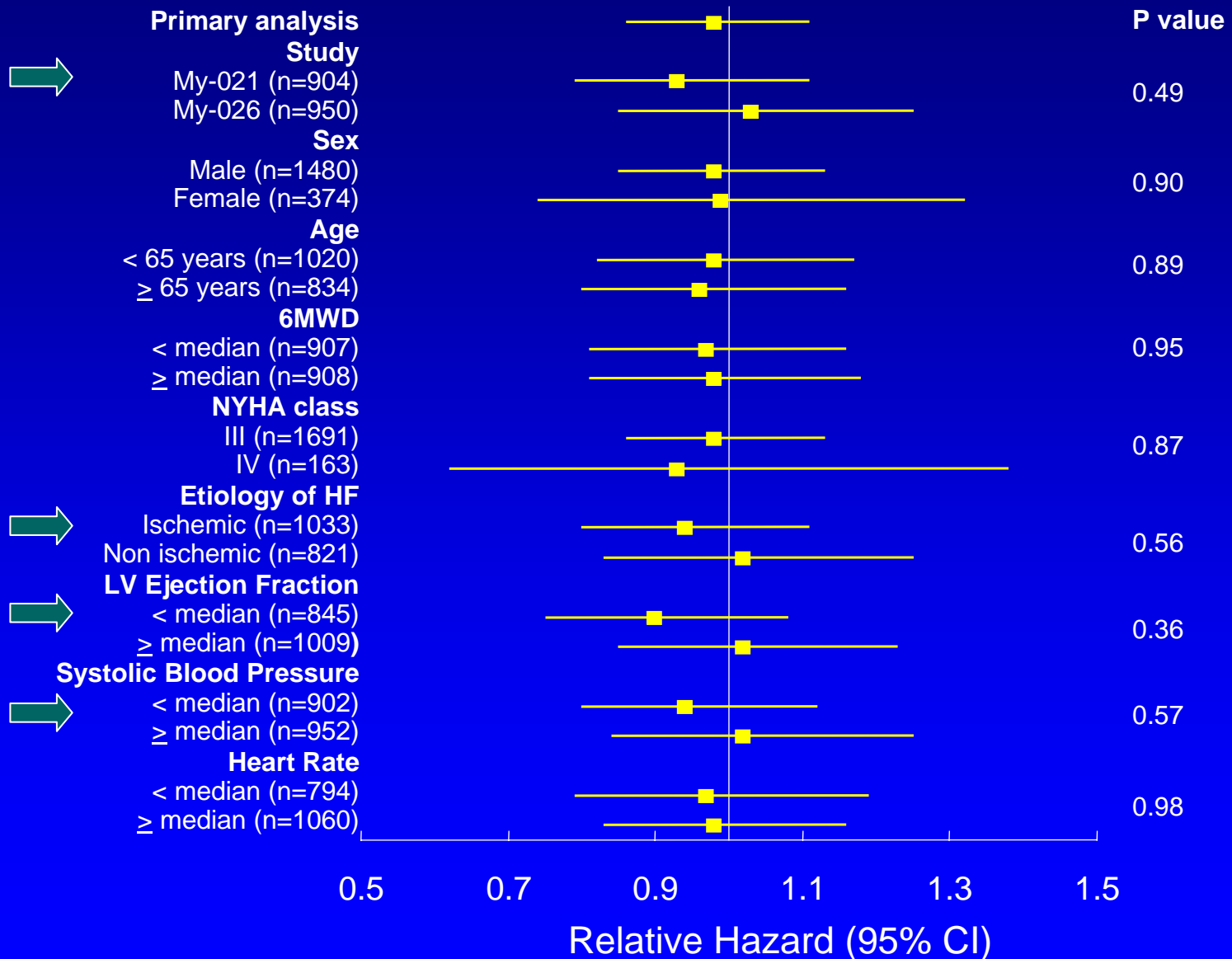
6 mwt is a robust estimate and surrogate endpoint in HF trials, affected by age, sex and severity

Learning effect in repeated testing

Low correlation with symptoms and MVO₂

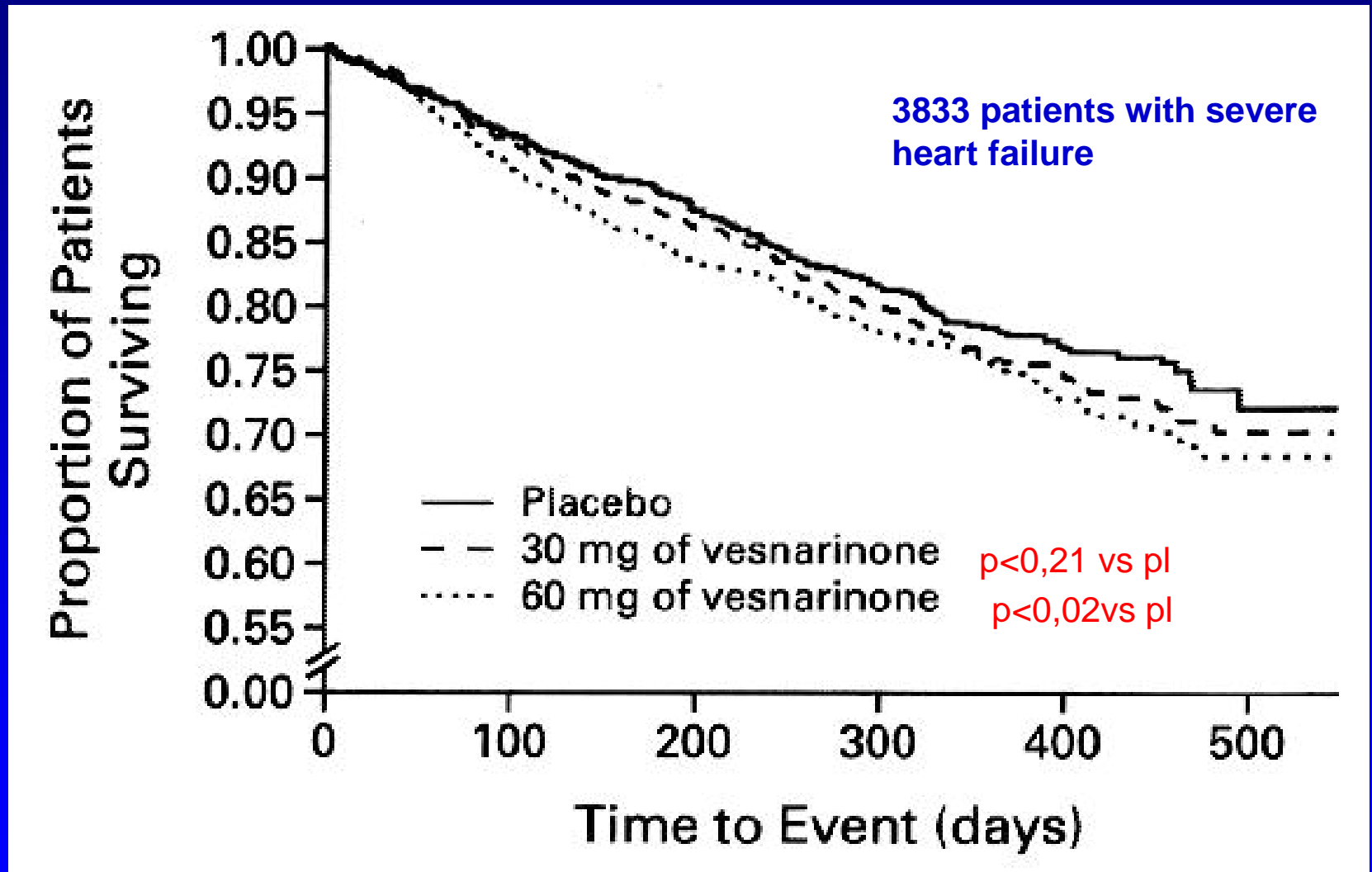
Lars G. Olsson¹, Karl Swedberg^{1*}, Andrew L. Clark², Klaus K. Witte², and John G.F. Cleland² European Heart Journal (2005) 26, 778–793

All-cause Mortality or CV Hospitalizations: Subgroup analysis



A Dose-Dependent Increase in Mortality with Vesnarinone among Patients with Severe Heart Failure

Cohn, J et al NEJM 1998



Cohn: N Engl J Med, Volume 339(25).December 17, 1998

Essentials observations from ESSENTIAL

- in most of the HF patients
 - No benefit (pt self estimation and m 6mwt)
 - No harm, (mortality not incr) was observed with low dose enoximone combined with conventional HF therapy including BBL

Essentials observations from ESSENTIAL

- **in most of the HF patients**
 - **No benefit (pt self estimation and m 6mwt)**
 - **No harm, (mortality not incr)**
- **No recommendation can be given based on Essential results although some patients may have benefitted in quality of life by 6mwt (low EF, low SBP), which requires further testing in prespecified group.**

Submaximal Exercise at 6 Months Post-Randomization

