Safety and Efficacy of Early Exercise Training after Elective Coronary Stenting in Patients with Stable Coronary Artery Disease.

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Background 1

• “Acute stent thrombosis associated with exercise testing after successful percutaneous transluminal coronary angioplasty.” *Am Heart J* 1995

• “Coronary dissection and thrombosis associated with exercise testing three months after successful coronary stenting.” *Clin Cardiol* 1999

Early exercise after coronary stenting has a risk of inducing stent thrombosis!!
However…
“Early exercise after coronary stenting is safe”
*J Am Coll Cardiol* 2003

In the current strong antiplatelet therapy, stent thrombosis is a very rare event.

Few studies have reported the safety of early exercise training after *elective* coronary stenting in patients with *stable* coronary artery disease.
Aim

- To investigate the safety of submaximal exercise training based on the Borg scale from the next day after coronary stenting.

Study Design

Single-centre prospective non-randomized trial.
Inclusion Criteria

• Patients who underwent successful elective coronary stenting (defined as residual stenosis <30% without complications).
Exclusion Criteria

- hemodialysis, uncontrollable hypertension, acute coronary syndrome within 4 weeks, symptomatic heart failure, hemorrhagic diatheses, severe valvular heart disease, dementia, inability to exercise due to orthopedic or neurological limitations, symptomatic main vessel or side branch stenosis, acute stent thrombosis, access site-related complications, persistent chest pain or new ST-segment deviation, or final coronary flow less than TIMI (Thrombolysis In Myocardial Infarction) grade 3
Participant Flow

Assessed for Eligibility (n = 2367)
16 (0.67%) excluded not meeting inclusion criteria

Enrollment (n = 2351)
All patients decided whether to do exercise or not by themselves

Allocated to Exercise group (n = 865)
60 lost to follow up
Completed follow-up (n = 805) Analyzed (n=865)

Allocated to control (n = 1486)
88 lost to follow up
Completed follow-up (n = 1398) Analyzed (n=1486)
Endpoint

• **Primary Endpoint**
  Incidence of stent thrombosis

• **Secondary Endpoints**
  1. **In-hospital Complication**
     (chest pain, hematoma, pseudoaneurysm, surgical repair, blood transfusion, deep venous thrombosis)
  2. **MACE**  (Death, non-fetal MI, Stroke)
  3. Unscheduled Hospital Visit for worsening angina
  4. Continuation Rate of Exercise Training
Definition: Stent thrombosis (ST) using the Academic Research Consortium (ARC) definition

Definite ST
Angiographic confirmation of ST and at least 1 of the following signs present within 48 hours: new onset of ischemic symptoms at rest, new electrocardiographic changes suggestive of acute ischemia, or typical rise and fall in cardiac biomarkers.

Probable ST
Any unexplained death within the first 30 days after intracoronary stenting.

Possible ST
Included all unexplained deaths occurring at least 30 days after the procedure.
Exercise Protocol

- All patients were prescribed dual antiplatelet medications (ticlopidine 200mg or clopidgrel 75mg + aspirin 100mg a day) before more than two days.
- Exercise training on a bicycle ergometer was performed on the day after coronary stenting.
- Exercise training was performed up to submaximal exercise based on Borg Index (up to 13). And exercise was continued for about 20 minutes.
- They continued the same degree exercise more than 3 times a week after discharge.
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Exercise(+)</th>
<th>Exercise(-)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>67.8 ± 9.5</td>
<td>68.4 ± 10.2</td>
<td>0.1605</td>
</tr>
<tr>
<td><strong>male gender (%)</strong></td>
<td>667 (77.1)</td>
<td>1112 (74.8)</td>
<td>0.2144</td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
<td>541 (62.5)</td>
<td>903 (60.8)</td>
<td>0.3936</td>
</tr>
<tr>
<td><strong>Hyperlipidemia (%)</strong></td>
<td>347 (40.1)</td>
<td>611 (41.1)</td>
<td>0.8841</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus (%)</strong></td>
<td>377 (43.6)</td>
<td>669 (45.0)</td>
<td>0.4991</td>
</tr>
<tr>
<td><strong>Smoking habit (%)</strong></td>
<td>216 (25.5)</td>
<td>384 (26.0)</td>
<td>0.9645</td>
</tr>
<tr>
<td><strong>Exercise habit (%)</strong></td>
<td>227 (26.2)</td>
<td>418 (28.1)</td>
<td>0.3229</td>
</tr>
<tr>
<td><strong>LV dysfunction (EF&lt;35%) (%)</strong></td>
<td>67 (7.7)</td>
<td>135 (9.1)</td>
<td>0.2639</td>
</tr>
<tr>
<td><strong>Body Mass Index &gt; 25 (%)</strong></td>
<td>334 (38.9)</td>
<td>584 (40.0)</td>
<td>0.7635</td>
</tr>
<tr>
<td><strong>prior PCI (%)</strong></td>
<td>151 (17.5)</td>
<td>223 (15.0)</td>
<td>0.1173</td>
</tr>
<tr>
<td><strong>Atrial fibrillation (%)</strong></td>
<td>46 (5.4)</td>
<td>68 (4.6)</td>
<td>0.4073</td>
</tr>
<tr>
<td><strong>Renal insufficiency (Cre&gt;1.5mg/dl)</strong></td>
<td>78 (9.0)</td>
<td>144 (9.7)</td>
<td>0.5894</td>
</tr>
</tbody>
</table>

EF: ejection fraction, PCI: percutaneous coronary intervention,
### Patient Characteristics 2

<table>
<thead>
<tr>
<th></th>
<th>Exercise(+)</th>
<th>Exercise(-)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multivessel Intervention (%)</strong></td>
<td>237 (27.4)</td>
<td>408 (27.5)</td>
<td>0.976</td>
</tr>
<tr>
<td><strong>Number of Stent</strong></td>
<td>1.33±0.63</td>
<td>1.35±0.67</td>
<td>0.667</td>
</tr>
<tr>
<td><strong>Stented Territory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD (%)</td>
<td>380 (44.0)</td>
<td>700 (47.1)</td>
<td>0.1362</td>
</tr>
<tr>
<td>RCA (%)</td>
<td>439 (50.8)</td>
<td>666 (44.8)</td>
<td>0.0054</td>
</tr>
<tr>
<td>LCX (%)</td>
<td>206 (23.8)</td>
<td>393 (26.4)</td>
<td>0.1579</td>
</tr>
<tr>
<td>Bypass Graft (%)</td>
<td>4 (0.5)</td>
<td>9 (0.6)</td>
<td>0.6515</td>
</tr>
<tr>
<td>Left Main Trunk (%)</td>
<td>11 (1.3)</td>
<td>38 (2.6)</td>
<td>0.0354</td>
</tr>
<tr>
<td>Use of statin (%)</td>
<td>359 (41.5)</td>
<td>618 (41.6)</td>
<td>0.9677</td>
</tr>
<tr>
<td>Use of β-blocker (%)</td>
<td>164 (19.0)</td>
<td>248 (16.7)</td>
<td>0.1626</td>
</tr>
<tr>
<td>Use of ACEI / ARB (%)</td>
<td>410 (47.4)</td>
<td>671 (45.6)</td>
<td>0.2924</td>
</tr>
<tr>
<td>Use of DES (%)</td>
<td>297 (34.3)</td>
<td>458 (31.0)</td>
<td>0.0784</td>
</tr>
<tr>
<td><strong>Approach Site</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial / Brachial / Femoral</td>
<td>175 / 285 / 405</td>
<td>283 / 480 / 723</td>
<td>0.6543</td>
</tr>
</tbody>
</table>

ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, DES: drug eluting stent
Result

In-hospital
Assessed for Eligibility (n = 2367)
16 (0.67%) excluded not meeting inclusion criteria

Enrollment (n = 2351)
Patients decided whether to do exercise or not by themselves

Allocated to Exercise group (n = 865)
60 lost to follow up
Completed follow-up (n = 805) Analyzed (n=865)

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Completed follow-up (n = 1398) Analyzed (n=1486)
Safety of Exercise Stress Test

Submaximal stress test: 865 pts

- Protocol Exercise: 800 pts (92.5%)
- Other Exercise: 46 pts (5.3%)
  - Physical Exercise: 11 pts
  - Walking Exercise: 35 pts
- Did not undergo: 19 pts (2.2%)
  - Lumber pain
  - Hematoma
  - Reject
  - Unknown
Safety of Exercise Stress Test

- Discontinuation of protocol exercise
  168 / 800 (21.0%)
  133: leg fatigue
  27: increased blood pressure
  2: chest discomfort without ECG change
  2: disphoria
  4: aggravation of hematoma of puncture site

* No serious complication developed during and after exercise training.
Complications after Procedure

Complication: Chest pain, Hematoma, pseudoaneurysm, pulmonary embolism, deep venous thrombosis, blood transfusion, Surgical repair.

The incidence of hematoma did not depend on the approach site or sheath size.
Result

Clinical Outcome @ 1-year
Cumulative Incidence of MACE and ST

MACE: death, non-fatal MI, stroke

At 30-day (EET vs Cntrl)
MACE: 1.4% vs. 1.3%, p=0.72
ST: 0.58% vs. 0.47%, p=0.73

At 1-year (EET vs Cntrl)
MACE: 4.9% vs. 4.5%, p=0.75
ST: 1.2% vs. 0.9%, p=0.52
### Multivariate predictors of ST

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD</td>
<td>5.50</td>
<td>1.61 – 18.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV dysfunction (&lt;35%)</td>
<td>5.54</td>
<td>1.59 – 19.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

EET (HR 1.32, 95% CI 0.40 to 4.36, p=0.64)

Prespecified risk factors: age, gender, LAD stenting, multivessel stenting, total stent length, stent diameter, use of a drug-eluting stent, use of clopidogrel, CKD, diabetes, LV dysfunction, and EET
Exercise Continuation Rate

* 30-day: 49.3% (EET) vs. 38.3% (Control) * P<0.0001
* 1-year: 28.3% (EET) vs. 30.5% (Control)
Unscheduled Hospital Visit for worsening angina

![Bar chart showing incidence of unscheduled hospital visits for worsening angina between EET (N=865) and Control (N=1486).]

- **EET (N=865):** 11.7%
- **Control (N=1486):** 17.4%

**P<0.001**
## Multivariate Predictors of Unscheduled Hospital Visit

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th></th>
<th></th>
<th>Multiivariate</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P value</td>
<td>HR</td>
<td>95% CI</td>
<td>P value</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.1</td>
<td>2.1 - 4.7</td>
<td>&lt;0.0001</td>
<td>2.88</td>
<td>1.87 - 4.42</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No Statin use</td>
<td>1.83</td>
<td>1.24 - 2.69</td>
<td>0.002</td>
<td>1.66</td>
<td>1.13 - 2.46</td>
<td>0.012</td>
</tr>
<tr>
<td>CKD</td>
<td>2.07</td>
<td>1.24 - 3.46</td>
<td>0.006</td>
<td>2.89</td>
<td>2.23 - 3.19</td>
<td>0.018</td>
</tr>
<tr>
<td>Non-Exercise habit</td>
<td>1.7</td>
<td>1.15 - 2.50</td>
<td>0.007</td>
<td>1.55</td>
<td>1.05 - 2.29</td>
<td>0.029</td>
</tr>
<tr>
<td>No use of β-blocker</td>
<td>1.55</td>
<td>0.99 - 2.42</td>
<td>0.055</td>
<td>1.06</td>
<td>0.67 - 1.69</td>
<td>0.81</td>
</tr>
<tr>
<td>Ejection Fraction &lt; 35%</td>
<td>1.31</td>
<td>0.71 - 2.43</td>
<td>0.39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivessel Disease</td>
<td>1.29</td>
<td>0.86 - 1.93</td>
<td>0.22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise Training</td>
<td>0.74</td>
<td>0.50 - 1.13</td>
<td>0.169</td>
<td></td>
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</tr>
</tbody>
</table>

HR: Hazard Ratio, CI: confidence interval
Limitation

• Single center, non-randomized trial despite large-scale prospective analysis.

• Non-supervised exercise monitoring (self-report)
Conclusion

• Submaximal exercise training based on Borg index from the day after elective coronary stenting does not increase the incidence of ST or postoperative complications.

• Early exercise training was effective for the acquirement or maintenance of exercise habit, and the reduction of unscheduled hospital visit for worsening angina