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Pragmatic clinical trials in cardiovascular medicine: trends over time in major medical journals

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Background: Pragmatic trials provide results that may be more applicable to the population in which the intervention will be eventually applied and are discussed extensively in the current healthcare environment. The aim of this study was to investigate how pragmatic or explanatory cardiovascular (CV) randomized controlled trials (RCT) are, if this was changing over time, and if they were more or less likely to meet their primary endpoint.

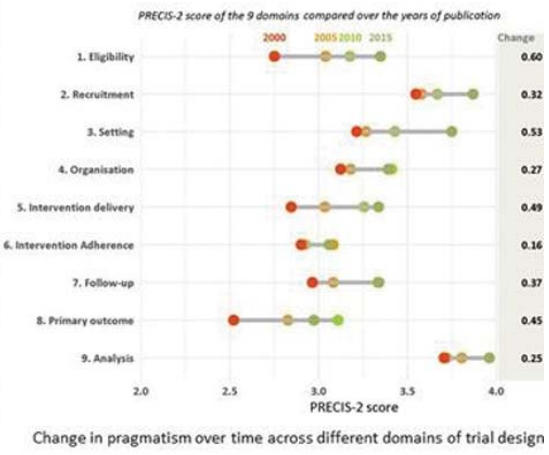
Methods: Using the six top-ranked (based on impact factors) medical and CV journals, all CV-related RCTs that were published during the years of 2000, 2005, 2010 and 2015 were identified, data extracted and reviewed by 2 adjudicators. The PRECIS-2 tool was used to evaluate the level of pragmatism. PRECIS-2 uses a 5-point ordinal scale (ranging from very pragmatic to very explanatory) across 9 domains of trial design, including eligibility, recruitment, setting, organization, intervention delivery, intervention adherence, follow-up, primary outcome, and analysis. A higher score indicates a more pragmatic score on an individual domain, and aggregated scores are a simplified formula across all domains. Cohen's D was used to quantify the mean difference relative to the variation.

Results: There were 616 RCTs, distributed evenly over the 2 decades, and 64% achieved their primary endpoint. The mean (±SD) PRECIS-2 score was 3.26±0.70 among 616 included RCTs. The level of pragmatism increased over time from a score of 3.07±0.74 in 2000 to 3.47±0.67 in 2015 ($p<0.0001$ for trend; Cohen's D relative effect size 0.57). The increase in pragmatism occurred mainly in the domains of eligibility, setting, intervention delivery, and primary endpoint (Figure). PRECIS-2 score was higher for neutral trials than those with positive results (p=0.0015) and in phase III/IV trials as compared to phase I/II trials ($p<0.0001$) (Figure). Furthermore, trials that involve more sites, with larger sample sizes, longer follow-ups, and those with mortality as the primary endpoint were found to be more pragmatic. There was no difference in the level of pragmatism between different sources of funding (public, industry, or both; p=0.52).

Conclusion: The PRECIS-2 tool can be used for appraising trials to assess their placement in the pragmatic-explanatory continuum. The level of pragmatism increased over time in CV trials. Greater focus on the design and delivery of CV trials will be required for the broad application.

Factors		N (%)	Mean PRECIS Score (SD)	Effect size: Cohen's D	P-value
Overall		616 (100)	3.26 (0.70)		
Year of publication	2000	172 (28)	3.07 (0.74)	Ref	<.0001
	2005	168 (27)	3.21 (0.64)	0.21	
	2010	136 (22)	3.36 (0.66)	0.42	
	2015	140 (23)	3.47 (0.67)	0.57	
Type of funding	Public only	213 (35)	3.33 (0.71)	Ref	0.52
	Industry only	199 (32)	3.27 (0.69)	-0.10	
	Public + Industry	122 (20)	3.28 (0.62)	-0.07	
	Not determined	82 (13)			
Phase of trial	I/II	246 (40)	2.97 (0.67)	Ref	<.0001
	III/IV	354 (57)	3.47 (0.64)	0.78	
	Unclear	16 (3)			
Trial result	Positive for 1^0 endpoint	396 (64)	3.19 (0.70)	-0.32	0.0015
	Not positive 1^0 but positive 2^0	50 (8)	3.36 (0.69)	-0.08	
	Neutral trial	170 (28)	3.41 (0.65)	Ref	

Study characteristics and pragmatism



Change in pragmatism over time across different domains of trial design