Canadian VIGOUR Centre
Bridging Hearts and Minds

# Cardiovascular Trials Over 2 Decades: Progress on Pragmatism?

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# 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

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**Adjudicators**

**Biostatistician:**

- Wendimagegn Alemayehu

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# Background

- 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”

Califf and Sugarman. Clin Trials 2015

# 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***

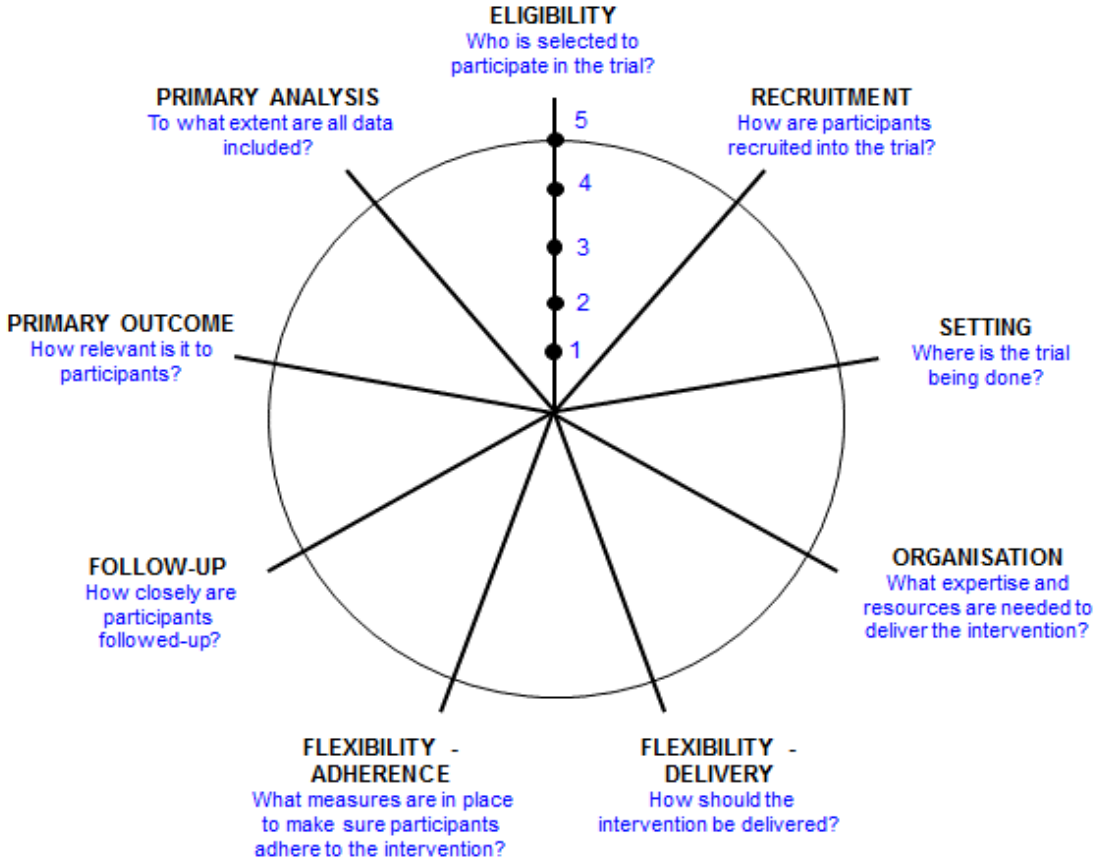
- Diverse / representative population
- Usual care setting
- Multiple, heterogeneous centres
- Faster recruitment
- Comparison w/ real-word alternatives
- Clinically-important outcomes
- May be less expensive

*much of this remains to be clearly demonstrated

# It snowed last night

# PRECIS-2

- **PR**agmatic **E**xplanatory **C**ontinuum **I**ndex **S**ummary
- Developed: 2009
- Updated: 2015
- 9 domains/aspects of trial design





Kevin Thorpe et al. J Clin Epid 2009
Kirsty Loudon et al. BMJ 2015

# Aims / Research Questions

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)


THE LANCET

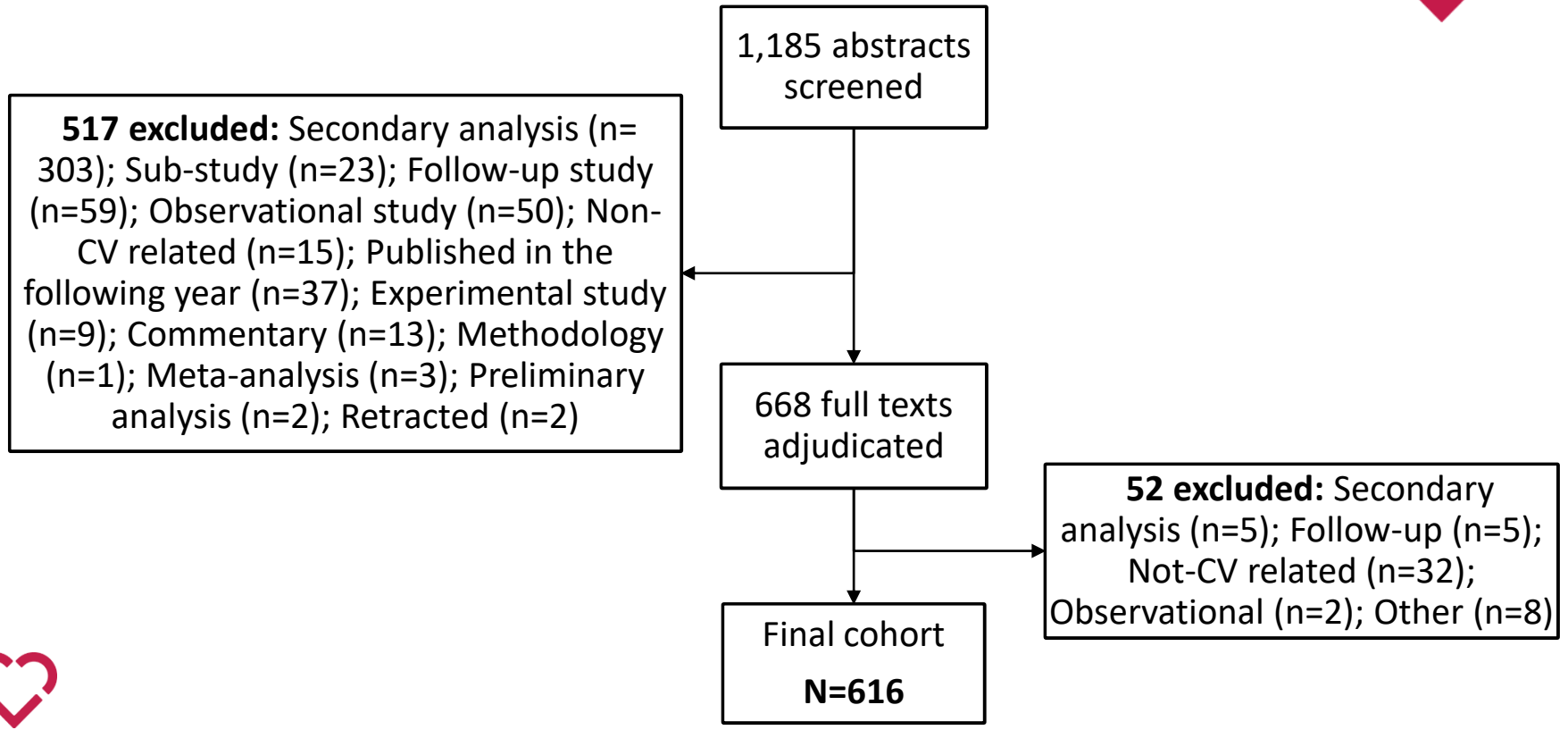

Circulation

European Heart Journal

- PubMed search for CV RCT years 2000, 2005, 2010, 2015
- Each adjudicated by 2 adjudicators using PRECIS-2 tool

Sepehrvand et al. JAMA Cardio 2019

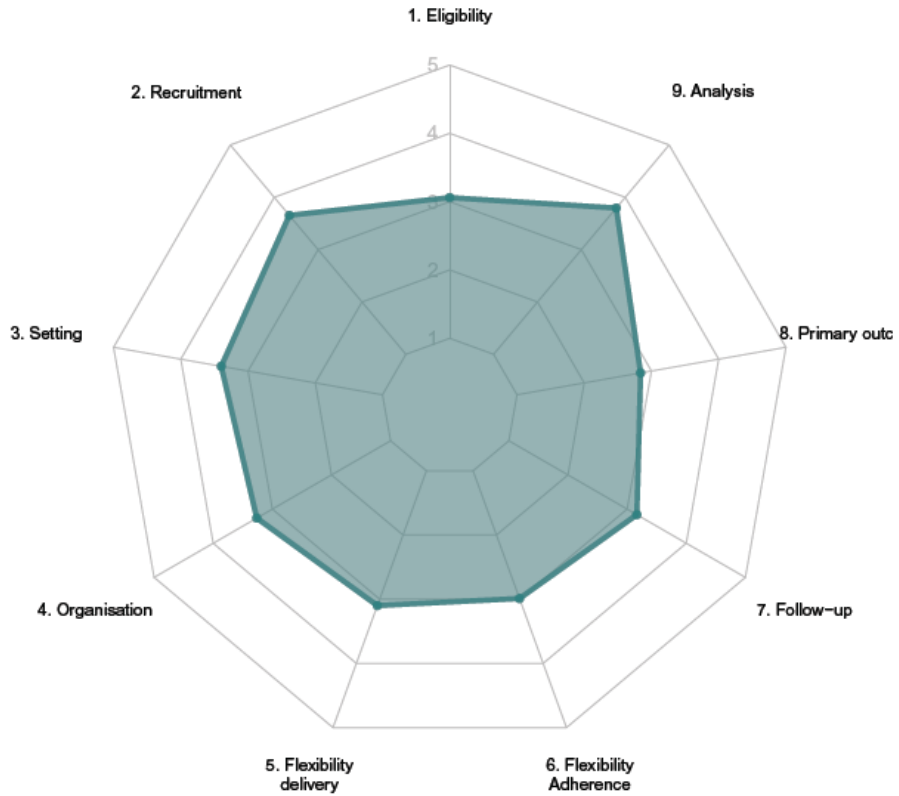
# Method: Study flow



# 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: 1$^{o}$ endpoint
- highest pragmatism: Statistical analysis

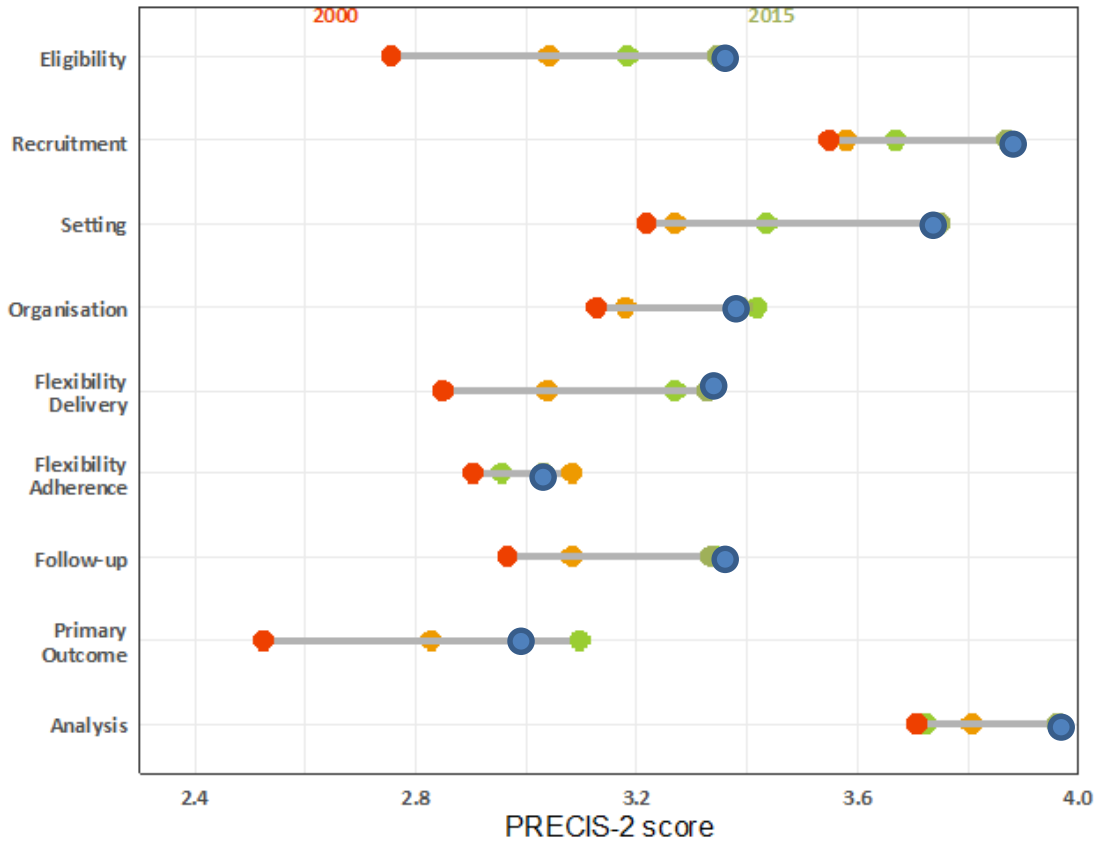
# Trend over time

- Pragmatism increased over time (p<0.0001)

| | N (%) | PRECIS score | Effect size: Cohen's D | Trend p-value |
|---|---|---|---|---|
| **Year** | | | | |
| **2000** | 172 (27.9) | 3.07 (0.74) | -ref- | <.0001 |
| **2005** | 168 (27.3) | 3.21 (0.64) | 0.21 | |
| **2010** | 137 (22.2) | 3.37 (0.66) | 0.43 | |
| **2015** | 139 (22.6) | 3.46 (0.67) | 0.56 | |

Values are mean (SD) unless otherwise stated

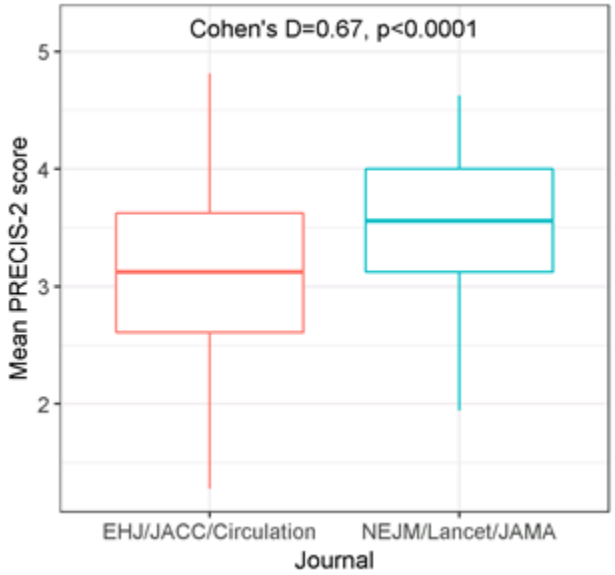
# PRECIS-2 score by year

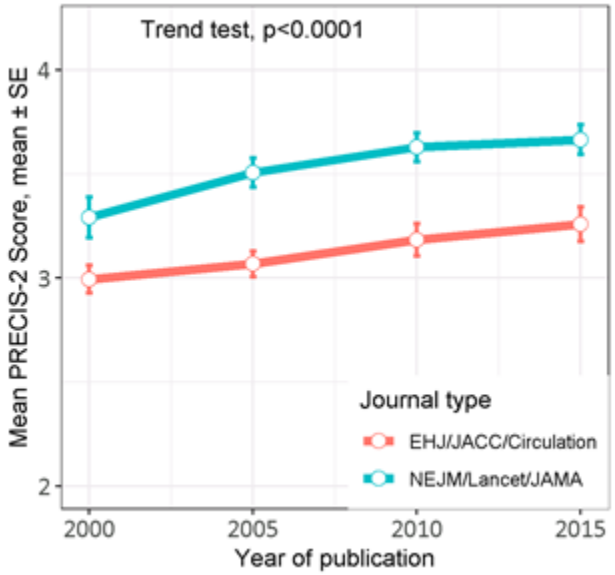



2000
2005
2010
2015

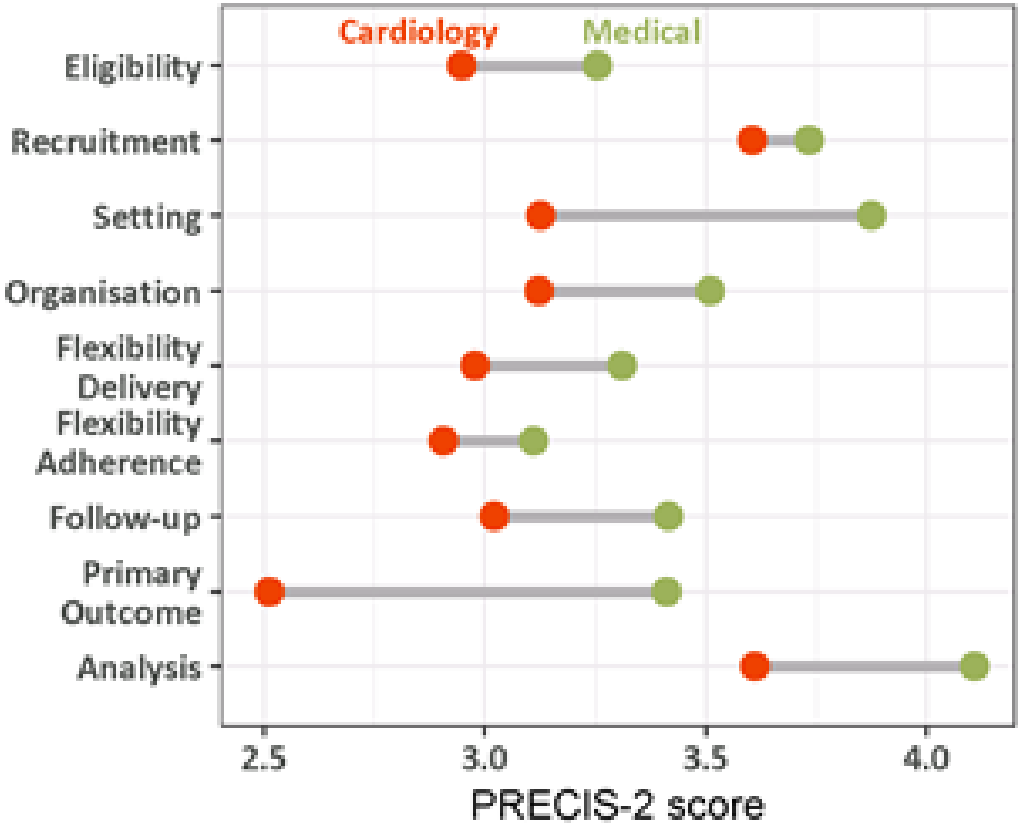
# Pragmatism by Journal

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



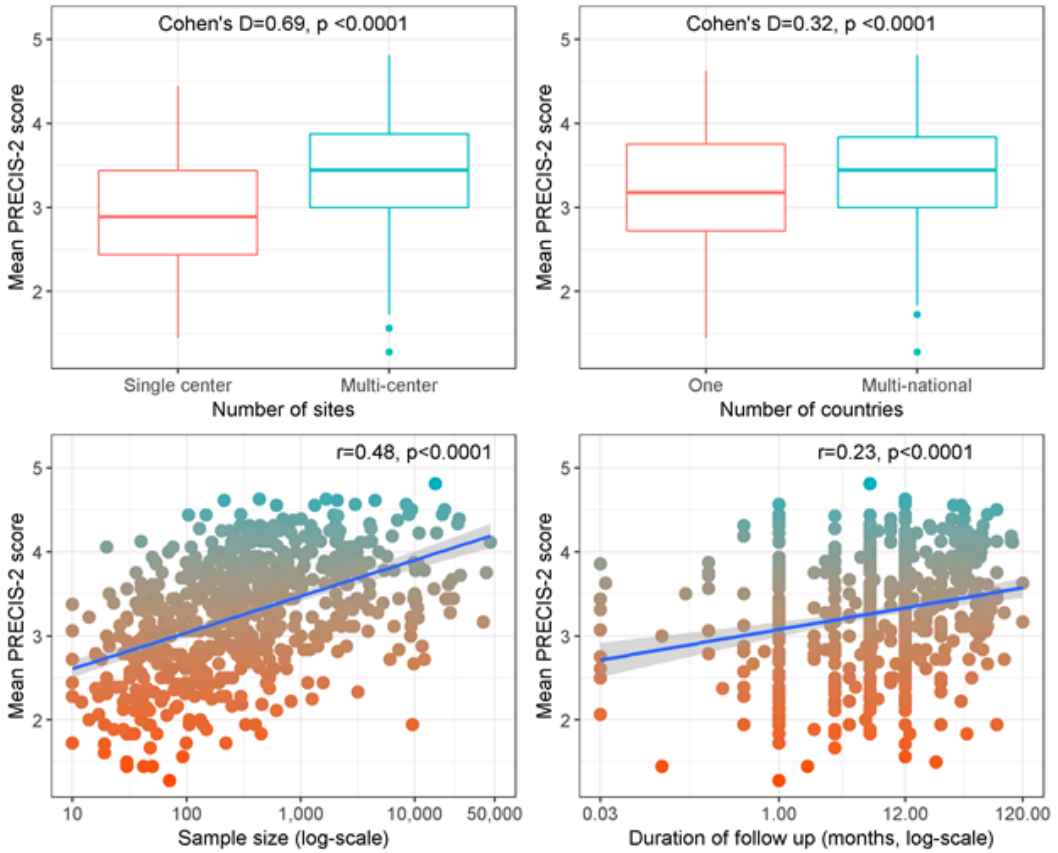



# PRECIS domain by Journal



# Trial characteristics

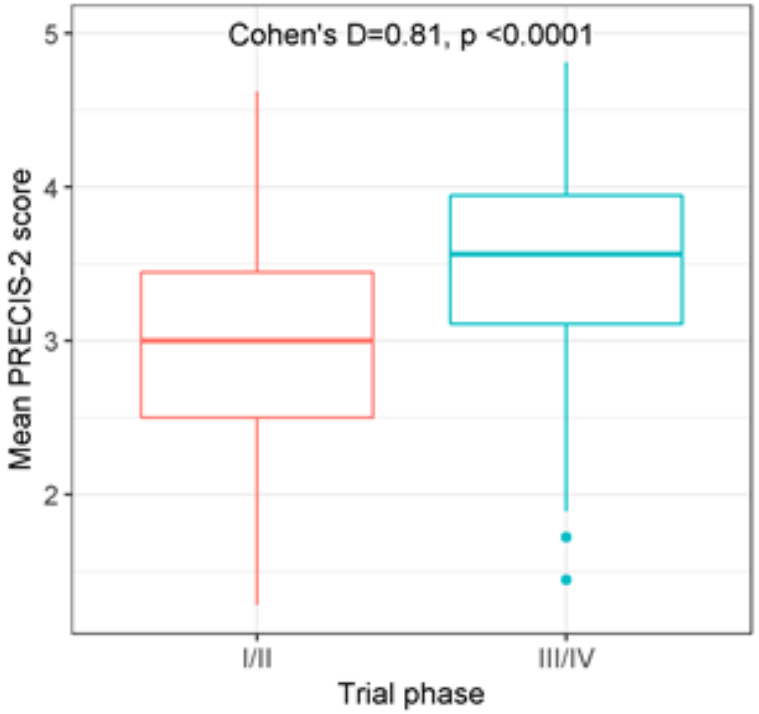
- PRECIS-2 score higher in RCTs w/
  - More sites/countries
  - Larger sample size
  - Longer F/U
  - mortality as primary endpoint



# Trial phase

- 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)

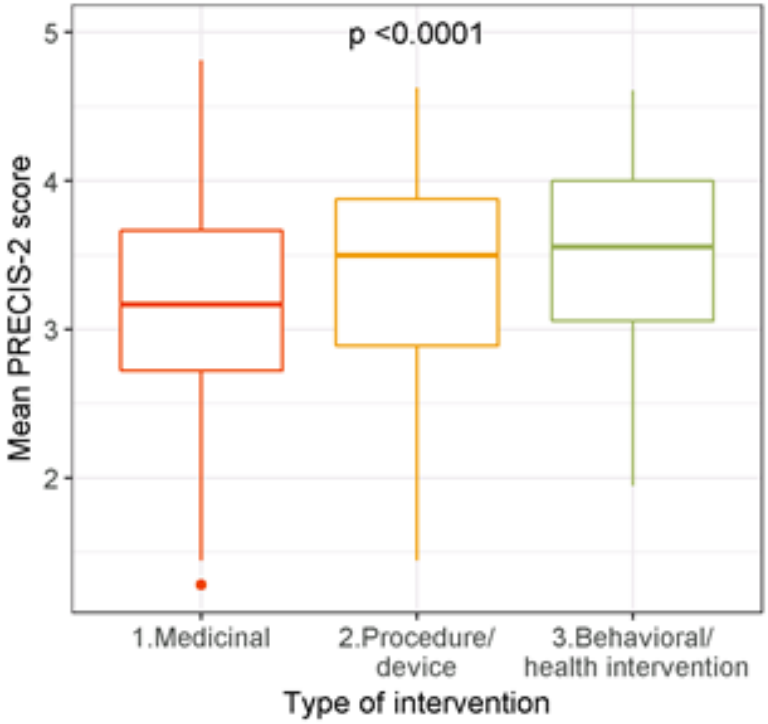



Values are mean (SD) unless otherwise stated

# Type of Intervention

- 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)

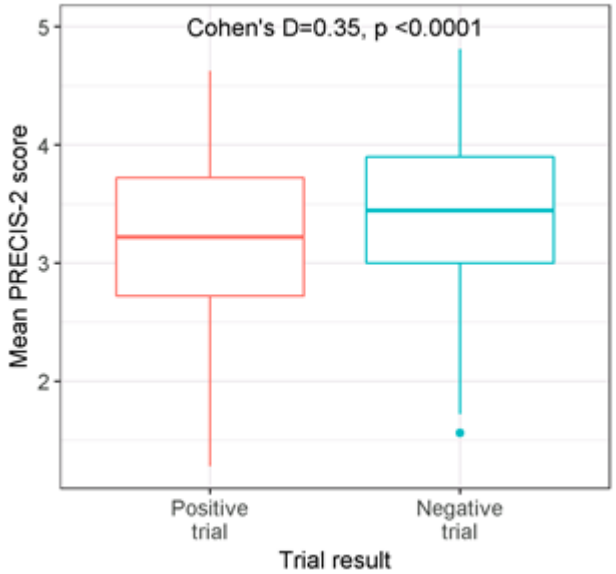
| | N (%) | PRECIS score | Cohen's D | p-value |
|---|---|---|---|---|
| **Funding** | | | | 0.38 |
| **Public only** | 210 (39.3) | 3.34 (0.71) | Ref | |
| **Industry only** | 215 (40.3) | 3.25 (0.69) | -0.13 | |
| **Public and Industry** | 109 (20.4) | 3.30 (0.60) | -0.07 | |

Values are mean (SD) unless otherwise stated

# Trial results

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

| | PRECIS-2 | Cohen's D |
|---|---|---|
| **Positive for 1$^{o}$ endpoint** | 3.17 (0.70) | 0.36 |
| **Neutral for 1$^{o}$ endpoint**<br>**Positive for 2$^{o}$ endpoints** | 3.38 (0.67) | 0.07 |
| **Neutral trial** | 3.42 (0.66) | -ref- |




Values are mean (SD) unless otherwise stated

# Trial results

- Pragmatism increased moderately over time
- Proportion of RCTs with positive results remained fairly stable
  - 65%, 62%, 55 %, and 62% respectively in RCTs from 2000, 2005, 2010, 2015
- Positive trials had lower PRECIS-2 compared to neutral trials, but Cohen *d* effect size of 0.36 denotes **small** difference in pragmatism

Sepehrvand et al. JAMA Cardio 2020

# Women in CV RCTs

- 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

Nguyen et al. Circ CQO 2018
Gong et al. Can J Cardiol 2019
Scott et al. JACC 2018

# Change in enrollment of women in RCT

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

| | N (%) | Female % (SD) | Effect size: Cohen's D | p-value |
|---|---|---|---|---|
| **Year** | | | | |
| **2000** | 168 (27.9) | 28.5 (20.2) | Ref | <.0001 |
| **2005** | 161 (26.7) | 30.7 (20.1) | 0.11 | |
| **2010** | 134 (22.3) | 34.0 (20.0) | 0.28 | |
| **2015** | 139 (23.1) | 35.8 (17.9) | 0.38 | |

Sepehrvand et al. CJC 2020

# Women in RCTs: disease states

- proportion of women enrolled varied among different CV fields

| | N (%) | Female % (SD) | Cohen's D | p-value |
|---|---|---|---|---|
| CAD | 256 (42.5) | 25.5 (16.2) | ref | <.0001 |
| HF | 79 (13.1) | 27.3 (20.6) | 0.10 | |
| Arrhythmia | 76 (12.6) | 31.8 (15.5) | 0.39 | |
| Stroke | 20 (3.3) | 46.2 (7.9) | 1.32 | |
| HTN | 28 (4.6) | 51.9 (22.7) | 1.57 | |
| Dyslipidemia | 15 (2.5) | 41.3 (23.7) | 0.95 | |
| Others | 128 (21.3) | 40.3 (21.2) | 0.83 | |

# Type of intervention

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

| | N (%) | Female % (SD) | Cohen's D | p-value |
|---|---|---|---|---|
| Type of Intervention | | | | |
| Medication | 334 (55.5) | 32.7 (21.8) | ref | 0.0279 |
| Device/procedural | 190 (31.6) | 29.2 (14.2) | 0.18 | |
| Health system | 78 (13.0) | 35.7 (21.6) | 0.14 | |

# 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

| | N (%) | Female % (SD) | Cohen's D | p-value |
|---|---|---|---|---|
| **Pragmatic*** | | | | 0.35 |
| No | 497 (82.6) | 31.7 (19.8) | ref | |
| Yes | 105 (17.4) | 33.6 (19.6) | 0.10 | |

# Funding

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

| | N (%) | Female % (SD) | Cohen's D | p-value |
|---|---|---|---|---|
| **Funding** | | | | 0.45 |
| **Private only** | 213 (40.6) | 31.2 (16.1) | ref | |
| **Public only** | 205 (39.1) | 33.4 (21.7) | 0.12 | |
| **Public and Private** | 106 (20.2) | 32.9 (19.6) | 0.10 | |

# Summary (1)

- 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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- Faster recruitment
- Comparison w/ real-word alternatives
- Clinically-important outcomes
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*much of this remains to be clearly demonstrated

# Summary (2)

- 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