Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA):

Long-Term Follow-Up of a 2 x 2 Factorial, Randomized, Placebo-Controlled, Double-Blind Clinical Trial of Candesartan and Metoprolol

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Disclosures

Siri Lagethon Heck: None

Torbjørn Omland (Principal Investigator)

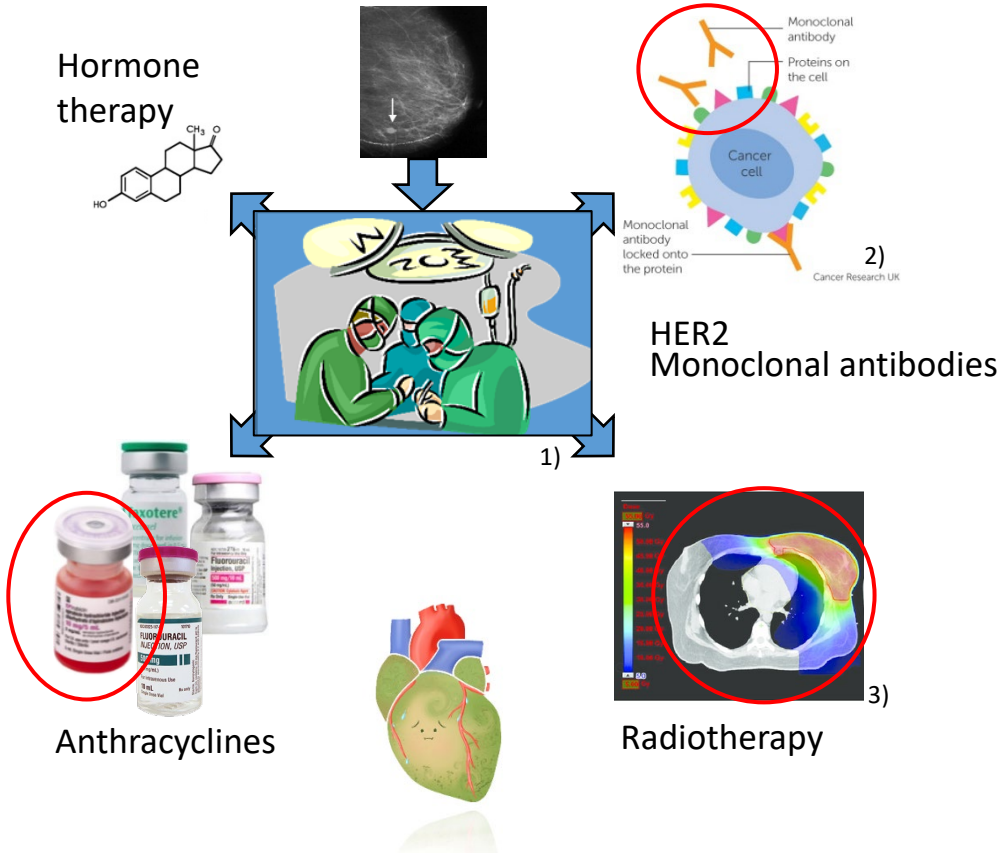
- Research support and/or honoraria from AstraZeneca, Abbott, Roche, Novartis, SomaLogic, Siemens and CardiNor

Adjuvant breast cancer therapy prolongs survival but may harm the heart

Anthracyclines, trastuzumab and radiotherapy have cardiotoxic effects

Neurohormonal blockade may attenuate the myocardial damage during cancer treatment

Long-term effects are unknown



1) Designed by Wannapik, 2) © Cancer Research UK Pham et al
3) Journal of Medical Imaging and Radiation Oncology 2016, [2002]

Trials on neurohormonal blockade during breast cancer treatment have shown modest and inconsistent beneficial effects

Study	Year	Intervention	Cancer therapy	n	Results
PRADA **Gulati et al**	2016	Candesartan Metoprolol	Anthracyclines Trastuzumab Radiotherapy	120	**Candesartan attenuated a decline in LVEF** Metoprolol attenuated troponin increase
Boekhout et al	2016	Candesartan	Trastuzumab	210	**No difference in cardiotoxic events** No difference in change in LVEF
MANTICORE **Pituskin et al**	2016	Perindopril Bisoprolol	Trastuzumab	94	**No difference in change in LVEDV** Attenuated decline in LVEF
CECCY **Avila et al**	2018	Carvedilol	Anthracyclines Taxanes	200	**No difference in cardiotoxic events** No difference in change in LVEF Attenuated troponin increase
Guglin et al	2019	Lisinopril Carvedilol	Trastuzumab	468	**No difference in cardiotoxic events** Effect in the subgroup who had received anthracyclines

LVEF= left ventricular ejection fraction

PRADA: a 2 x 2 factorial, randomized, placebo-controlled, double-blind trial

Women 18-70 years with early breast cancer
Anthracycline containing adjuvant treatment

No serious concomitant illness
No significant cardiovascular disease
No prior chemo/radiotherapy
No indication/contraindications for the study drugs

Hypothesis

Long-term decline in cardiac function can be prevented by treatment with metoprolol and candesartan during adjuvant treatment for early breast cancer

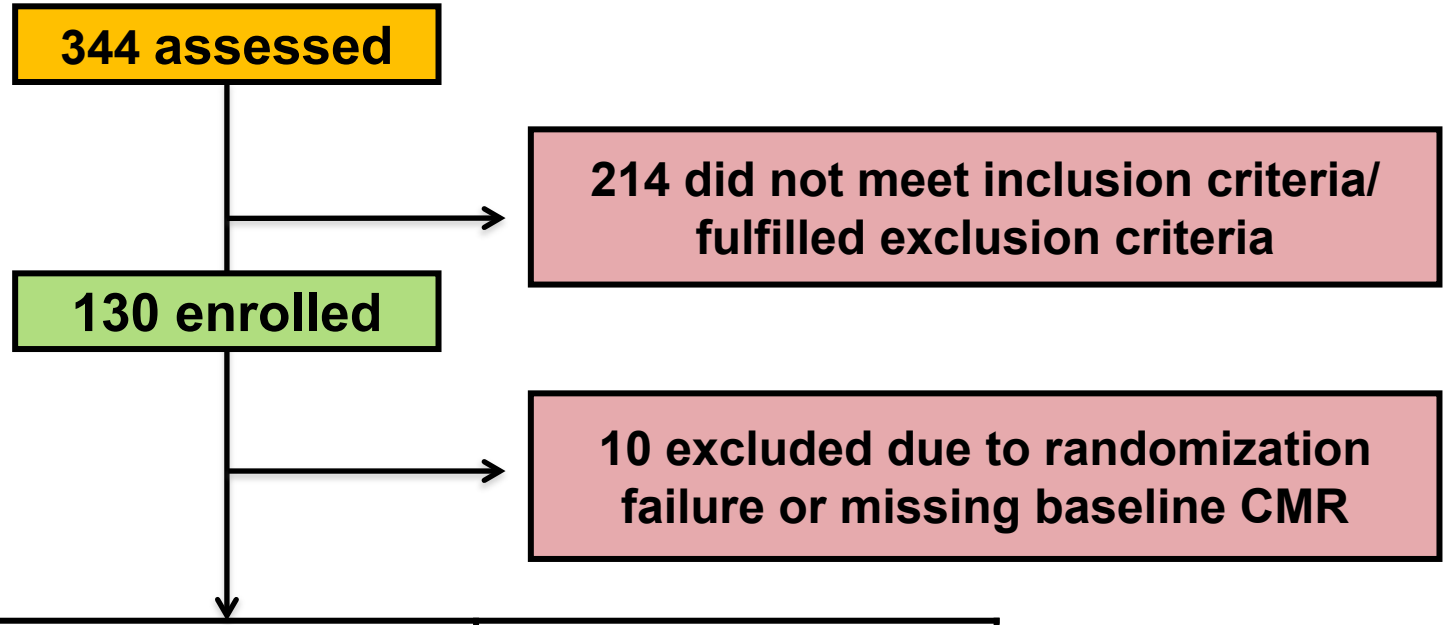
Power calculations

Change in LVEF	Sample size	Power
5±5%	120	95%
3±5%	120	90%
2±5%	120	60%

α= 0.05

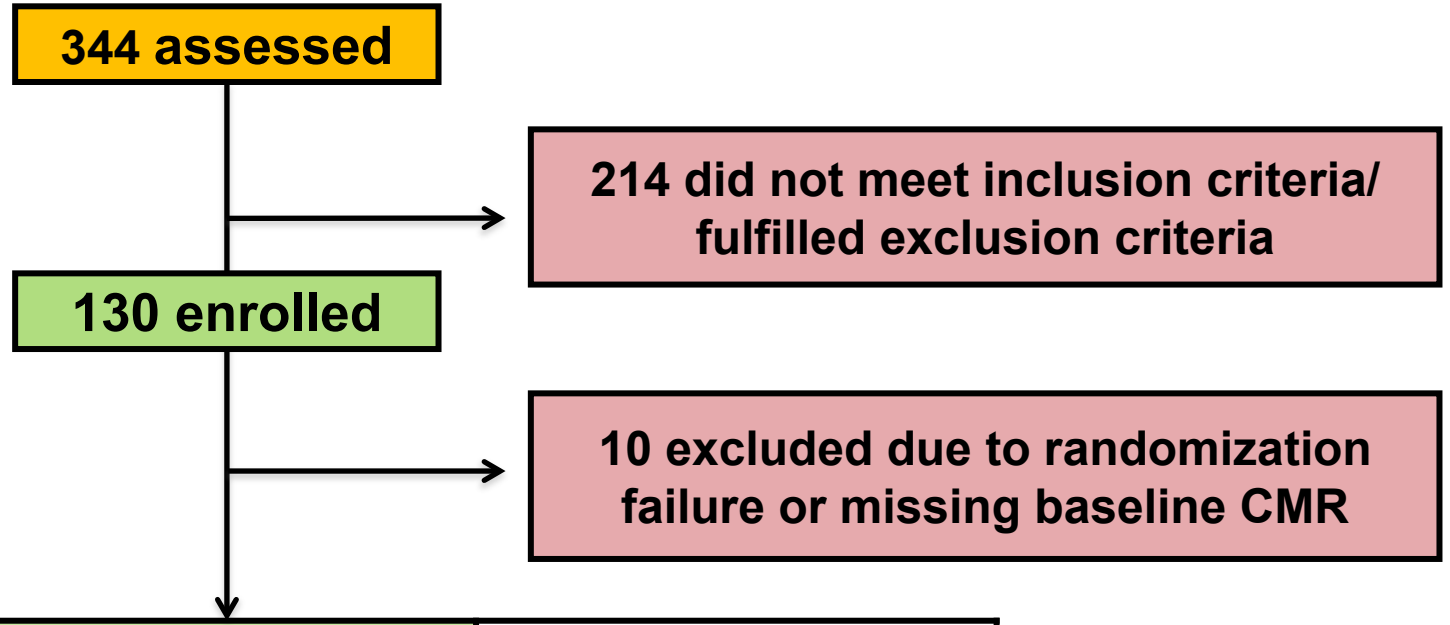
LVEF= left ventricular ejection fraction

CONSORT diagram



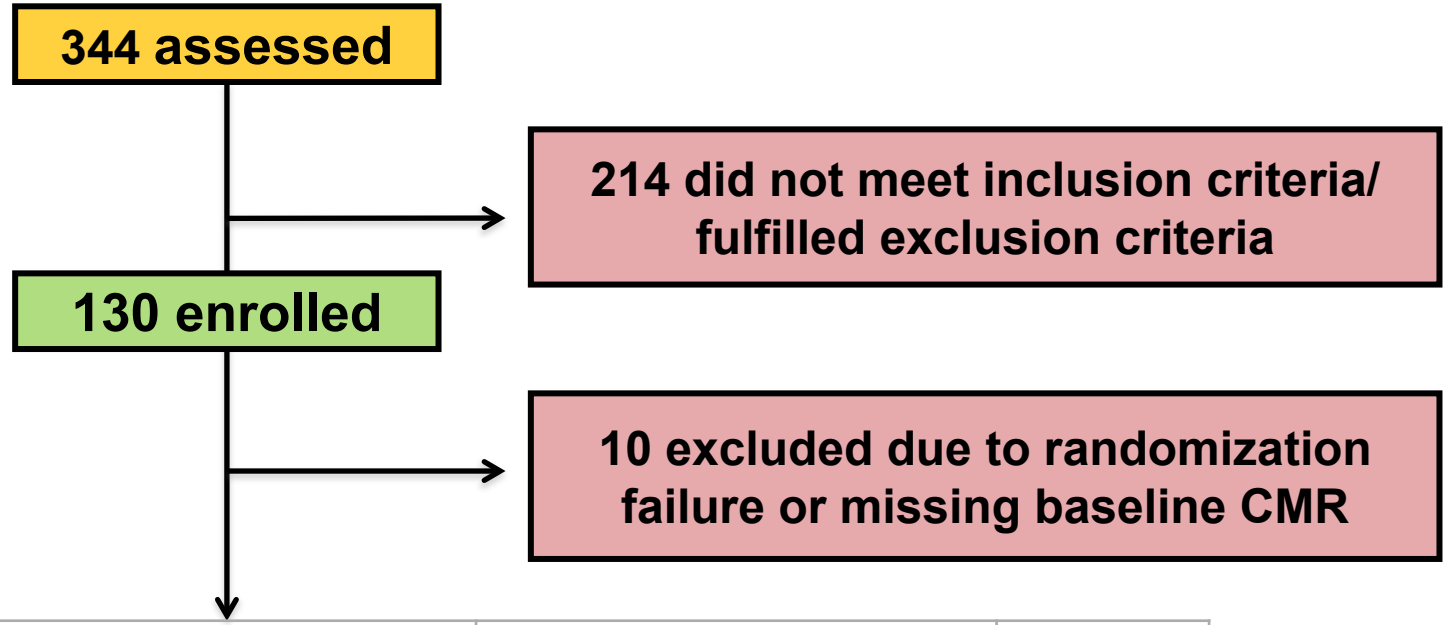
	Candesartan	Candesartan placebo
Metoprolol	28	30
Metoprolol placebo	32	30

CONSORT diagram



	Candesartan	Candesartan placebo
Metoprolol	28	30
Metoprolol placebo	32	30
	60	60

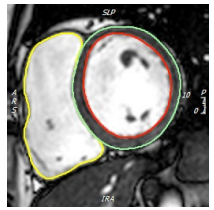
CONSORT diagram



	Candesartan	Candesartan placebo	
Metoprolol	**28**	**30**	**58**
Metoprolol placebo	**32**	**30**	**62**

Study flowchart

Primary endpoint: Change in LVEF



HER2-: Radiotherapy

Surgery | Anthracyclines | HER2+: Trastuzumab/ radiotherapy

Median 2 years

Study drug during adjuvant therapy | No study drug

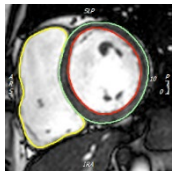
LVEF= left ventricular ejection fraction

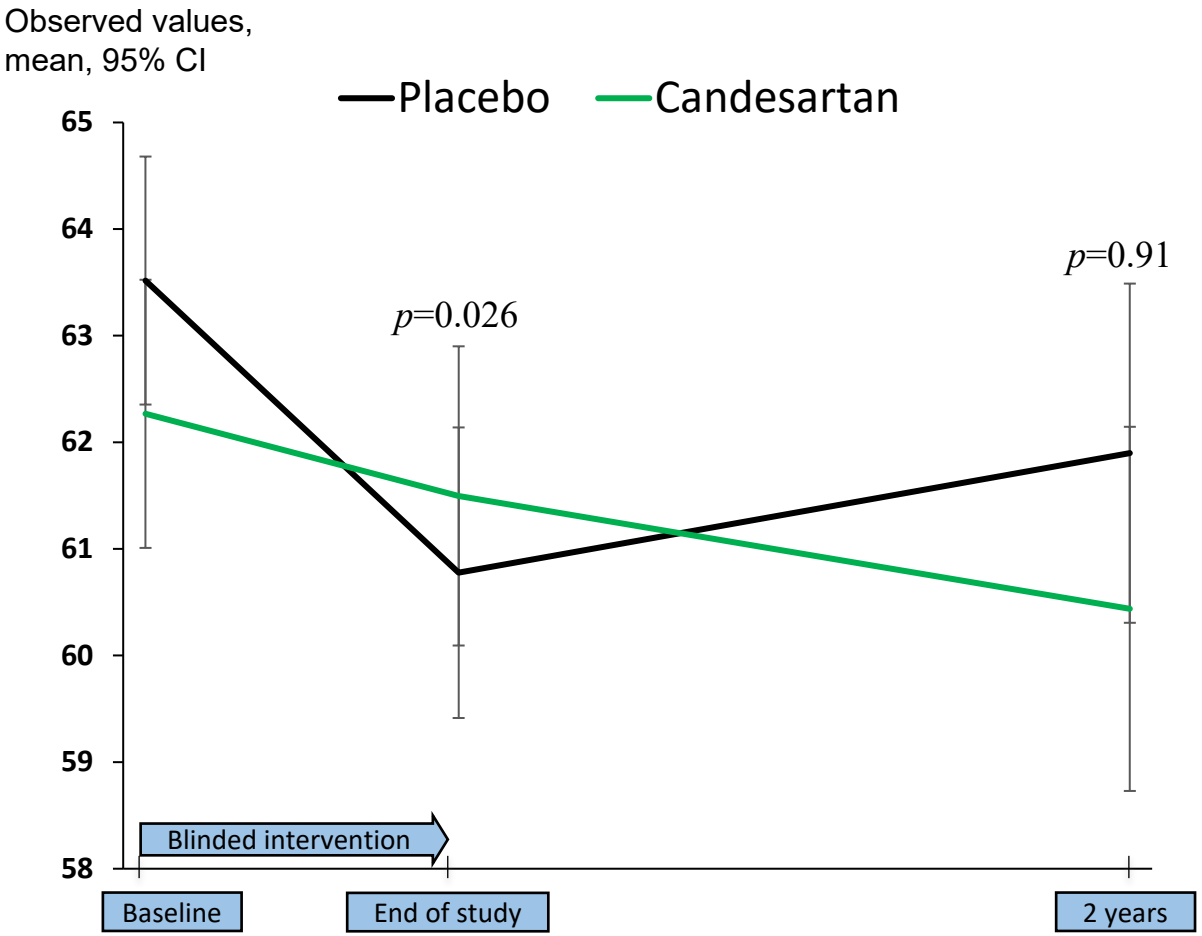
Baseline and cancer treatment characteristics

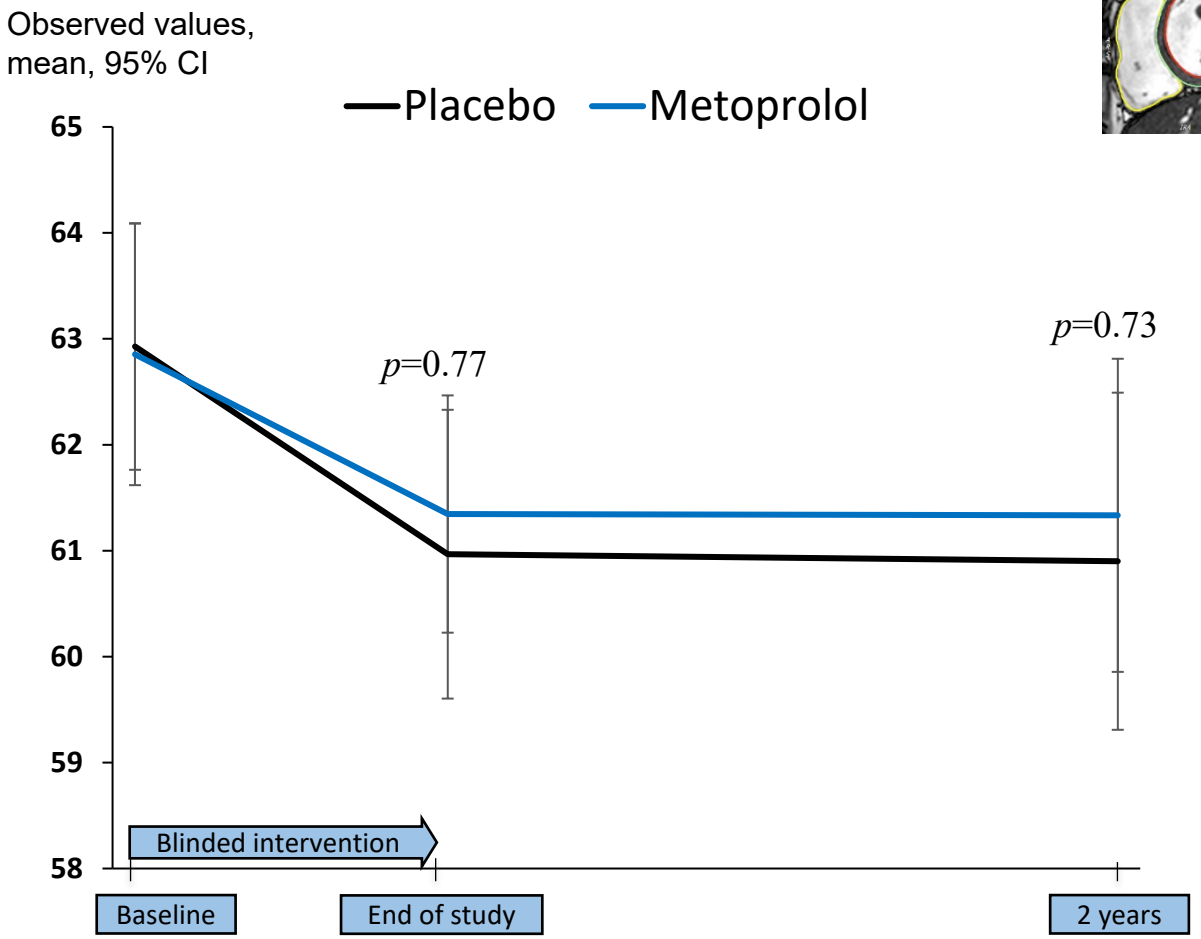
	Candesartan-Metoprolol	Candesartan-Placebo	Placebo-Metoprolol	Placebo-Placebo
N	**28**	**32**	**30**	**30**
Age at recruitment (years)	50 ± 9	52 ± 11	51 ± 9	51 ± 9
Systolic blood pressure (mmHg)	125 ± 13	132 ± 14	133 ± 12	130 ± 13
Heart rate (beats/min)	68 ± 11	68 ± 10	70 ± 12	65 ± 11
BMI	24 ± 3	26 ± 4	27 ± 6	26 ± 4
Current smokers	5/28 (18 %)	7/32 (22%)	4/30 (13%)	5/30 (17%)
Hypertension	1/28 (4%)	5/32 (16%)	2/30 (7%)	0/30 (0%)
Diabetes	0/28 (0%)	1/32 (3%)	1/30 (3%)	0/30 (0%)
Epirubicin, median dose mg/m²	240 (240, 400)	240 (240, 400)	240 (240, 400)	240 (240, 400)
Trastuzumab	7/28 (25%)	7/32 (22%)	6/30 (20%)	7/30 (23%)
Radiation	16/28 (57%)	19/32 (59%)	20/30 (67%)	21/30 (70%)
Taxanes	24/28 (86%)	25/32 (78%)	25/30 (83%)	22/30 (73%)

Mean ± SD, numbers (percent) or median (range)

At 2 years, there were no between-group differences in change in LVEF

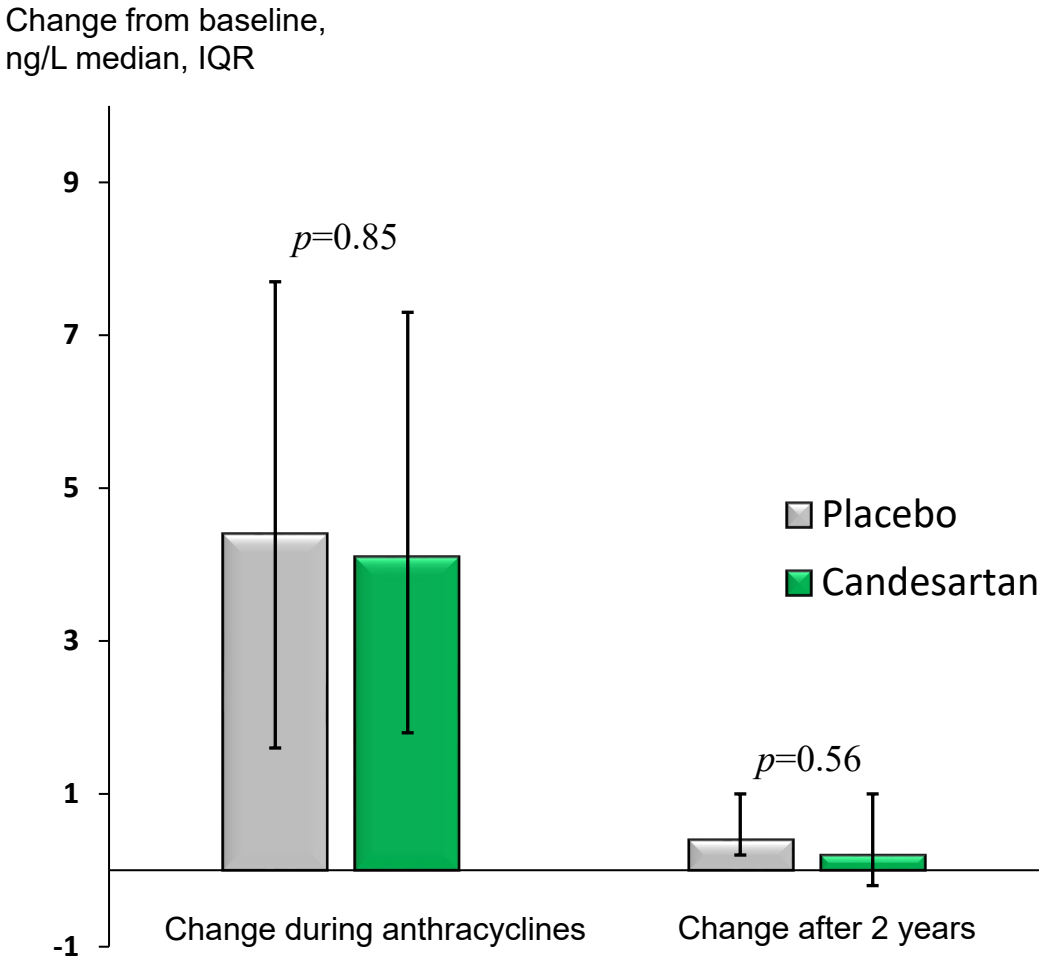


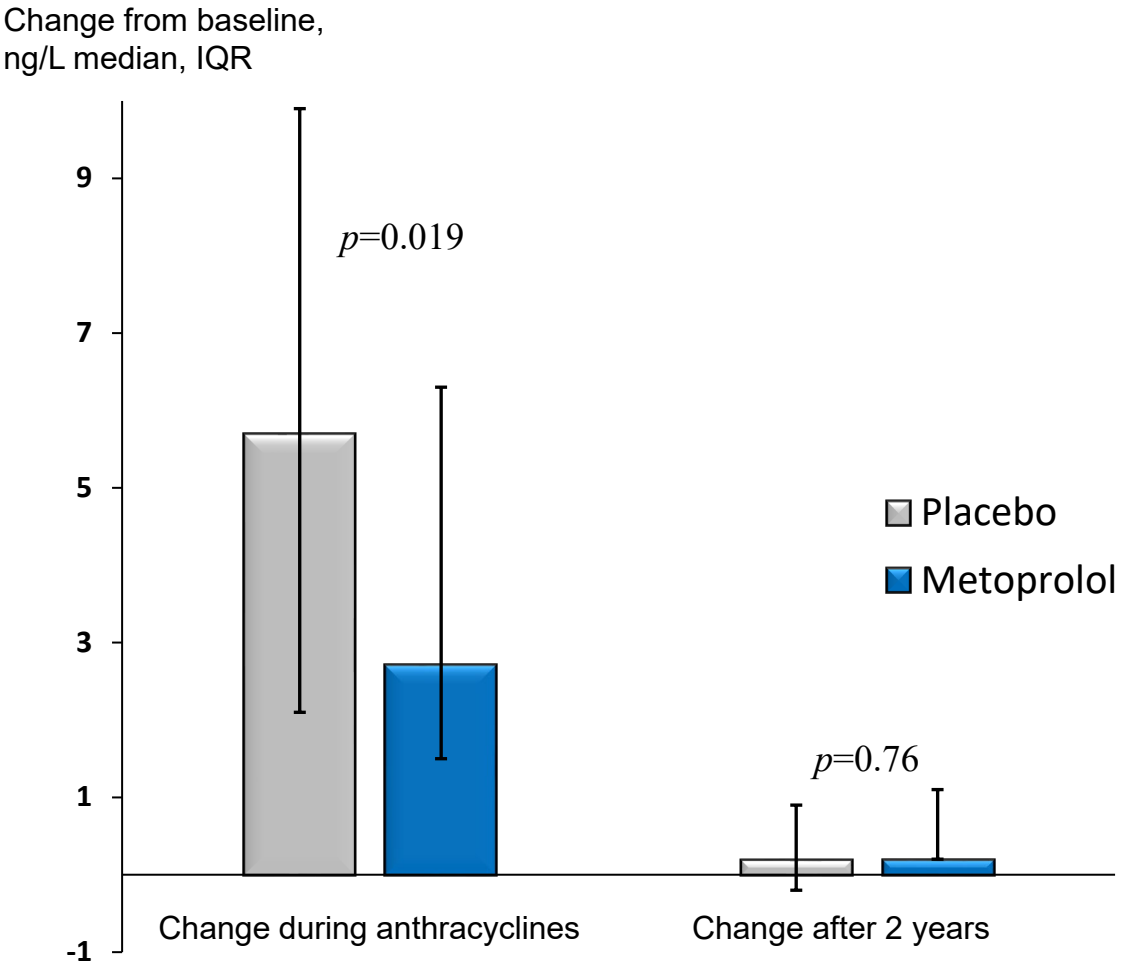




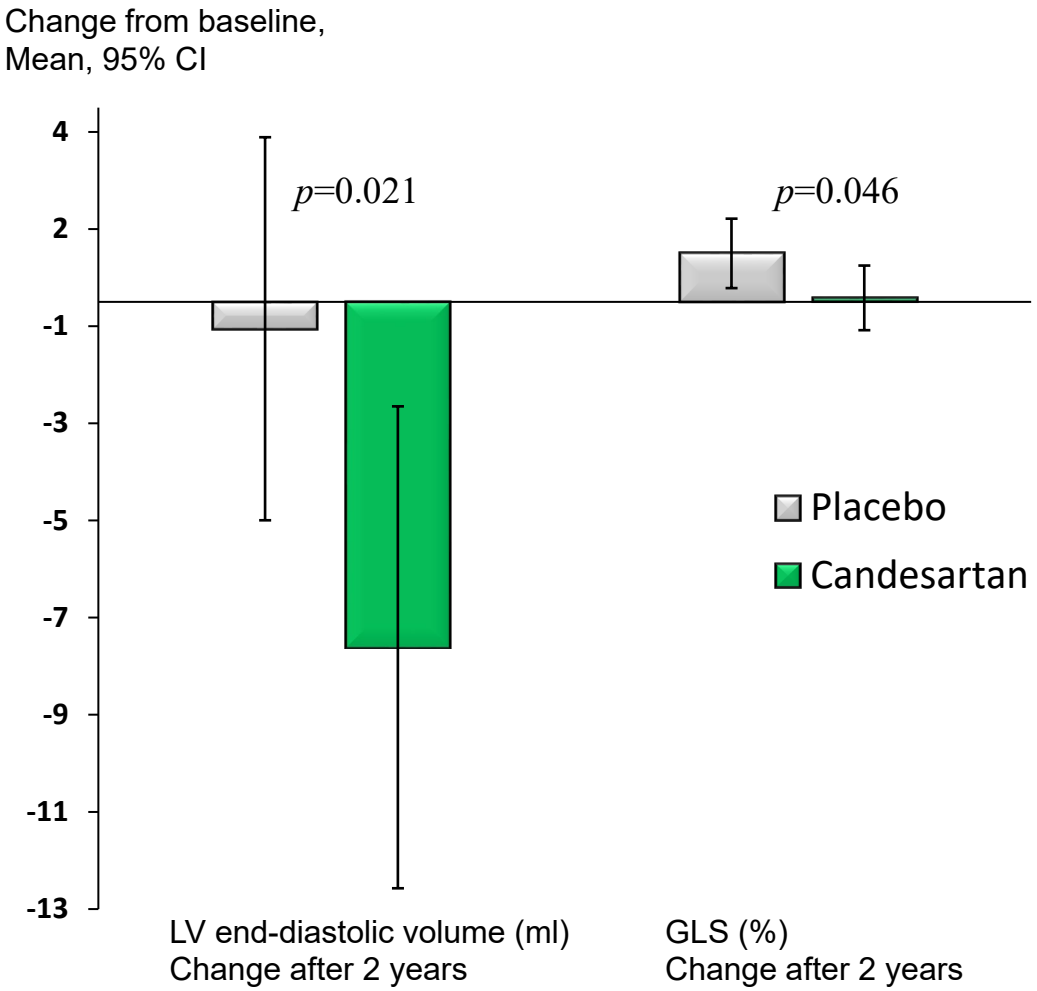
p-values are for between-group differences in the linear mixed model in the intention to treat analysis

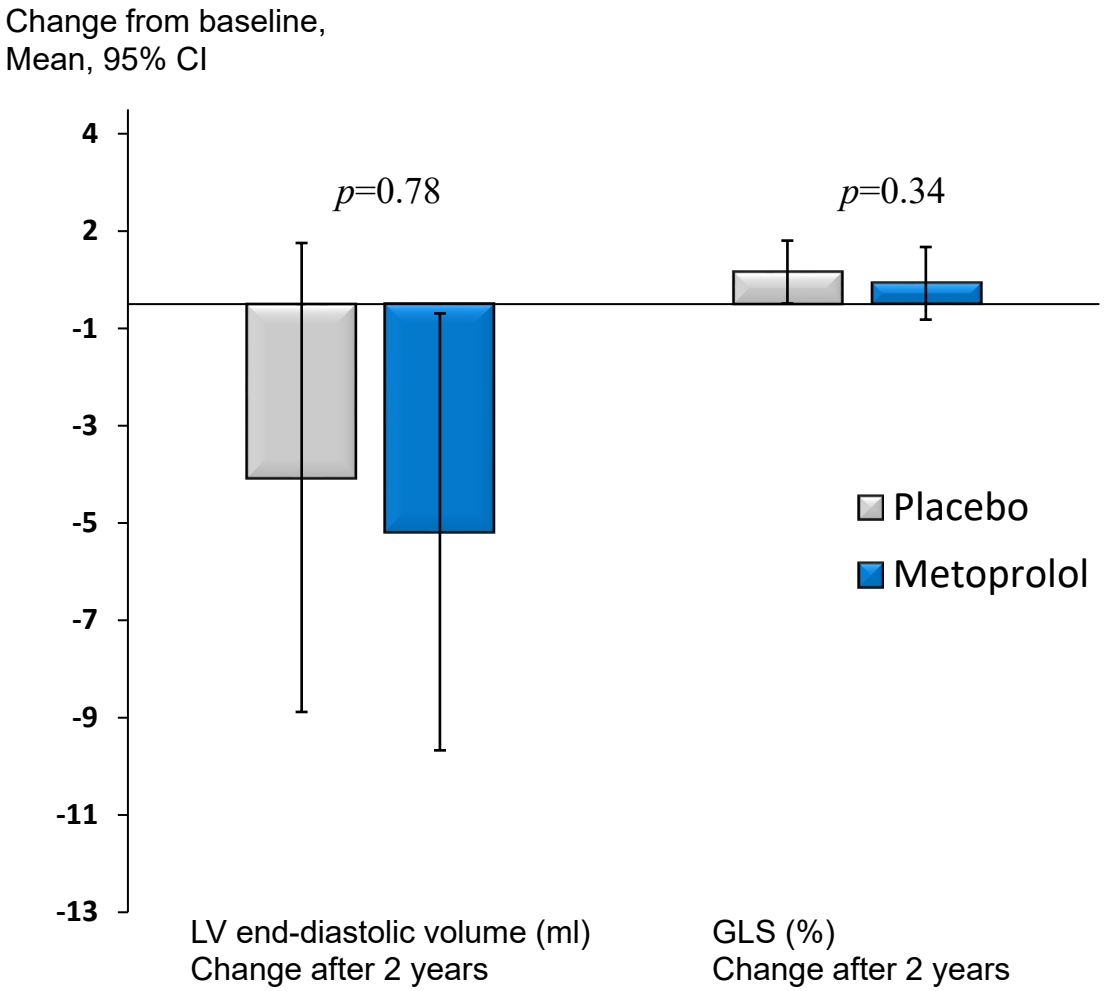
At 2 years, there were no between-group differences in change in troponin I





At 2 years, LV end-diastolic volume was reduced and GLS decline attenuated in the candesartan arm





GLS= Global Longitudinal Strain (%)

Strengths

Trial design

LVEF assessed by serial CMR

2 year follow-up

Limitations

Single center

18% of participants did not have 2-year CMR

Less decline in LVEF than anticipated

Conclusion

Candesartan and metoprolol during adjuvant therapy for early breast cancer did not protect against long-term decline in LVEF

LVEF= left ventricular ejection fraction

Clinical implications

Broadly administered cardioprotective therapy may not be required during adjuvant breast cancer therapy, as decline in systolic function was minor and not prevented by neurohormonal blockade

Study organization

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)

Investigators

SL Heck
G Gulati
A Mecinaj
J Schulz-Menger (Cardiac MRI)
B Gravdehaug (Surgery)

Study statistician

MW Fagerland

Data safety and monitoring board

P Smith (Chair)
O Engebråten (Clinical oncology)
FA Dahl (Biostatistician)

Akershus University Hospital

Clinical Research Unit
Division of Radiology, Surgery, Oncology and Cardiology

Oslo University Hospital

Charitè Campus Buch/HELIOS Berlin

Funding

University of Oslo, The Extra Foundation for Health and Rehabilitation, The Norwegian Cancer Society, Akershus University Hospital, The South-Eastern Norway Regional Health Authority

Industry Support

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