



PEP-CHF

Perindopril in Elderly People with Chronic Heart Failure

**John GF Cleland, Michal Tendera, Jerzy Adamus,
Nick Freemantle, Lech Polonski, Jacqueline Taylor
on behalf of PEP-CHF investigators**

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Background

- About 50% of patients with a clinical diagnosis of HF have neither a low LV ejection fraction nor major valve disease
- Many of these patients are believed to have HF due to diastolic dysfunction
- The prevalence of HF and the proportion due to ‘diastolic’ dysfunction increase with age
- It is uncertain whether treatments for HF, including ACE inhibitors, are effective in this group of patients



Death and Readmission for Heart Failure

Study	Yr	N & %	Age#	FU	Mortality		HF re-admission	
					LVSD	PLVSF	LVSD	PLVSF
Philbin	00	312 (24%)	75	6	18%	15%	24%	22%
Ahmed	01	430 (55%)	NA	6	35%	27%	54%	52%
Smith	03	200 (48%)	73	12	21%	13%	22%	16%
EHFS-1	03	3,148 (46%)	71	3	12%	10%	22%	16%
Owan	06	2,167 (47%)	74	12	32%	29%	NA	NA
Bhatia	06	880 (31%)	75	12	26%	22%	36%*	31%*

>30% patients in surveys <70 years
Older patients have worse outcome

* Death or re-admission for heart failure



Aim

To compare the effects of perindopril and placebo on morbidity and mortality in older patients with clinical evidence of heart failure secondary to left ventricular diastolic dysfunction



Main Inclusion / Exclusion criteria

- Age ≥ 70 years
- Cardiovascular hospitalisation in the previous 6 months
- Clinical diagnosis of heart failure (≥ 3 of 9 clinical criteria)
- Treated with diuretics
- Evidence of diastolic dysfunction
- Serum creatinine $< 200 \mu\text{mol/L}$



Diagnosis: *Echocardiography*

≥ 2 of 4 echocardiographic criteria had to be fulfilled

- **LV wall motion index of 1.4 to 1.6 inclusive**
- **Left atrial diameter $>25\text{mm}/\text{m}^2$ or > 40 mm**
- **Septal or posterior LV wall $>12\text{mm}$ in thickness**
- **Impaired LV filling by ≥ 1 criteria recommended by ESC Study Group on DHF (1998) or AF**



Intervention

- **Randomization**
 - Blocks of 4 within treatment centres
 - Centrally administered process blind to the study investigators
- **No diuretic for 24 hours prior to 1st dose of perindopril 2mg open-label**
- **Patients tolerating the test dose randomly assigned to**
 - Perindopril 2mg/day or matching placebo
- **Weekly monitoring of BP and renal function for first 5 wks then at 8 wks and then every 12 wks thereafter**
- **Perindopril or matching placebo increased to 4mg/day provided there was no contra-indication**



Primary composite endpoint

- **All-cause mortality or unplanned HF-related hospitalisation**
 - Time-to-first-event analysis
 - Included hospitalisations for HF due to declining renal function, acute vascular events, arrhythmias, infection or unknown causes
 - Independently classified blind to treatment allocation



Secondary Outcomes & Additional Measures

- **Secondary Outcomes**
 - All-cause mortality
 - Cardiovascular mortality
 - HF hospitalisation
 - HF requiring increased diuretic treatment
 - Hospital bed-days (all-cause and CV)
 - NYHA class at one year
- **Additional Measures**
 - 6 minute corridor walk test at 1 year (n=642)
 - NT-proBNP at 1 year (n=279)



Statistical Methods

- **Assumptions:**
 - 500 patients per treatment group
 - Minimum follow-up of one year
 - Annual rate of the primary composite - 50%
 - Reduced by Perindopril to 40%
 - Predicted hazard ratio of 0.74
- **Conventional one sided α of 0.025**
- **90% power assuming 451 primary outcome events**
- **Logrank tests for analysis of the time to first event**
- **Cox's proportional-hazards model to assess risk reduction**
- **Changes in NYHA class, 6MWT and NT-proBNP analysed using ANCOVA or Fisher tests**



Conduct of the Study

- **Enrollment began in year 2000**
- **852 patients enrolled at 53 centres in Bulgaria (3), Czech Republic (5), Hungary (10), Ireland (1), Poland (26), Russia (1), Slovakia (2) and the UK (5)**
 - 209 from UK and Ireland
 - 641 from Central/Eastern Europe
 - Two patients not randomised for administrative reasons
- **All patients tolerated the test dose of perindopril**
- **Mean follow-up 26 months (range 12 to 54)**
- **4 patients lost to follow-up after 9, 28, 28 and 33 months**



Baseline Characteristics

Variable	Perindopril (n = 424)	Placebo (n = 426)
Age, years (<i>IQR</i>)	75 (72 to 79)	75 (72 to 79)
Women, %	54%	57%
Duration of HF, months (<i>IQR</i>)	8 (2 to 38)	11 (2 to 39)
History of high blood pressure (%)	333 (79%)	337 (79%)
Prior MI (%)	116 (27%)	110 (26%)
Diabetes (%)	88 (21%)	87 (20%)
NYHA class I/II (%)	327 (77%)	317 (74%)
6-minute walk distance, meters (<i>IQR</i>)	290 (200 to 372)	297 (200 to 380)
BMI, kg/m ² (<i>IQR</i>)	27.5 (25.1 to 30.0)	27.6 (25.3 to 30.7)
AF (%)	79 (19%)	93 (22%)
Systolic BP (<i>sitting</i>), mmHg (<i>IQR</i>)	138 (128 to 150)	140 (129 to 150)
Creatinine, μmol/L (<i>IQR</i>)	95 (81 to 110)	97 (84 to 111)
NT-proBNP, pg/ml (<i>IQR</i>)	335 (160 to 1014)	453 (206 to 1045)



Baseline Echocardiography

Variable (<i>IQR</i>)	Perindopril (n=424)	Placebo (n=426)
WMI, <i>units</i>	2.0 (1.7 to 2.0)	2.0 (1.7 to 2.0)
LVEF, %	65 (56 to 66)	64 (56 to 66)
LVEED, <i>mm</i>	46 (41 to 51)	46 (42 to 51)
IVS, <i>mm</i>	13 (12 to 15)	13 (12 to 15)
PLV, <i>mm</i>	13 (11 to 14)	12 (11 to 14)
LA Diameter, <i>mm</i>	45 (41 to 48)	44 (41 to 48)
E/A ratio	0.70 (0.50 to 0.90)	0.70 (0.60 to 0.90)
IVRT, <i>msec</i>	107 (80 to 120)	106 (85 to 120)
DCT, <i>msec</i>	210 (165 to 270)	206 (160 to 267)



Baseline Treatment

Variable (%)	Perindopril (n=424)	Placebo (n=426)
Aspirin	283 (67%)	280 (66%)
Oral anticoagulants	71 (17%)	65 (15%)
Beta-blockers	235 (55%)	228 (54%)
Nitrates	226 (53%)	208 (49%)
Calcium channel blockers	135 (32%)	140 (33%)
Loop diuretics	198 (47%)	186 (44%)
Thiazide diuretics	227 (54%)	236 (55%)
Spirolactone	37 (9%)	48 (11%)
Digoxin	45 (11%)	55 (13%)



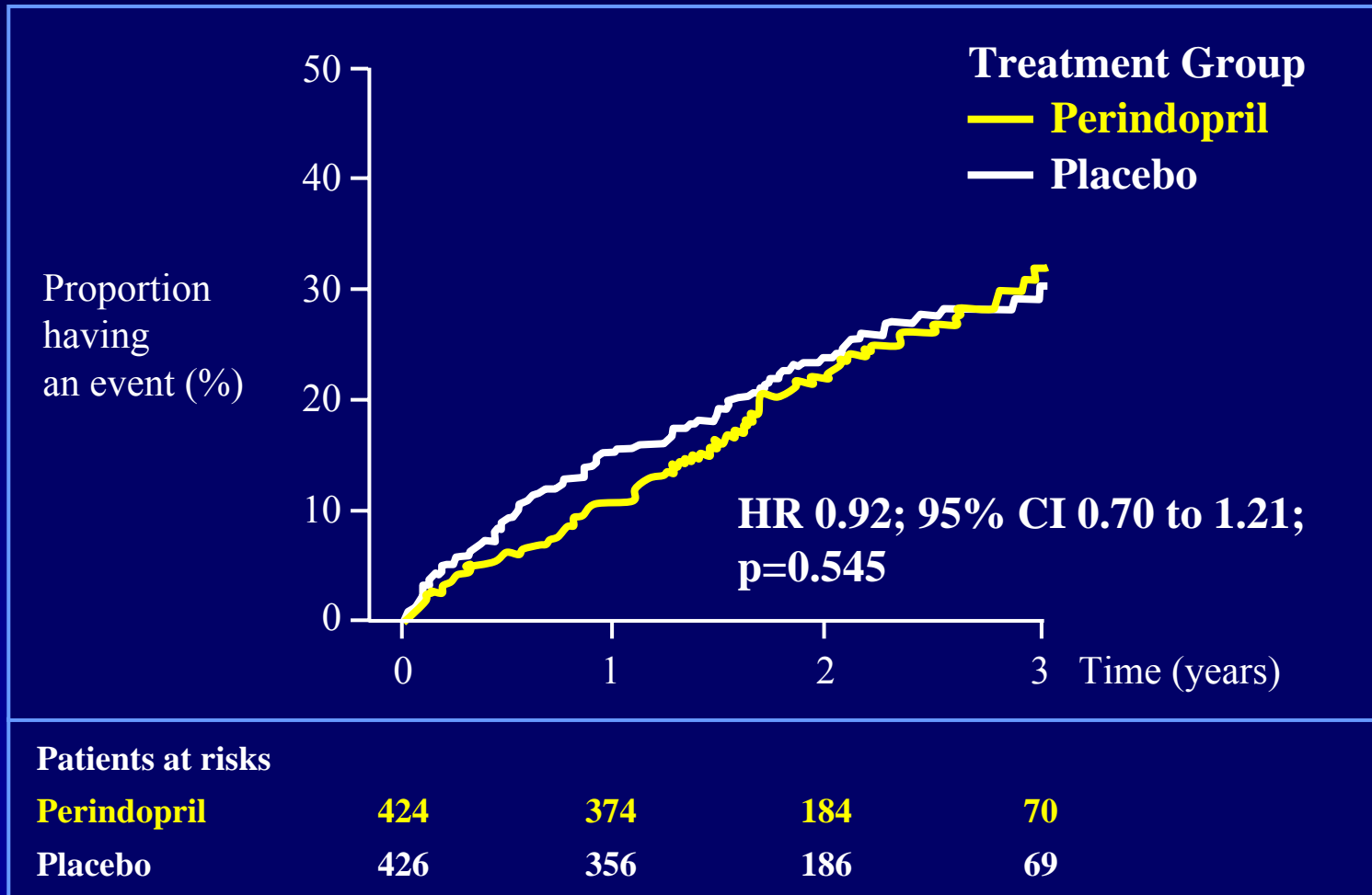
Conduct of the Study

- **Recruitment**
 - Planned enrolment ≤ 1 year & Completion ≤ 2 years
 - Administrative delays and slow recruitment
- **Lower than expected event rate**
- **Adherence to therapy**
 - 90% on assigned therapy at one year
 - By 18 months blinded therapy stopped in
 - 40% assigned to perindopril (~90% started open-label)
 - 36% assigned to placebo (~90% started open-label)
- **Recruitment terminated after 850 patients randomised**
 - All patients followed for a further year to obtain data on symptoms and exercise capacity



Primary end-point

Time to first occurrence of total mortality and unplanned HF

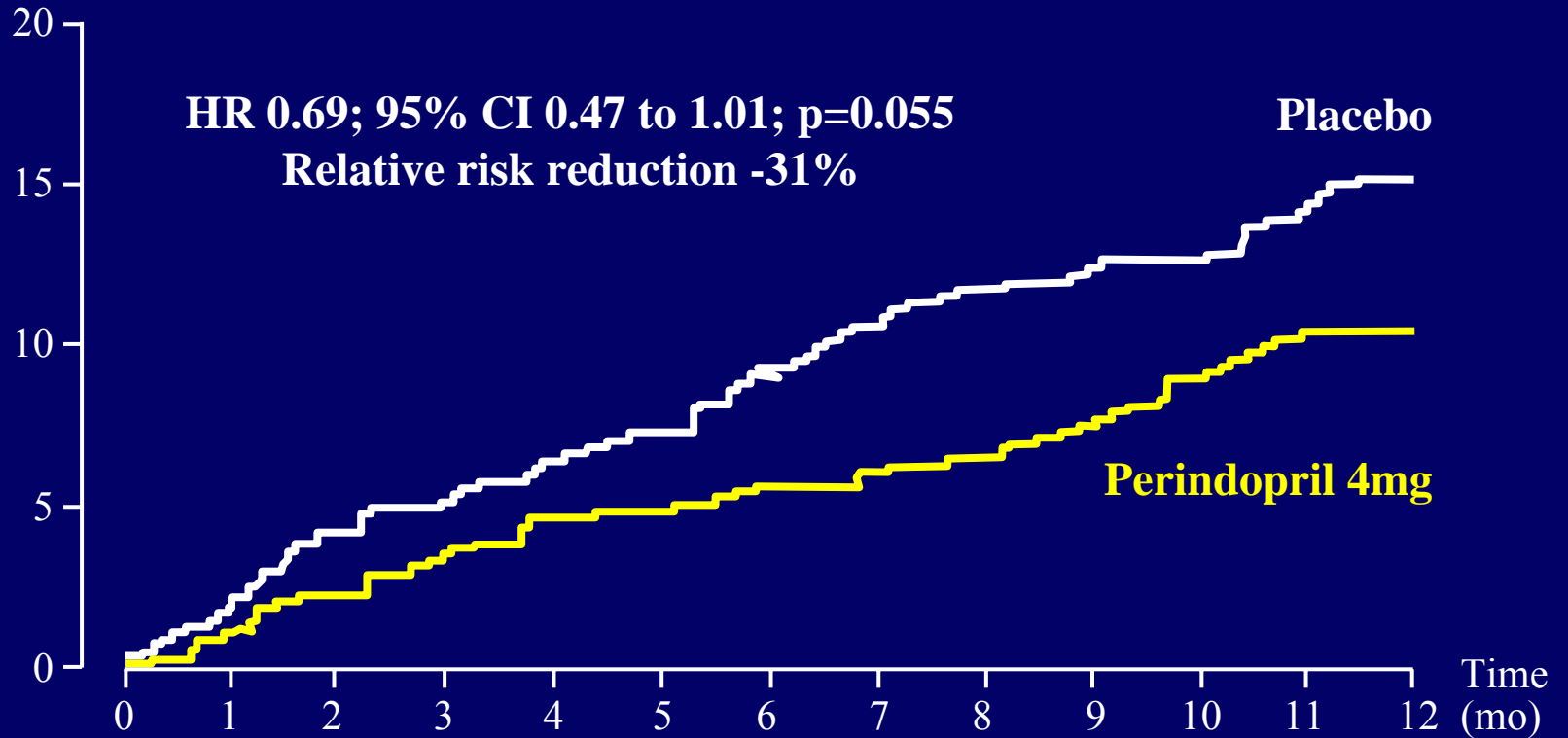




Primary end-point at one year

Time to first occurrence of primary endpoint at 1 year

Proportion having an event (%)



Patients at risks

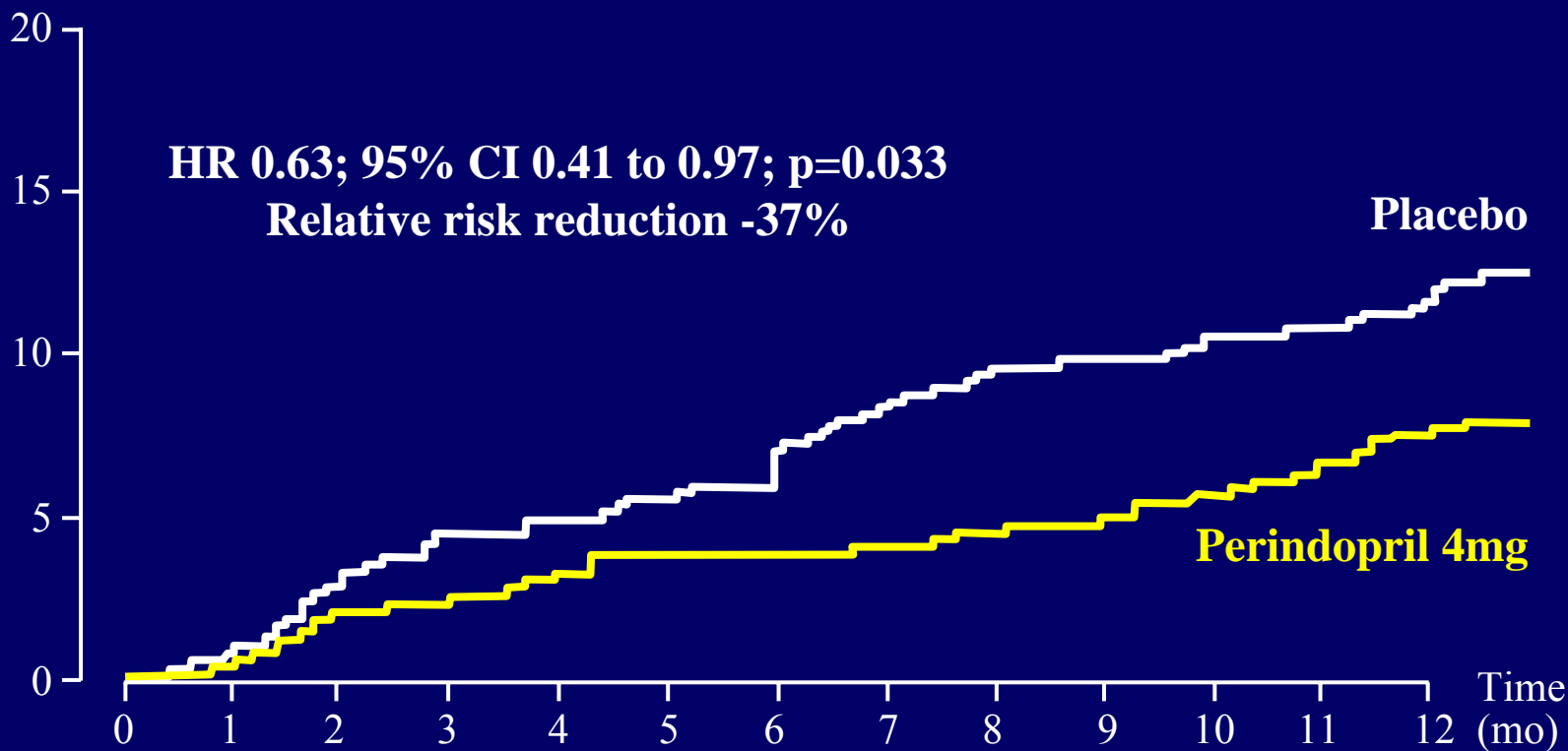
Perindopril	424	408	399	390	374
Placebo	426	405	387	374	356



Unplanned HF at one year

Time to first occurrence of unplanned heart failure related hospitalization at 1 year

Proportion having an event (%)

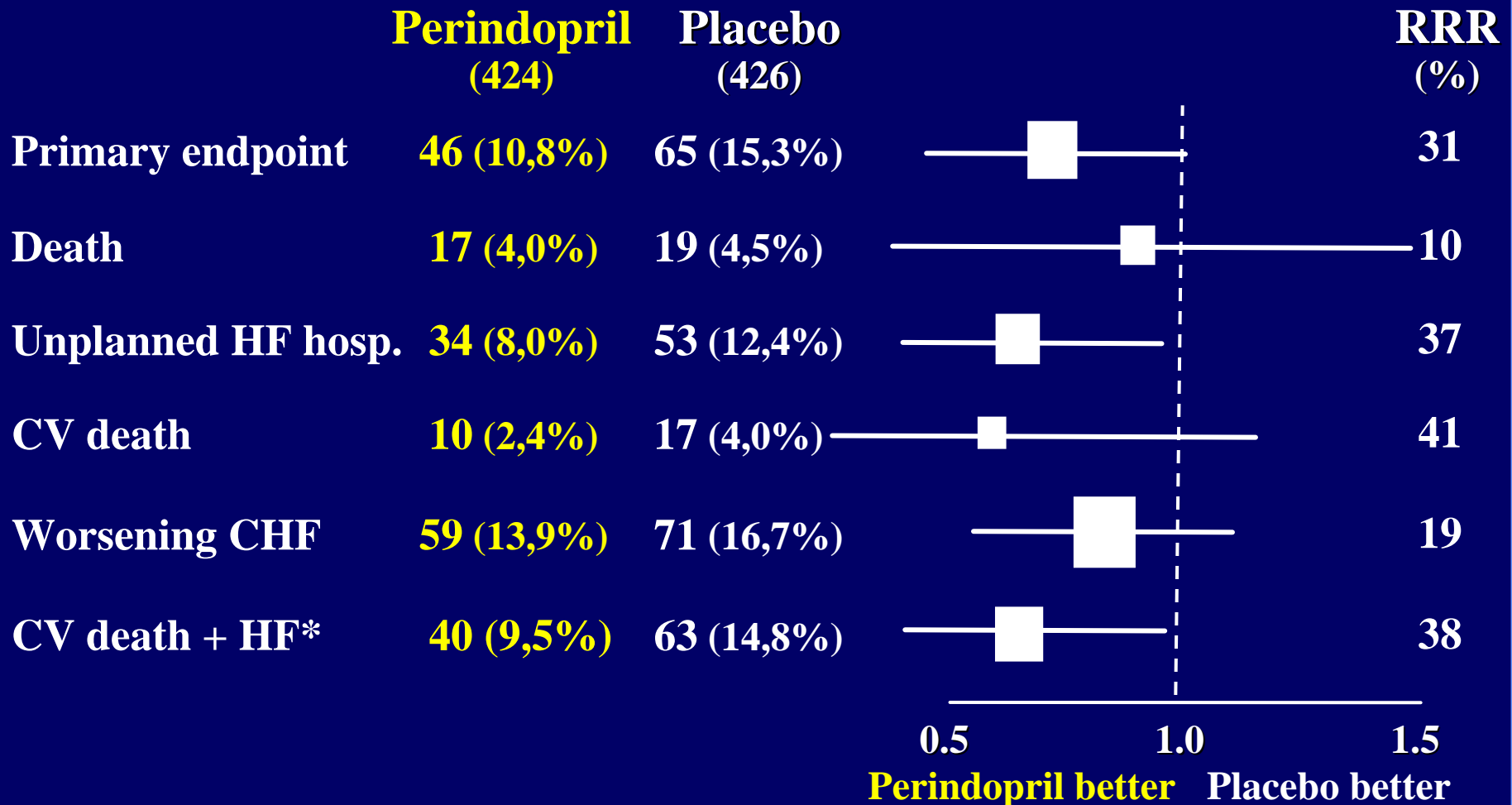


Patients at risks

Perindopril	424	408	399	390	374
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Summary of endpoints at one year



* Primary endpoint in CHARM Preserved



Total Bed-Days Occupancy

	Hospitalisation	Perindopril	Placebo
≥ 1	Patients	201	204
	Median days (<i>IQR</i>)	14 (8 to 35)	19 (9 to 40)#
	Total days	5,692	7,009
≥ 1 CV	Patients	139	143
	Median days (<i>IQR</i>)	12 (7 to 26)	15 (7 to 35)*
	Total days	2,862	4,078

p = 0.229

* p = 0.056
(adjusted for MI)



Secondary Outcomes NYHA Class

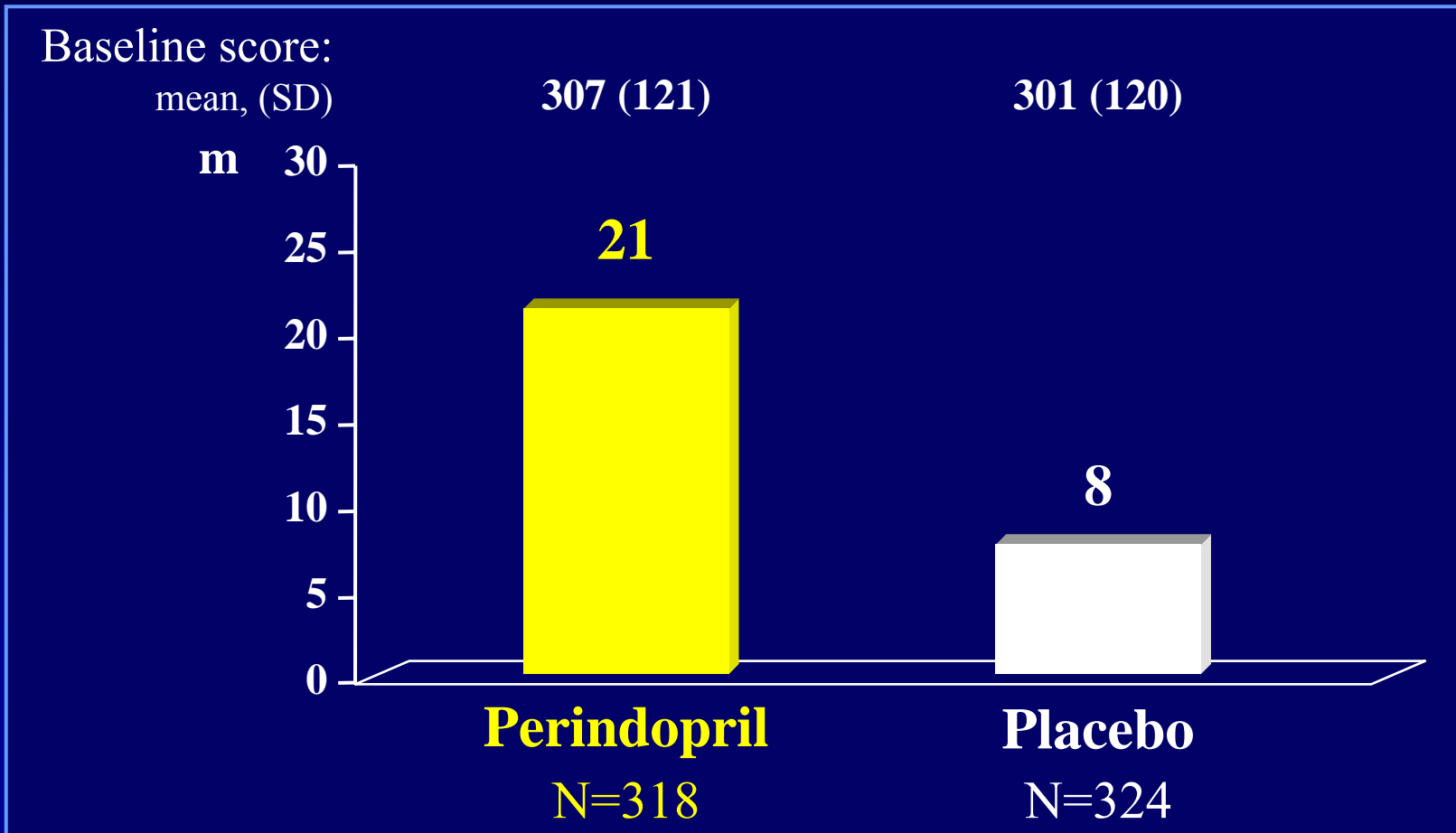
NYHA class	Perindopril	Placebo
I	75 (20.3%)	47 (12.4%)
II	235 (63.7%)	268 (70.5%)
III/IV	59 (16%)	65 (17.1%)

P=0.030



6 minute Corridor walk test

Change from baseline to One Year



Difference between groups adjusted to baseline
= 14 metres 95% CI [3 to 25] p=0.011



Power estimation

	Number of patients	Follow-up (years)	Annual event rate	Event risk Placebo	Event risk Perindopril	RRR	N events	Power
Protocol hypothesis	1004	1.5	50%	50%	40%	26%	451	90%
Real	850	2.2	12.7%	40.7% (at 2.2 y)	34.3% (at 2.2 y)	8%	207	35%

RRR=Reduction of relative risk



Conclusion

- **PEP-CHF had insufficient power to show an effect on its primary endpoint due to a lower than predicted event rate**
- **In the 1st year, when most patients were on assigned therapy, Perindopril**
 - **Improved symptoms and exercise capacity**
 - **Reduced hospitalisations for heart failure**
- **Perindopril also reduced total and CV hospital bed-days**
- **Perindopril might be of benefit in this patient population**
- **Patients with NT pro-BNP below median had few events**



Investigators

UK JGF Cleland, C Gray, J Taylor, M Lye, M Brack.

Poland M Tendera, J Adamus, L Polonski, M Cholewa, J Goch, M Gutowska Jabłonska, M Janion, P Kardaszewicz, M Krzeminska-Pakula, B Kusnierz, K Łoboz-Grudzień, M Krauze-Wielicka, W Musiał, A Nowicki, W Piwowarska, L Walasek, J Wolkowski, W Rubin, R Szelemej, M Zebrowska, B Engel, M Galewicz, T Kawka-Urbaneck, S Malinowski, B Mikłaszewicz, J Skwarna

Slovak Republic I Riecansky, J Urbanova, M Faltin

Russia V Mareyev

Ireland D O'Mahony

Hungary A Ronaszeki, J Tomcsanyi, K Toth, F Poor, A Cziraki, L Rostas, G Lupkovics, L Illyes, M Gurzo, L Horvath

Czech Republic J Widimsky, P Gregor, J Hradec, J Matouskova, J Spinar, L Spinarova.

Bulgaria T Daskalov, A Djurdjev, T Donova, N Penkov