Effects of selective serotonin re-uptake inhibition on **MO**rtality, m**O**rbidity and mood in **D**epressed **H**eart **F**ailure patients **(MOOD-HF)**

MOOD-HF

A double-blind, randomized, placebo-controlled, parallel group study to determine the effects of serotonin re-uptake inhibition with the SSRI escitalopram on morbidity, mortality and mood in depressed patients with chronic systolic heart failure

Christiane E. Angermann MD
on behalf of the MOOD-HF Investigators

ACC.2015
FEATURED CLINICAL RESEARCH

Trial Registration ISRCTN33128015; **Eudra-CT-number** 2007-006609-25

Bundesministerium für Bildung und Forschung

Competence Network Heart Failure

Zentrum für Klinische Studien Leipzig

Comprehensive Heart Failure Center

Disclosures

MOOD-HF

CE Angermann declares financial / logistic support for MOOD-HF

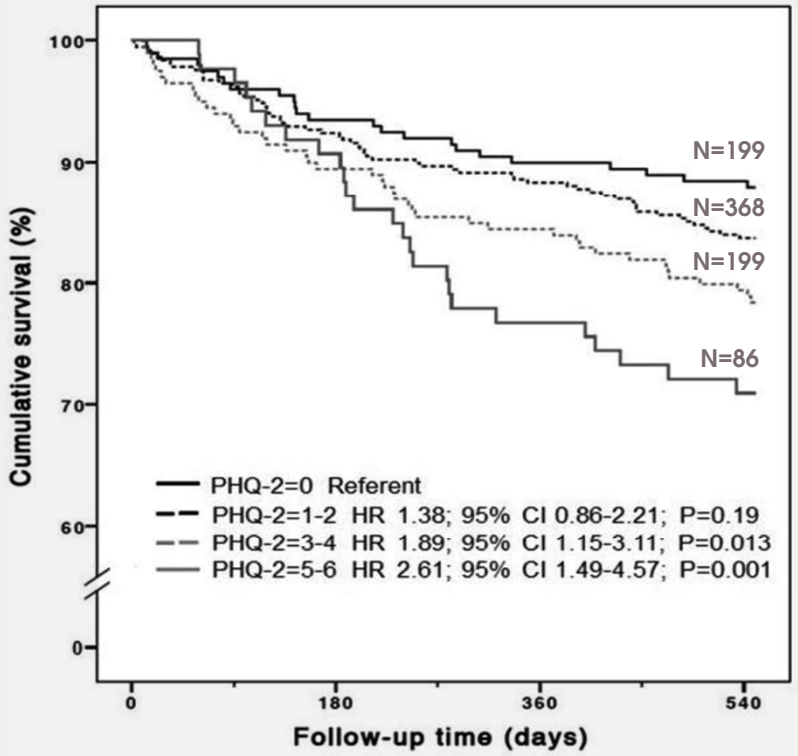
- German Ministry of Education and Research (BMBF, grant 01KG0702, funding of study)
- Lundbeck A/S Denmark (study drug, co-funding of patient identification and recruitment)
- Competence Network Heart Failure (logistic support)
- Comprehensive Heart Failure Center & University of Würzburg (project management, personnel)

Background

MOOD-HF

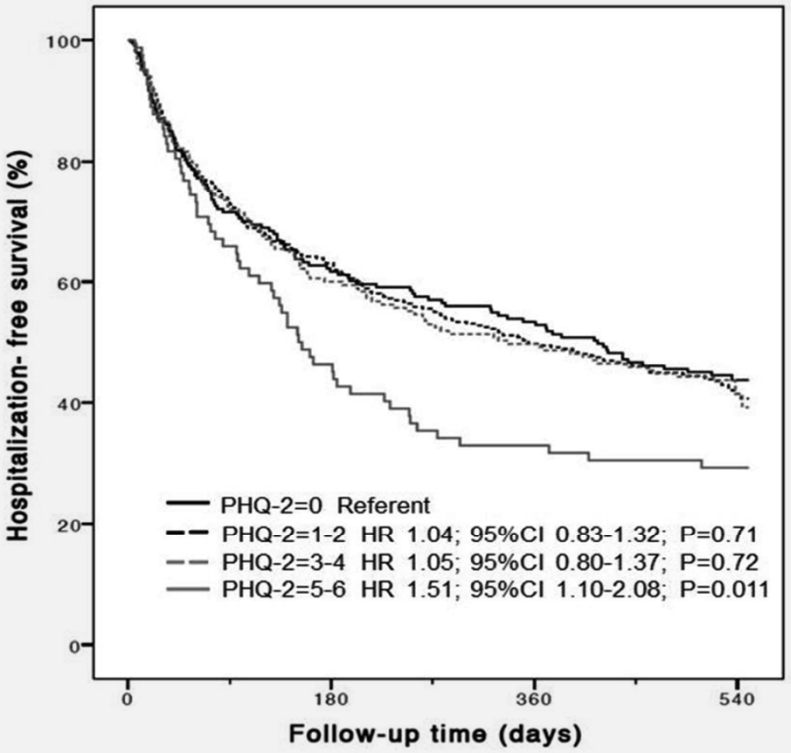
‚Dose-response' relationship between depression severity and the risk of death/re-hospitalization in patients with systolic heart failure and co-morbid depression (N=852)

All-cause death



A

All-cause re-hospitalization



B

Piepenburg S,…Angermann CE Circ Heart Fail 2015 (in revision)

Objectives

MOOD-HF

Primary

- Investigate effects of escitalopram (E) vs. placebo (P) on mortality and morbidity in patients with chronic systolic heart failure (CHF) and a current episode of major depression (MDD)

Major secondary

- Estimate improvement of depression by E vs. P (12 weeks)

Secondary (selection)

- Effects of E on components of primary endpoint (total population & subgroups) and clinical / laboratory / imaging parameters of CHF severity
- Safety and tolerability

Patient Population

MOOD-HF

Inclusion criteria

- Age >18 years, stable symptomatic systolic CHF (NYHA II – IV, LV ejection fraction <45%)
- Current major depression diagnosed by Structured Clinical Interview (SCID) performed by psychiatrist
- Written informed consent

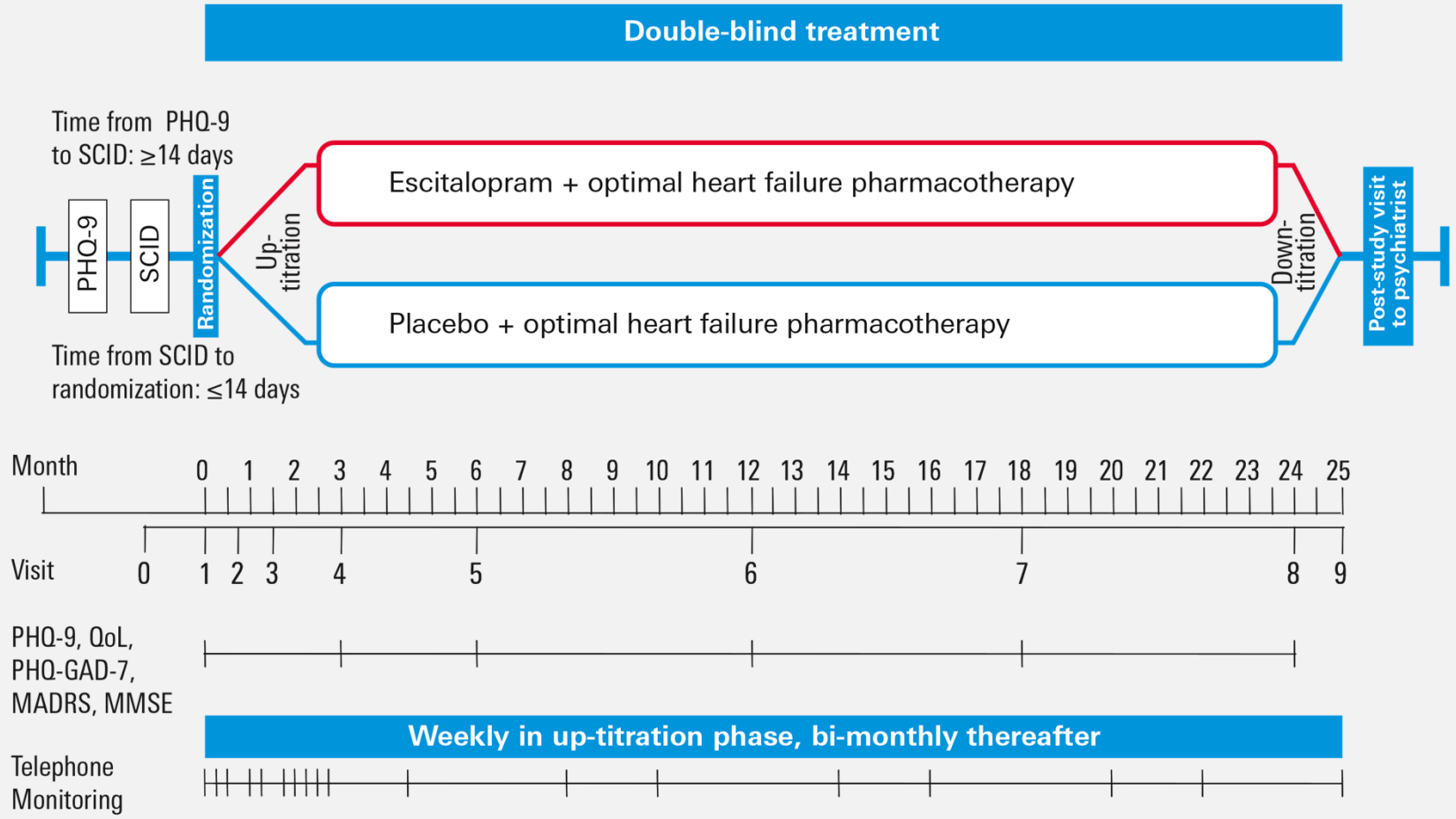
Important exclusion criteria

- Current treatment with a SSRI or other antidepressant
- Previous treatment failure / contraindications to escitalopram
- Acute MI (<3 months), AHF, recent / planned (<3 /12 m) heart surgery, advanced renal failure (MDRD<30)
- Imminent risk / history of suicide, dementia (≥ moderate) or severe depressive episode with psychotic features

Study Flow –'Cardiologist-Psychatrist-Nurse' care

MOOD-HF

Multicenter multidisciplinary double-blind phase IV RCT, 16 academic German centers, randomization 1:1 to either E or P 20 (10) mg once daily. Strata: age, sex, NYHA III/IV, last hospitalization < vs. ≥ 4 weeks



Endpoints

MOOD-HF

Primary endpoint

- Time to all-cause death or hospitalization*

Major secondary endpoint

- Montgomery-Åsberg Depession Rating Scale (MADRS) score after 12 weeks**

Prespecified secondary endpoints (selection)

- Components of primary endpoint, CV death, HF-related hospitalization
- Changes in HF severity (e.g. NYHA class, NT-proBNP, LVEF)
- Safety (SAE, ECG time intervals, renal function)

* Adjudicated by independent blinded endpoint committee

** Applied by trained and certified MOOD-HF cardiologist

Data Analysis

MOOD-HF

Intention to treat population (ITT)

- Patients who took at least one dose of study drug (evaluated as randomized) – primary mode of analysis

Population on study medication (OSM)

- Patients censored at the time they stopped taking the study medication (no restart) – prespecified exploratory analysis

Patient Disposition

	N	% (of previous)
• Screened	**11 086**	
• PHQ-9 sum score ≥12	**1 979**	**18**
• Underwent SCID	**773**	**39**
• SCID indicative of MDD	**508**	**66**
• Randomized	**376**	**74**
• Took ≥1 dose of study drug (ITT population)	**372**	**99**

Statistics / Study Termination

MOOD-HF

- Assumed a 36% annual primary outcome rate on placebo
- Hypothesized a 25% relative reduction in primary events (all-cause death or hospitalization) on escitalopram
- HR=0.705, α=0.05, power=0.8
  $\rightarrow$ **257 adjudicated endpoint events needed**

DSMB recommendation & consequences (January, 2014)

- To prematurely stop recruitment as of February 28, 2014
- To terminate study participation of individual patients at the next scheduled visit if subjects were then $\geq$6 months in the study
- End of study by August, 2014
- 376 patients randomized
- **235 patients with adjudicated endpoint events**

Patient Participation over Time

MOOD-HF

- Median participation time: 18.4 (E) and 18.8 (P)months
- Total patient-years in study /on study medication: 503 / 428
- Mean daily dose of study drug at 12 weeks: 13.7(E) / 13.4 mg (P)
- Comparable participation over time in E and P arms

	Escitalopram (100%: N=185)	**Placebo** (100%: N=187)
3 weeks	94	97
6 weeks	89	95
12 weeks	85	93
6 months	82	86
12 months	65	72
18 months	51	56
24 months	42	45

Baseline Characteristics I

MOOD-HF

	Escitalopram	Placebo
Demographics		
Age (y) – mean	62	62
Female sex – %	24	25
HF etiology/severity/measurements		
Ischemic HF – %	63	66
NYHA class III-IV – %	48	58
LVEF (%) – mean	35	35
LVD_{ED} (mm) – mean	60	60
RR sys/diast (mmHg) – mean	124/76	124/76
Heart rate (bpm) – mean	69	70
NTproBNP (ng/L) – median	837	781
(IQR)	*(289-2512)*	*(313-1935)*

Baseline Characteristics II

MOOD-HF

	Escitalopram	Placebo
Co-morbidities (%)		
Atrial fibrillation	21	18
Diabetes mellitus	32	32
COPD	14	15
Renal dysfunction*	35	28
Anemia**	20	20
HF therapy (%)		
ACE inhibitor and/or ARB	95	94
Beta-blocker	91	93
MR-antagonist	58	58
Diuretic	81	81

* eGFR <60 mL/min/1.73 m^2

** Hb <12g/dL (women), <13g/dL (men)

Baseline Characteristics III

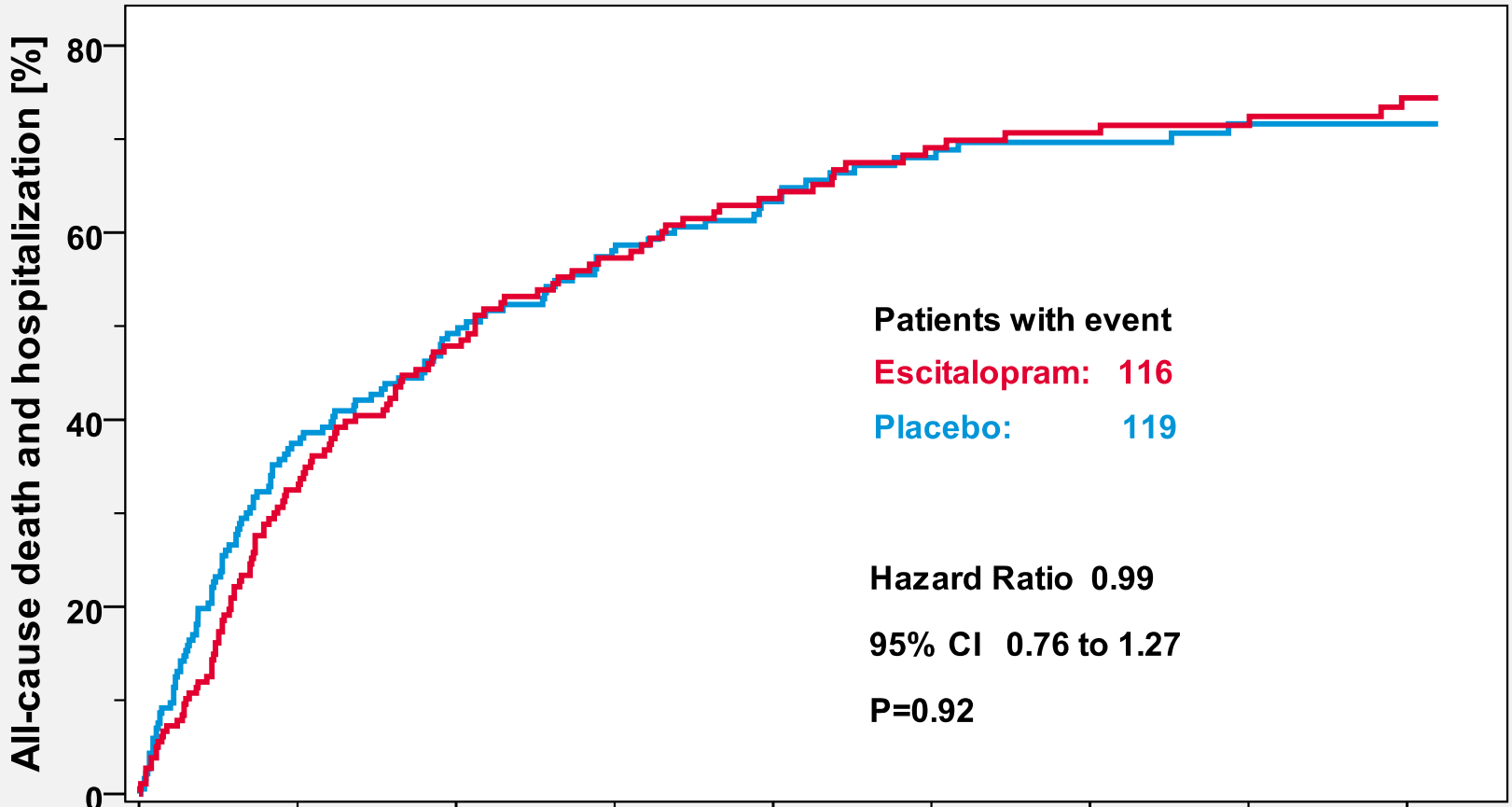
MOOD-HF

	Escitalopram	Placebo
Depression characteristics		
History of depression – %	12	12
PHQ-9 score – mean ± SD		
at the time of screening	15 ± 4	15 ± 4
at randomization	12 ± 5	13 ± 5
MADRS score – mean ± SD	20 ± 9	22 ± 9
GAD-7 score – mean ± SD	13 ± 7	14 ± 7

1° Outcome

Time to all-cause death or hospitalization

MOOD-HF

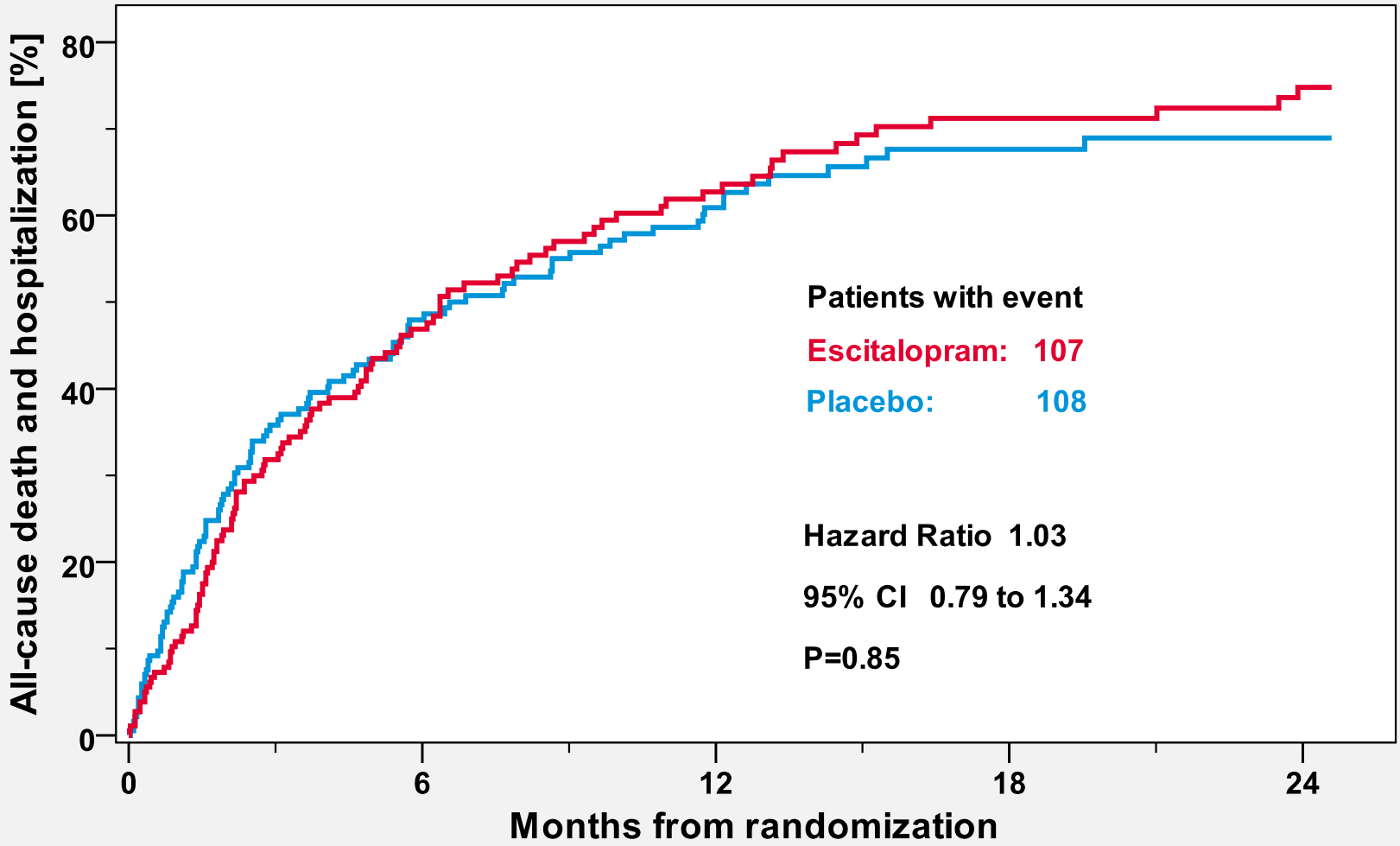


N at risk				
E: 185	81	50	36	26
P: 187	83	53	34	25

1° Outcome – OSM

Time to all-cause death or hospitalization

MOOD-HF

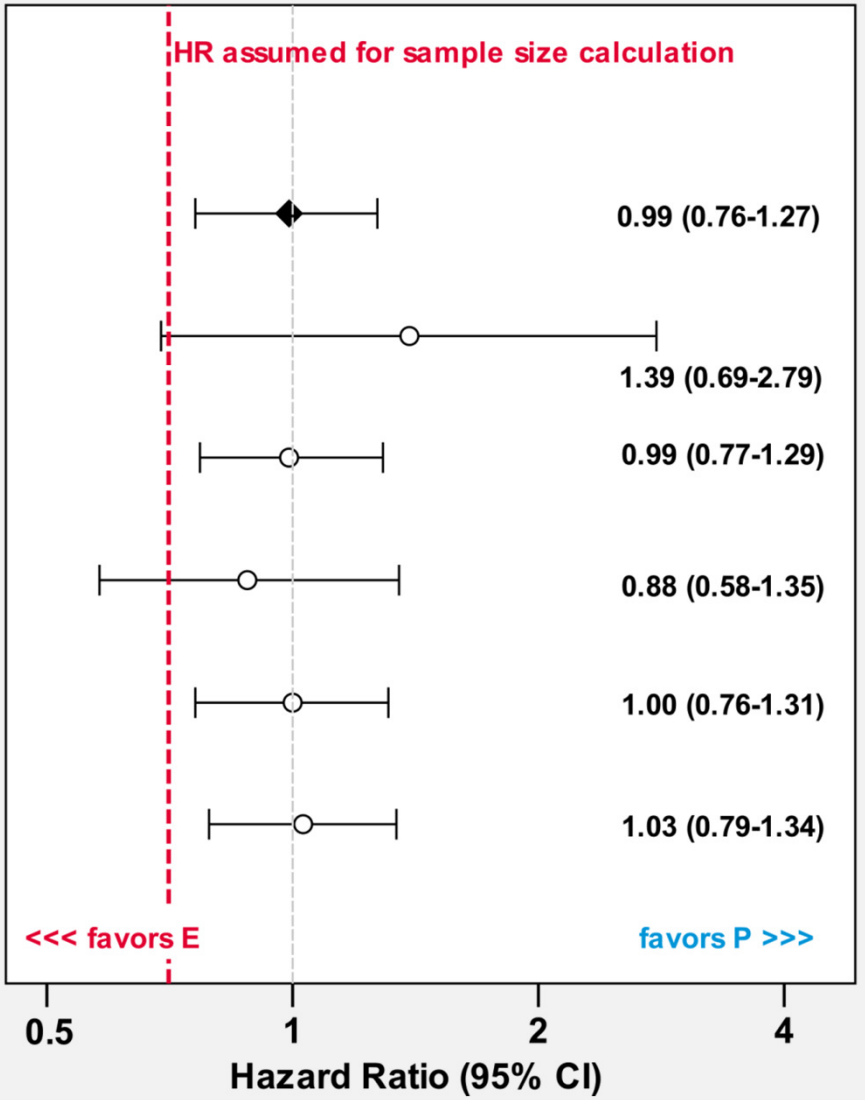


N at risk				
E: 185	72	43	30	21
P: 187	76	48	30	22

Components of 1° Outcome
and other time-to-event outcomes

MOOD-HF

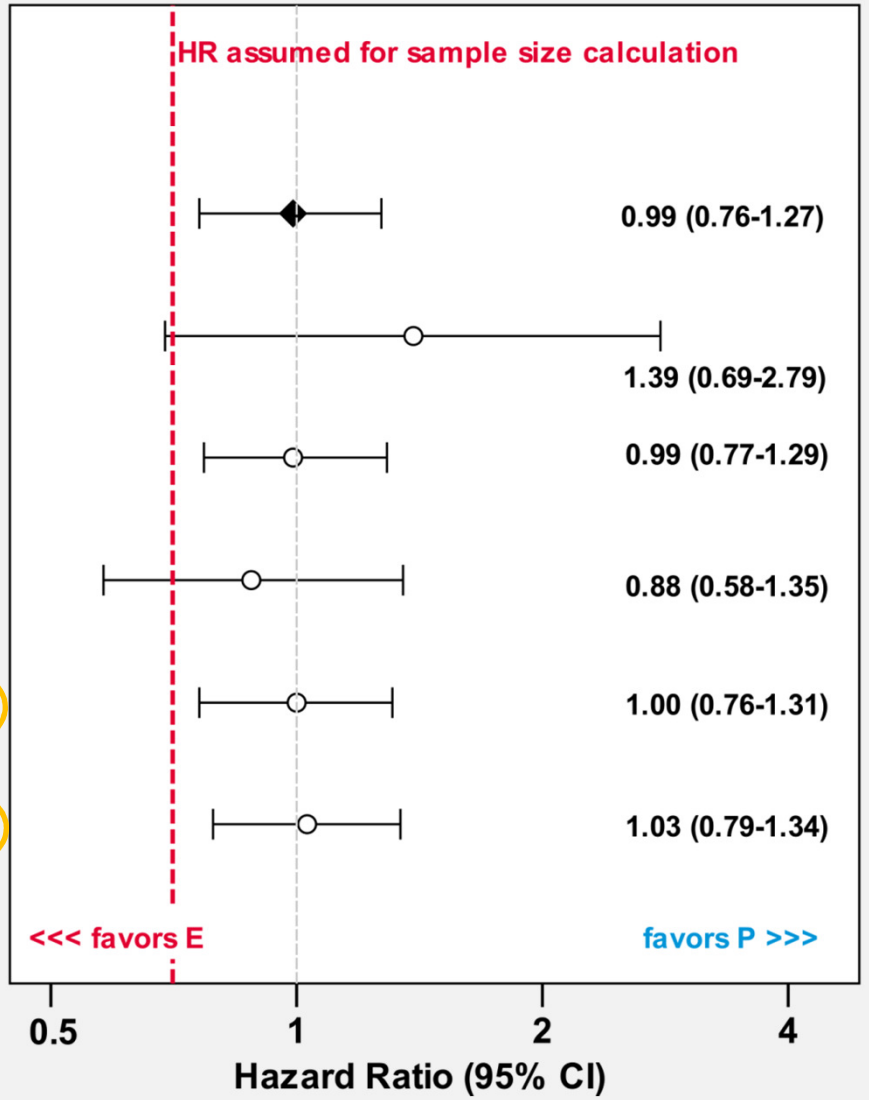
ENDPOINTS	N of events E	N of events P
All-cause death & hospitalization (primary)	116	119
All-cause death	18	14
All-cause hospitalization	116	118
CV death & HF hospitalization	40	46
Non-CV death & non-HF hospitalization	102	108
Primary endpoint, on study medication	107	108



Components of 1° Outcome
and other time-to-event outcomes

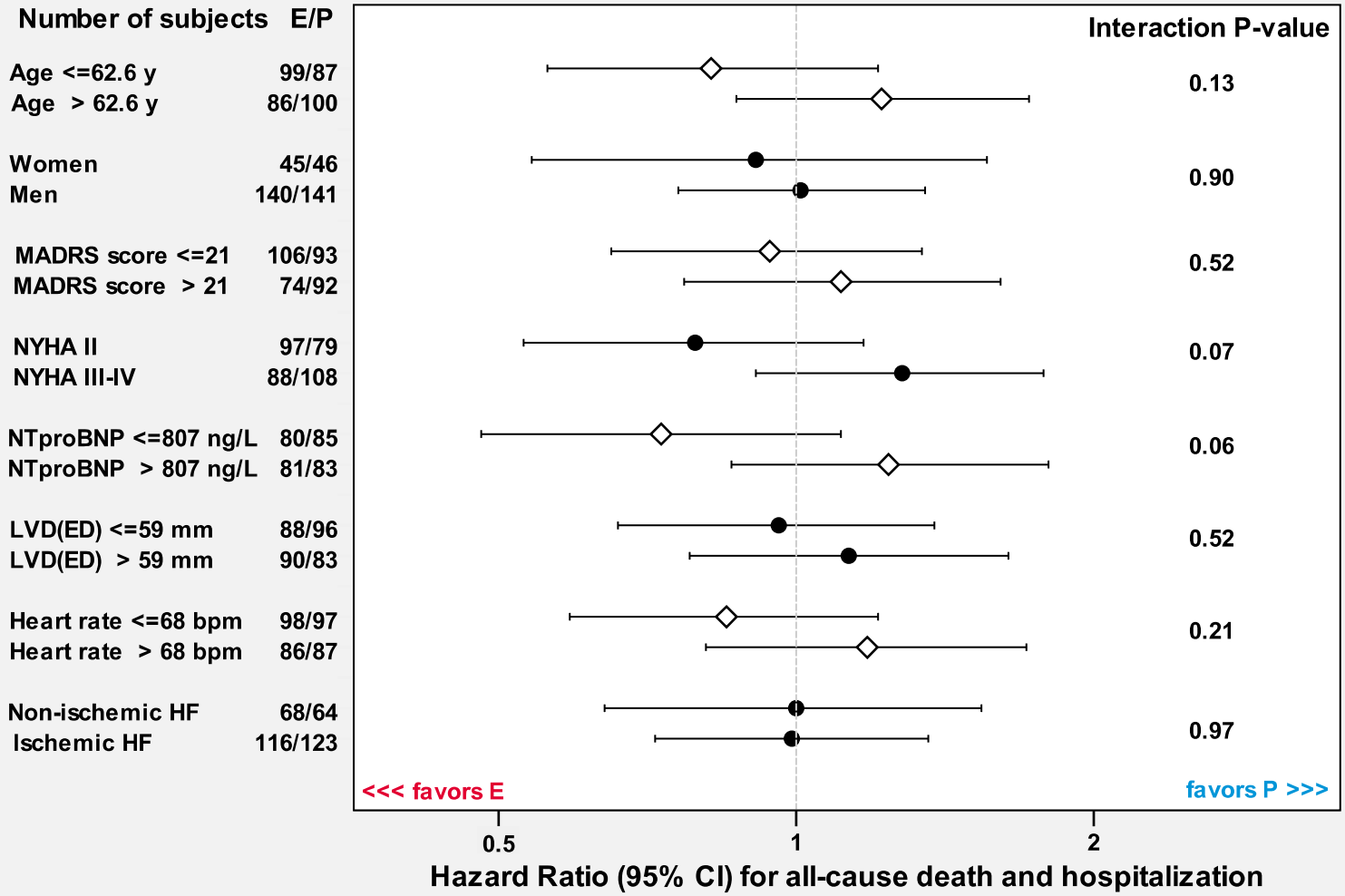
MOOD-HF

ENDPOINTS	N of events E	N of events P
All-cause death & hospitalization (primary)	116	119
All-cause death	18	14
All-cause hospitalization	116	118
CV death & HF hospitalization	40	46
Non-CV death & non-HF hospitalization	102	108
Primary endpoint, on study medication	107	108



1° Outcome
Subgroups

MOOD-HF



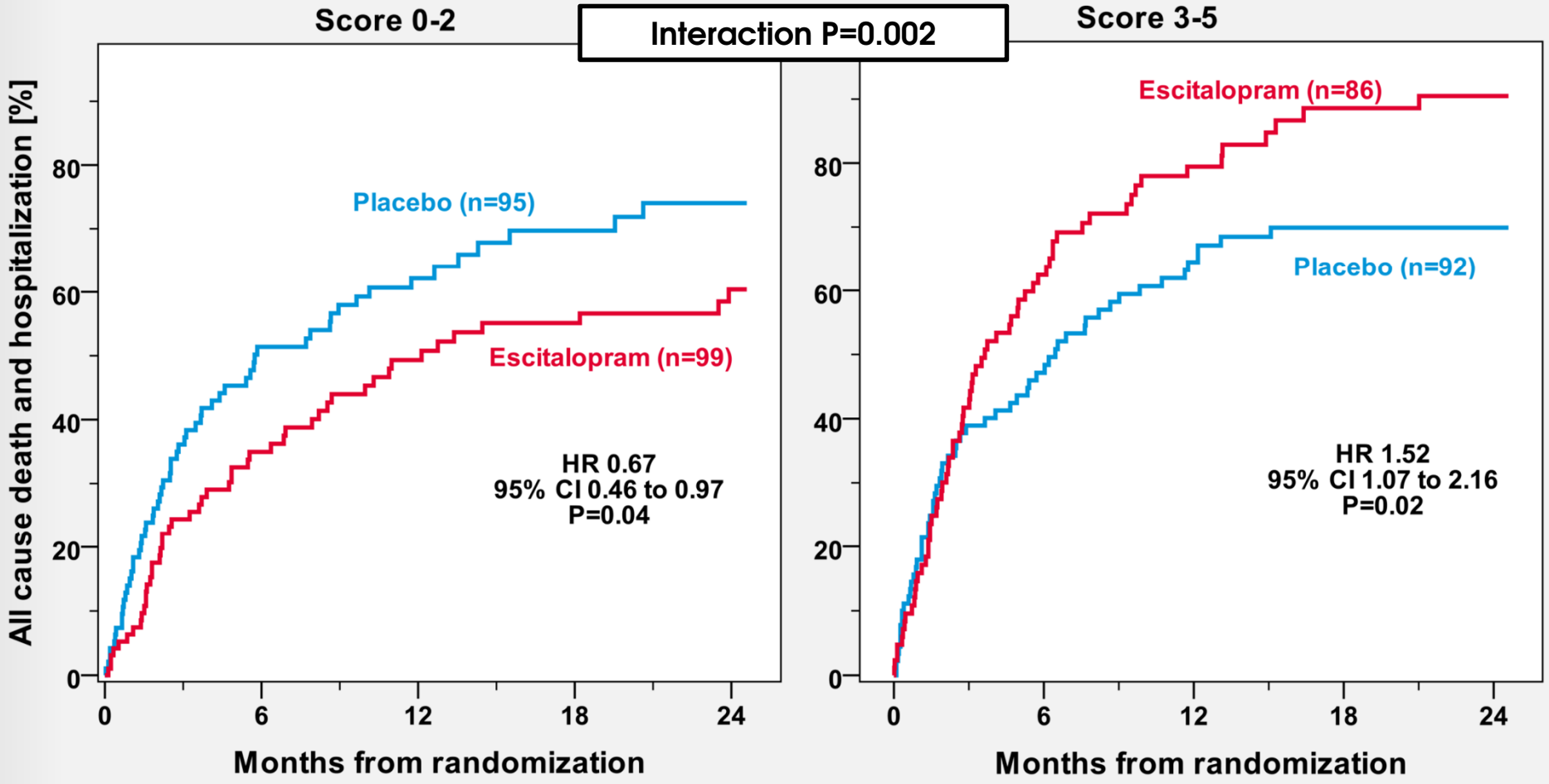
1° Outcome

Posthoc analysis of selected subgroups

MOOD-HF

Risk score (1 score point each)

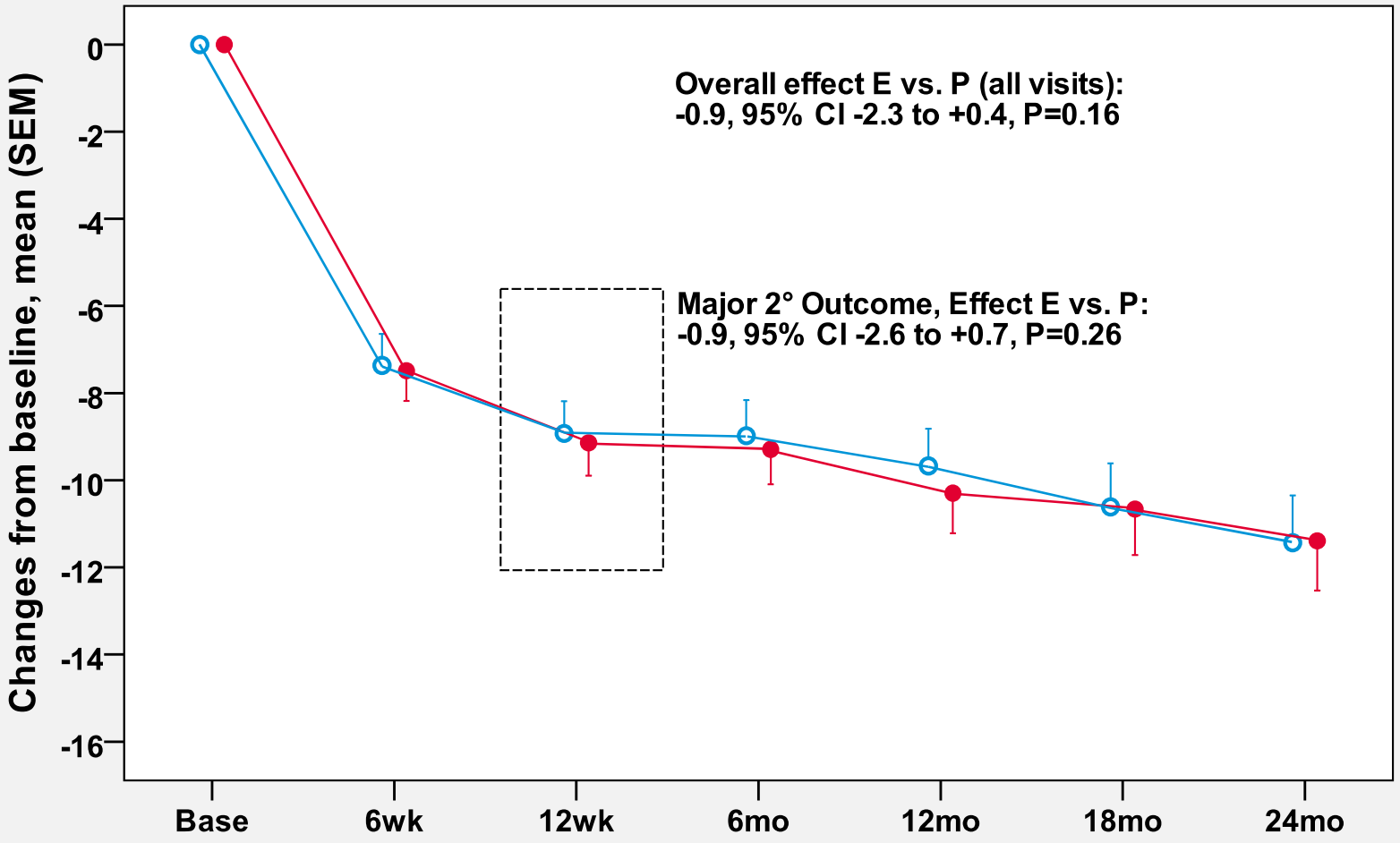
Age > 62.6 years; NYHA III-IV; NTproBNP > 807 ng/L; HR > 68 bpm; LVD_{ED} > 59 mm



Major 2° Outcome

10- item Montgomery–Åsberg Depression Rating Scale

MOOD-HF

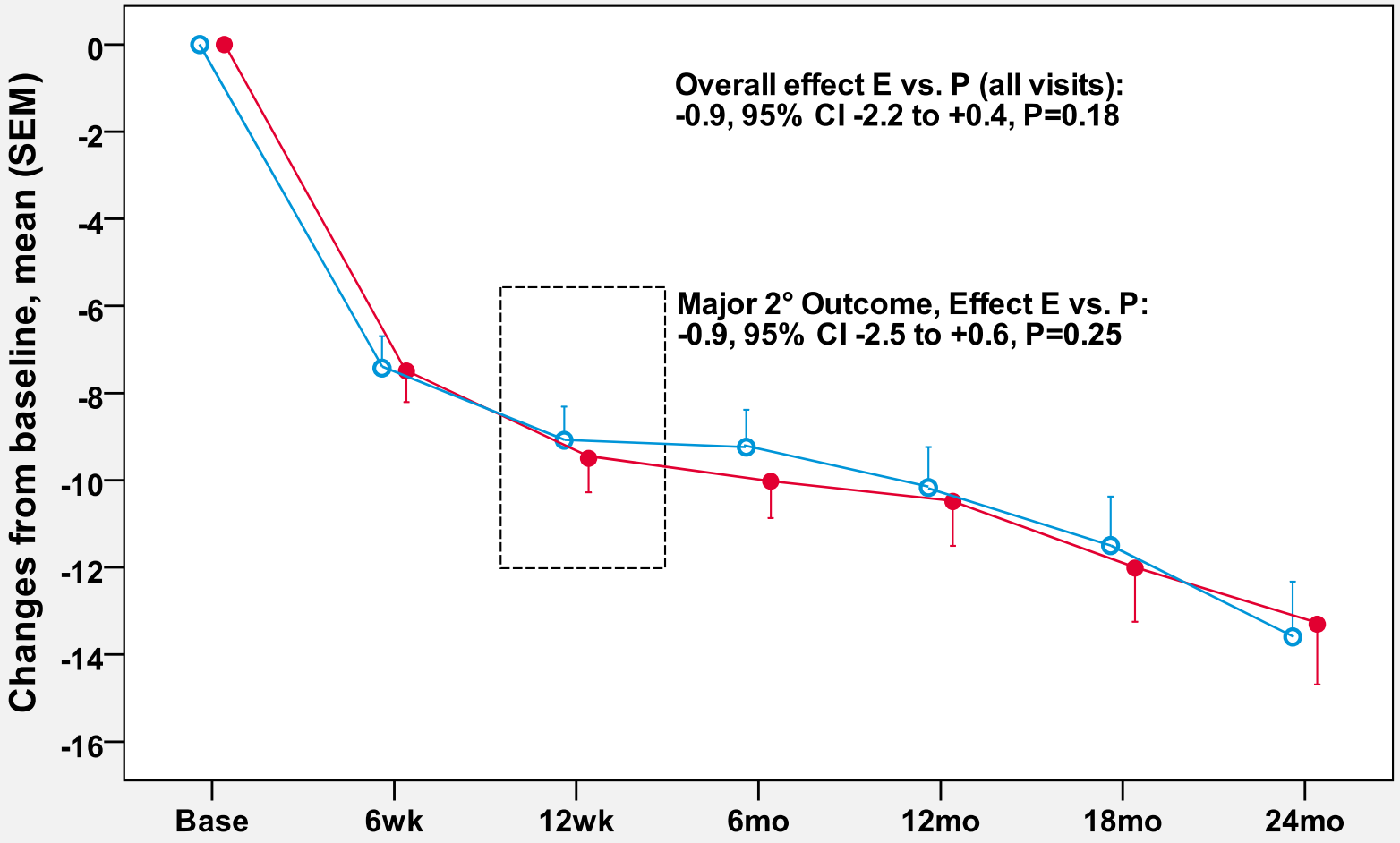


	Base	6wk	12wk	6mo	12mo	18mo	24mo
E:	180	152	149	141	105	83	69
P:	185	162	151	142	119	90	76

Major 2° Outcome – OSM

10- item Montgomery–Åsberg Depression Rating Scale

MOOD-HF

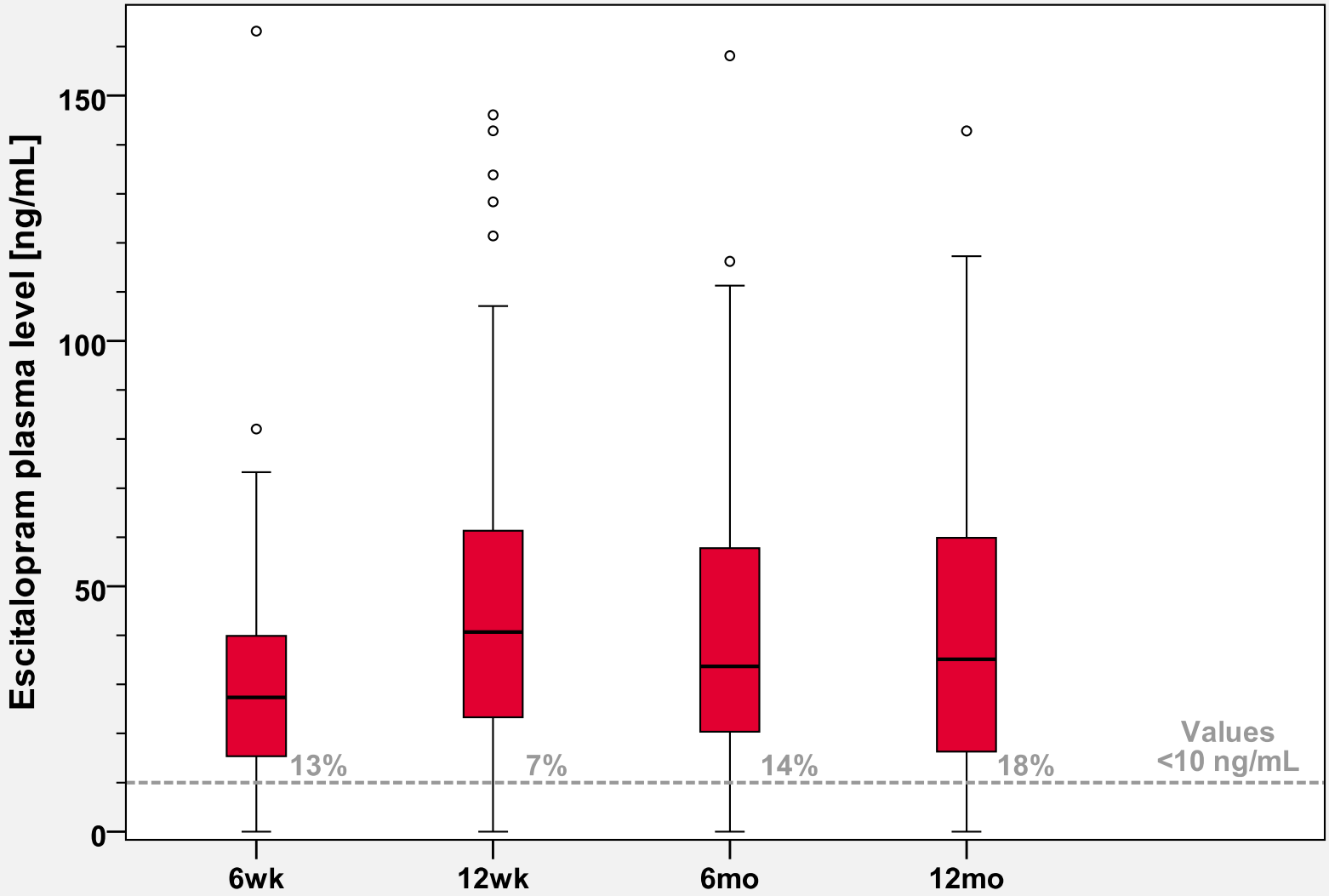


	Base	6wk	12wk	6mo	12mo	18mo	24mo
E:	180	148	141	122	86	66	49
P:	185	159	144	132	100	72	52

Adherence to Study Medication

Escitalopram Plasma Levels

MOOD-HF



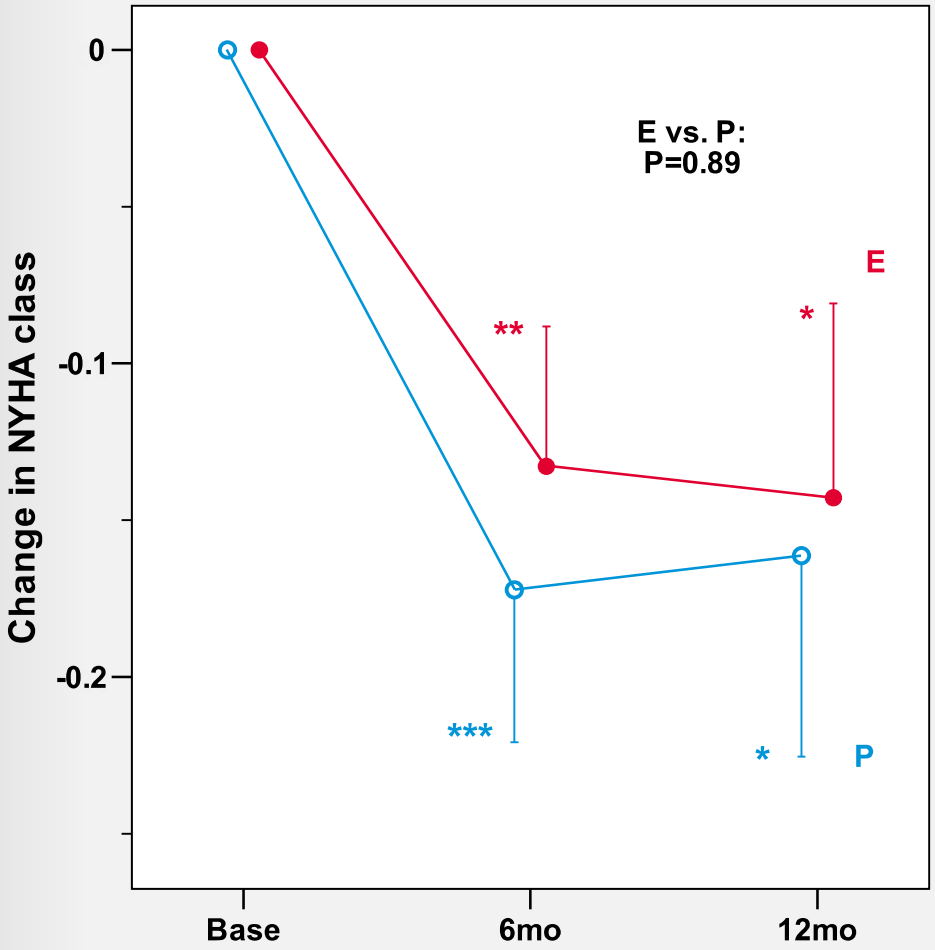
Heart Failure Medication

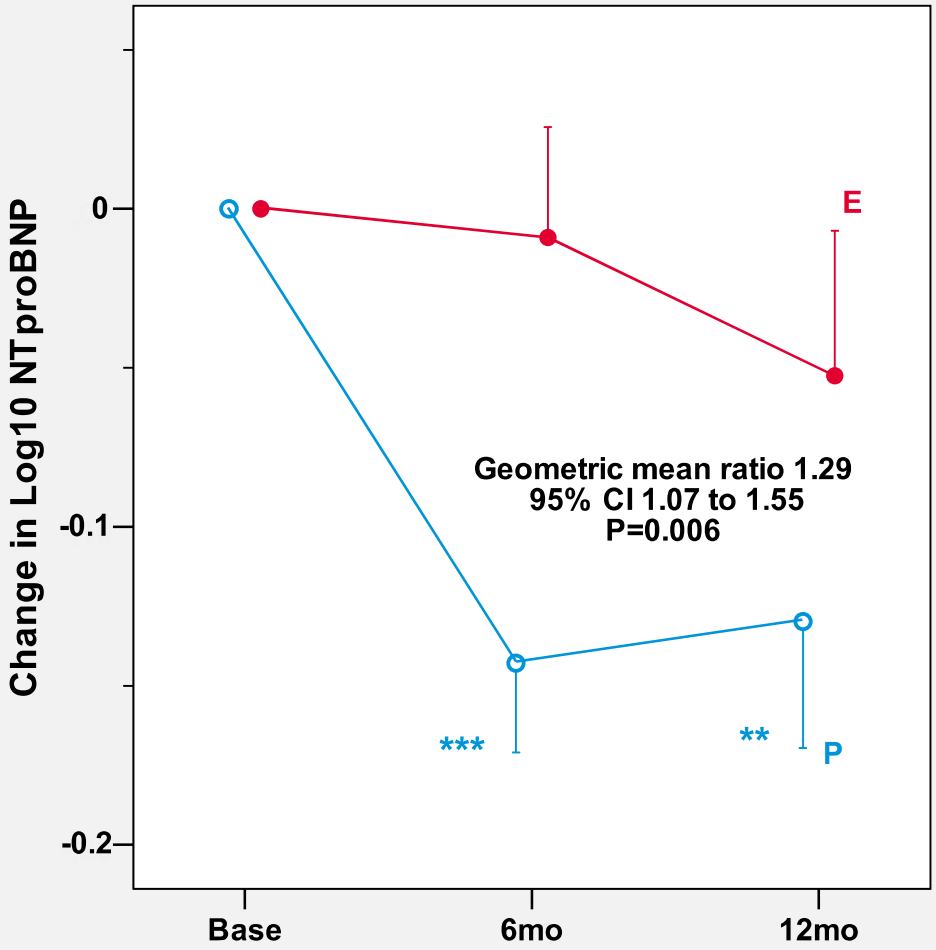
MOOD-HF

	Baseline	12 week follow-up
ACE-I / ARB*		
On medication	93 %	95 %
On target dose	27 %	35 %
Dose as % of target dose	56±38	64±39
Beta-blocker*		
On medication	91 %	95 %
On target dose	27 %	33 %
Dose as % of target dose	58±40	63±39

*Uptitration did not differ significantly between study arms

Changes in NYHA Class and NT-proBNP

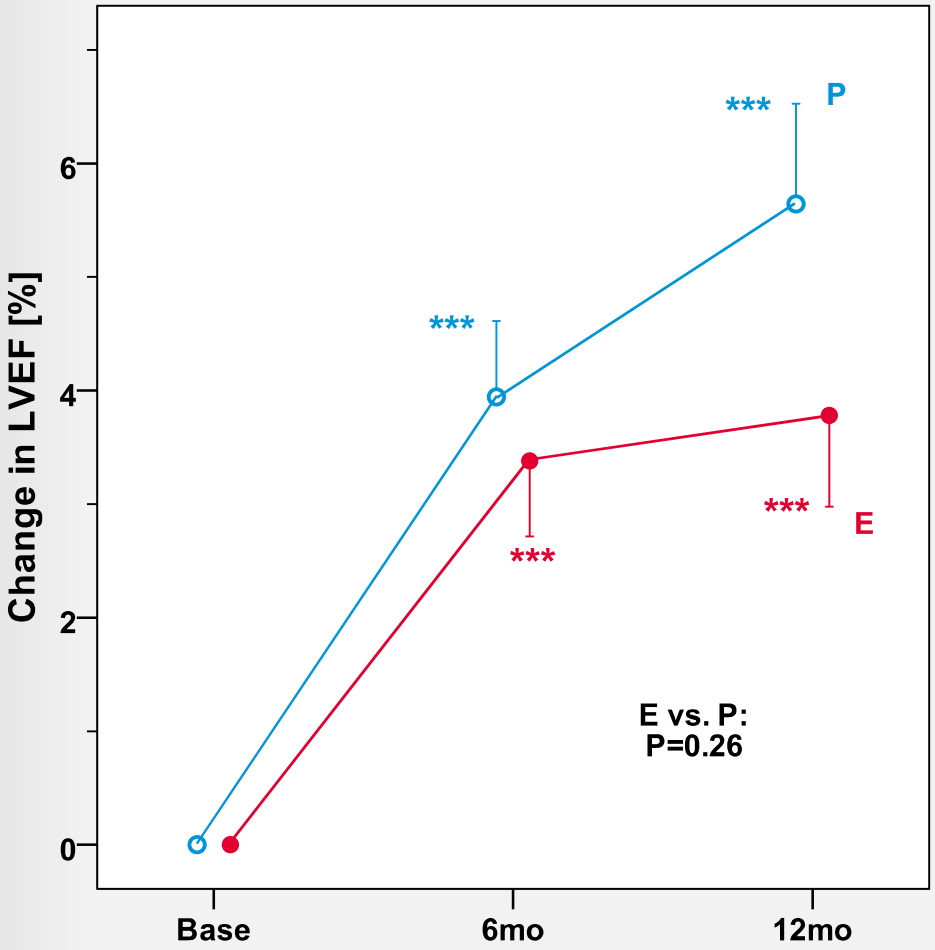


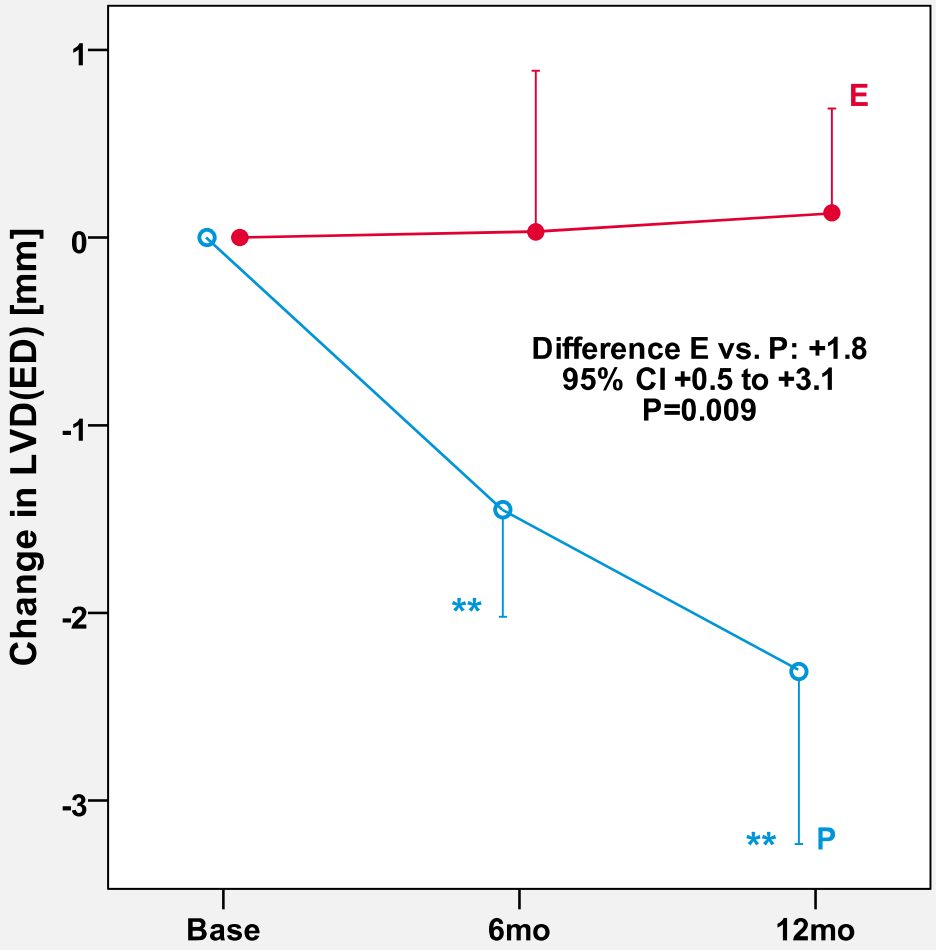


* P<0.05 ** P<0.01 *** P<0.001 vs. Baseline

Changes in LV Function and Morphology

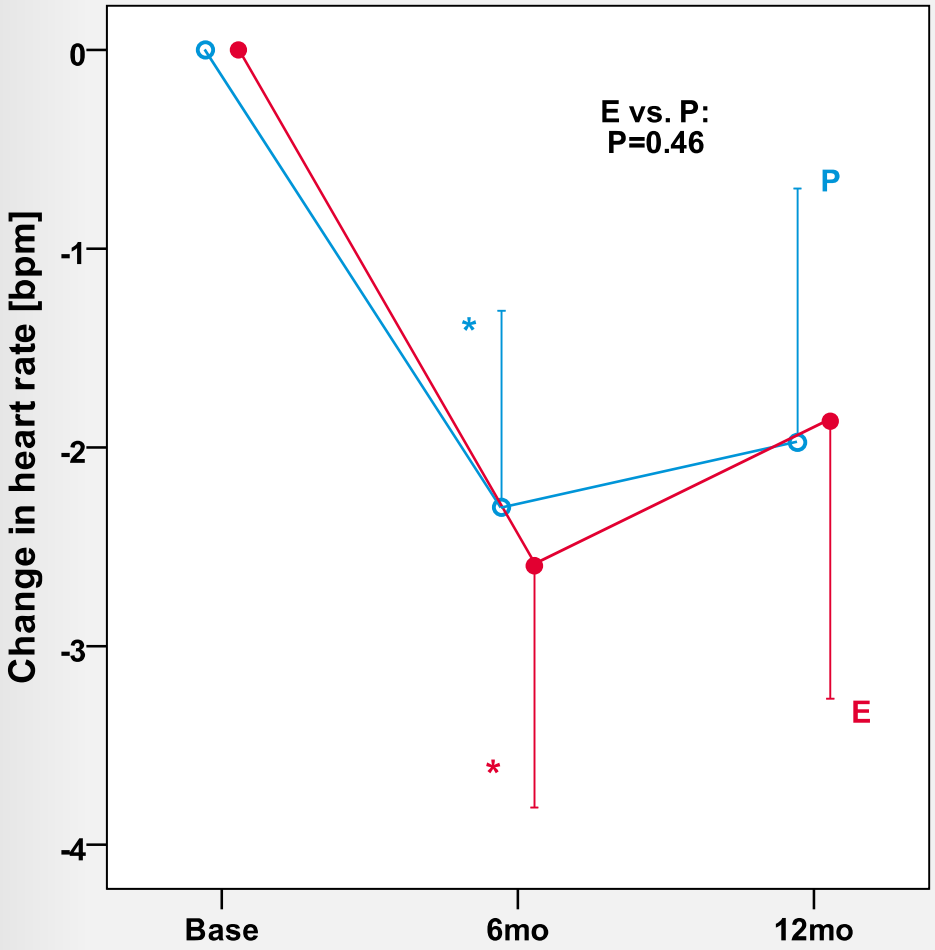
MOOD-HF

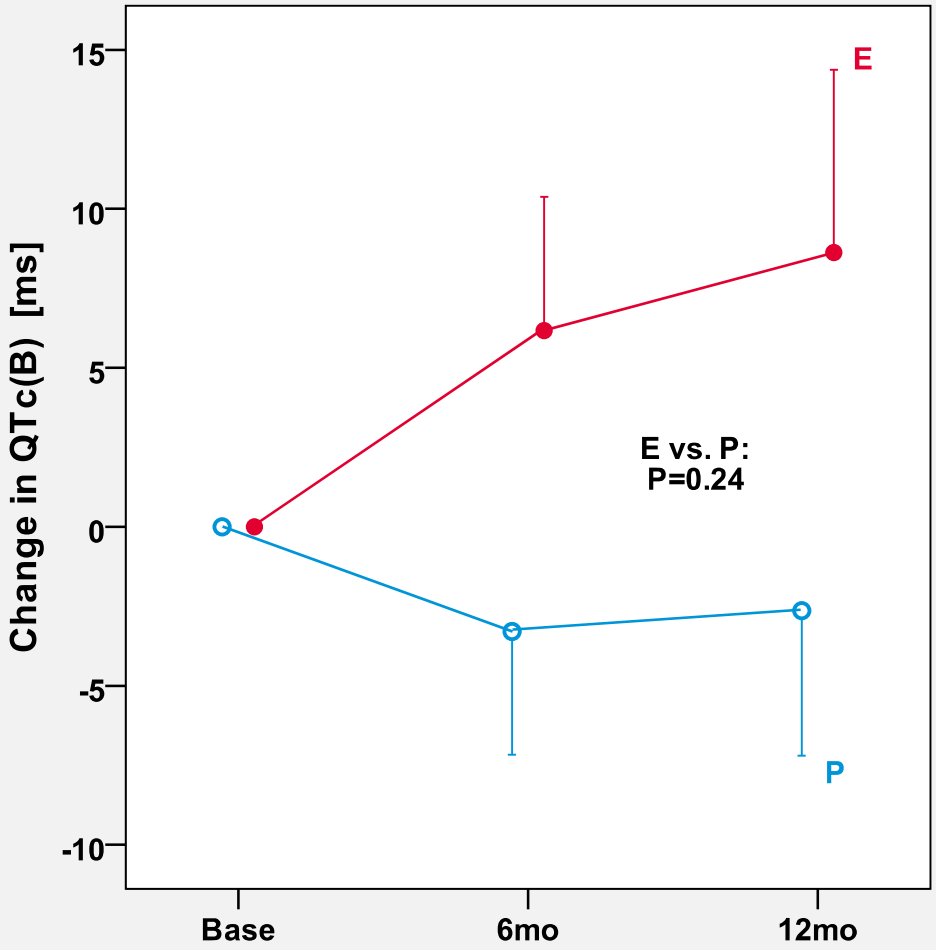




* P<0.05 ** P<0.01 *** P<0.001 vs. Baseline

Changes in Heart Rate and QTc Time





* P<0.05 ** P<0.01 *** P<0.001 vs. Baseline

Serious Adverse Events

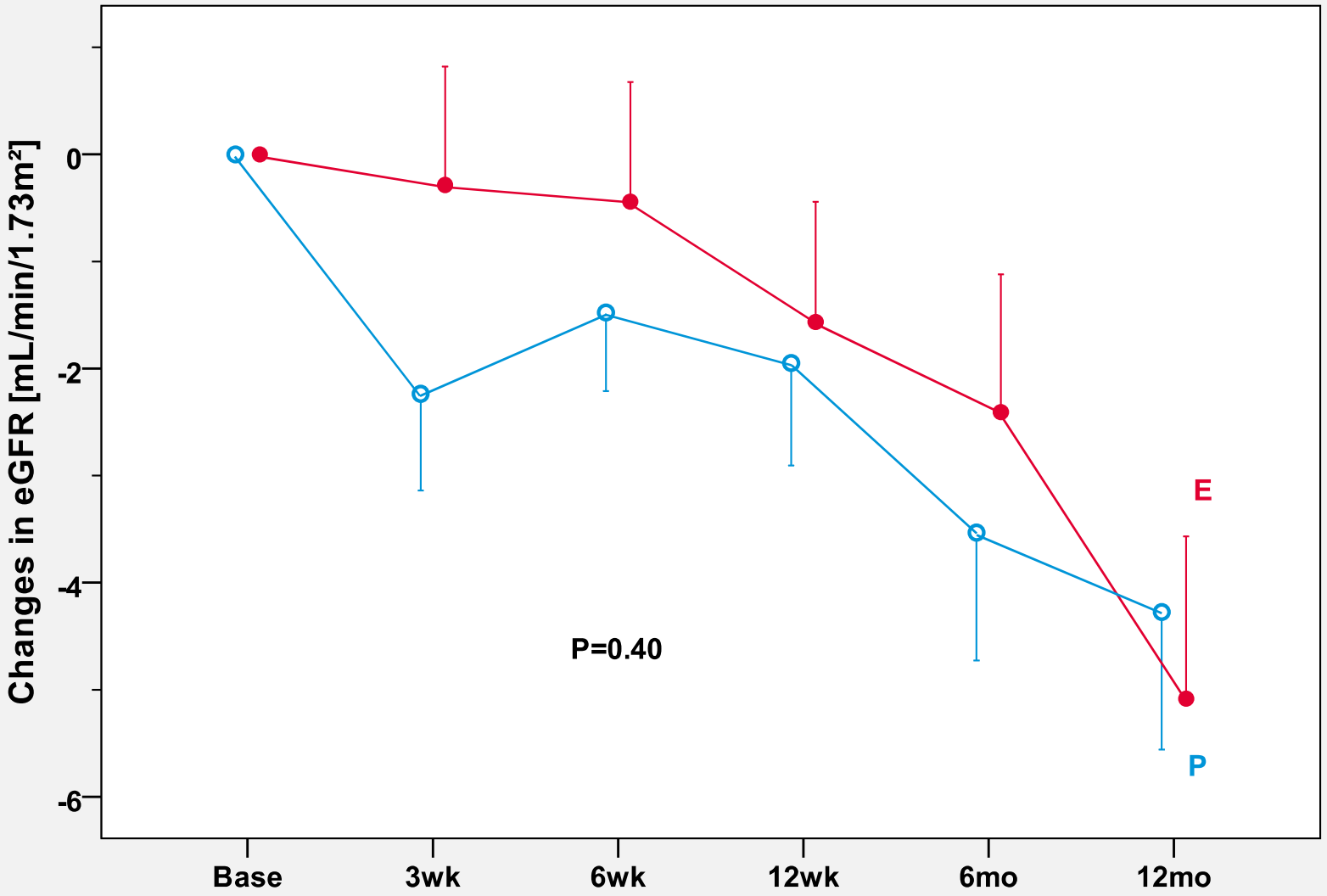
MOOD-HF

- Total number of hospitalizations per patient:
  E 1.6±2.3, **P** 1.8±2.3, P=0.47 (adjusted for time alive in study)

- SAE reports not including hospitalization and death

	Escitalopram	Placebo	P-value
Patients with SAE	46 %	48 %	0.68
# of SAE per patient	0.77	0.93	0.56
severe (% of SAE)	86 %	80 %	0.37

Safety – Renal Function



MOOD-HF – Summary

- First larger-scale RCT on long-term efficacy / safety of a SSRI in systolic CHF patients with co-morbid depression
- Escitalopram neither improved the composite primary outcome, nor depression in this population
- Co-morbid depression as well as HF signs and symptoms improved significantly in *both* study arms
- Although escitalopram proved generally safe, posthoc analyses suggest differential effects in younger subjects with milder HF versus older subjects with more severe HF

MOOD-HF – Conclusions

- Results are in accordance with the concept of heterogenous pathomechanisms and possibly treatment requirements in co-morbid depression in CHF
- MOOD-HF does **not** provide a rationale for escitalopram therapy in such patients
- Confirms the need for optimal CHF management suggesting that this might also be a means to improve co-morbid depression.
- These findings could be considered for future guidelines

Thank You!

- **Patients:** All consenting to be screened and considering to participate
- **Steering Committee:** CE Angermann, M Böhm, J Deckert, G Ertl, H Faller, G Gelbrich, B Pieske, B Maisch, H Schunkert
- **Biometry:** G Gelbrich
- **Clinical Trial Centre Leipzig:** A Beyer, B Binder, C Prettin
- **DSMB:** G Breithardt, M Gottwik, HW Hense, K Laederach, B Löwe
- **Endpoint Adjudicating Committee**: E Erdmann, V Hombach, T Meinertz
- **Principal Investigators & Teams:** CE Angermann (PI), J Baulmann, U Bavendiek, R Braun-Dullaeus, F Edelmann, R Erbel, H Gunold, M Haass, I Kindermann, V Mitrovic, K Müllerleile, M Pauschinger, M Rauchhaus, B Schieffer, S Störk, L Weil, N Werner, R Westenfeld
- **BMBF/DLR:** I Hahn, M Schnitzler / **Lundbeck A/S:** M Friede
- **Competence Network Heart Failure:** G Ertl, S Störk, R Dietz