Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA): Primary Results of a Randomized, 2 x 2 Factorial, Placebo-Controlled, Double-Blind Clinical Trial

Geeta Gulati[1], Siri Lagethon Heck[1], Anne Hansen Ree[1], Pavel Hoffmann[2], Jeanette Schulz-Menger[3], Morten W Fagerland[2], Berit Gravdehaug[1], Florian von Knobelsdorff-Brenkenhoff[3], Åse Bratland[2], Tryggve H Storås[2], Tor-Arne Hagve[1], Helge Røsjø[1], Kjetil Steine[1], Jürgen Geisler[1],Torbjørn Omland[1]

[1] Akershus University Hospital, Lørenskog, Norway; [2] Oslo University Hospital, Oslo, Norway; [3] Charité Campus Buch/HELIOS, Berlin, Germany

UiO : University of Oslo

AKERSHUS UNIVERSITY HOSPITAL

Background

PRADA-STUDY

- Anthracycline-containing chemotherapy and trastuzumab prolong survival in patients with early breast cancer
- High-dose anthracyclines and trastuzumab have well known cardiotoxic side effects
- Cardiotoxicity may limit anti-cancer treatment both in a primary setting and in relapsing cancer
- Neurohormonal blockade may prevent decline in LVEF during cancer treatment
- Randomized, placebo-controlled, double blind trials in homogenous study populations using imaging methods with high accuracy and low variability are missing

Cardioprotective role of β-blockers and angiotensin antagonists in early-onset anthracyclines-induced cardiotoxicity in adult patients: a systematic review and meta-analysis

(Yun et al. Postgrad Med J, September 2015)

PRADA-STUDY

Study	Intervention	Initiation of study medication and time of treatment	Malignancy (n)	LVEF definition and imaging modality	Study design
Kalay et al 2006	Carvedilol	Before chemo., maintained for 6 months	Breast cancer 34 Other 16	LVEF <50 Echocardiography	Single blinded Placebo controlled Randomized
Kaya et al 2013	Nebivolol	Before chemo., continued for 6 months	Breast Cancer 45	No definition Echocardiography	Double blinded Placebo controlled Randomized
Cardinale et al 2006	Enalapril	After chemo., maintained for 1 year	Breast Cancer 29 Other 85	LVEF <50% and >10% LVEF reduction Echocardiography	Open labeled Randomized
Dessi et al 2013	Telmisartan	Before chemo., maintained up to 6 months after epirubicin discontinuation	Breast Cancer 18 Other 31	No definition Echocardiography	Single blinded Placebo controlled Randomized

Modified from Yun et al. Postgrad Med J Sept. 2015

Hypothesis and power calculations

PRADA-STUDY

Hypothesis

In patients treated for early breast cancer, decline in cardiac function can be prevented by concomitant use of metoprolol or candesartan

Power calculations:

120 women included

- if baseline LVEF 60%(±5% (SD)),
- two-sided $p<0.05$
- difference in LVEF of 5%
- anticipated dropout rate 17%

Power of 95%

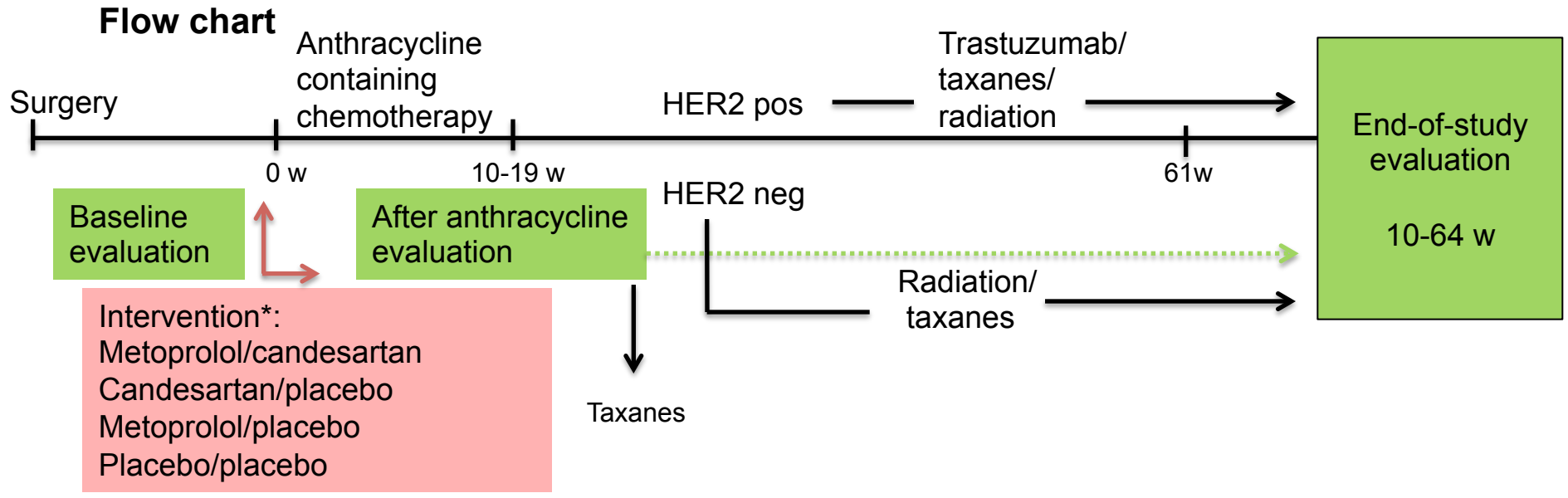
Trial design and flow chart

PRADA-STUDY

Trial design

- 2 x 2 factorial, randomized, placebo-controlled, double-blind, single centre trial
- Stratified for anthracycline dose and for trastuzumab

Flow chart



*Candesartan starting dose 8 mg, target dose 32 mg
Metoprolol starting dose 25 mg, target dose 100 mg

Eligibility

PRADA-STUDY

Inclusion criteria

- Women aged 18-70 years
- Eastern Cooperative Oncology Group (ECOG) performance status 0–1
- Serum creatinine < 1.6 mg/dL or eGFR ≥ 60 ml/min/1.73 m^2
- Systolic blood pressure ≥ 110 mg Hg and < 170 mm Hg
- Left ventricular ejection fraction ≥ 50%

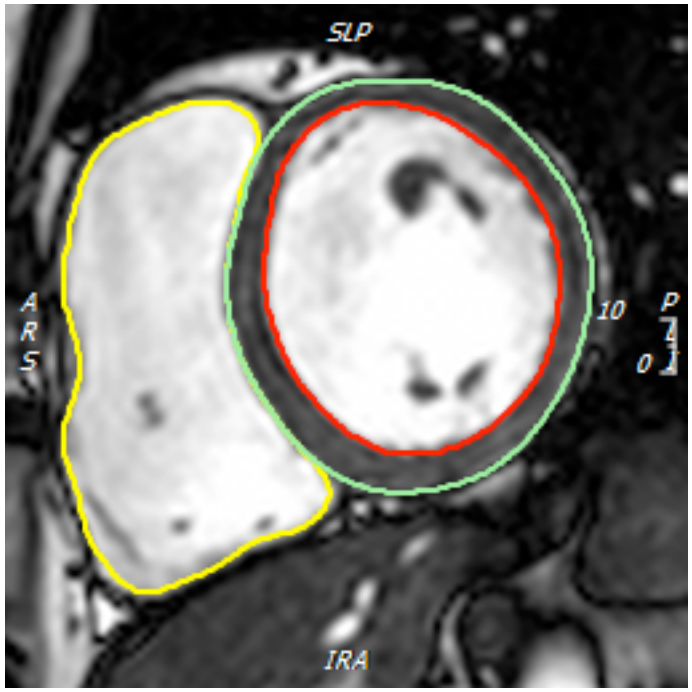
Key exclusion criteria

- Prior malignancy requiring chemotherapy or chest radiotherapy
- Symptomatic heart failure
- Clinically significant coronary artery disease, valvular heart disease, significant arrhythmias, or conduction delays
- Treatment with ACEI, ARB or beta-blocker within the last 4 weeks prior to study start

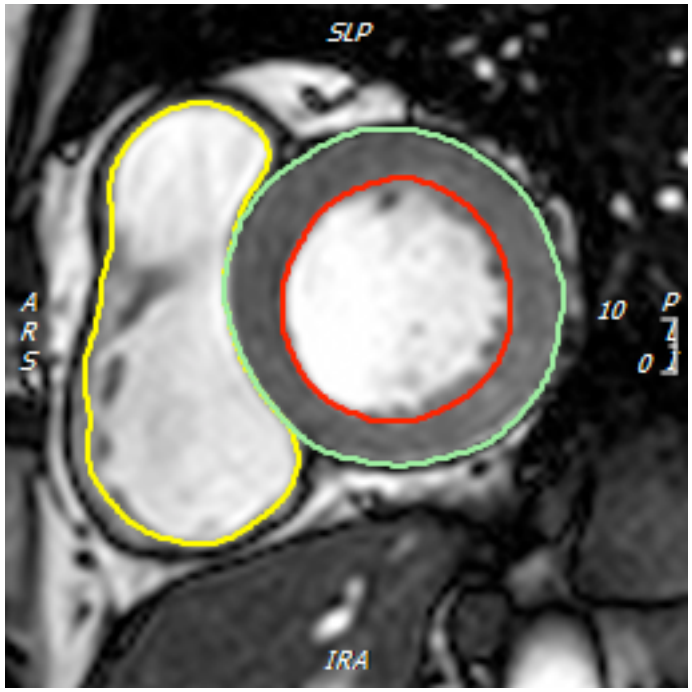
Primary endpoint

PRADA-STUDY

Change in LVEF using cardiac MRI from baseline to end of study



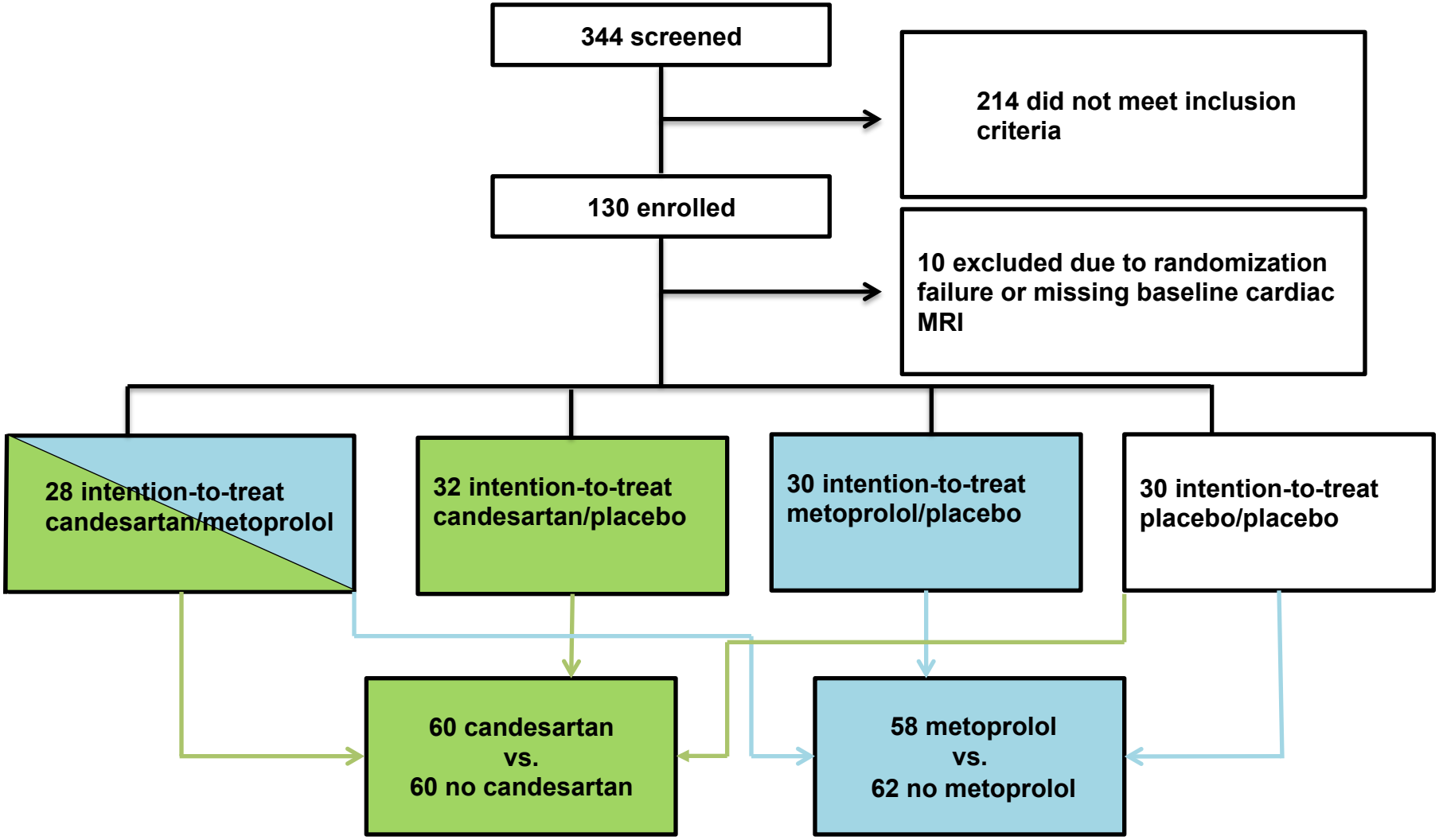
End-diastolic contour on cardiac MRI



End-systolic contour on cardiac MRI

Screening and randomization

PRADA-STUDY



Baseline characteristics

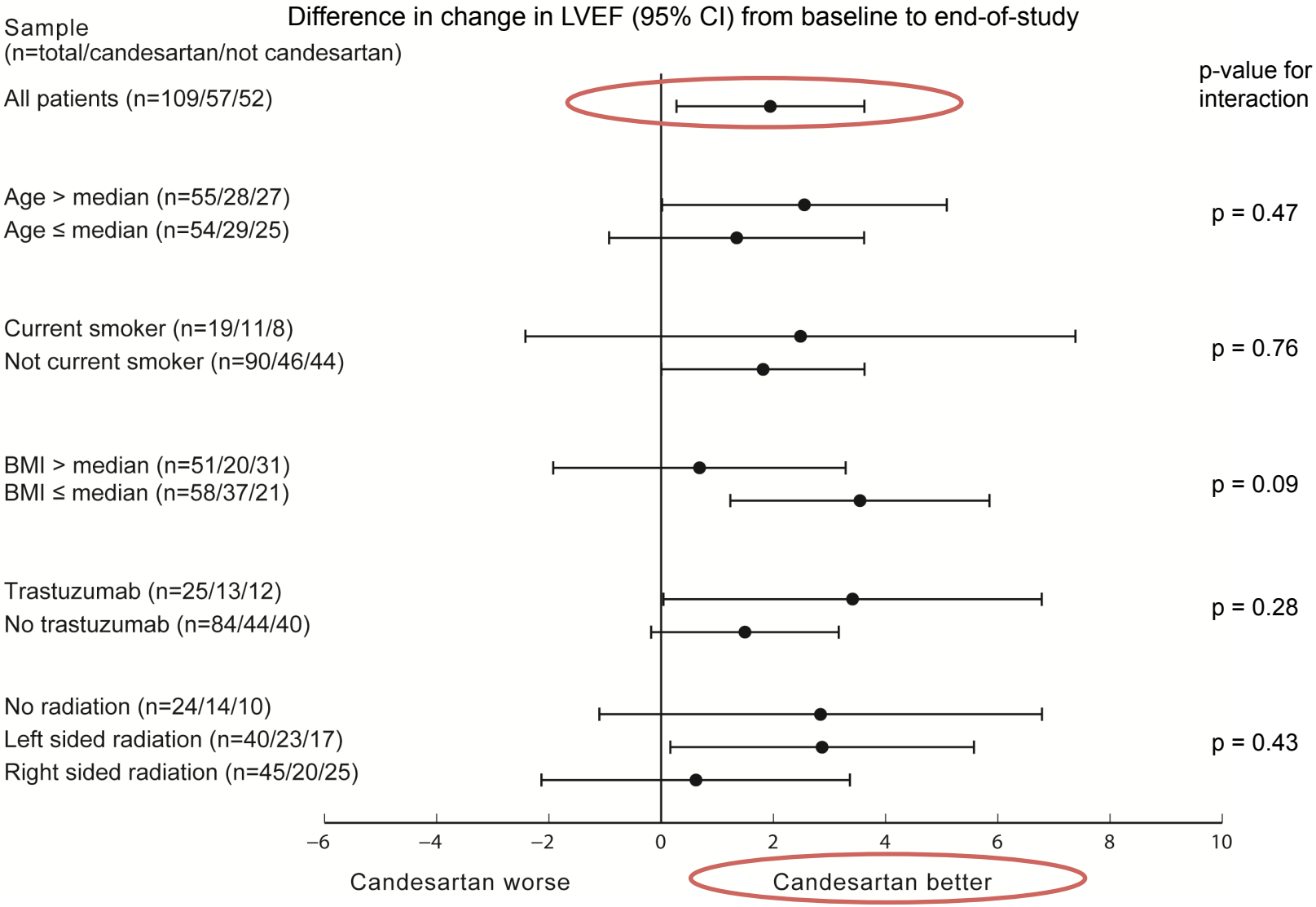
PRADA-STUDY

	Candesartan/Metoprolol	Candesartan/Placebo	Metoprolol/Placebo	Placebo/Placebo
Mean age at recruitment (years)	50.0 ± 8.9	51.7 ± 10.7	50.5 ± 9.1	50.8 ± 9.2
Systolic blood pressure (mmHg)	124.7 ± 12.8	131.9 ± 14.1	134.4 ± 13.1	130.3 ± 12.9
Diastolic blood pressure (mmHg)	78.2 ± 11.5	80.5 ± 8.5	80.5 ± 11.3	80.2 ± 9.9
Heart rate (beats/min)	70.8 ± 11.4	71.7 ± 6.7	73.3 ± 10.1	68.3 ± 11.6
Body mass index kg/m²	25.3 ± 3.6	25.9 ± 4.3	27.8 ± 6.3	25.6 ± 4.5
Current smokers	6/30 (20.0 %)	7/32 (21.9%)	5/32 (15.6%)	7/32 (21.9%)
Hypertension	1/30 (3.3%)	5/32 (15.6%)	2/32 (6.3%)	0/32 (0%)
Diabetes mellitus	0/30 (0%)	1/32 (3.1%)	1/32 (3.1%)	0/32 (0%)
Left ventricular ejection fraction (%)	62.2 ± 4.4	62.3 ± 5.3	63.5 ± 5.0	63.6 ± 4.1
Additional therapy after FEC*				
Trastuzumab	7/30 (23.3%)	7/32 (21.9%)	7/32 (21.9%)	7/32 (21.9%)
Radiation	18/30 (60.0%)	19/32 (59.4%)	22/32 (68.8%)	23/32 (71.9%)
Taxanes	25/30 (83.3%)	25/32 (78.1%)	26/32 (81.3%)	24/32 (75%)

* FEC – 5-fluorouracil, epirubicin, cyclophosphamide

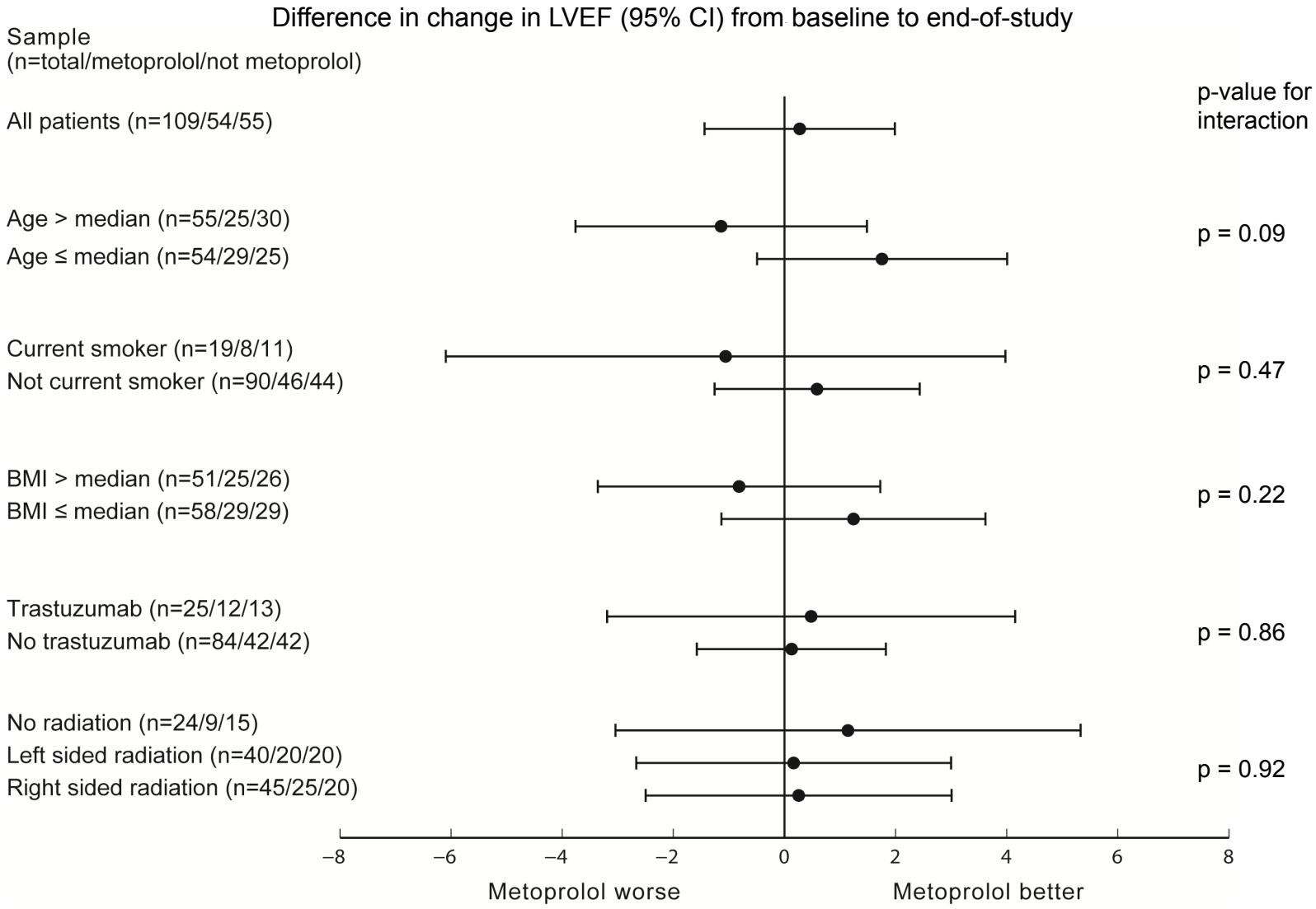
Primary results of candesartan

PRADA-STUDY



Primary results of metoprolol

PRADA-STUDY



Clinical implications

PRADA-STUDY

- In the PRADA-study anti-cancer treatment for breast cancer was associated with a modest, short-term decline in ventricular function, long term assessment is necessary

- If a sustained, long-term effect of early angiotensin inhibition can be confirmed, preventive therapy may be indicated as standard care

Strengths and limitations

PRADA-STUDY

Strengths

- Design; Randomized, placebo controlled, double blind trial in a 2 x 2 factorial design permitting comparison of 2 drugs with only a minimal loss of power
- Methodology; Serial imaging with cardiac MRI, the gold standard for LVEF
- Sample size; The largest RCT on intervention of cardiac dysfunction in breast cancer

Limitations

- Follow up; Currently follow up to end of cancer treatment
- Low risk group; Exclusion of patients with established cardiovascular disease

Conclusion

PRADA-STUDY

- In patients treated for early breast cancer, concomitant treatment with candesartan provides protection against early decline in global left ventricular function

- In contrast metoprolol did not alleviate decline in global left ventricular function

Study organization

PRADA-STUDY

Investigators

G Gulati

SL Heck

Study steering committee

T Omland (Chair and Primary Investigator)

J Geisler (Clinical oncology)

AH Ree (Radiation oncology)

P Hoffmann (Cardiac MRI)

H Røsjø (Biobank)

K Steine (Echocardiography)

Data safety and monitoring board

P Smith (Chair)

O Engebråten (Clinical oncology)

FA Dahl (Biostatistician)

Independent statistician in study structure

L Diep

Study statistician

MW Fagerland

Akershus University Hospital (involved units)

Clinical Research Unit

Division of Radiology

Division of Surgery

Division of Oncology

Division of Cardiology

Oslo University Hospital

P Hoffmann

Å Bratland

AD Hoff

Charitè Campus Buch/HELIOS Berlin

J Schulz-Menger

F von Knobelsdorff-Brenkenhoff

Funding

University of Oslo, The Extra Foundation for Health and Rehabilitation, The Norwegian Cancer Society, Akershus University Hospital

Industry Support

Abbott Diagnostic (Abbott Park, IL), AstraZeneca (Mölndal, Sweden)