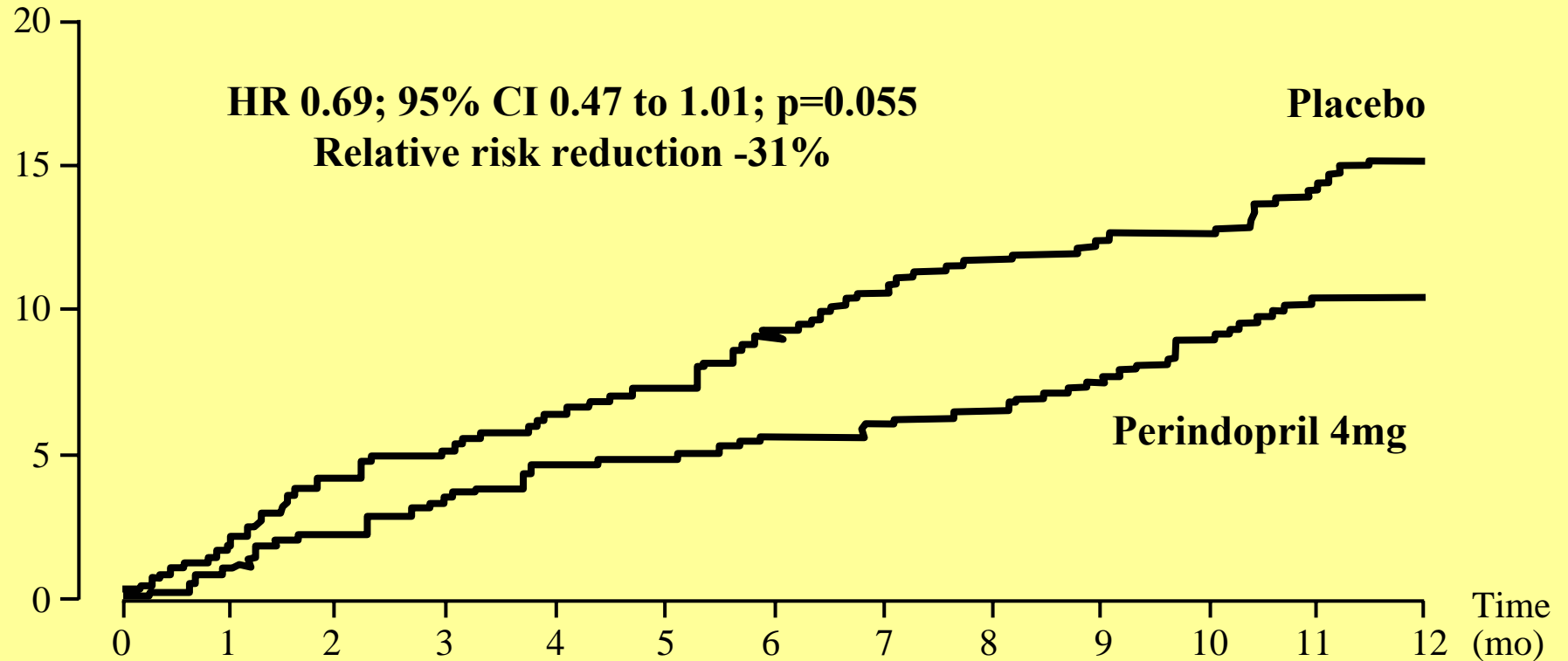


# PEP-CHF Primary end-point at one year

Time to first occurrence of total mortality  
or HF Hospitalisation

Proportion having an event (%)

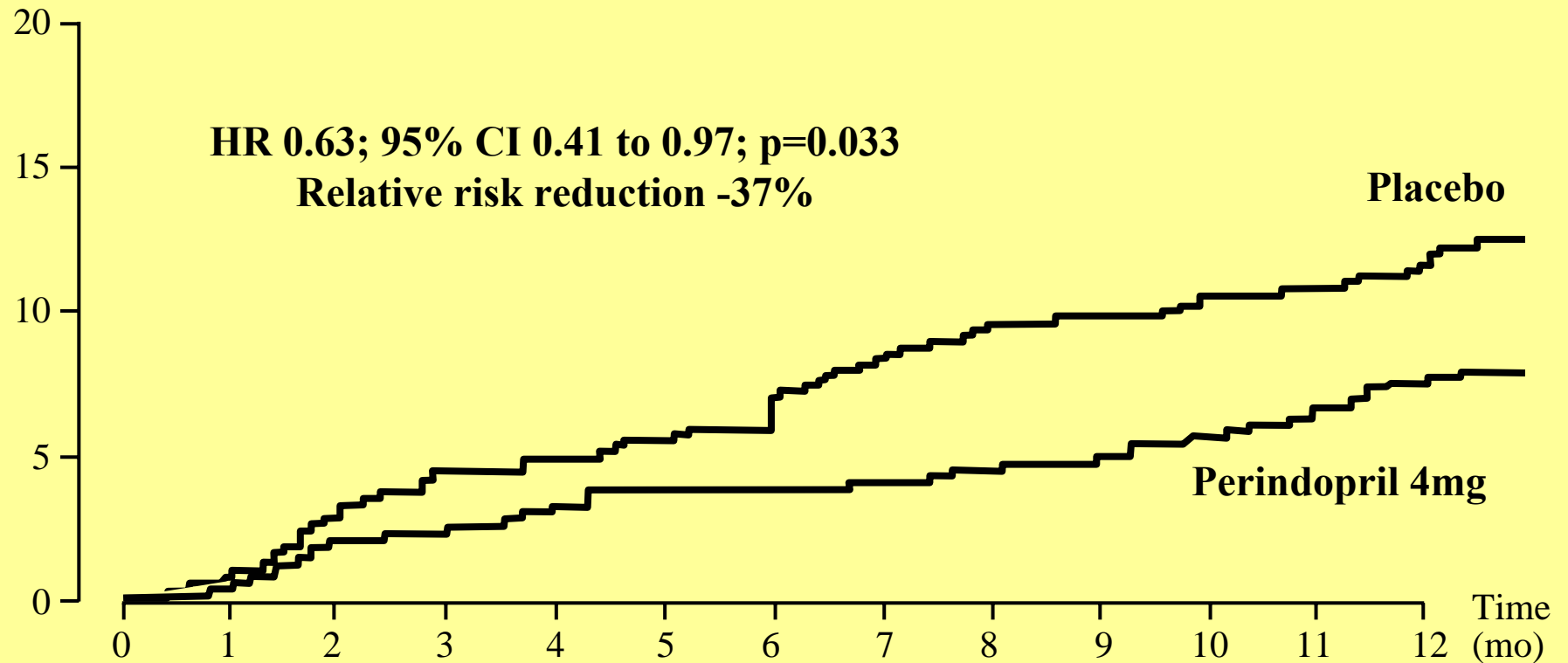


Patients at risks

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

# HF Hospitalisation at one year

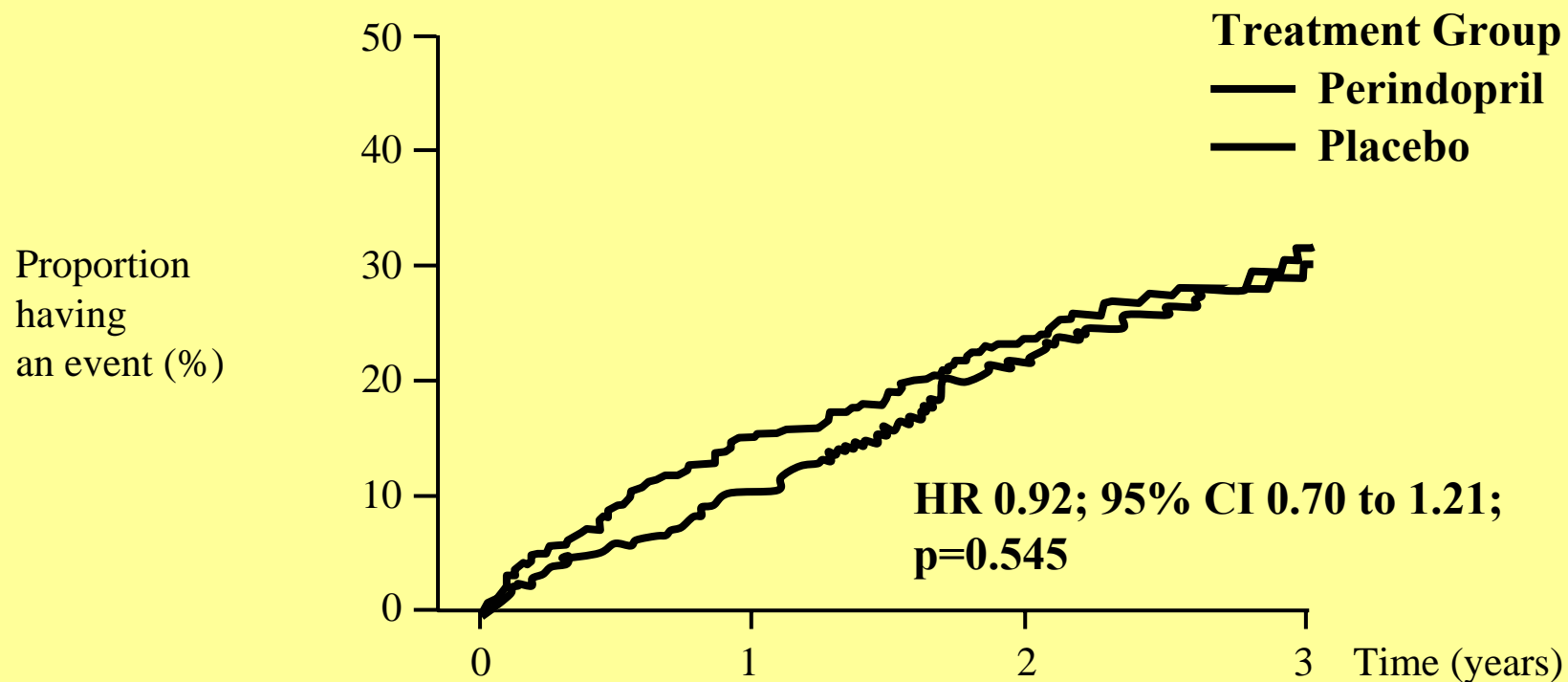
Proportion having an event (%)



Patients at risks

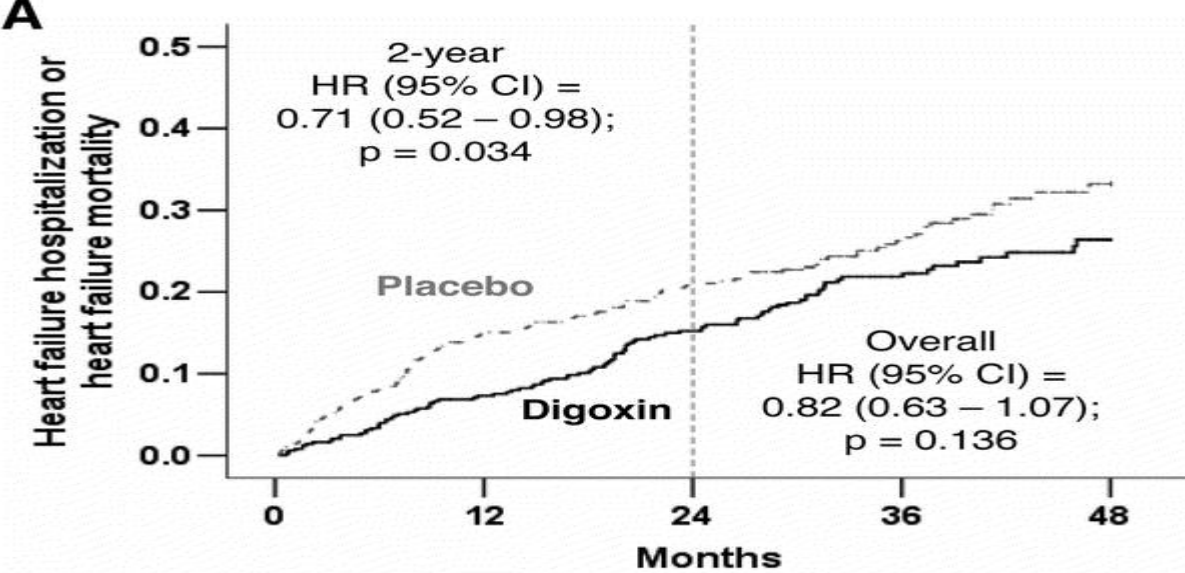
Perindopril	424	408	399	390	374
Placebo	426	405	387	374	356

# Primary end-point during follow-up



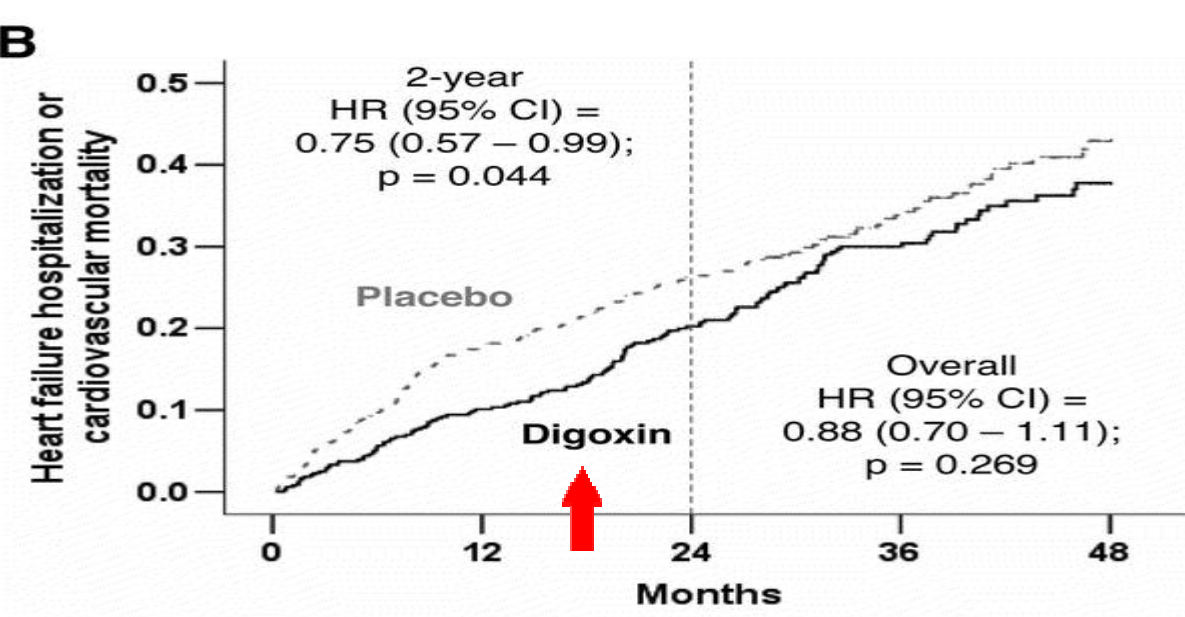
## Patients at risks

Perindopril	424	374	184	70
Placebo	426	356	186	69



**Number of patients at risk**

Placebo	496	408	366	240	84
Digoxin	492	440	387	248	98

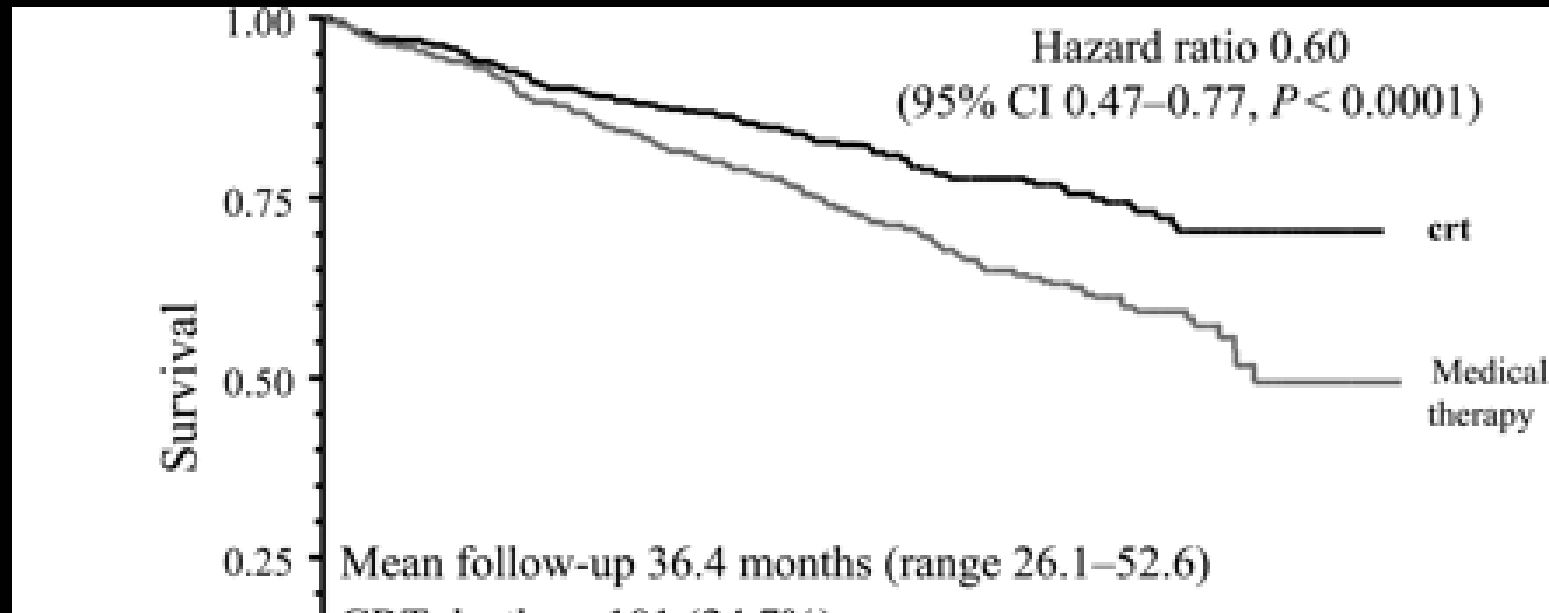


**Number of patients at risk**

Placebo	496	408	366	240	84
Digoxin	492	440	387	248	98

Dangers of Short studies

# CARE-HF EXTENSION



“The benefits of CRT observed in the main trial persist or increase with longer follow-up”

Cleland et al. Eur Heart J 2006;27;1928 August

# Conduct of the Study

- Lower than expected event rate
- Discontinuation
  - 90% on assigned therapy at 12 months
  - By 18 months blinded therapy stopped in:
    - 40% assigned to perindopril (~90% started open-label)
    - 36% assigned to placebo (~90% started open-label)

Loss of power

# Power estimation

	Number of patients	Follow-up (years)	Annual event rate	Event risk Placebo	Event risk Perindopril	RRR	N events	Power
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Protocol hypothesis	1004	1	60%	50%	40%	26%	451	90%
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Real	850	2.2	12.7%	40.7% (at 2.2 y)	34.3% (at 2.2 y)	8%	207	35%
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## CHARM Preserved

## PEP-CHF

Population

3023

852

Age yr

67

75

Women %

40

56

Mean EF %

54

65

Hypertension %

64

79

Previous MI %

44

26

Intervention

candesartan

perindopril

Follow-up months

37

26

Events

699

207

Discontinuation %

16

CHARM  
29% non-CV deaths

10/38

Endpoints

CV Death

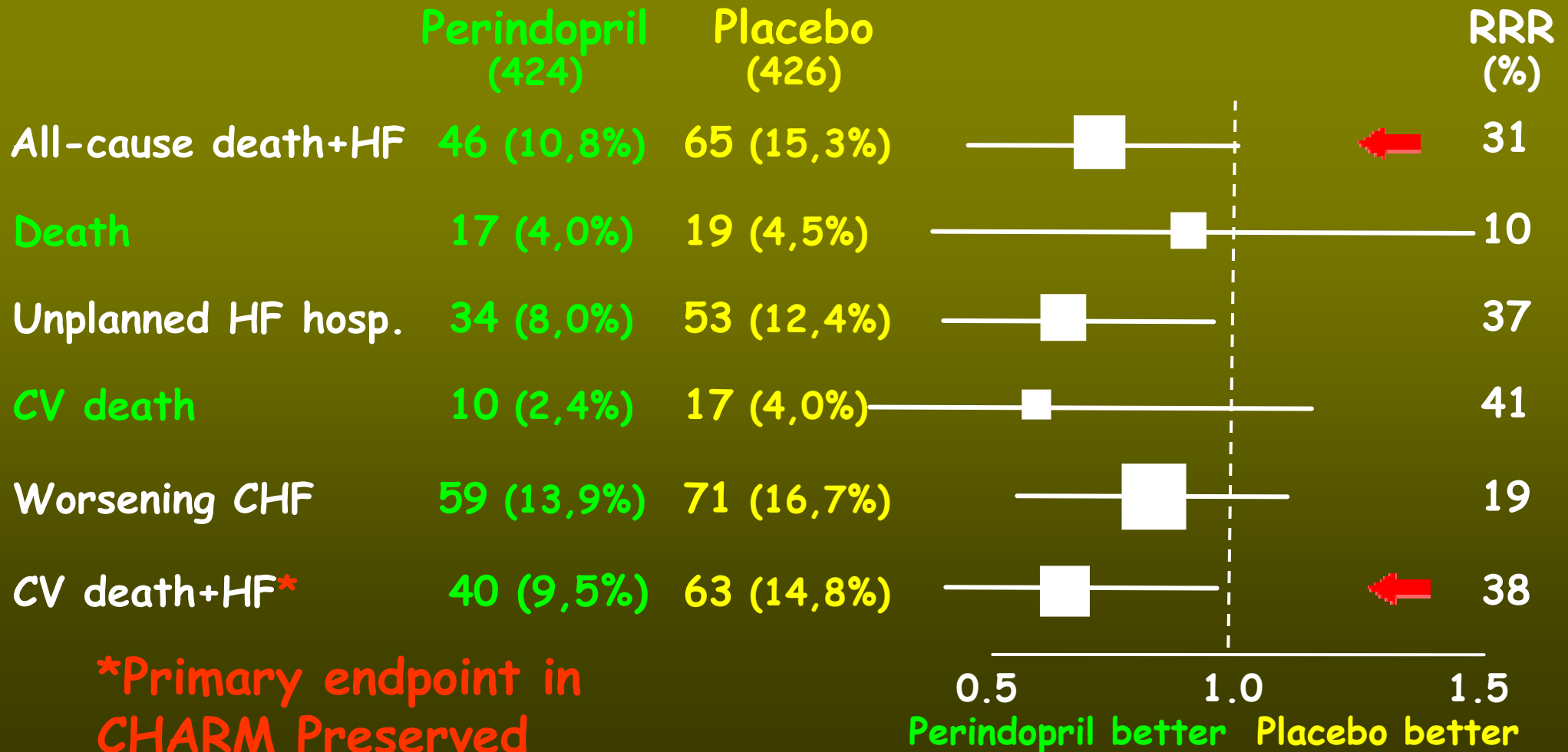
All-cause death

HF Hospitalisation

HF Hospitalisation

# Endpoints at one year

## PEP-CHF



**CHARM  
Preserved**

**PEP-CHF**

**I-PRESERVE**

**Population**

3023

852

4128

**Age yr**

67

75

72

**Women %**

TOPCAT

60

**Mean EF %**

4500 patients

59

**Hypertension %**

NYHA II

88

**Previous MI %**

EF > 45%

23

**BNP**

CV Death/HF hospitalisation

864

**Intervention**

Spiroonolactone

irbesartan

**Follow-up months**

ON TARGET/TRANSCEND

45?

**Events**

333

207

1440?

**Discontinuation %**

16

10/38

?

**Endpoints**

CV Death

All-cause death

All-cause death

HF Hospitalisation

HF Hospitalisation

CV Hospitalisation

# Concerns

- Slow recruitment
- Low event rate
- 36 deaths at 1 year (19/17)
- High discontinuation rate
- Form of KM curve
- When was the trial really over?

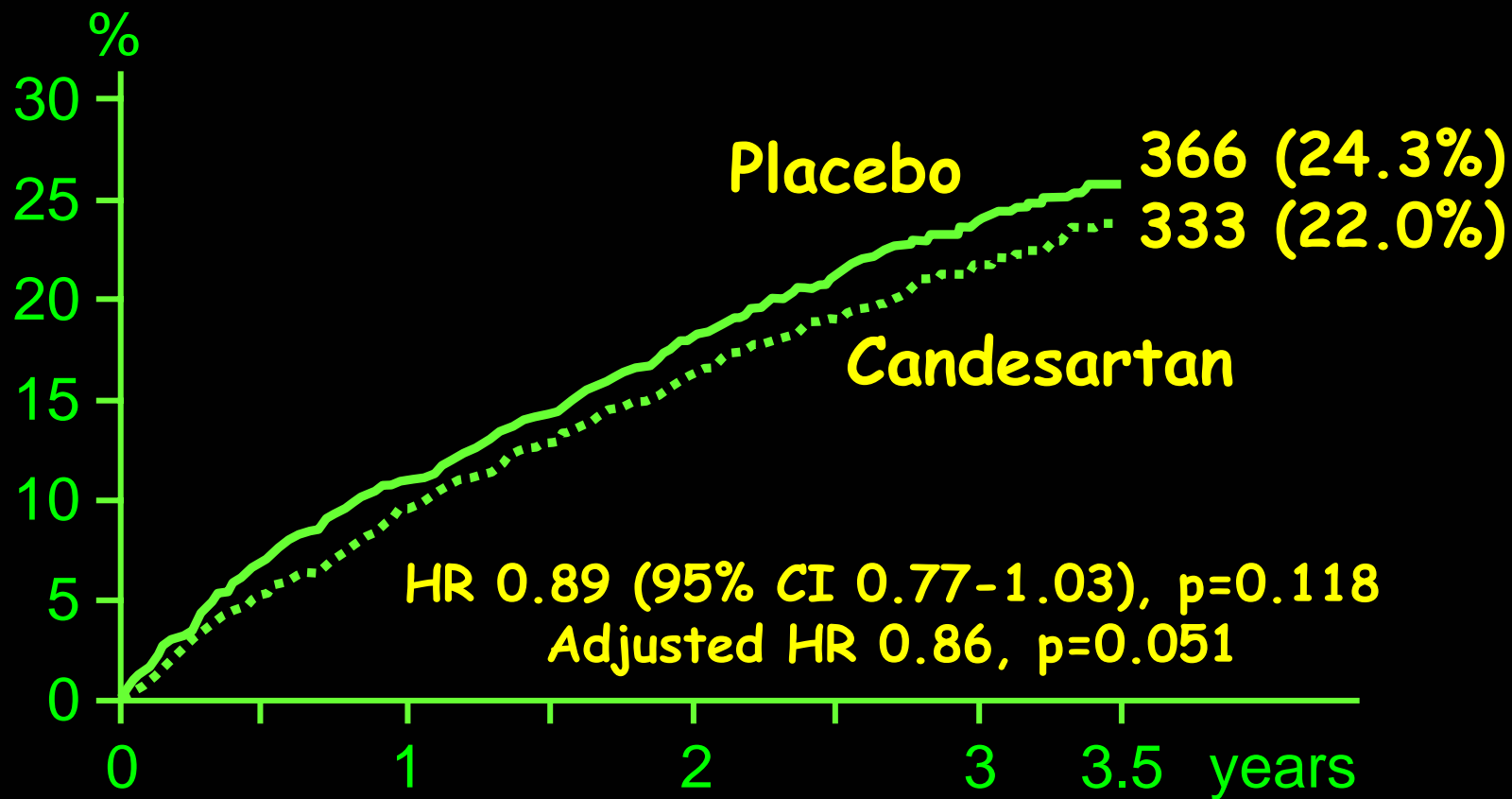
# My take on PEP-CHF:

- Interpretation complicated by methodological limitations
- Results are consistent with CHARM and support a role for inhibition of the renin-angiotensin system in patients with heart failure and preserved systolic function (morbidity)
- Other important measures were strongly supportive (hospitalisation, NYHA, 6 min walk)
- Clinicians will understand the message

# Perils of trials

- Too small
- Too short
- Too late
- Wrong protocol
- Wrong population - too few events
- Wrong dose
- Not controlled
- Non-randomised
- Discontinuation
  
- Wrong endpoint!

# CHARM-Preserved: Primary outcome CV death or HF hospitalisation

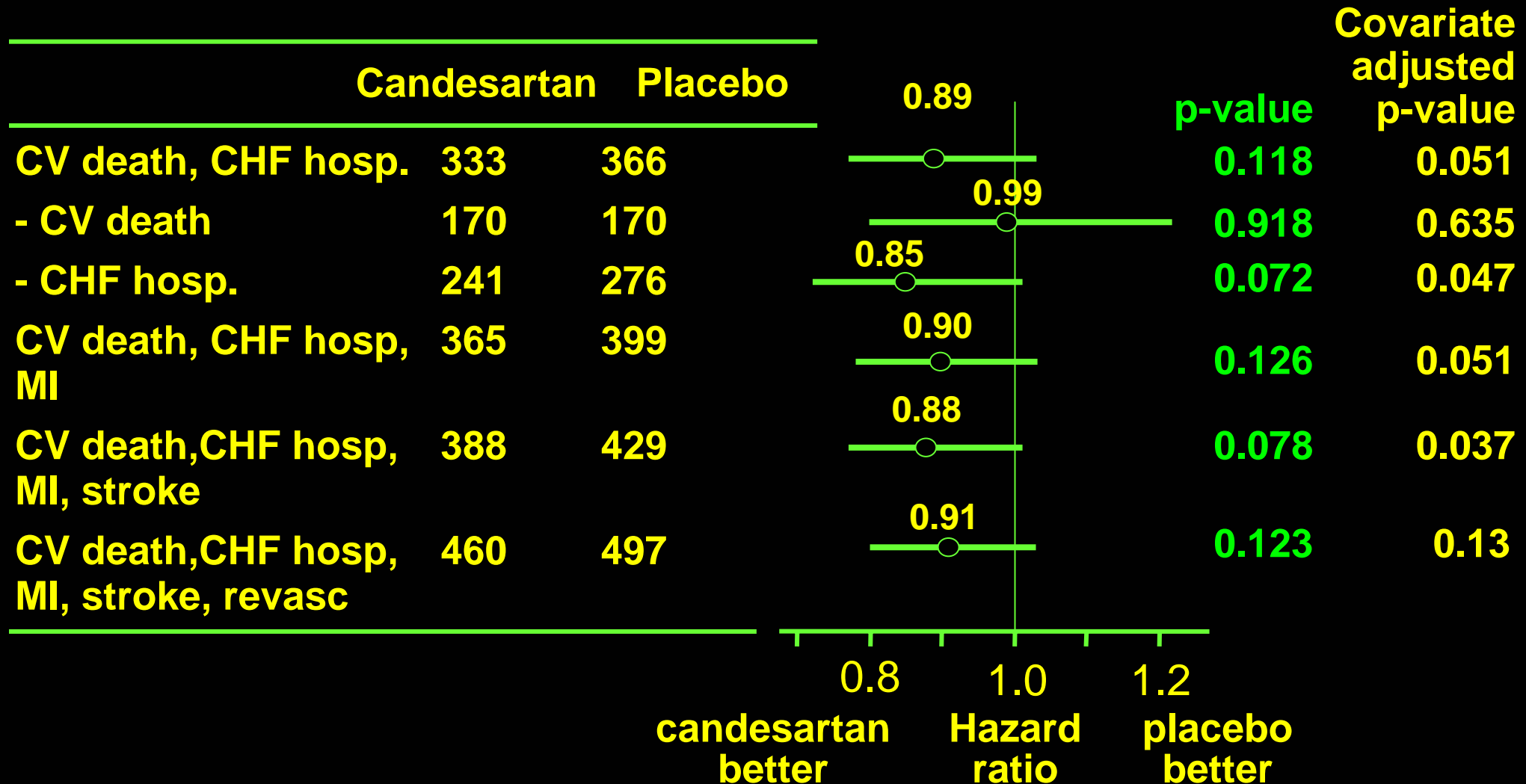


# PHARMA RCTs

Title	N	EF	Intervention	Endpoint	Status
I-PRESERVE	4133	>45 %	irbesartan	All-cause mortality, CV hospitalisation	2008
TOPCAT	4500	>45 %	spironolactone	CV Mortality, RCA, HF hospitalisation	2010
ONTARGET	27,500	>40 %	telmisartan	CV death, MI, stroke, HF hospitalisation	2008
TRANSCEND	5000	>40 %	telmisartan	CV death, MI, stroke, HF hospitalisation	2008

# CHARM-Preserved

## Primary and secondary outcomes



## PEP-CHF

## I-PRESERVE

Population

852

4128

Mean EF

65%

59%

Age

75

72

Women

56%

60%

Hypertension

79%

88%

Previous MI

26%

23%

Intervention

perindopril

irbesartan

Follow-up

26 months

45 months?

Events

207

1440?

Discontinuation

10/38

?

Endpoints

All-cause death  
HF Hospitalisation

All-cause death  
CV Hospitalisation

BNP

~394

864

# The updated ESC guidelines

"Most, if not all, patients with systolic dysfunction have changes in **diastolic function**"

"Therefore, diastolic and systolic heart failure should not be considered as separate pathophysiologic entities"

# I-PRESERVE

- **Hypothesis:** irbesartan in HF and preserved LV systolic function
- **Population:** 4133 pts  $\geq 60$  yrs with clinical HF and  $EF \geq 45\%$ , NYHA class II-IV and HF hospitalisation.
- **Intervention:** irbesartan (300 mg) vs. placebo
- **Primary endpoint:** all-cause mortality and CV hospitalisation
- **Status:** reports 2008
  - **VOTE!**
  - ✓ irbesartan
  - ✓ placebo
  - ✓ neutral

# TOPCAT

- **Hypothesis:** spironolactone in mild HF and preserved LV function
- **Population:** 4500 patients with NYHA II HF, EF>45%
- **Intervention:** spironolactone (45 mg), placebo
- **Primary endpoint:** CV mortality, RCA, HF hospitalisation
- **Status:** 2010
  - **VOTE!**
  - ✓ spironolactone
  - ✓ placebo
  - ✓ neutral

# Updated Treatment guidelines

- "Recommendations are largely speculative (level of evidence C)
- We do not have clear evidence that patients with primary diastolic heart failure benefit from any specific drug regimen
- It is most logical to treat the patients according to general principles"

# Issues:

- Discontinuation
- Crossover
- Diff at 12 and 18 months
- Unplanned HF
- Eastern Europe
- Assumptions
- Explain CV in hosp data
- Event rate in table?

# CHARM (candesartan)

## Baseline characteristics

	Alternative n=2028	Added n=2548	Preserved n=3023	Overall n=7599
Mean age (years)	67	64	67	66
Women (%)	32	21	40	32
NYHA class (%)				
II	48	24	60	45
III	49	73	38	52
IV	3	3	2	3
Mean LVEF	57	57	54	39
Medical history (%)				
myocardial infarction	26	26	44	53
diabetes	27	30	28	28
hypertension	50	48	64	55
atrial fibrillation	25	26	29	27

• Older

• More women

• More hypertension

• Less CAD & MI

# Summary of endpoints at one year PEP-CHF

