THE VALUE OF 24 H HEART RATE VARIABILITY IN PREDICTING THE MODE OF DEATH IN PATIENTS WITH HEART FAILURE AND SYSTOLIC DYSFUNCTION IN BETA-BLOCKING ERA

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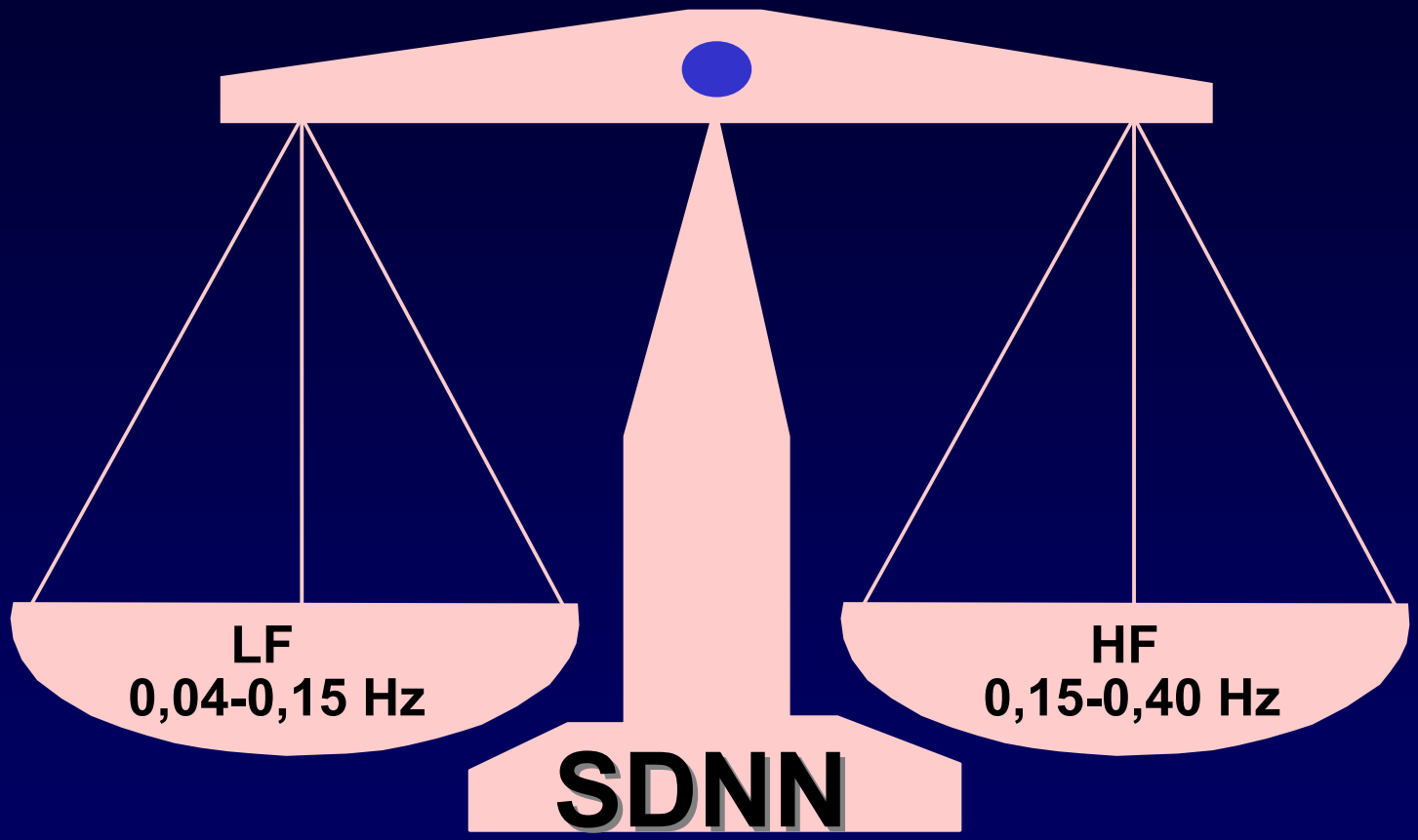
Heart Rate Variability (HRV)



Sympathetic/vagal modulation

Parasympathetic modulation

Objectives:

To assess the relationship between parameters of HRV and traditional clinical markers of unfavorable prognosis with total mortality and mode of death in pts with heart failure and LV dysfunction in beta-blocking era.

Inclusion criteria

- ❑ Symptomatic heart failure (NYHA II-IV)
- ❑ Sinus rhythm
- ❑ Left ventricle systolic dysfunction (LVEF ≤ 40%)
- ❑ Stable clinical condition

Exclusion criteria

- non-sinus rhythm
- myocardial infarction (< 3 months)
- diabetes mellitus
- SA and AV-block
- renal failure
- severe non-cardiac diseases (with poor prognosis)

Study design

- Prospective observational study

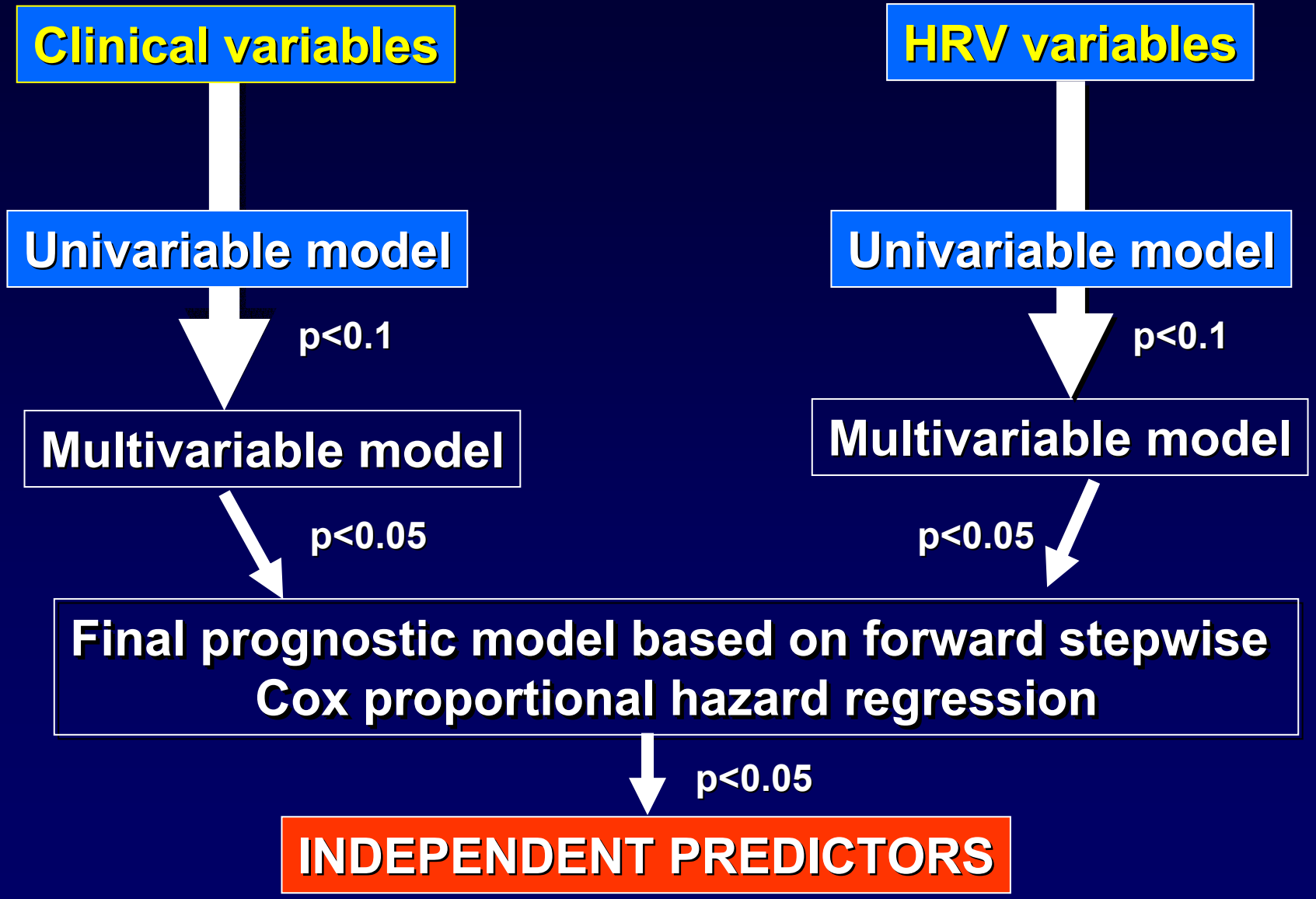
End points

- Primary endpoint – all-cause mortality

- Secondary endpoints –
- pump failure death (PFD)
- sudden death (SD)

Statistical analysis

(stepwise regression analysis)



Baseline patients clinical characteristics

Characteristics	Total (n=135)
Age, yrs	52.4 ± 11.9
Gender (m/f)	111/23 (82%/17%)
Etiology (isch/nonisch)	91/43 (68%/32%)
LVEF, %	30.1 ± 6.7
NYHA	2.9 ± 0.8
•NYHA II	56 (42%)
•NYHA III	55 (40%)
•NYHA IV	24 (18%)
VPCs (24h)	219 (34 -817)*
NSVT (n)	57 (35%)

* Presented as median with 25th and 75th percentiles

Baseline treatment

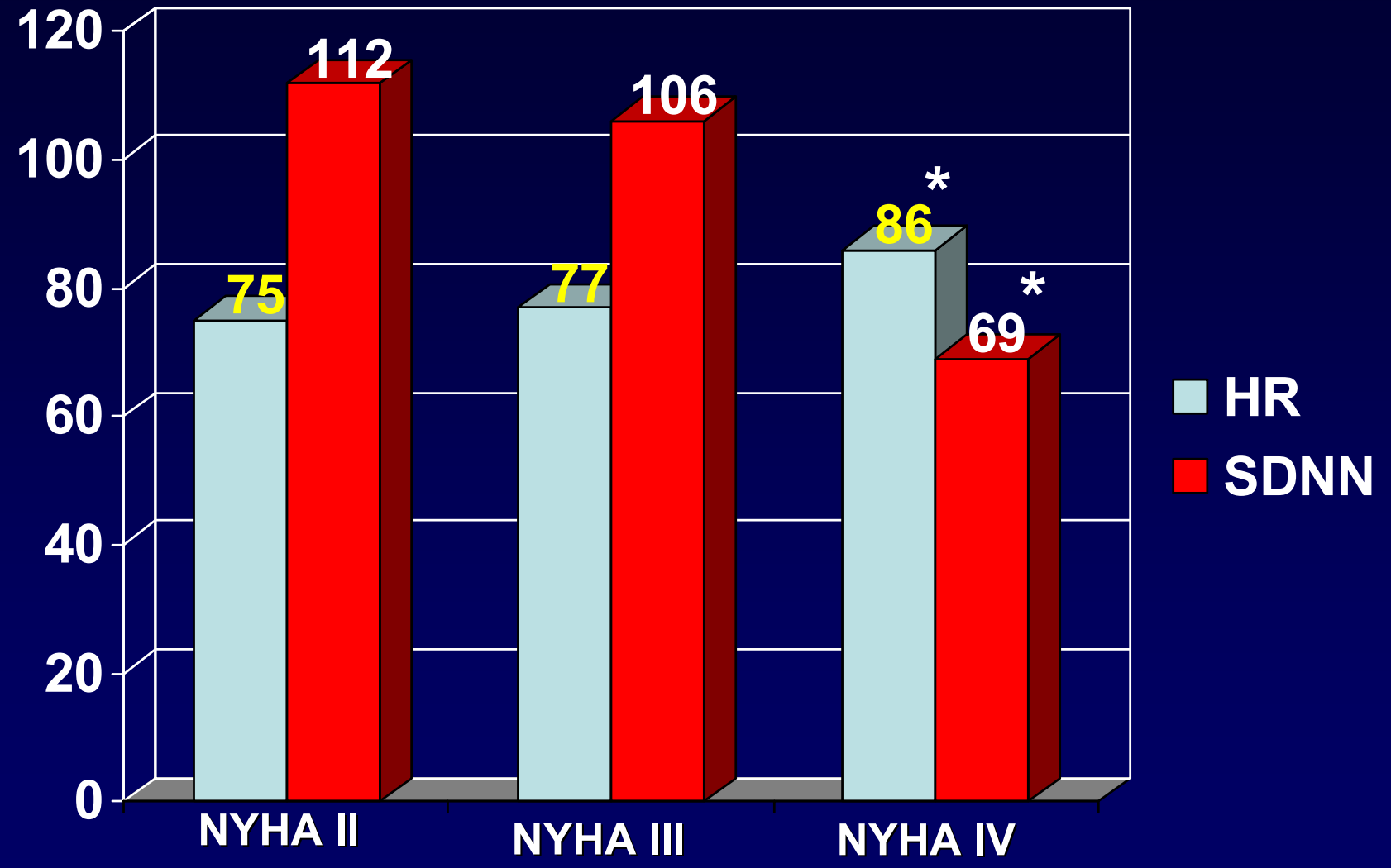
Treatment	%
Diuretics	90.3%
ACE Inhibitors	89.1%
Beta-blockers	79.4%
Digoxin	45.1%
Spironolactone	68.6%
Aspirin	76.4%
Nitrates	11.1%
Amiodarone	14.8%
Warfarin	5.6%

Heart Rate Variability in Heart Failure

HRV measures

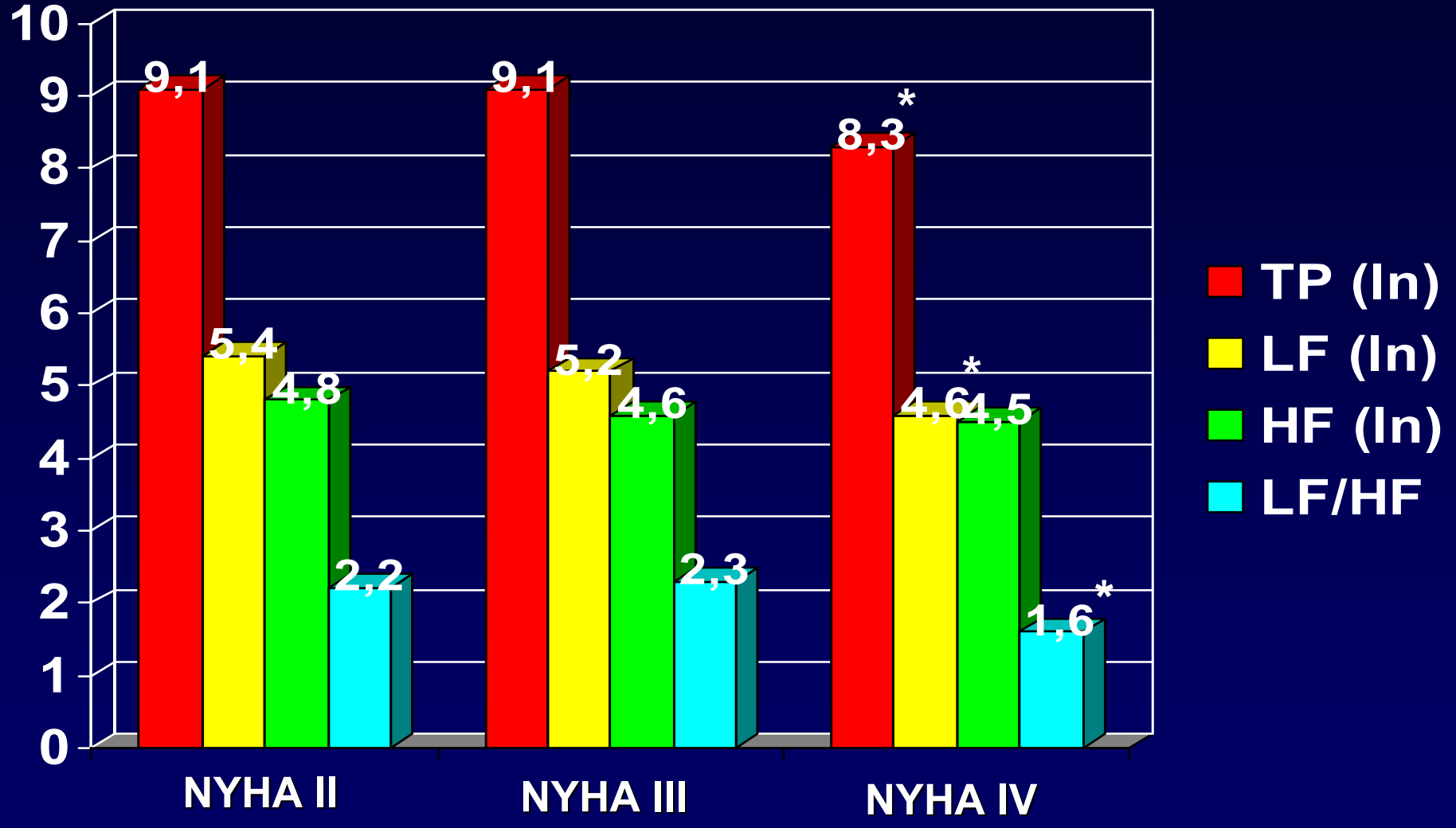
Measures	Value
SDNN, ms	107 ± 44.2
SDANN, ms	90.2 ± 29.1
SD, ms	38.1 ± 18.3
RMSDD, ms	28.9 ± 14.8
pNN50, %	3.9 ± 7.4
TP, ln ms ^{2}	9.5 ± 2,5
LF, ln ms ^{2}	5.9 ± 1.2
HF, ln ms ^{2}	5.6 ± 1.4
LF/HF	2.0 ± 1.4
VLF, ln ms ^{2}	7.9 ± 1.4
ULF, ln ms ^{2}	9.8 ± 1.6

Changes of Heart Rate and SDNN by NYHA



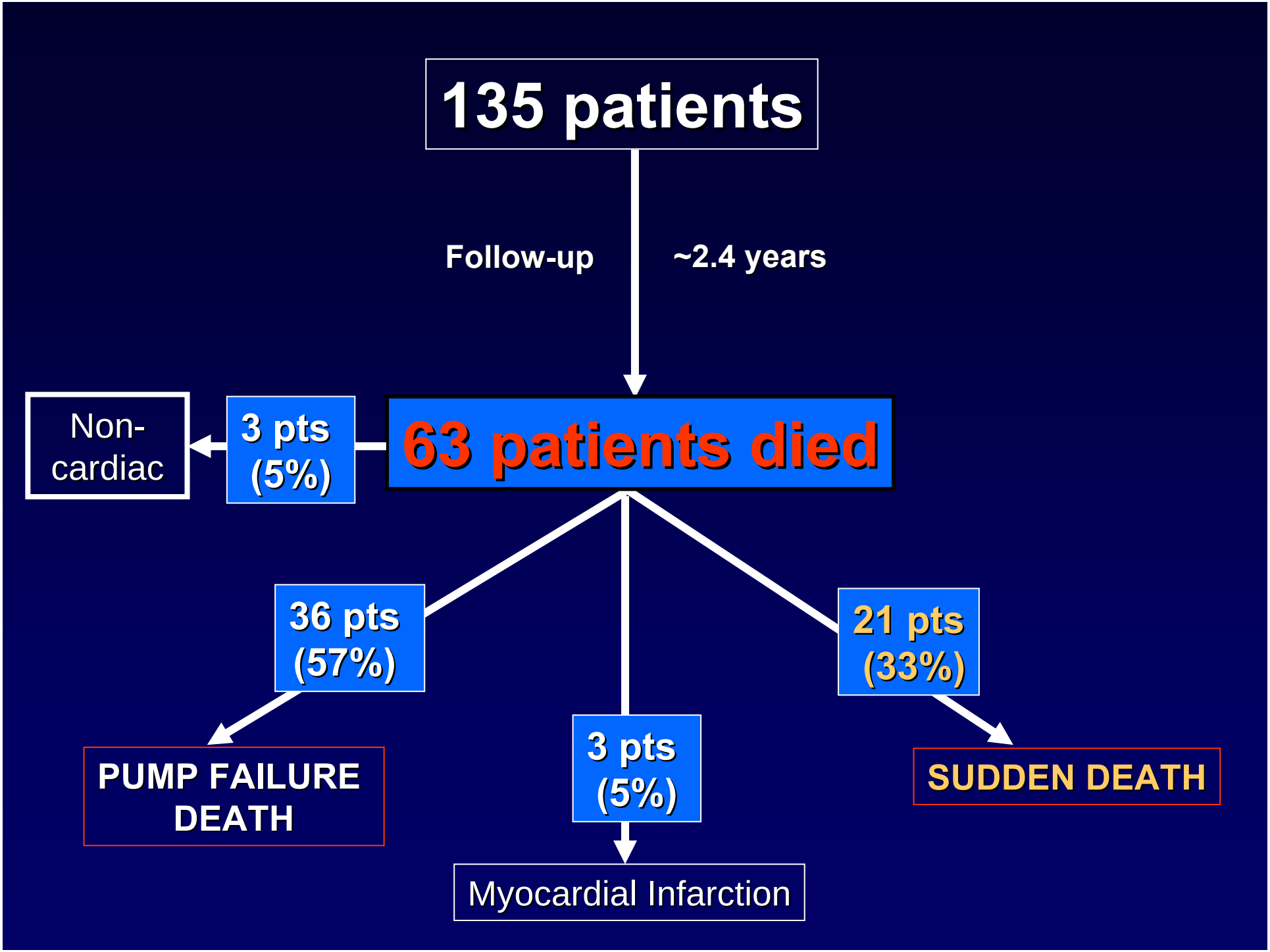
*p value < 0.05

Changes of Frequency Domain HRV measures by NYHA



* p value < 0.05

TOTAL MORTALITY


135 patients
Follow-up
~2.4 years
63 patients died
3 pts (5%)
Non-cardiac
36 pts (57%)
3 pts (5%)
21 pts (33%)
PUMP FAILURE DEATH
Myocardial Infarction
SUDDEN DEATH

Univariable predictors of total mortality among clinical variables

Variable (cut-off value)	RR	p	95% CI
NYHA, III-IV	3.5	0.003	1.2 - 4.25
NSVT	1.1	0.04	0.2 – 3.4
LVEF ≤ 30 %	1.5	0.03	0.8 – 1.7

Univariable predictors of total mortality among HRV measures

Variable (cut-off value)	RR	p	95% CI
RR $\leq$ 746 ms	1.5	0.01	0.9-1.9
SDNN < 90 ms	3.0	0.0003	1.3 – 4.2
SDANN < 70 ms	1.5	0.006	0.9 – 2.0
TP ln < 9.05 ms^2	1.7	0.002	1.1 – 2.5
LF ln < 5.1 ms^2	1.6	0.005	1.1 – 2.3
VLF ln < 6.35 ms^2	1.3	0.04	0.9 – 2.1
ULF ln < 8.1 ms^2	1.2	0.002	0.8 – 1.6

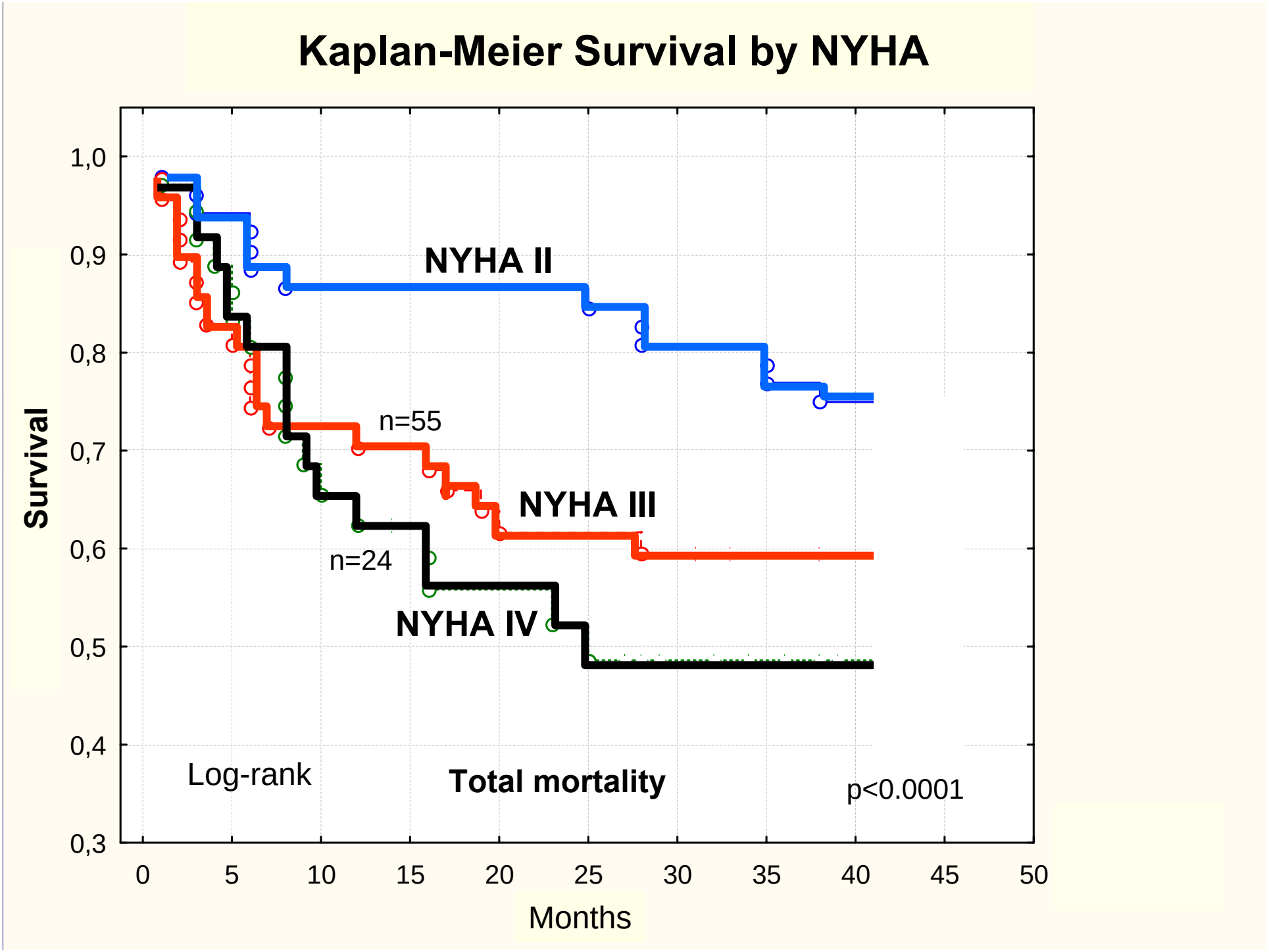
Multivariable predictors of total mortality

Clinical variables			
Variable (cut-off value)	RR	p	95% CI
NYHA, III-IV	2.0	0.02	1.0 - 3.3

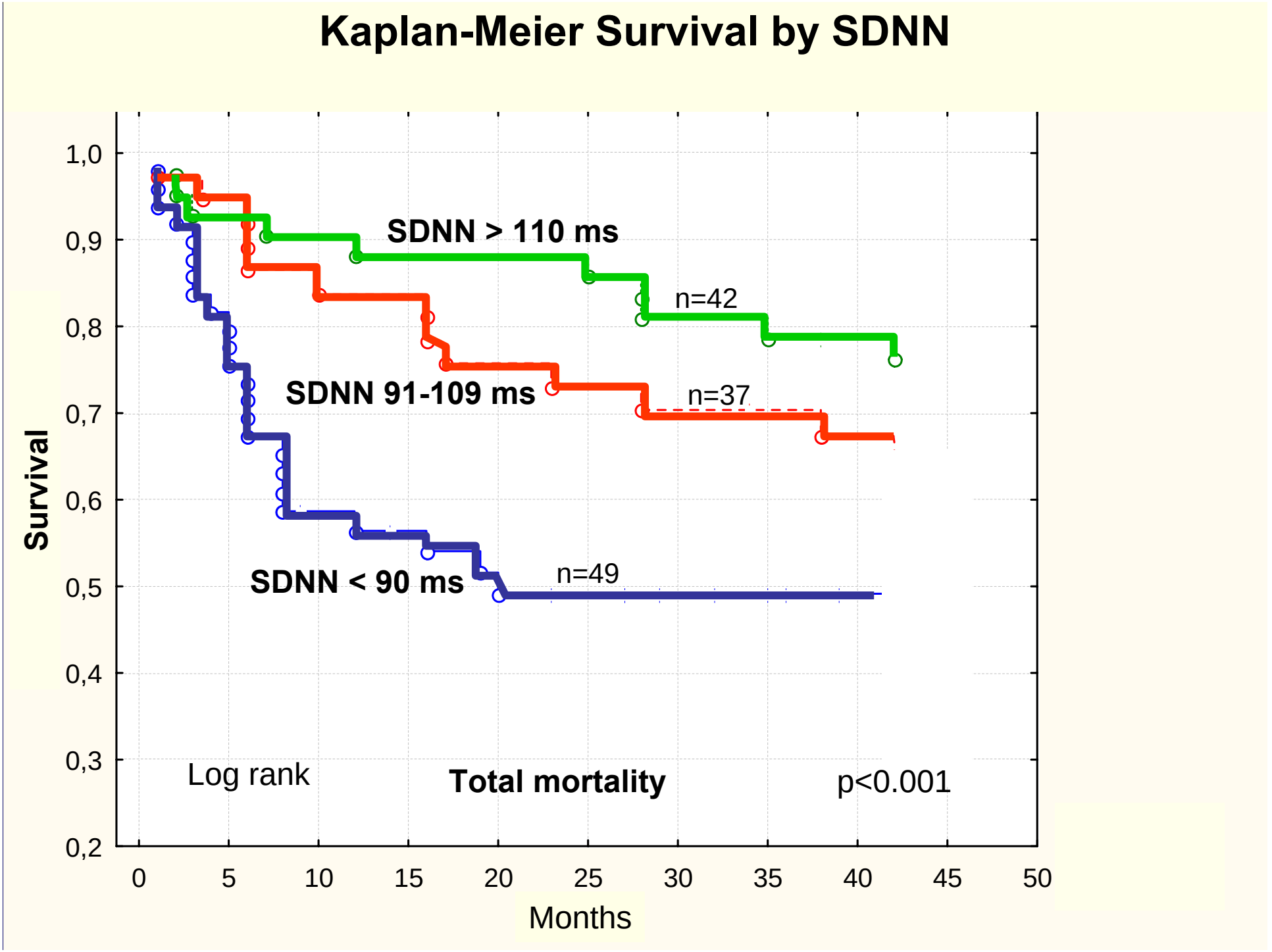
HRV measures			
Variable (cut-off value)	RR	p	95% CI
SDNN ≤ 90 мс	1.5	0.002	0.6 - 1.8

Final prognostic multivariable model for total mortality (forward stepwise Cox proportional hazard regression)

Variable (cut-off value)	RR	p	95% CI
NYHA, III-IV	1.8	0.001	0.7 - 2.8
SDNN ≤ 90 ms	1.2	0.002	0.2 - 1.9


Kaplan-Meier Survival by NYHA
Survival
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
NYHA II
n=55
NYHA III
n=24
NYHA IV
Log-rank
Total mortality
p<0.0001
0
5
10
15
20
25
30
35
40
45
50
Months

Kaplan-Meier Survival by SDNN



PUMP FAILURE DEATH

Univariable predictors of pump failure death

Clinical variables			
Variable (cut-off value)	RR	p	95% CI
NYHA, III-IV	9.5	0.0003	2.9 - 16.8
NSVT	1.3	0.003	0.3 – 3.5
LVEF ≤ 28 %	1.6	0.02	0.8 – 2.4

HRV measures			
Variable (cut-off value)	RR	p	95% CI
RR ≤ 705 MC (85')	2.3	0.0004	1.2-3.3
SDNN ≤ 85 ms	1.3	0.03	0.7 – 2.2

Multivariable predictors of pump failure death

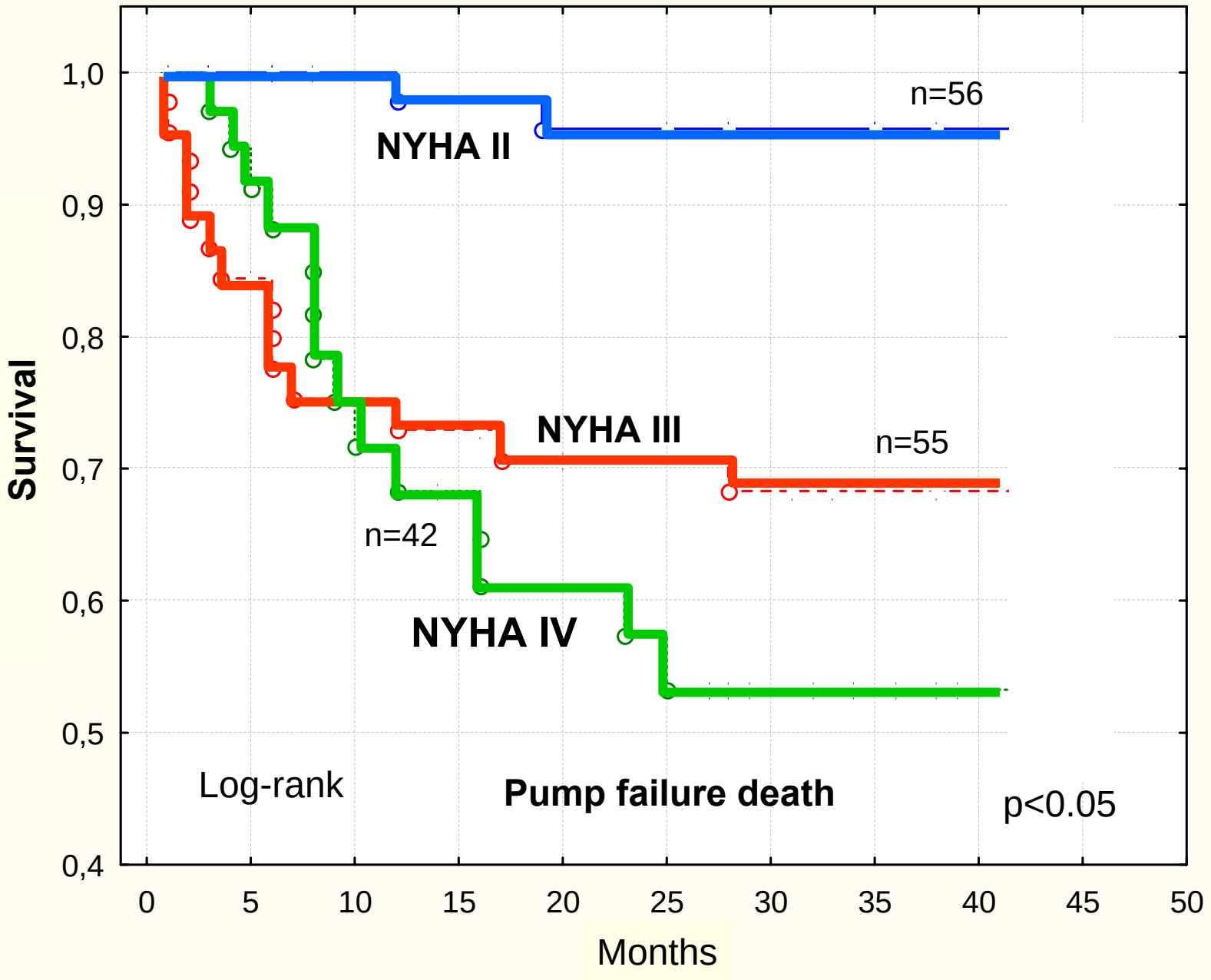
Clinical variables			
Variable (cut-off value)	RR	p	95% CI
NYHA, III-IV	8.1	0.001	2.3 - 15.7

HRV measures			
Variable (cut-off value)	RR	p	95% CI
RR ≤ 705 ms (85')	2.0	0.001	1.1-3.0

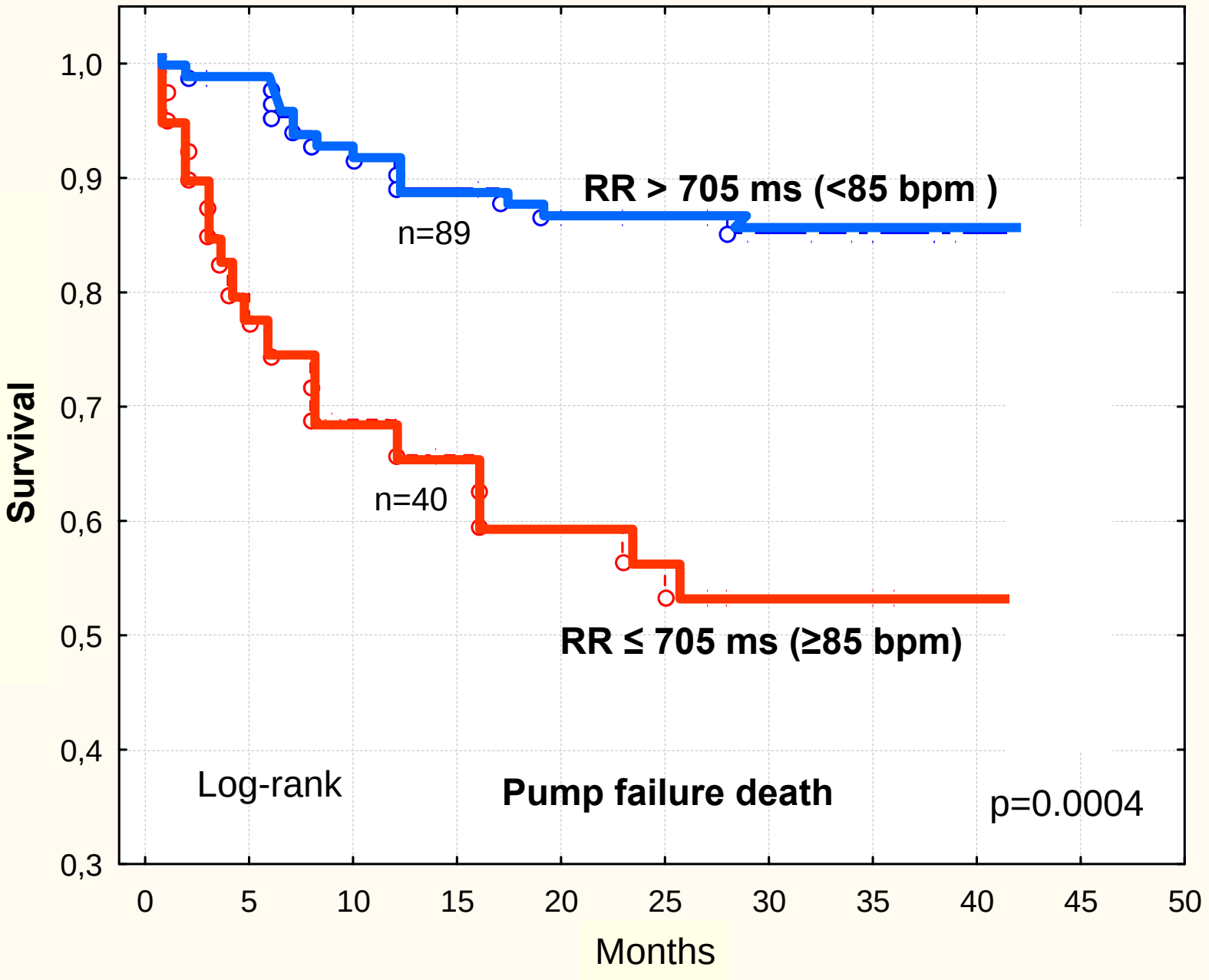
Final prognostic multivariable model for pump failure death (forward stepwise Cox proportional hazard regression)

Variable (cut-off value)	RR	p	95% CI
NYHA, III-IV	8.0	0.001	2.1 - 14.8
RR $\leq$ 705 ms (85')	1.5	0.002	0.6 – 3.8

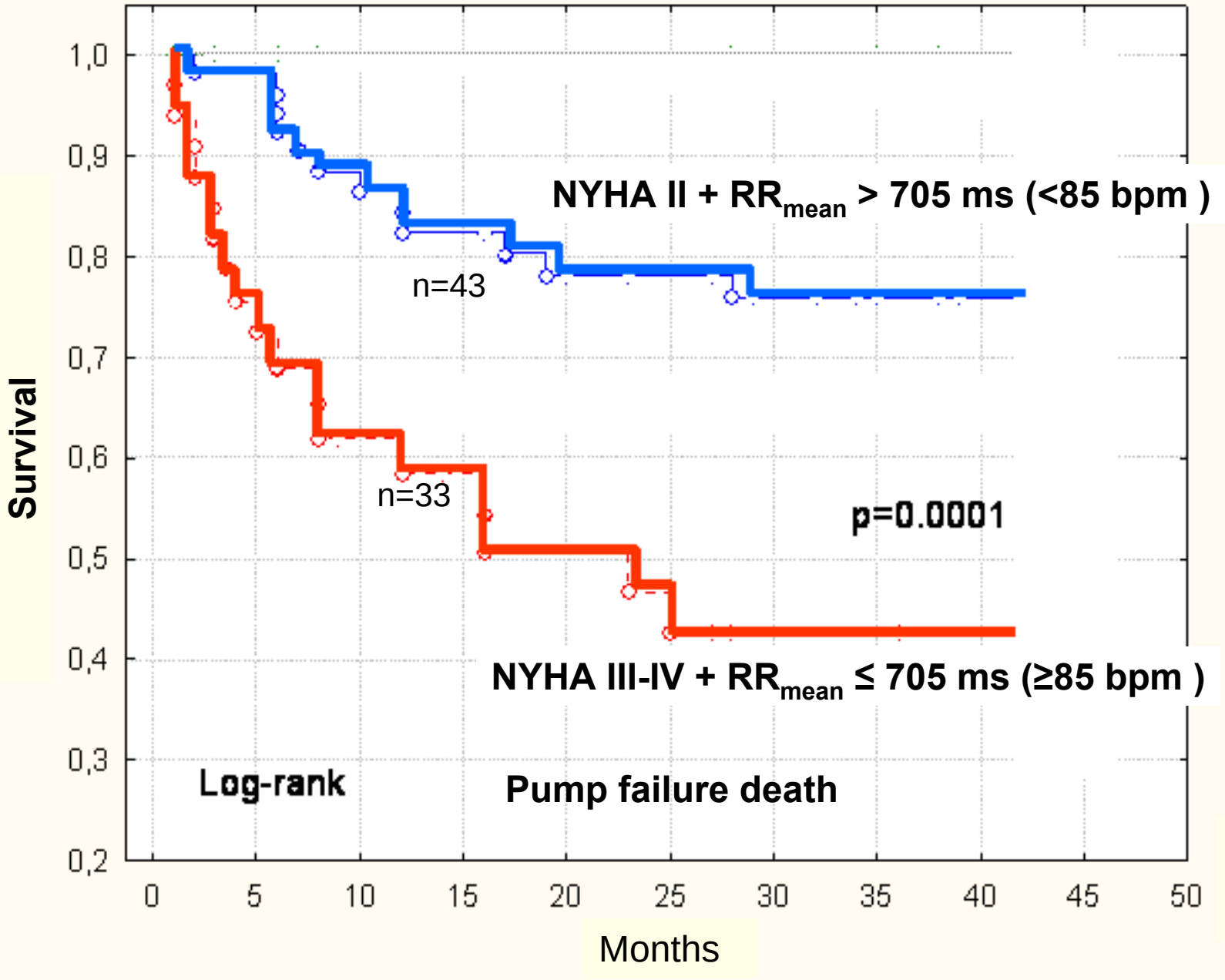
Kaplan-Meier Survival by NYHA



Kaplan-Meier Survival by mean RR



Kaplan-Meier Survival in 2 independent risk factor model



SUDDEN DEATH

Univariable predictors of sudden cardiac death

Clinical variables			
Variable (cut-off value)	RR	p	95% CI
NYHA, II	6.5	0.0002	2.4 – 9.5
LVEF $\leq$ 26 %	2.4	0.004	1.1 – 3.6

HRV measures			
Variable (cut-off value)	RR	p	95% CI
LF< 4.5, ln ms^2	2.1	0.006	0.9 – 5.5
LF/HF < 1.5	3.5	0.001	1.45 – 4.49

Multivariable predictors of sudden cardiac death

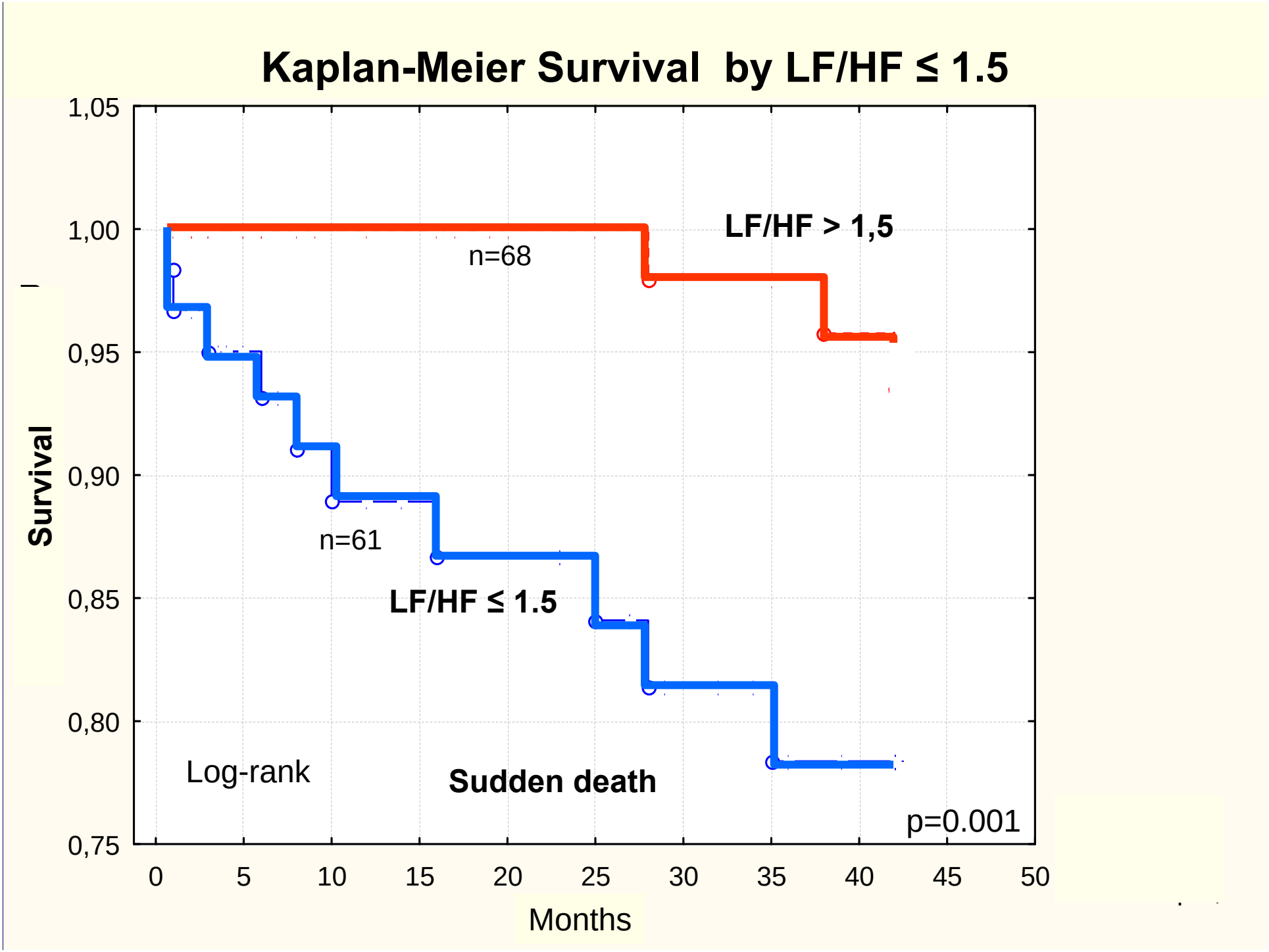
Clinical variables			
Variable (cut-off value)	RR	p	95% CI
NYHA, II	2.0	0.002	1.0 - 3.3
LVEF ≤ 26 %	1.1	0,04	0.2 – 4.6

Multivariable predictors of sudden cardiac death

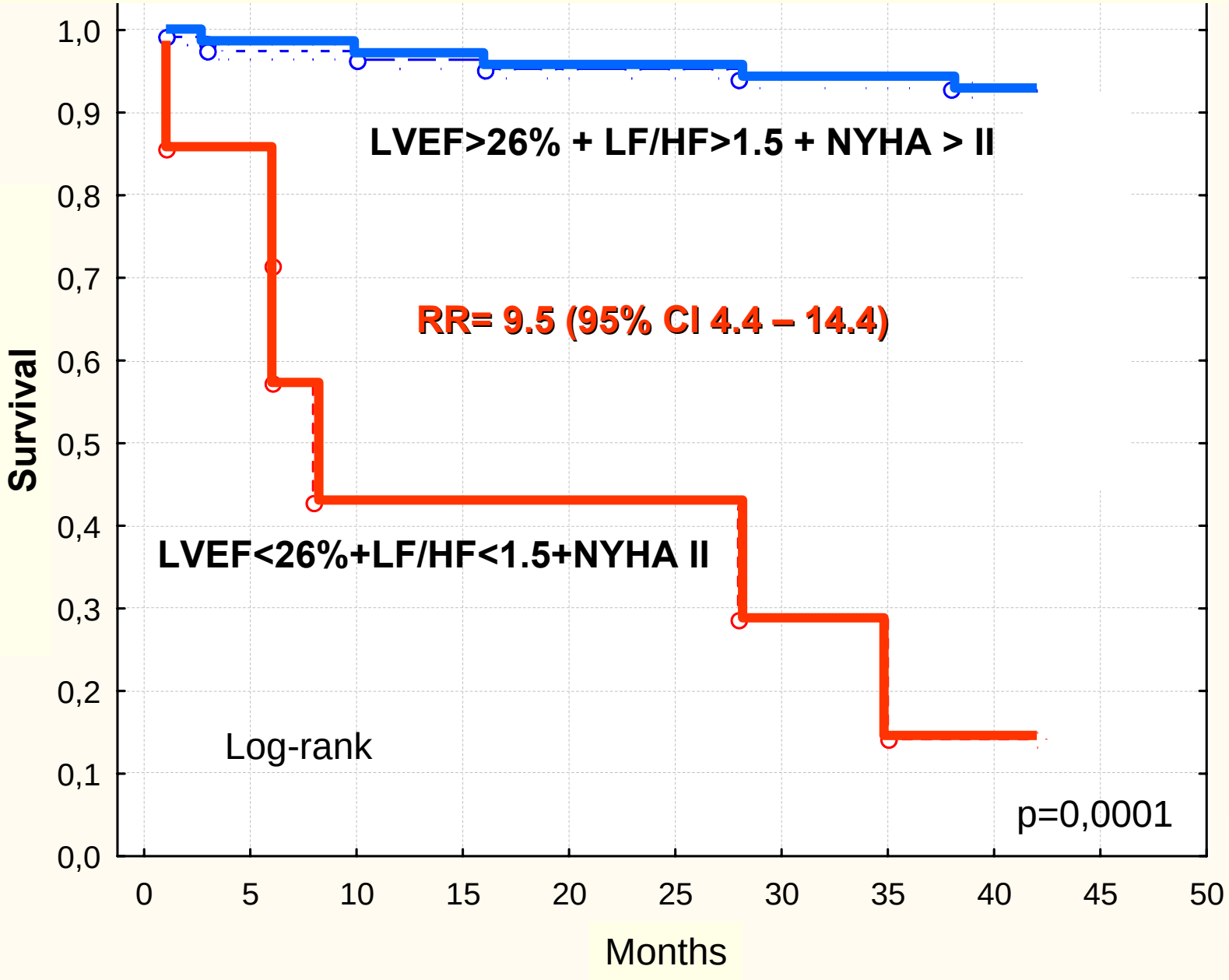
HRV measures			
Variable (cut-off value)	**RR**	**p**	**95% CI**
LF/HF < 1.5	**3.5**	**0.001**	**1.45 – 4.49**

Final prognostic multivariable model for sudden cardiac death (forward stepwise Cox proportional hazard regression)

Variable (cut-off value)	RR	p	95% CI
NYHA, II	3.5	0.003	2.0 – 9.5
LVEF ≤ 26 %	1.4	0,04	0.4 – 3.0
LF/HF < 1.5	1.5	0.001	0.5 – 2.9


Kaplan-Meier Survival by LF/HF ≤ 1.5
1,05
1,00
0,95
0,90
0,85
0,80
0,75
Survival
0
5
10
15
20
25
30
35
40
45
50
Months
LF/HF > 1,5
n=68
n=61
LF/HF ≤ 1.5
Log-rank
Sudden death
p=0.001

Kaplan-Meier Survival in 3 independent risk factor model



Conclusions

1. The main HRV indices (both time- and frequency domain) are depressed in heart failure which relates to the severity of heart failure

2. III-IV NYHA and SDNN ≤ 90 ms are independent predictors of all-cause mortality.

3. III-IV NYHA and mean RR ≤ 705 ms (HR≥85') are independent predictors of death from progressive pump failure. Their combination singles out pts at the most increased risk of pump failure death.

Conclusions (continued)

5. Patients in II NYHA, depressed LVEF ≤ 26%, and decreased LF/HF ≤ 1.5 are independent predictors of sudden death. Their combination singles out patients with heart failure at the most increased risk of sudden death.

6. HRV measures are advantageous over traditional markers of unfavorable prognosis (VPCs, NSVT) in identifying patients with heart failure at increased risk of sudden death.