The Cardiovascular Safety of Aromatase Inhibitors and Tamoxifen in Post-Menopausal Women with Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Farzin Khosrow-Khavar MSc1,2, Kristian B. Filion PhD1,2,3, Shatha Al-Qurashi MD4, Nazi Torabi MLIS5, Nathaniel Bouganim MD6, Samy Suissa PhD1,2, Laurent Azoulay PhD1,2,4

1 Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Quebec, Canada
2 Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada
3 Division of Clinical Epidemiology, Department of Medicine, McGill University, Montreal, Quebec, Canada
4 Department of Oncology, McGill University, Montreal, Quebec, Canada
5 McGill Library, McGill University, Montreal, Quebec, Canada
6 Department of Oncology, Cedar Cancer Center, McGill University Health Center, Montreal, Quebec, Canada

NOYCIA 2016
Background

• Aromatase inhibitors (AI) and tamoxifen are widely used in treatment of post-menopausal women with hormone-receptor positive breast cancer

• Meta-analysis indicate better efficacy associated with AIs in RCTs directly comparing AIs to tamoxifen

• However, these studies also indicate increased risk of cardiovascular adverse events associated with AIs
American Society of Clinical Oncology Guidelines

THE BOTTOM LINE (CONTINUED)

Tradeoffs of Benefits and Risks
- Benefits: increasing overall survival and distant disease-free survival (DFS), reducing breast cancer-specific mortality, decreased risk of recurrence, decreased risk of contralateral breast cancer
- Harms: endometrial cancer (if continuing tamoxifen), hot flashes and other menopausal symptoms (with either tamoxifen or AIs), deep vein thrombosis or pulmonary embolism (tamoxifen), ischemic heart disease (AI), osteopenia/osteoporosis (AI), uterine cancer (tamoxifen)

CONTRAINDICATIONS
- Women of premenopausal endocrine status, including pregnant women (4.1, 8.1)
- Patients with demonstrated hypersensitivity to ARIMIDEX or any excipient (4.2)

WARNINGS AND PRECAUTIONS
- In women with pre-existing ischemic heart disease, an increased incidence of ischemic cardiovascular events occurred with ARIMIDEX use compared to tamoxifen use. Consider risks and benefits (5.1, 6.1)
- Decreases in bone mineral density may occur. Consider bone mineral density monitoring (5.2, 6.1)
- Increases in total cholesterol may occur. Consider cholesterol monitoring (5.3, 6.1)
Cardioprotective Mechanisms of Tamoxifen

- Tamoxifen decreases levels of total cholesterol, LDL-C, and increases HDL-C levels in RCTs
- Tamoxifen decreases levels of C-reactive protein and fibrinogen
- Tamoxifen has anti-oxidant activities which protect cholesterol from harmful oxidation
Objectives

- To conduct a comprehensive systematic review and meta-analysis of cardiovascular safety of AIs and tamoxifen

Adjuvant Trials
- Upfront AI vs T
- Al vs Sequential T+Al
- Upfront T vs P

Extended-Adjuvant Trials
- Al vs P
- T vs P
Methods

- **Search Strategy:**
  - *Databases:* Pubmed, Embase, Cochrane CENTRAL, WHO ICRTP, Clinicaltrials.gov
  - *Population:* Female
  - *Intervention:* Aromatase Inhibitors (letrozole, anastrozole, exemestane) or tamoxifen
  - British Medical RCT Hedge where appropriate

- **Inclusion Criteria:**
  - *Population:* Post-menopausal women with diagnosis of breast-cancer
  - *Outcome:* Studies reporting cardiovascular events (excluding VTE, hypertension, hypercholesterolemia)

- **Exclusion Criteria:**
  - 1st or 2nd generations AIs or raloxifene
  - Pre-menopausal population
  - Primary prevention trials
  - Less 100 patients
  - Studies where primary indication for endocrine therapy is not breast cancer
Quality Assessment and Analysis

Quality Assessment:
• Cochrane collaboration tool for assessing risk of bias
• Screening and quality assessment conducted independently by two reviewers

Analysis:
• Relative risk of cardiovascular adverse events obtained for each RCT
• Pooled analysis by RCT design using DerSimonian-Laird Random-Effects Analysis
• Secondary analysis: Ischemic heart disease as the outcome
• Sensitivity Analysis: Fixed-effects analysis
Study Flow Diagram

Records identified through database search (n=15352)

Duplicates (n=5388)

Records undergoing title/abstract screening (n=9964)

Not relevant topic-journal title/abstract (n=8957)
Not relevant topic-conference abstract (n=394)
Full text-does not include CV endpoints (n=217)
Prevention RCTs (n=149)
Reviews (n=112)
Pre-menopausal population (n=63)
Not English (n=22)
Observational (n=17)

Studies meeting inclusion criteria (n=33)

RCTs included in the quantitative analysis (n=16)
### Meta-Analysis of Cardiovascular Adverse Events by RCT Design

<table>
<thead>
<tr>
<th>Trials</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>RR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjuvant-Upfront (AI vs T)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC</td>
<td>127</td>
<td>104</td>
<td></td>
<td>19.89</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>169</td>
<td>152</td>
<td></td>
<td>28.68</td>
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<tr>
<td>Abou-Touk et al.</td>
<td>4</td>
<td>3</td>
<td></td>
<td>0.61</td>
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<tr>
<td>N-SAS-BCO3</td>
<td>2</td>
<td>3</td>
<td></td>
<td>0.4</td>
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<tr>
<td>ITA</td>
<td>17</td>
<td>14</td>
<td></td>
<td>2.76</td>
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<tr>
<td>ARNO95</td>
<td>9</td>
<td>4</td>
<td></td>
<td>0.94</td>
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<tr>
<td>IES</td>
<td>259</td>
<td>211</td>
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<td>43.88</td>
</tr>
<tr>
<td>Paridaens et al.</td>
<td>22</td>
<td>12</td>
<td></td>
<td>2.84</td>
</tr>
<tr>
<td><strong>Subtotal (I-squared: 0%)</strong></td>
<td>100</td>
<td></td>
<td></td>
<td>1.19 [1.07, 1.34]</td>
</tr>
</tbody>
</table>

| **Adjuvant - Upfront vs Sequential (AI vs T->AI)**| | | | |
| BIG 1-98                      | 103                 | 108            |        | 40.17       | 0.96 [0.74, 1.24] |
| TEAM                          | 405                 | 326            |        | 59.83       | 1.23 [1.07, 1.42] |
| **Subtotal (I-squared: 64.29%)**| 100                 |                |        | 1.11 [0.87, 1.42] |

**Experimental decreases risk**

**Experimental increases risk**
### Meta-Analysis of Cardiovascular Adverse Events by RCT Design

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<tr>
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<th>Weight</th>
<th>RR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extended Adjuvant (AI vs P)</strong></td>
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<td></td>
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<tr>
<td>MA.17</td>
<td>149</td>
<td>144</td>
<td></td>
<td>1.04 [0.83, 1.29]</td>
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<tr>
<td><strong>Extended Adjuvant (T vs NT)</strong></td>
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<td></td>
</tr>
<tr>
<td>ATLAS</td>
<td>127</td>
<td>163</td>
<td>31.34</td>
<td>0.78 [0.62, 0.98]</td>
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<td>SITAM-01</td>
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<td>17</td>
<td>4.41</td>
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<td>NSABP-B14</td>
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<td>1.05</td>
<td>1.95 [0.49, 7.77]</td>
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<td>UK Over 50s</td>
<td>302</td>
<td>319</td>
<td>63.2</td>
<td>0.95 [0.82, 1.09]</td>
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<td>Subtotal (I-squared: 10.83%)</td>
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<td><strong>Adjuvant - Upfront (T vs P or NT)</strong></td>
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<td>Scottish</td>
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<td>47</td>
<td>78.58</td>
<td>0.67 [0.43, 1.04]</td>
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<td>12</td>
<td>18.79</td>
<td>0.67 [0.28, 1.64]</td>
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<td>Cummings et al.</td>
<td>1</td>
<td>2</td>
<td>2.63</td>
<td>0.49 [0.05, 5.28]</td>
</tr>
<tr>
<td>Subtotal (I-squared: 0%)</td>
<td>100</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Experimental decreases risk

Experimental increases risk

RR

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Novartis Oncology Young Canadian Investigator Awards 2016
Secondary Analysis-Ischemic Heart Disease

• Upfront Adjuvant Al vs T → RR: 1.30 (95% CI: 1.11-1.53)

• Extended adjuvant Al vs P → RR: 1.04 (95% CI: 0.83-1.29)

• Extended Adjuvant T vs P → RR: 0.91 (95% CI: 0.60-1.40)

• Upfront adjuvant T vs P → RR: 0.66 (95% CI: 0.45-0.98)
Conclusions

• The increased risk of cardiovascular disease associated with AIs in RCTs comparing AIs to tamoxifen should be interpreted with caution.

• The augmented cardiovascular risk associated with AIs in adjuvant trials can be accounted for by the cardioprotective effects of tamoxifen.

• This new evidence may guide the assessment of risk and benefit ratio of aromatase inhibitors and tamoxifen.
Acknowledgements

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