Cardiovascular Trials Over 2 Decades: Progress on Pragmatism?

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Director, Cardiovascular Research, University of Alberta
Cardiologist, Mazankowski Alberta Heart Institute
Disclosures

• JAE is an associate editor of Circulation
• Other disclosures available online at thecvc.ca

• Work published in JAMA Cardiology (2019) and Canadian Journal of Cardiology (2020)

• Work formed part of PhD thesis of Dr. Nariman Sepehrvand
Acknowledgement

Adjudicators

Biostatistician:
  • Wendimagegn Alemayehu

Funding agency:
Alberta Innovates
• Schwartz / Lellouch (1967): modern concept of pragmatic RCT

• Trial purpose:
  – efficacy of an intervention in ideal condition
  – effectiveness of an intervention over another in usual care

• “Designed for the primary purpose of informing decision-makers regarding the comparative balance of benefits, burdens and risks of a biomedical or behavioral health intervention at the individual or population level”
Pragmatic vs Explanatory Clinical Trials

**Explanatory trials**
- Strict in/exclusion criteria
- Ideal setting
- Specialized centres
- Slow recruitment
- Comparison with placebo
- Physiological endpoints
- More expensive

**Pragmatic trials**
- Diverse / representative population
- Usual care setting
- Multiple, heterogeneous centres
- Faster recruitment
- Comparison w/ real-word alternatives
- Clinically-important outcomes
- May be less expensive

*much of this remains to be clearly demonstrated
It snowed last night
**PRagmatic Explanatory Continuum Index Summary**

- Developed: 2009
- Updated: 2015
- 9 domains/aspects of trial design

Kevin Thorpe et al. J Clin Epid 2009
Kirsty Loudon et al. BMJ 2015
1. How pragmatic or explanatory are cardiovascular (CV) randomized controlled trials (RCT)?

2. Has the level of pragmatism in CV trials changed over two decades?

3. Has the proportion of women enrolled in CV trials changed over 2 decades?
Method

• Top 3 medical / CV journals (based on impact factor)


• Each adjudicated by 2 adjudicators using PRECIS-2 tool
Method: Study flow

1,185 abstracts screened

668 full texts adjudicated

Final cohort N=616

517 excluded: Secondary analysis (n=303); Sub-study (n=23); Follow-up study (n=59); Observational study (n=50); Non-CV related (n=15); Published in the following year (n=37); Experimental study (n=9); Commentary (n=13); Methodology (n=1); Meta-analysis (n=3); Preliminary analysis (n=2); Retracted (n=2)

52 excluded: Secondary analysis (n=5); Follow-up (n=5); Not-CV related (n=32); Observational (n=2); Other (n=8)
Methods: Analysis

- PRECIS-2 score for domain: average of 2 adjudicator scores
- Mean PRECIS-2 score: averaging scores over 9 domains
- Cohen’s D to quantify standardized difference between the groups
  - small   0.2-0.49
  - medium  0.5-0.79
  - large    ≥ 0.8
Results

• Mean PRECIS-2 score: 3.26 (0.70)
• Domain w/ lowest level of pragmatism: 1⁰ endpoint
• highest pragmatism: Statistical analysis
### Trend over time

- Pragmatism increased over time (p<0.0001)

<table>
<thead>
<tr>
<th>Year</th>
<th>N (%)</th>
<th>PRECIS score</th>
<th>Effect size: Cohen’s D</th>
<th>Trend p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>172 (27.9)</td>
<td>3.07 (0.74)</td>
<td>-ref-</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>2005</td>
<td>168 (27.3)</td>
<td>3.21 (0.64)</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>137 (22.2)</td>
<td>3.37 (0.66)</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>139 (22.6)</td>
<td>3.46 (0.67)</td>
<td>0.56</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean (SD) unless otherwise stated.
PREMIS-2 score by year

2000
2005
2010
2015
Pragmatism by Journal

- general medical more pragmatic than in cardiology journals
  - 3.55 (0.58) vs 3.10 (0.71); p<0.0001
PRECIS domain by Journal

[Diagram showing the comparison of Cardiology and Medical domains across various PRECIS-2 score categories: Eligibility, Recruitment, Setting, Organisation, Flexibility, Delivery, Flexibility, Adherence, Follow-up, Primary, Outcome, Analysis. Each category is represented with dots indicating the score range.]
 Trial characteristics

- PRECIS-2 score higher in RCTs w/
  - More sites/countries
  - Larger sample size
  - Longer F/U
  - mortality as primary endpoint
Higher PRECIS-2 score in phase III/IV than in phase I/II trials

- Phase III/IV: 3.49 (0.63)
- Phase I/II: 2.97 (0.67)

Values are mean (SD) unless otherwise stated.
Higher PRECIS-2 score in RCTs of behavioral/health system > medications or device

- Health system: 3.48 (0.67)
- Medication: 3.14 (0.69)
- Device/procedural: 3.38 (0.67)

Values are mean (SD) unless otherwise stated.
Funding

- No difference in pragmatism between different sources of funding (public, industry)

<table>
<thead>
<tr>
<th>Funding</th>
<th>N (%)</th>
<th>PRECIS score</th>
<th>Cohen’s D</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding</td>
<td></td>
<td></td>
<td></td>
<td>0.38</td>
</tr>
<tr>
<td>Public only</td>
<td>210 (39.3)</td>
<td>3.34 (0.71)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Industry only</td>
<td>215 (40.3)</td>
<td>3.25 (0.69)</td>
<td>-0.13</td>
<td></td>
</tr>
<tr>
<td>Public and Industry</td>
<td>109 (20.4)</td>
<td>3.30 (0.60)</td>
<td>-0.07</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean (SD) unless otherwise stated
Trial results

- PRECIS-2 score higher for neutral trials than those with positive results

<table>
<thead>
<tr>
<th></th>
<th>PRECIS-2</th>
<th>Cohen’s D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive for 1&lt;sup&gt;o&lt;/sup&gt; endpoint</td>
<td>3.17 (0.70)</td>
<td>0.36</td>
</tr>
<tr>
<td>Neutral for 1&lt;sup&gt;o&lt;/sup&gt; endpoint</td>
<td>3.38 (0.67)</td>
<td>0.07</td>
</tr>
<tr>
<td>Positive for 2&lt;sup&gt;o&lt;/sup&gt; endpoints</td>
<td>3.38 (0.67)</td>
<td>0.07</td>
</tr>
<tr>
<td>Neutral trial</td>
<td>3.42 (0.66)</td>
<td>-ref-</td>
</tr>
</tbody>
</table>

Values are mean (SD) unless otherwise stated.
Pragmatism increased moderately over time.

Proportion of RCTs with positive results remained fairly stable:

Positive trials had lower PRECIS-2 compared to neutral trials, but Cohen's $d$ effect size of 0.36 denotes small difference in pragmatism.

Sepehrvand et al. JAMA Cardio 2020
Women account for ~45% of the burden of CV diseases

Potentially underrepresented in CV RCTs

- 500 highly-cited CV RCTs (1996-2015): 28% women; proportion of women increased slightly over time (**0.29% per year**)
- 598 CV RCTs, 3 major journals (1986-2015); increased from 21% in 1986-1990 to **33%** in 2011-2015
- RCTs supporting 36 FDA drug approvals; participation in the range of disease prevalence for Pulm HTN, HTN, and AF, but below expected for ACS/CAD, HF
### Change in enrollment of women in RCT

- Enrollment in 602 CV RCT: 32.0% (19.8) women

<table>
<thead>
<tr>
<th>Year</th>
<th>N (%)</th>
<th>Female % (SD)</th>
<th>Effect size: Cohen’s D</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>168 (27.9)</td>
<td>28.5 (20.2)</td>
<td>Ref</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>2005</td>
<td>161 (26.7)</td>
<td>30.7 (20.1)</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>134 (22.3)</td>
<td>34.0 (20.0)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>139 (23.1)</td>
<td>35.8 (17.9)</td>
<td>0.38</td>
<td></td>
</tr>
</tbody>
</table>

Sepehrvand et al. CJC 2020
Women in RCTs: disease states

- proportion of women enrolled varied among different CV fields

<table>
<thead>
<tr>
<th>Disease State</th>
<th>N (%)</th>
<th>Female % (SD)</th>
<th>Cohen’s D</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>256 (42.5)</td>
<td>25.5 (16.2)</td>
<td>ref</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HF</td>
<td>79 (13.1)</td>
<td>27.3 (20.6)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>76 (12.6)</td>
<td>31.8 (15.5)</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>20 (3.3)</td>
<td>46.2 (7.9)</td>
<td>1.32</td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>28 (4.6)</td>
<td>51.9 (22.7)</td>
<td>1.57</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>15 (2.5)</td>
<td>41.3 (23.7)</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>128 (21.3)</td>
<td>40.3 (21.2)</td>
<td>0.83</td>
<td></td>
</tr>
</tbody>
</table>
Type of intervention

- Slightly higher proportion of women enrolled in RCTs of behavioral/health system > medications or device

<table>
<thead>
<tr>
<th>Type of Intervention</th>
<th>N (%)</th>
<th>Female % (SD)</th>
<th>Cohen’s D</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td>334 (55.5)</td>
<td>32.7 (21.8)</td>
<td>ref</td>
<td>0.0279</td>
</tr>
<tr>
<td>Device/procedural</td>
<td>190 (31.6)</td>
<td>29.2 (14.2)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Health system</td>
<td>78 (13.0)</td>
<td>35.7 (21.6)</td>
<td>0.14</td>
<td></td>
</tr>
</tbody>
</table>
Pragmatism and women’s enrollment

- weak correlation between pragmatism (PRECIS-2 score) & percentage of women in trials
  - Total PRECIS-2 score: $r=0.13$, $p=0.002$
  - Eligibility domain: $r=0.12$, $p<0.001$

- No difference between pragmatic trials and others in terms of women’s enrollment

<table>
<thead>
<tr>
<th></th>
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<th>Female % (SD)</th>
<th>Cohen’s D</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pragmatic*</td>
<td></td>
<td></td>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td>No</td>
<td>497 (82.6)</td>
<td>31.7 (19.8)</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>105 (17.4)</td>
<td>33.6 (19.6)</td>
<td>0.10</td>
<td></td>
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</table>
Funding

- No difference in the enrollment of women between different sources of funding (public, industry)

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<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding</td>
<td></td>
<td></td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>Private only</td>
<td>213 (40.6)</td>
<td>31.2 (16.1)</td>
<td>ref</td>
<td></td>
</tr>
<tr>
<td>Public only</td>
<td>205 (39.1)</td>
<td>33.4 (21.7)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Public and Private</td>
<td>106 (20.2)</td>
<td>32.9 (19.6)</td>
<td>0.10</td>
<td></td>
</tr>
</tbody>
</table>
• Women underrepresented in CV RCTs (< ⅓ of trial participants)
• Slight increase in women’s enrollment in CV RCTs over 2 decades
• Initiatives that focus on patient, clinician, and trial design factors are needed to address the gender gap in trial enrollment
Conclusions: Can we get there?

Explanatory trials*
- Strict in/exclusion criteria
- Ideal setting
- Specialized centres
- Slow recruitment
- Comparison with placebo
- Physiological endpoints
- More expensive

Pragmatic trials*
- Diverse / representative population
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*much of this remains to be clearly demonstrated
Pragmatism increased over time in CV trials

The increase in pragmatism was mainly in Eligibility, Setting, Flexibility of Intervention Delivery, and Primary Endpoint domains of trial design

No clinical trial is completely explanatory or pragmatic

Future RCTs should consider the domains of the PRECIS-2 in the design as well as the knowledge translation / dissemination phase