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

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Background

- 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)

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

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

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

Flow chart

- Surgery
- Anthracycline containing chemotherapy
- Baseline evaluation
- After anthracycline evaluation
- Intervention*:
  - Metoprolol/candesartan
  - Candesartan/placebo
  - Metoprolol/placebo
  - Placebo/placebo
- HER2 pos
- Trastuzumab/taxanes/radiation
- HER2 neg
- Radiation/taxanes
- Taxanes
- End-of-study evaluation
  - 10-64 w

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

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 m²
- 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

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

End-diastolic contour on cardiac MRI

End-systolic contour on cardiac MRI
CONSORT diagram for the intention to treat analysis in the primary endpoint population.

Screening and randomization:
- 344 screened
- 130 enrolled
- 214 did not meet inclusion criteria
- 10 excluded due to randomization failure or missing baseline cardiac MRI

- 28 intention-to-treat candesartan/metoprolol
- 32 intention-to-treat candesartan/placebo
- 30 intention-to-treat metoprolol/placebo
- 30 intention-to-treat placebo/placebo

- 60 candesartan vs. 60 no candesartan
- 58 metoprolol vs. 62 no metoprolol
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Candesartan/Metoprolol</th>
<th>Candesartan/Placebo</th>
<th>Metoprolol/Placebo</th>
<th>Placebo/Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at recruitment (years)</td>
<td>50.0 ± 8.9</td>
<td>51.7 ± 10.7</td>
<td>50.5 ± 9.1</td>
<td>50.8 ± 9.2</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>124.7 ± 12.8</td>
<td>131.9 ± 14.1</td>
<td>134.4 ± 13.1</td>
<td>130.3 ± 12.9</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78.2 ± 11.5</td>
<td>80.5 ± 8.5</td>
<td>80.5 ± 11.3</td>
<td>80.2 ± 9.9</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>70.8 ± 11.4</td>
<td>71.7 ± 6.7</td>
<td>73.3 ± 10.1</td>
<td>68.3 ± 11.6</td>
</tr>
<tr>
<td>Body mass index kg/m²</td>
<td>25.3 ± 3.6</td>
<td>25.9 ± 4.3</td>
<td>27.8 ± 6.3</td>
<td>25.6 ± 4.5</td>
</tr>
<tr>
<td>Current smokers</td>
<td>6/30 (20.0 %)</td>
<td>7/32 (21.9%)</td>
<td>5/32 (15.6%)</td>
<td>7/32 (21.9%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1/30 (3.3 %)</td>
<td>5/32 (15.6%)</td>
<td>2/32 (6.3%)</td>
<td>0/32 (0%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0/30 (0%)</td>
<td>1/32 (3.1%)</td>
<td>1/32 (3.1%)</td>
<td>0/32 (0%)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>62.2 ± 4.4</td>
<td>62.3 ± 5.3</td>
<td>63.5 ± 5.0</td>
<td>63.6 ± 4.1</td>
</tr>
</tbody>
</table>

### Additional therapy after FEC*

<table>
<thead>
<tr>
<th></th>
<th>Candesartan/Metoprolol</th>
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<th>Metoprolol/Placebo</th>
<th>Placebo/Placebo</th>
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<tr>
<td>Trastuzumab</td>
<td>7/30 (23.3 %)</td>
<td>7/32 (21.9%)</td>
<td>7/32 (21.9%)</td>
<td>7/32 (21.9%)</td>
</tr>
<tr>
<td>Radiation</td>
<td>18/30 (60.0 %)</td>
<td>19/32 (59.4%)</td>
<td>22/32 (68.8%)</td>
<td>23/32 (71.9%)</td>
</tr>
<tr>
<td>Taxanes</td>
<td>25/30 (83.3 %)</td>
<td>25/32 (78.1%)</td>
<td>26/32 (81.3%)</td>
<td>24/32 (75%)</td>
</tr>
</tbody>
</table>

* FEC – 5-fluorouracil, epirubicin, cyclophosphamide
Primary results of candesartan

Sample (n=total/candesartan/not candesartan)

All patients (n=109/57/52)

Age > median (n=55/28/27)
Age ≤ median (n=54/29/25)

Current smoker (n=19/11/8)
Not current smoker (n=90/46/44)

BMI > median (n=51/20/31)
BMI ≤ median (n=58/37/21)

Trastuzumab (n=25/13/12)
No trastuzumab (n=84/44/44)

No radiation (n=24/14/10)
Left sided radiation (n=40/23/17)
Right sided radiation (n=45/20/25)

Difference in change in LVEF (95% CI) from baseline to end-of-study

p-value for interaction

p = 0.76
p = 0.09
p = 0.43
p = 0.47
p = 0.28
Primary results of metoprolol

Difference in change in LVEF (95% CI) from baseline to end-of-study

Sample
(n=total/metoprolol/not metoprolol)

All patients (n=109/54/55)

Age > median (n=55/25/30)  p = 0.09
Age ≤ median (n=54/29/25)  p = 0.47

Current smoker (n=19/8/11)  p = 0.86
Not current smoker (n=90/46/44)  p = 0.92

BMI > median (n=51/25/26)  p = 0.22
BMI ≤ median (n=58/29/29)

Trastuzumab (n=25/12/13)  p = 0.86
No trastuzumab (n=84/42/42)

No radiation (n=24/9/15)  p = 0.92
Left sided radiation (n=40/20/20)
Right sided radiation (n=45/25/20)
Clinical implications

• 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

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

- 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**

**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

**Charité Campus Buch/HELIOS Berlin**
- J Schulz-Menger
- F von Knobelsdorff-Brenkenhoff

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