Association of medical therapy with cardiovascular outcomes in patients with myocardial infarction with nonobstructive coronary arteries

M. Tao¹, S. Dhaliwal¹, A. Miller¹, D. Ghosalkar¹, R. Masson¹, T. Rahman¹, R. Pyo¹

¹Stony Brook University Hospital, Stony Brook, United States of America

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Background: Myocardial infarction with nonobstructive coronary arteries (MINOCA) is a disease that has been poorly characterized with unclear clinical and therapeutic outcomes. The association of medical therapy with cardiovascular outcomes in patients with MINOCA has been inadequately assessed. The purpose of this meta-analysis is to evaluate the association of medical therapy with cardiovascular outcomes in patients with MINOCA.

Methods: A literature search was conducted for studies reporting on the association of medical therapy with clinical endpoints in patients with MINOCA. Clinical endpoints include all-cause mortality, recurrence of acute coronary syndrome (ACS), and major adverse cardiovascular events (MACE). Databases searched included Ovid MEDLINE, EMBASE, Web of Science, and Google Scholar.

Results: A total of 9 studies with 27731 MINOCA patients (17816 on medical therapy, 9915 not on medical therapy) met inclusion criteria. Mean follow-up duration was 56 months, mean age was 63 years old, 52% were men. Medical therapy did not significantly reduce risk of MACE compared to no medical therapy (OR 0.99, 95% CI 0.91-1.07; p=0.73). Subgroup analysis demonstrated no significant reduction in risk of MACE regardless of ACE inhibitors/ARBs, antiplatelet therapy, or beta blocker therapy (OR 1.03, 95% CI 0.91-1.17; p=0.62; OR 1.00, 95% CI 0.87-1.14; p=0.98; OR 0.92, 95% CI 0.79-1.06; p=0.22). However, there is a trend toward lower risk of MACE in MINOCA patients on beta blocker therapy.

Analysis of MINOCA patients by presence of vasospasm did not demonstrate any significant reduction in risk of MACE with antiplatelet use in either subgroups (OR 1.03, 95% CI 0.71-1.49; p=0.89 without vasospasm; OR 0.92, 95% CI 0.74-1.14; p=0.44 with vasospasm). Use of antiplatelet therapy in patients with vasospasm did not significantly reduce risk of mortality or recurrent ACS (OR 0.80, 95% CI 0.37-1.75; p=0.58; OR 1.21, 95% CI 0.89-1.64; p=0.22).

Conclusions: Standard medical therapy using antiplatelet agents, beta blockers, or ACE inhibitors/ARBs are not associated with lower risk of cardiovascular outcomes in patients with MINOCA regardless of presence of vasospasm. However, there is a paucity in literature evaluating agents other than antiplatelet therapies. Additional high-quality studies are required to evaluate the utility of specific medication classes for treatment of specific etiologies of MINOCA.
### Association of Medical Therapy with MACE in Patients with MINOCA

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Medical Tx</th>
<th>No Medical Tx</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACEI/ARB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciliberti 2021</td>
<td>78/340/28/191</td>
<td>2.4%</td>
<td>1.29 (0.81, 2.06)</td>
</tr>
<tr>
<td>Lindahl 2016</td>
<td>596/3019/563/2885</td>
<td>35.2%</td>
<td>1.01 (0.89, 1.15)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>3449/3076/191/37.7%</td>
<td>1.03 (0.91, 1.17)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>674/591</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.93, df = 1 (p = 0.33); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.50 (p = 0.62)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1.1.2 Antiplatelet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho 2019</td>
</tr>
<tr>
<td>Ciliberti 2021</td>
</tr>
<tr>
<td>Dias 2016</td>
</tr>
<tr>
<td>Ishi 2016</td>
</tr>
<tr>
<td>Lim 2016</td>
</tr>
<tr>
<td>Lindahl 2017</td>
</tr>
<tr>
<td>Mori 2020</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
</tr>
<tr>
<td>Total events</td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 33.52, df = 6 (p &lt; 0.00001); I² = 82%</td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.02 (p = 0.98)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1.1.3 Beta Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciliberti 2021</td>
</tr>
<tr>
<td>Lindahl 2017</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
</tr>
<tr>
<td>Total events</td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 1.86, df = 1 (p = 0.17); I² = 46%</td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.22 (p = 0.22)</td>
</tr>
</tbody>
</table>

| Total (95% CI)      | 17443/9764/100.0% | 0.99 (0.91, 1.07) |
| Total events        | 2425/1319 |              |                               |
| Heterogeneity: Chi² = 37.81, df = 10 (p < 0.0001); I² = 74% |
| Test for overall effect: Z = 0.35 (p = 0.71) |
| Test for subgroup differences: Chi² = 1.61, df = 2 (p = 0.45); I² = 0% |

### Association of Antiplatelet Therapy with MACE in MINOCA Patients with or without Vasospasm

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Medical Tx</th>
<th>No Medical Tx</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1.1 Not Vasospasm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciliberti 2021</td>
<td>99/546/7/75</td>
<td>4.4%</td>
<td>2.15 (0.96, 4.83)</td>
</tr>
<tr>
<td>Dias 2016</td>
<td>23/88/67/188</td>
<td>13.7%</td>
<td>0.64 (0.36, 1.12)</td>
</tr>
<tr>
<td>Femoral 2019</td>
<td>39/296/9/74</td>
<td>5.4%</td>
<td>1.10 (0.51, 2.38)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>930/337/23.5%</td>
<td>1.03 (0.71, 1.49)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>161/83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 5.99, df = 2 (p = 0.05); I² = 67%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.11 (p = 0.89)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3.1.2 Vasospasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho 2019</td>
</tr>
<tr>
<td>Ishi 2016</td>
</tr>
<tr>
<td>Lim 2016</td>
</tr>
<tr>
<td>Mori 2020</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
</tr>
<tr>
<td>Total events</td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 14.78, df = 3 (p = 0.002); I² = 80%</td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.78 (p = 0.44)</td>
</tr>
</tbody>
</table>

| Total (95% CI)    | 3019/2932/100.0% | 0.94 (0.78, 1.14) |
| Total events      | 363/285 |              |                               |
| Heterogeneity: Chi² = 20.81, df = 6 (p = 0.002); I² = 71% |
| Test for overall effect: Z = 0.61 (p = 0.54) |
| Test for subgroup differences: Chi² = 0.35, df = 1 (p = 0.62); I² = 0% |
Association of Antiplatelet Therapy with All-Cause Mortality in Patients with Vasospasm

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Medical Tx Events</th>
<th>Total Events</th>
<th>No Medical Tx Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho 2019</td>
<td>5</td>
<td>827</td>
<td>7</td>
<td>1011</td>
<td>26.7%</td>
<td>0.87 [0.82, 2.76]</td>
</tr>
<tr>
<td>Ishii 2016</td>
<td>2</td>
<td>137</td>
<td>1</td>
<td>503</td>
<td>9.0%</td>
<td>7.44 [0.67, 82.64]</td>
</tr>
<tr>
<td>Lim 2016</td>
<td>10</td>
<td>456</td>
<td>9</td>
<td>321</td>
<td>34.1%</td>
<td>0.78 [0.31, 1.94]</td>
</tr>
<tr>
<td>Mori 2020</td>
<td>5</td>
<td>669</td>
<td>14</td>
<td>760</td>
<td>30.3%</td>
<td>0.40 [0.14, 1.12]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2089</strong></td>
<td><strong>2595</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>0.80 [0.37, 1.75]</strong></td>
</tr>
</tbody>
</table>

Total events: 22
Heterogeneity: Tau² = 0.24; Chi² = 4.99, df = 3 (P = 0.17); I² = 40%
Test for overall effect: Z = 0.55 (P = 0.58)

Association of Antiplatelet Therapy with Recurrent ACS in Patients with Vasospasm

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Medical Tx Events</th>
<th>Total Events</th>
<th>No Medical Tx Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho 2019</td>
<td>29</td>
<td>827</td>
<td>28</td>
<td>1011</td>
<td>32.3%</td>
<td>1.28 [0.75, 2.16]</td>
</tr>
<tr>
<td>Ishii 2016</td>
<td>4</td>
<td>137</td>
<td>17</td>
<td>503</td>
<td>9.4%</td>
<td>0.86 [0.28, 2.60]</td>
</tr>
<tr>
<td>Lee 2018</td>
<td>2</td>
<td>77</td>
<td>13</td>
<td>77</td>
<td>16.8%</td>
<td>0.13 [0.03, 0.60]</td>
</tr>
<tr>
<td>Lim 2016</td>
<td>9</td>
<td>456</td>
<td>2</td>
<td>321</td>
<td>3.1%</td>
<td>3.21 [0.69, 14.96]</td>
</tr>
<tr>
<td>Mori 2020</td>
<td>44</td>
<td>669</td>
<td>33</td>
<td>760</td>
<td>38.4%</td>
<td>1.55 [0.98, 2.47]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2166</strong></td>
<td><strong>2672</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>1.21 [0.89, 1.64]</strong></td>
</tr>
</tbody>
</table>

Total events: 88
Heterogeneity: Chi² = 11.20, df = 4 (P = 0.02); I² = 64%
Test for overall effect: Z = 1.22 (P = 0.22)