Critical Appraisal of Non-Inferiority Randomized Controlled Trials

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Non-inferiority (NI) randomized controlled trials (RCTs) are becoming increasingly popular types of clinical trials, particularly in cardiovascular, infectious disease, and oncology research. In this issue of the Journal, the Evidence-Based Practice Review Section includes our first critical appraisal of a NI trial. A brief primer on NI trials is included below to complement the critical appraisal. We base our NI trial appraisal on the concepts in the JAMA Users' Guide to the Medical Literature: How to use a Noninferiority Trial.[1] Further details can be found in this Users' Guide reference.

The purpose of traditional RCTs is to determine whether a new therapy is superior to a placebo or an active control. However, NI trials are different, in that their purpose is to examine whether a new therapy is non-inferior or "not that much worse" than the comparison. The new therapy in a NI trial should offer some type of advantage, such as, decreased toxicity or greater convenience, relative to the standard therapy.

Most NI trials have an objective to examine an efficacy outcome. With this objective, the comparison arm should be an active control that is the gold standard therapy for the condition being treated. However, more recently, NI trials have also been designed with the objective of assessing whether a new therapy is "not that much more harmful", and these have typically evaluated cardiovascular harms compared to a placebo control.

Three key pointers to critically appraise a NI trial differently than a traditional superiority RCT include examining whether the study has been designed to ensure that:

1. The target population, comparison arm, and outcomes measured are chosen optimally, rather than chosen to find a minimal difference between the new therapy and the comparison (that is, biased towards a NI conclusion);

2. The analysis is conducted as both intention to treat (which is biased towards a NI conclusion) and per protocol (a biased analysis in general, but less likely to falsely conclude NI), with minimal difference in results between both types of analyses; and

3. The NI margin (how much worse the new therapy can be) is clinically reasonable, and does not allow excessive harm, or excessive loss of benefit with the new therapy. Often statistically derived NI margins are too large to be clinically reasonable to clinicians and patients.

We hope these pointers will help readers become comfortable with critically appraising and using NI trials in their practice.

About the Section Editor

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Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis (PRECISION)

Citation: Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. N Engl J Med 2016;375:2519-29

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Patient Population: Adult patients diagnosed with osteoarthritis (OA) and/or rheumatoid arthritis (RA) requiring treatment with a nonsteroidal anti-inflammatory drug (NSAID) for at least 6 months were included. Participants were required to have an established or be at increased risk for cardiovascular disease.

Intervention: The intervention group received celecoxib 100 mg twice daily (n=8,072; mean daily dose, 209 mg).

Comparison: The control group received either ibuprofen 600 mg thrice daily (n=8,040; mean daily dose, 2045 mg) or naproxen 375 mg twice daily (n=7,969; mean daily dose, 852 mg).

Outcome: The primary composite outcome was measured by the number of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The mean treatment duration was 20.3 months and the mean follow-up time was 34.1 months.

Trial Validity	Risk of Bias		
START OF TRIAL	High	Possible / Unclear	Low
Randomization / Concealment			
• A random 1:1:1 assignment to celecoxib 100 mg BID, ibuprofen 600 mg TID, or naproxen 375 mg BID was done using a computerized randomization system. Randomization was stratified according to the primary diagnosis (OA and/or RA), aspirin use, and geographic region. If a patient was diagnosed with both OA and RA, s/he was stratified to the RA group. • Allocation concealment was not discussed in the article.		X	
Baseline Characteristics			
• The baseline characteristics between the three groups were well matched. • Patients were on average 63 years old. The majority of patients were female (64.1%), white (74.6%) and diagnosed with OA (90.0%). At the time of randomization, some participants were concurrently taking aspirin (45.9%) and statin (53.9%), and these patients were equally distributed across the three arms. Other reported comorbidities included diabetes (35.3%), hypertension (77.8%), and dyslipidaemia (62.5%). About 23% of study participants had established cardiovascular disease. On average, patients had good renal function with a serum creatinine level of 0.9 mg/dl.			X

Comparison Arm			
• Naproxen was associated with less cardiovascular risk based on limited data. Ibuprofen is one of the widely used NSAIDs for pain control in arthritis and many other conditions. • Comparing celecoxib with these two drugs seems reasonable.			X

DURING TRIAL	High	Possible / Unclear	Low
Blinding			
• The patients, clinicians, and outcome assessors were blinded. The authors did not discuss the blinding of the data collectors and data analysts.			X
Equal Treatment			
• Patients in the ibuprofen and naproxen groups were allowed to uptitrate their doses regardless of OA or RA diagnosis. However, per study protocol, dose escalation of celecoxib was allowed in patients with RA, but not those diagnosed with OA. About 90% of study subjects were diagnosed with OA; those who were allocated to the celecoxib group would not have received dose titration like those in the ibuprofen or naproxen groups. More patients in the celecoxib group reported insufficient clinical response potentially due to suboptimal dosing, which may have caused a bias towards non-inferiority. • Contamination could have been an issue. Ibuprofen and naproxen were available over-the-counter; therefore, patients in the celecoxib group might add ibuprofen or naproxen to the study drug. However, any measures to avoid contamination were not discussed in the study. • Co-intervention could have been an issue. Equal percentages of patients received statin (54%) and aspirin (45%) across the three arms at baseline; however, the status of taking these medications during the trial was not assessed. Additionally, aspirin has been shown to decrease antiplatelet effect when used with nonselective NSAIDs. If patients were on aspirin for primary CV prevention, this known drug-drug interaction between aspirin and nonselective NSAIDs could have negatively affected the study outcome within the comparison groups.	X		

END OF TRIAL	High	Possible / Unclear	Low
Completeness of Outcome Data			
• Of the 8000 patients randomized to each group, about 5000 had stopped taking the assigned therapy (68.8%) by the end of the study. Although patients who discontinued the study drug were still followed, roughly, 22.9% of the randomized patients either withdrew consent in writing (8.3%), verbally expressed unwillingness to continue participation (7.4%), or were lost to follow-up (7.2%). These subjects who remained event-free were assumed to be alive using the last observation carried forward. The percentage of missing data is greater than the absolute risk difference of the primary endpoint (0.2% for celecoxib vs. naproxen, and 0.4% for celecoxib vs. ibuprofen), which may have contributed to a bias towards non-inferiority.	X		
Method of Outcome Analysis			
• Both intention-to-treat (ITT) and on-treatment analyses were performed, as recommended for non-inferiority studies. • Patients who took at least one dose of the study drug and had at least one post-baseline follow-up visit that wer included in the final on-treatment analysis. This allowed the majority of the study participants to be included in the on-treatment analysis in spite of the high therapy discontinuation rate (68.8%) and the follow-up discontinuation rate (30%). Similar outcome event rates were reported in both ITT and on-treatment analyses.			X
Non-inferiority Margin			
• The non-inferiority margin (<1.40) was defined to allow up to 40% more primary outcome events in the celecoxib group. With 2% of the estimated annual cardiac event rate, this means that the study was designed to accept 8 additional CV-related events per 1000 patients as non-inferior. Given the seriousness of an outcome, adjusting the non-inferiority margin to less than 1.20 would have been more appropriate. • Additionally, the actual annual cardiac event rate was 1% with the recruited study population. By including the low CV risk population (instead of the high-risk patients as the trial originally intended), it is premature to conclude that celecoxib carries no worse CV risk compared to naproxen or ibuprofen.		X	

Trial Result of Intention-to-Treat Population

Safety Outcome	Celecoxib N = 8072	Naproxen N = 7969	Ibuprofen N = 8040	Celecoxib vs. Naproxen			Celecoxib vs. Ibuprofen		
				Hazard Ratio (HR) and 95% Confidence Interval (CI)	Relative Risk Reduction (RRR)	Absolute Risk Reduction (ARR)	HR (95% CI)	RRR	ARR
Primary Endpoint									
Death by CV cause, nonfatal MI, and nonfatal stroke**	188 (2.3%)	201 (2.5%)	218 (2.7%)	0.93 (0.76-1.13) P<0.001*	7.7%	0.2%	0.85 (0.70-1.04) P<0.001*	14.1%	0.4%
Secondary and Tertiary Endpoints									
Major adverse CV events***	337 (4.2%)	346 (4.3%)	384 (4.8%)	0.97 (0.83-1.12) P = 0.64	3.8%	0.2%	0.87 (0.75-1.01) P = 0.06	12.6%	0.6%
GI events	86 (1.1%)	119 (1.5%)	130 (1.6%)	0.71 (0.54-0.93) P = 0.01	28.7%	0.4%	0.65 (0.50-0.85) P = 0.02	34.1%	0.6%
Renal events	57 (0.7%)	71 (0.9%)	92 (1.1%)	0.79 (0.56-1.12) P = 0.19	20.7%	0.2%	0.61 (0.44-0.85) P = 0.04	38.3%	0.4%

Trial Result of On-Treatment Population

Safety Outcome	Celecoxib N = 8030	Naproxen N = 7933	Ibuprofen N = 7990	Celecoxib vs. Naproxen			Celecoxib vs. Ibuprofen		
				HR (95% CI)	RRR	ARR	HR (95% CI)	RRR	ARR
Primary Endpoint									
Death by CV cause, nonfatal MI, and nonfatal stroke**	134 (1.7%)	144 (1.8%)	155 (1.9%)	0.90 (0.71-1.15) P<0.001*	8.1%	0.2%	.81 (0.65-1.02) P<0.001*	14.0%	0.3%
Secondary and Tertiary Endpoints									
Major adverse CV events***	247 (3.1%)	253 (3.2%)	284 (3.6%)	0.95 (0.80-1.13)	3.6%	0.1%	0.82 (0.69-0.97)	13.5%	0.5%
GI events	54 (0.7%)	115 (1.4%)	115 (1.4%)	0.45 (0.33-0.63)	53.6%	0.8%	0.44 (0.27-0.68)	53.3%	0.8%
Renal events	42 (0.5%)	62 (0.8%)	73 (0.9%)	0.66 (0.44-0.97)	33.1%	0.3%	0.54 (0.37-0.80)	42.7%	0.4%

CV=cardiovascular, GI=gastrointestinal, MI=myocardial infarction

*P-value for non-inferiority; other P-values for superiority. **The primary composite endpoint included death from cardiovascular cause, nonfatal myocardial infarction, and nonfatal stroke. This composite endpoint is also known as the antiplatelet trialists collaboration (APTC) outcome.

***Major cardiovascular adverse events include each component of the APTC outcome plus coronary revascularization or hospitalization for unstable angina or transient ischemic attack (TIA).

The primary composite outcome included death from CV causes, nonfatal MI, or nonfatal stroke. Each individual component of the composite outcome was reported separately. Celecoxib was also found to be non-inferior to ibuprofen for each outcome component. Overall, the result of the composite outcome suggested that the potential CV risk associated with celecoxib may not be greater than that seen with naproxen or ibuprofen. The upper bound of confidence interval was less than 1.40, as to meet the predefined non-inferiority margin. On-treatment analysis showed celecoxib may be associated with up to 15% higher CV events compared to naproxen, which is still less than the non-inferiority margin (40%).

The trial was primarily focusing on the safety outcomes of celecoxib compared to the other two nonselective NSAIDs, so the efficacy of the therapy in controlling arthritis pain was not well emphasized. The investigators used three different patient-reported outcome measures to assess the anti-arthritic efficacy as an exploratory outcome. These measures were (1) change in global assessment of arthritis, (2) change in visual analog scale (VAS), and (3) change in health assessment questionnaire disability index. The magnitude of changes of most components was not statistically significant. However, the VAS was slightly worse in celecoxib, and more patients in celecoxib were observed with insufficient clinical response compared to other groups, which may suggest a suboptimal dosing of celecoxib.

Trial Applicability	Risk of Bias		
	High	Possible / Unclear	Low
Patient Applicability			
• This study applies to patients who are Caucasian females aged 55 to 75 years old and diagnosed with osteoarthritis (OA) requiring NSAIDs for pain. • The trial originally intended to include high-risk CV patients; however, <25% of patients in the study had established CV disease. Therefore, the study result is applicable to the low CV risk population. • One in 10 patients were diagnosed with rheumatoid arthritis (RA). In general, patients with RA are at higher CV risk compared to those with OA (almost two-fold). In a subgroup analysis of RA patients, the primary endpoint revealed a wide range of confidence interval from 0.5% to 1.6% in both comparing the celecoxib group with ibuprofen and naproxen groups. It is inconclusive to establish CV safety of using celecoxib in RA patients based on this trial result.		X	
Intervention Applicability			
• Celecoxib requires prescription, while both naproxen and ibuprofen are available over-the-counter. Celecoxib may not be as accessible and obtainable for patients because of the cost and inconvenience of having to see a provider to get a prescription.			X
Patient-Important Outcomes Measured			
• The safety outcomes reported in this study included: 1. Primary clinical endpoints directly measuring the number of cardiovascular deaths, nonfatal MIs, or nonfatal strokes 2. Secondary clinical endpoints measuring the number of GI or renal events • An additional endpoint assessing effectiveness of pain control was reported using three different patient-reported outcomes. All the outcomes assessed in this study are clinically relevant.			X
Balance of Benefits vs. Harms			
• Comparable rates of the primary composite outcome occurred in the celecoxib group compared to the naproxen group (2.3% vs 2.5%; HR 0.93, p<0.001 for non-inferiority), and compared to the ibuprofen group (2.3% vs. 2.7%; HR 0.85, p<0.001 for non-inferiority). • Serious GI events were lower in the celecoxib group compared to either group. • Based on these results, the potential CV risk associated with celecoxib may not be greater than that seen with naproxen or ibuprofen, while the celecoxib group may benefit from lower risk of serious GI and renal complications compared to the nonselective NSAIDs. • However, clinicians should be reminded of several issues in the study design, specifically related to the dosing restriction in the celecoxib group resulting in low-dose celecoxib therapy compared to the other treatment groups. • In this trial, the annual CV event rate was 1%, which is lower than expected (2%). One potential explanation for this lower incidence rate is the enrolment of subjects who were at low risk, rather than established or at high risk of CVD.		X	

Health Care Professionals Summary

The trial result only demonstrated the CV safety profile of low-dose celecoxib (200 mg daily) in the low CV risk population diagnosed with OA (90% of studied subjects). In spite of the high discontinuation and follow-up rates, both ITT and on-treatment analysis included the majority of subjects randomized at the beginning of the study. This may have introduced a bias and underestimated the safety events, which could have resulted in the CV-related outcome favoring the celecoxib group. The use of NSAIDs in high-risk patients from a CV safety perspective remains inconclusive.

Patient Summary

All NSAIDs carry a warning on package inserts about increased risk of heart attack and stroke. The PRECISION trial attempted to investigate whether the cardiac-related outcomes (death from cardiac cause, nonfatal heart attack, or stroke) were similar in patients receiving celecoxib compared to either naproxen or ibuprofen. Overall, it is safe to use low-dose celecoxib (200 mg daily) for patients with OA who did not have any previous cardiac events, such as a heart attack. However, it is unclear whether the use of celecoxib in patients with high risk of cardiac events would be as safe as using either naproxen or ibuprofen.

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