

NT-proBNP guided management
of chronic heart failure based on
an **individual** target value

PRIMA-study

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Presenter disclosure information

The following relationships exist related to this presentation:

Luc Eurlings: *No relationships to disclose*

Yigal Pinto: *Consulting fees, Roche Diagnostics* *Modest level*

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Study funding	Netherlands Heart Foundation	Significant level
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Unrestricted grant	Astra Zeneca	Modest level
Unrestricted grant	Roche diagnostics	Modest level

(NT-pro)BNP guided therapy in Heart Failure

Rationale

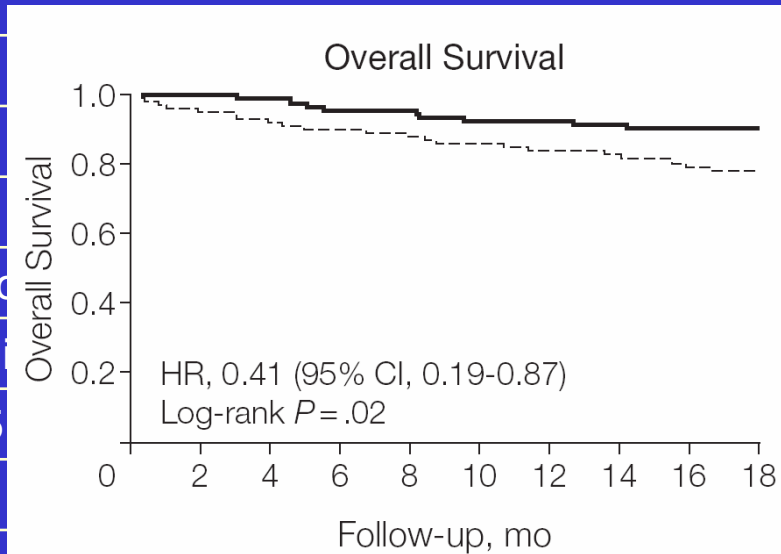
- (NT-pro)BNP levels are known to react upon HF therapy
- Decrease in NT-proBNP levels during HF admission reflects better outcome
- Can (NT-pro)BNP guided therapy of chronic heart failure decrease morbidity and mortality?
- What NT-proBNP target-value should be used?

(NT-pro)BNP guided therapy in Heart Failure

Current evidence

Benefit in subjects younger than 75 years

Study		BATTLESCARRED
N		364
Fixed target		g/ml 1300 pg/ml
Reduction: primary endpoint		no
overall mortality		no
Mortality < 75		yes, 10.9% vs 21.7%
Target reached		Not yet published



TIME-CHF
JAMA 2009;301:383

Current evidence (NT-pro)BNP guided management of CHF

- All studies use a general, fixed target of natriuretic peptide
- No overall reduction in mortality
- Favorable in patients under 75 years
- Fixed (NT-pro)BNP target value reached only in minority
- Value of individual (NT-pro)BNP target values?

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Can pro-brain-natriuretic peptide guided therapy of chronic heart failure
Improve heart failure morbidity and mortality?

Hypothesis:

NT-proBNP guided management of chronic heart failure based on an **individually set** target value reduces morbidity and mortality compared to therapy guided by standard clinical judgement.

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Can pro-brain-natriuretic peptide guided therapy of chronic heart failure
Improve heart failure morbidity and mortality?

- Prospective, randomized, single-blinded study
- 12 participating Dutch university and large general hospitals
- Patients recruited between June 2004 and September 2007

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Inclusion criteria

- Admitted with symptomatic heart failure
- Elevated NT-proBNP levels $\geq 1,700$ pg/ml (200 pmol/L) on hospital admission

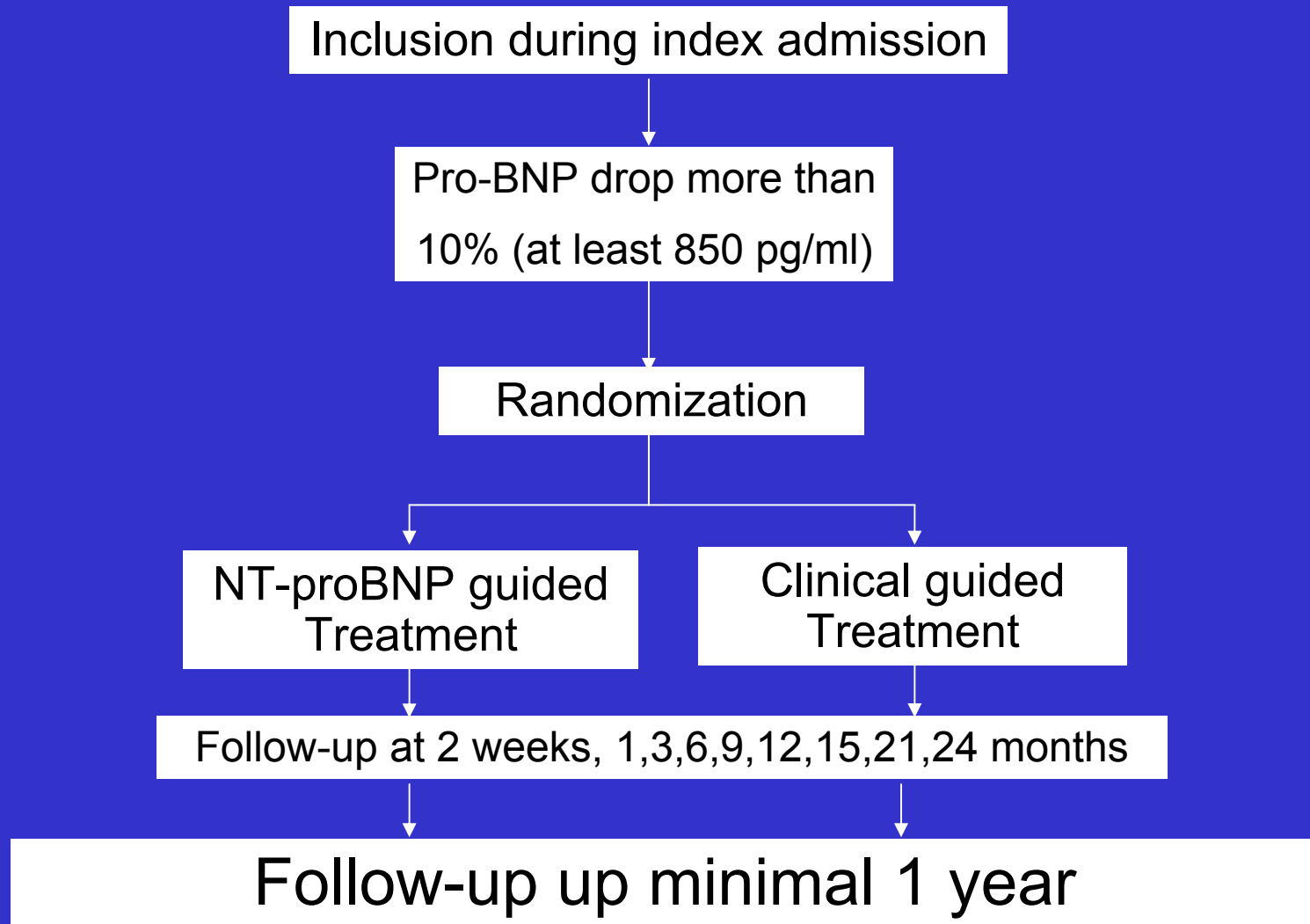
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Exclusion criteria

- Life threatening cardiac arrhythmias
- Urgent invasive or surgical intervention
- Severe COPD or recent pulmonary embolism
- Non Heart Failure related expected survival <1 year
- Patients undergoing Haemodialysis / CAPD
- Renal dysfunction allowed

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Trial outline



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Inclusion

Inclusion during index admission

Pro-BNP drop more than
10% (at least 850 pg/ml)

Randomization
345 pts

NT-proBNP guided
Treatment
174pts

Clinical guided
Treatment
171 pts

Follow-up at 2 weeks, 1,3,6,9,12,15,21,24 months

Follow-up up minimal 1 year

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Treatment Targets

- NT-proBNP guided group:
 - Clinical assessment
 - Individual NT-proBNP target level
(Lowest level at discharge or 2 weeks follow-up)
- Clinical guided group:
 - Clinical assessment only

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Preliminary analysis

- Primary endpoint: Number of days alive outside hospital
- Prespecified secondary endpoints:
 - (cardiovascular) mortality
 - (HF, CV and total) hospitalization
 - Composite endpoint death/hospitalization
 - Use of evidence based HF medication
 - Analysis in patients that maintain their NT-proBNP target level
 - Age and renal function subgroups

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Baseline characteristics (I)

	NT-proBNP	Clinical
n	174	171
Age (mean, SD)	71 (12)	73 (12)
Gender (%M)	55	60
Myocardial Infarction (%)	37	43
CABG (%)	18	17
Hypertension (%)	48	49
Diabetes (%)	25	28
BP systolic (mean, SD)	117 (19)	119 (22)
BP diastolic (mean, SD)	69 (11)	69 (12)
Heart rate (mean, SD)	72 (11)	75 (16)
Creatinine (mcm/L)(median, IQR)	121 (98 - 157)	126 (104 - 166)
LVEF (% , median, IQR)	31 (24 - 46)	35 (25 - 48)

All = ns

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Characteristics at discharge (II)

	NT-proBNP	Clinical
n	174	171
NYHA class at discharge		
I	11.5	9.9
II	64.9	70.8
III	23.6	19.3
IV	0	0
NT-proBNP levels, pg/ml (pmol/L)		
Admission, median	8034 (948)	8169 (964)
Discharge, median	2958 (349)	2932 (346)
Target , median	2492 (294)	---

All = ns

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Results follow-up

- Median follow-up (IQR): 702 days (488 – 730)
- In 80% of the NT-proBNP group target level was achieved at one year follow-up

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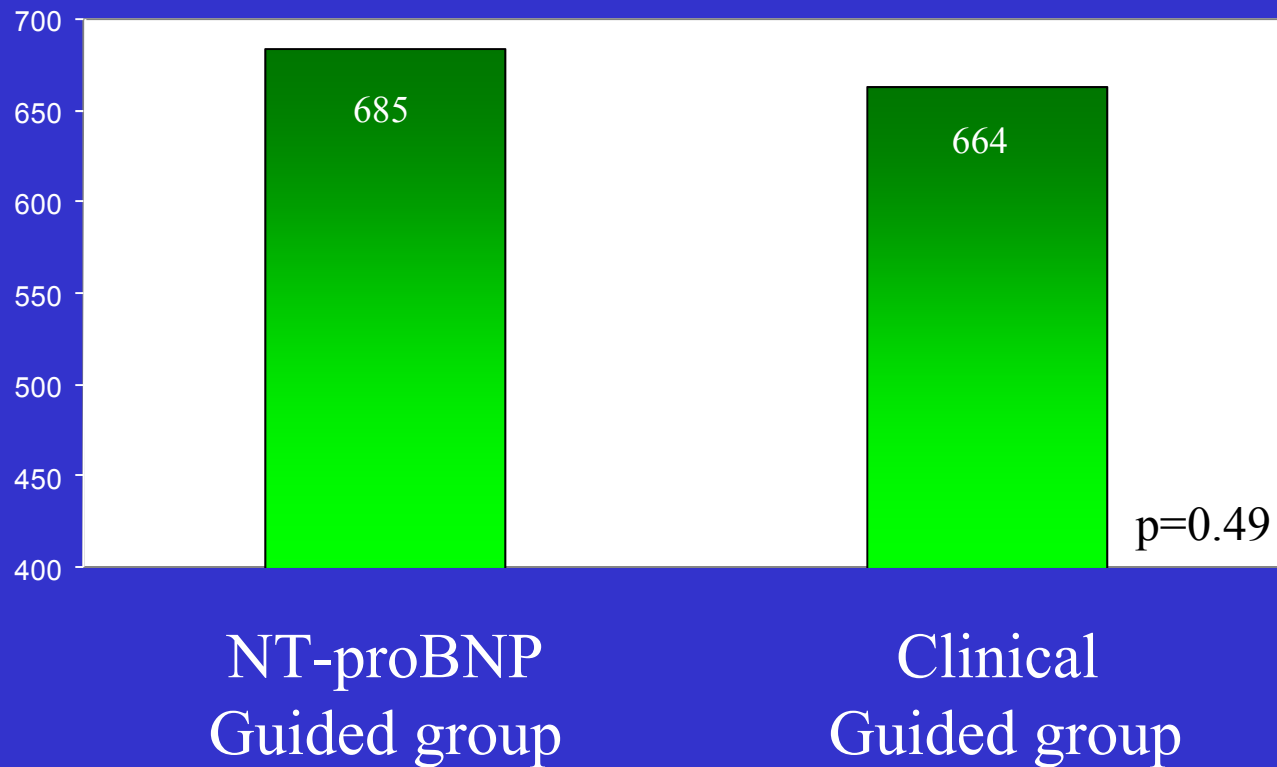
Increase or start evidence based medication during follow-up

Number of increases HF medication	NT-proBNP	Clinical	P
n	174	171	
Diuretics	168	120	0.018
Beta blockers	105	95	ns
ACE-inhibitors	77	55	0.099
AT-II antagonists	41	22	ns
Aldosteron antagonists	19	15	ns
Digoxin	14	19	ns
Total	424	326	0.006

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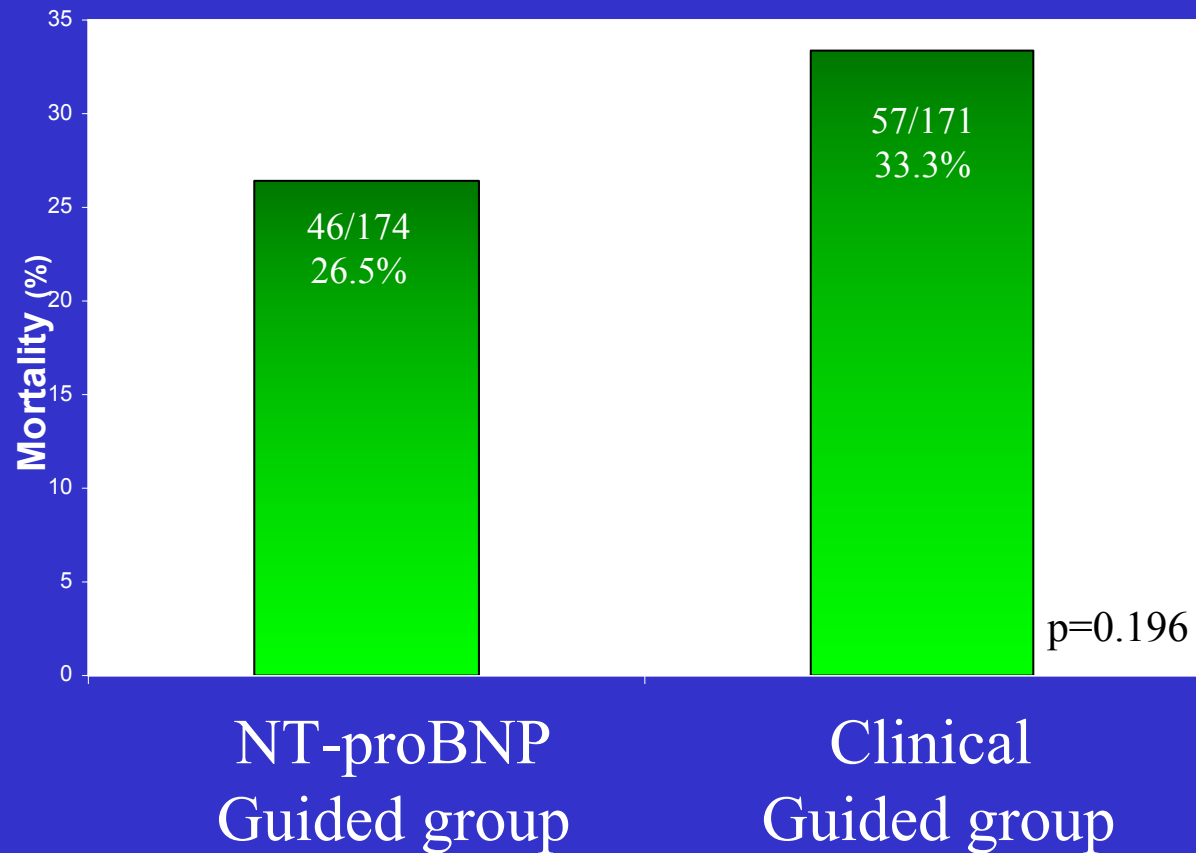
Primary outcome measure

Number of days alive outside the hospital



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Total Mortality



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Secondary analysis

- Cardiovascular mortality ns
- Combined endpoint CV mortality / readmissions ns
- HF related readmissions ns
- Creatinine above / below the median ns
- Age above / below the median ns
- Discharge NT-proBNP above / below the median ns

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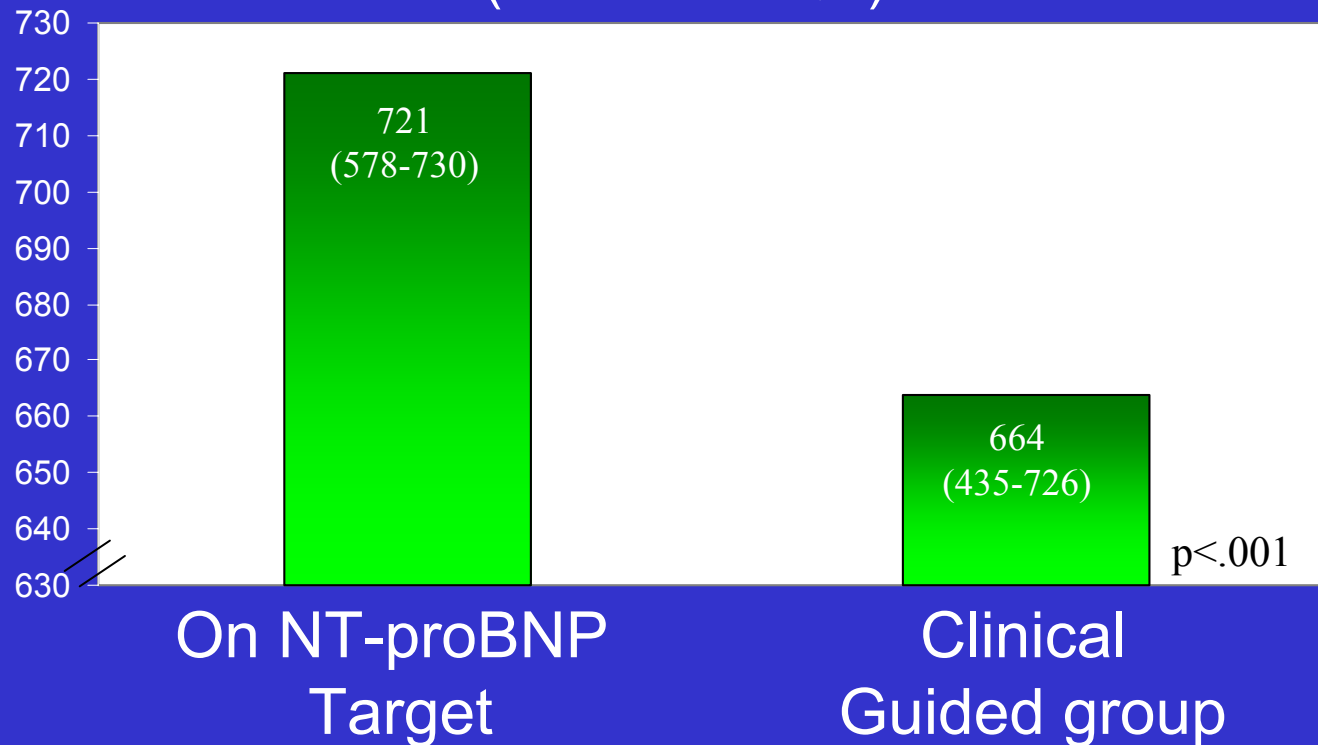
Prespecified on target analysis

- Definition:
 - At least 75% of outpatient visits NT-proBNP level at the individual target value
- 101 of 174 patients in NT-proBNP guided group (58%) maintained their target in more than 75% of visits

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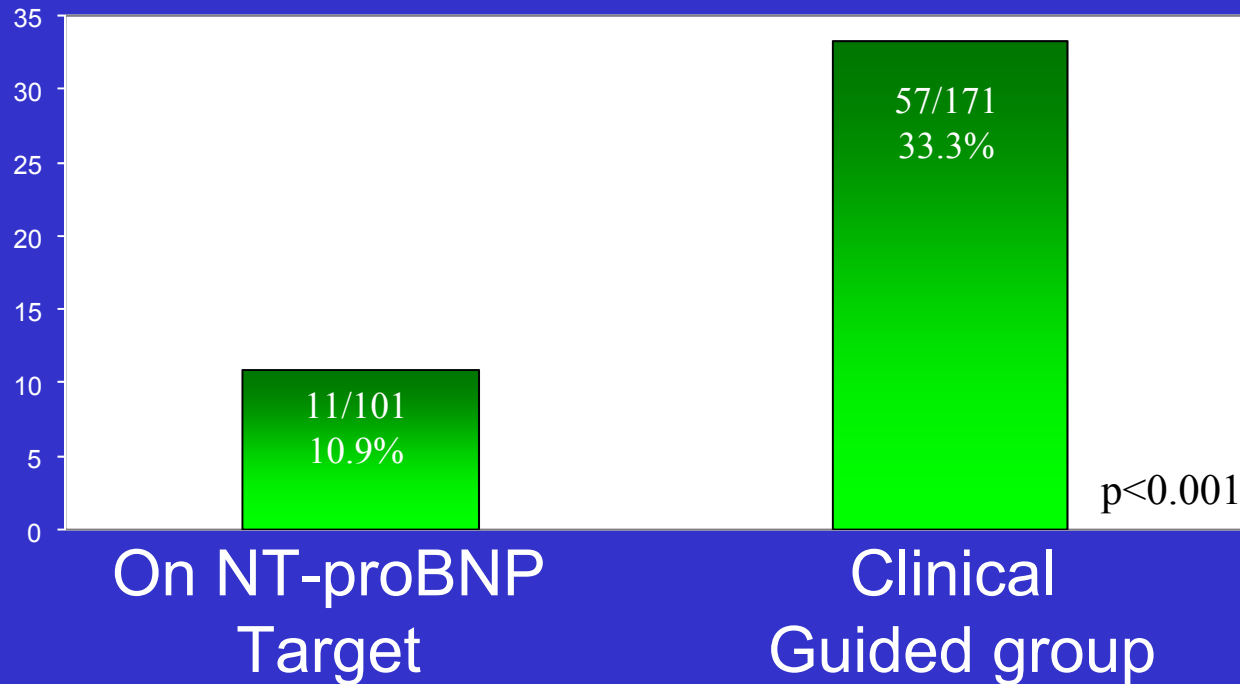
On NT-proBNP target analysis: Primary endpoint

Number of days alive outside the hospital
(median + IQR)



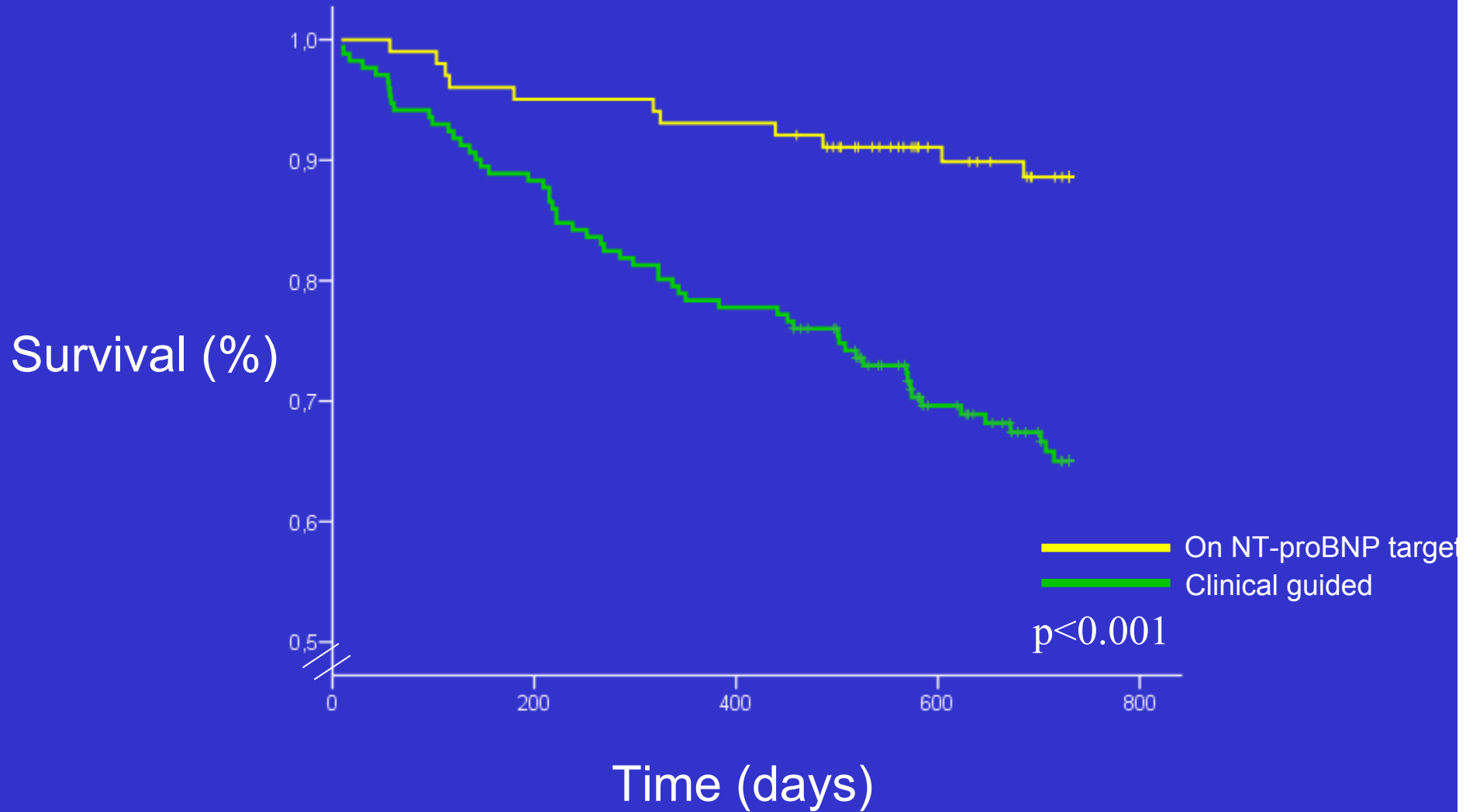
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On NT-proBNP target: Mortality (%)



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On NT-proBNP target: Mortality



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Conclusions

- The PRIMA-study did not show significant effect of NT-proBNP guided management on main endpoints
- NT-proBNP guided management resulted in significantly more frequent start or increase in HF medication
- 80% of patients achieved their individual NT-proBNP target value after one year follow-up
- Patients who consistently reached their target had better outcome.
- Prospective identification of this subgroup of patients would be of clinical interest.

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Implications

- Management of heart failure guided by an individually defined optimal NT-proBNP level does not appear favorable in the overall population
- However, maintaining this individual optimal NT-proBNP level potents significantly better outcome
- The PRIMA-study allows to identify patients where it is feasible to maintain the optimal NT-proBNP level and who may benefit from treatment guided by their own optimal NT-proBNP

Acknowledgements

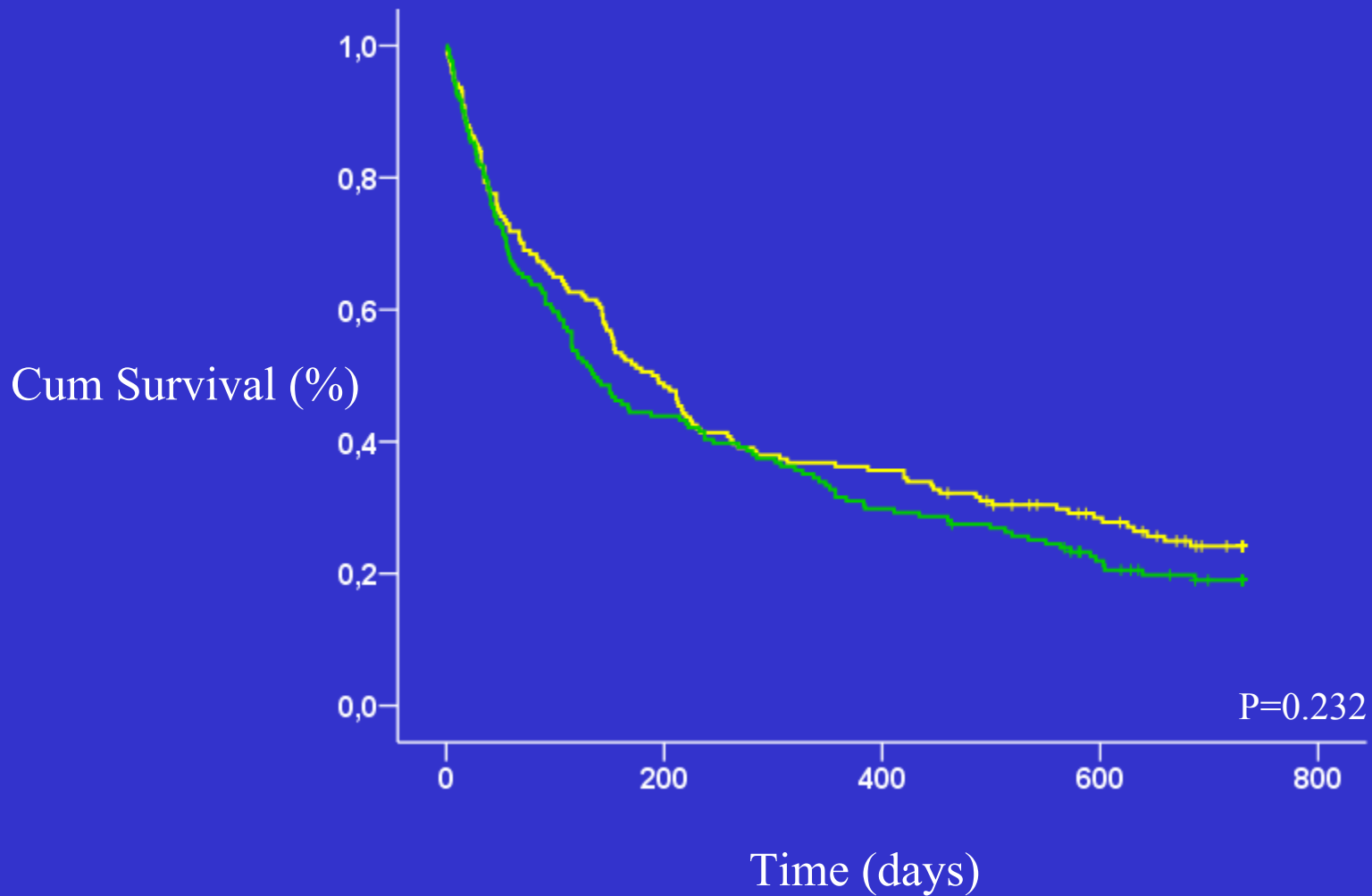
Participating centers

• Academic Medical Center	Amsterdam	Wouter Kok*
• Amphia Hospital	Breda	Peter Dunselman
• Atrium Medical Center	Heerlen	Cara Lodewijks*
• Erasmus Medical Center	Rotterdam	Aggie Balk*
• Hospital Deventer	Deventer	Dirk Lok*
• Maastricht University Medical Center	Maastricht	Harry Crijns
• Meander Medical Center	Amersfoort	Thierry Wildbergh
• Orbis Medical Center	Sittard	Dave van Kraaij*
• Reinier de Graaf Gasthuis	Delft	Petra van Pol*
• University Medical Center	Utrecht	Nicolaas de Jonge*
• VieCuri Medical Center	Venlo	Joan Meeder*
• VU Medical Center	Amsterdam	Otto Kamp

* Member of the Steering Committee

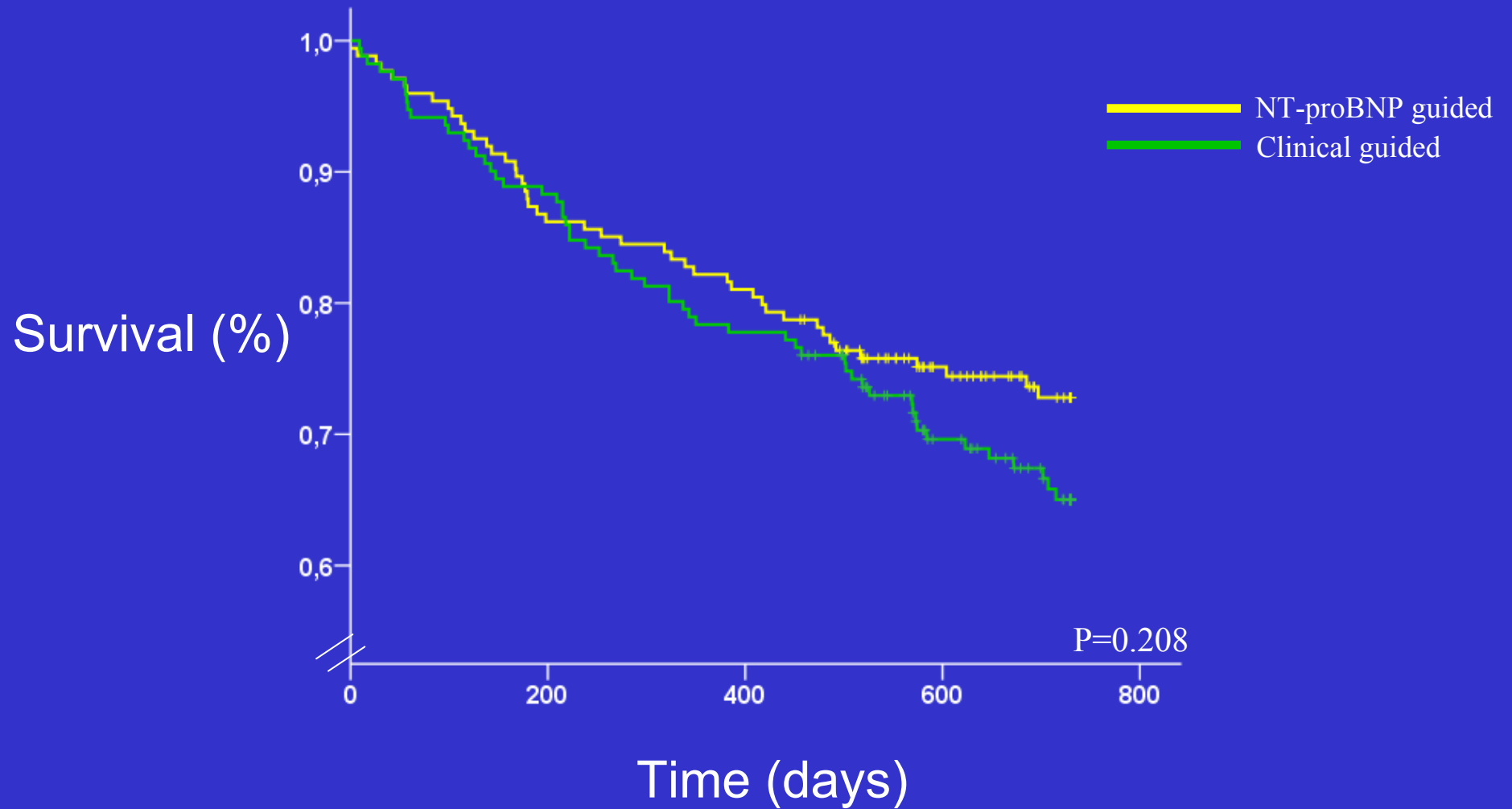
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Composite endpoint Death / Rehospitalization



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Total Mortality



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Inclusion

Patients screened

Approx 2,900 pts

Informed consent

447 pts

Randomisation

345 pts

NT-proBNP guided
174 pts

Clinical guided
171 pts

Excluded before informed consent

23% Unable to give IC

13% Unwilling to give IC

13% Admission NT-proBNP < 1,700 pg/ml

9% HF not primary diagnosis

9% Discharge before IC could be obtained

7% (Planned) intervention

4% COPD / pulmonary embolism

Excluded before randomisation

6 pts

1 PCI

2 ICD implantations

3 HF not primary diagnosis

Insufficient NT-proBNP drop

96 pts