Fifteen-year mortality outcomes in the APEX-AMI trial compared to the general ST-elevation myocardial infarction population in Canada: Exploring lessons from numerators and denominators

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Funding Acknowledgements: None.

Background: It is well established that patients enrolled in clinical trials tend to be younger, more likely male, and have fewer comorbidities. Moreover, sites that enroll patients in randomized trials (RT) are often tertiary care centres in urban areas especially in the setting of STEMI. The impact of these potential selection biases on clinical outcomes both within and well beyond the proscribed RT follow-up window have not been adequately explored.

Objective: To compare 15-year mortality of ST elevation myocardial infarction of Canadian (STEMI) patients with high-risk electrocardiographic findings enrolled within 6 hours of symptom onset undergoing primary PCI in the APEX-AMI clinical trial of Pexelizumab (APEX-AMI group) with STEMI patients presenting to 25 APEX-AMI enrolling sites (APEX-AMI sites group); and STEMI patients presenting to 400 other sites (non-APEX-AMI site group).

Methods: APEX-AMI enrolled patients between 07/13/2004 – 05/11/2006. We conducted a probabilistic linkage (based on admission date, discharge date, age, sex, province, diagnosis of MI, presence of comorbidities) between APEX-AMI and the Canadian national Discharge Abstract Database (DAD), excluding Quebec, for the same time period. These data were further linked to tax files (for socio-economic data) and vital statistics data to obtain mortality status as of 2020.

Results: Of the 335 Canadian participants in APEX-AMI, 143 were from Quebec and were excluded. Of the remaining 192 patients, 188 (97.9%) were linked with the DAD. There were 8,470 patients in the APEX-AMI sites and 10,940 in the non-APEX-AMI sites groups, respectively (Table 1). Patients enrolled in APEX-AMI were less likely to be female, more affluent, have a lower comorbidity burden as measured by the Charlson Comorbidity Index, and higher PCI rates. Ninety-day all-cause mortality in the three groups was 4.3%, 8.5%, 12.7% in the APEX-AMI, APEX-AMI site, and non-APEX-AMI site groups, respectively. At 15-years, mortality rates were 34.0%, 45.8%, and 52.2% in the three groups (p<0.01, Figure). Enrollment in APEX-AMI was associated with an unadjusted 45% reduction in risk of 15-year mortality (HR 0.55, 95% CI: 0.43-0.70). However, this association was attenuated after adjusting for demographic and clinical factors (adjusted HR (aHR), 0.69, 95% CI: 0.54-0.88), and completely nullified after adjusting for PCI (aHR, 0.82, 95% CI: 0.64-1.05).

Conclusions: Our study demonstrates the feasibility and value of extending clinical trial follow-up via linkage with routinely collected administrative data. While enrollment in clinical trials appears to be associated with better long-term outcomes, our findings highlight the need to be vigilant to the potential for selection bias, the generalizability of trial findings and the potential to more broadly enhance long-term STEMI outcomes.
### Table 1. Baseline characteristics by trial enrollment status

<table>
<thead>
<tr>
<th></th>
<th>Enrolled in RT</th>
<th>Not Enrolled in RT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APEX-AMI patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>200**</td>
<td>8,470</td>
</tr>
<tr>
<td>Female, %</td>
<td>15.8</td>
<td>28.6</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>62.6 (12.5)</td>
<td>63.3 (13.5)</td>
</tr>
<tr>
<td>Rural residence, %</td>
<td>10.5</td>
<td>18.7</td>
</tr>
<tr>
<td>Marital Status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With Partner</td>
<td>64.7</td>
<td>65.7</td>
</tr>
<tr>
<td>Divorced/Separated</td>
<td>17.7</td>
<td>10.7</td>
</tr>
<tr>
<td>Single</td>
<td>11.8</td>
<td>10.3</td>
</tr>
<tr>
<td>Widowed</td>
<td>5.9</td>
<td>13.3</td>
</tr>
<tr>
<td>Family Income, median (IQR)</td>
<td>50,750 (30,050-79,600)</td>
<td>45,200 (25,750-77,450)</td>
</tr>
<tr>
<td>Charlson score, median (IQR)</td>
<td>1 (1-2)</td>
<td>1 (1-3)</td>
</tr>
<tr>
<td>PCI, %</td>
<td>85.0</td>
<td>61.4</td>
</tr>
</tbody>
</table>

* all comparisons significant at p<0.0001; **rounded to nearest 100; SD: Standard deviation; IQR: Interquartile range; PCI: Percutaneous coronary intervention

### Figure 1. Fifteen-year survival by trial enrollment status

![Figure 1. Fifteen-year survival by trial enrollment status](image-url)