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An analysis of randomized controlled trials underpinning ST-elevation myocardial infarction management guidelines

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ABSTRACT

Background: The fragility index (FI) is calculated by iteratively changing one outcome "event" to a "non-event" within a trial until the associated p-value exceeds 0.05.
Purpose: To investigate the FI and fragility quotient (FQ) of trial endpoints referenced in the ACCF/AHA/SCAI guidelines in the management of ST-elevation myocardial infarctions. Secondarily, we assess the post-hoc power and risk of bias for these specific outcomes and whether differences exist between adequately and inadequately powered studies on fragility measures.
Basic procedures: All citations referenced in the guideline were screened for inclusion criteria. The FI and FQ for all included trials were then calculated. The Cochrane 'risk of bias' Tool 2.0 was used to evaluate the likelihood and sources of bias in the included trials.
Main findings: Forty-two randomized controlled trials were included for assessment. The median FI was 10 with a FQ of 0.0055. Seven trials were at a high risk of bias, all due to bias in the randomization process. Fifteen trials were found to be underpowered. Adequately powered studies had higher FIs and FQs compared to underpowered studies.
Principal conclusions: Our findings support the use of FI and FQ analyses with power analyses in future methodology of randomized control trials. With understanding and reporting of FI and FQ, evidence of studies can be readily available and quickly eliminate some readers' concern for possible study limitations.

1. Introduction

Cardiovascular disease is the leading cause of death in the United States. Myocardial infarctions (MI) have affected approximately 735,000 Americans [1,2]. Currently, ST-elevation myocardial infarctions (STEMI) account for 25 to 40% of all MI presentations [3-6], and despite a recent decline in incidence, STEMIs remain at the forefront of cardiovascular attention owing to their high mortality rate [4,7]. To address this prevalent issue, clinical practice guidelines (CPGs) are developed to aid practitioners in the management of STEMI.

The American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) released a CPG for the management of STEMI in 2013 [7] and published a focused update in 2015 [8]. These CPGs detail the class of recommendations (I-III) and level of evidence (A–C) that support them. The guideline panel provided these assignments as a mechanism for researchers and physicians to evaluate the scientific validity of the evidence that underpin each recommendation. Recommendations comprising the STEMI CPG are substantiated by various study designs; however, randomized controlled trials (RCTs) represent the gold standard for assessing intervention effectiveness [9-12]. Recent studies have challenged the value of RCTs due to potential flaws in design, implementation, and reporting [13-15]. Schulz et al. purported that trials with inadequate or unclear reporting yielded larger treatment effects compared to adequately reported trials [16]. Likewise, sample size can bias RCT results, as smaller sample sizes have been associated with overestimated treatment effects [17,18]. While much attention has been devoted to the quality, design, and sample size in RCTs, little is known about the robustness of trial results [14,19-24].

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In this study, we apply the Fragility Index [25] (FI) and the Fragility Quotient [26] (FQ) to determine the robustness of the RCT outcomes that underpin recommendations set forth by the ACCF/AHA/Society for Cardiovascular Angiography and Interventions (SCAI). The FI estimates the number of events required to change a statistically significant outcome to a non-significant outcome. The FI is calculated by iteratively changing one outcome "event" to a "non-event" within a trial until the associated p-value exceeds 0.05. A small FI indicates a more fragile trial outcome, whereas a large FI indicates a more robust trial outcome. The FQ was calculated by dividing the FI by total sample size. The FQ is reported as a decimal between 0 and 1 with a smaller FQ indicating a less robust FI (i.e., a small FI relative to sample size) while a larger FQ indicates a more robust FI (i.e., a large FI relative to sample size). Our study uses the FQ to assess a trial's FI irrespective of its sample size. The FQ is calculated by dividing the FI by the sample size and provides another means to interpret the FI [26]. The FI measures the robustness of the outcome, whereas the FQ measures the robustness of the FI. The FI and FQ enable practitioners to assess the strength of individual trial outcomes underlying guideline recommendations, thus giving them greater confidence in the management and treatment of STEMI. In cases where the FI exceeds the number of participants lost to follow up, statistical significance for that outcome is uncertain.

Given the importance of clinical trials for advancing STEMI management, our primary outcome is to evaluate the FI and FQ of all applicable RCT outcomes from the ACC/AHA/SCAI STEMI practice guidelines. Secondarily, we assess the post-hoc power and risk of bias for these specific RCT outcomes and whether differences exist between adequately powered and underpowered trials on the FI and FQ.

2. Material and methods

This study was not subject to Institutional Review Board oversight since it did not meet the regulatory definition of human subject research as defined in 45 CFR 46.102(d) and (f) of the Department of Health and Human Services' Code of Federal Regulations [27]. We applied relevant Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines [28] for reporting descriptive statistics.

2.1. Eligibility criteria

We obtained all CPGs currently published by the ACC/AHA/SCAI pertaining to ST-elevation myocardial infarction (STEMI) and extracted all RCTs cited as the supporting evidence for the recommendations. We screened all RCTs for inclusion. For an RCT to qualify for inclusion it had to contain 2 arms or have used a 2-by-2 factorial design. Each study contained a 1:1 random assignment of participant to condition and reported at least 1 statistically significant dichotomous outcome ($p < 0.05$).

2.2. Full-text screening and data extraction

Two investigators (CM and AB) performed a pilot test of a devised extraction form to ensure uniformity and clarity. Following the pilot test, CM and AB dually extracted and validated all data. Each author was blinded to the responses of the other. Any disagreements were resolved by consensus. Only the significant, dichotomous outcomes reported in the CPGs were analyzed.

We extracted the following for the included trial outcomes: year of trial publication, sample size in each arm, number of patient events in each arm, number lost to follow up in each arm, associated p-value, the primary outcome of the RCT, statistical test(s) used, and the number of times the RCT has been cited using the Web of Science, Science Citation Index.

2.3. Fragility index and quotient evaluation

The FI for each endpoint was calculated according to the method described by Walsh et al. [25]. We iteratively added events to the group with the smaller number of events, while subtracting non-events to keep the total number of participants constant. The smallest number of additional events added to that smaller group that obtained a p-value ≥ 0.05 represented the FI. The FQ was then calculated by dividing the FI by the sample size of that trial [26]. An online calculator is available at https://clincalc.com/Stats/FragilityIndex.aspx.

2.4. Risk of bias evaluation

Using the Cochrane Risk of Bias Tool 2.0 (ROB 2.0), we evaluated the risk of bias in the included trials. ROB 2.0 addresses the lack of clarity and uniformity in risk of bias assessments derived from the previous tool. Additionally, the new tool shifts focus of risk of bias judgements from the clinical trial to the trial outcome [29]. Furthermore, ROB 2.0 contains decision algorithms to limit subjectivity in assigning bias judgements. The scaling is modified: the unclear risk of bias option has been replaced with "some concerns". ROB 2.0 redefined and standardized the bias domains, which now include (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result.

Prior to performing the ROB evaluation, MV, CM, and AB read the ROB 2.0 test manual and viewed all training videos from the Cochrane Collaboration. Afterward, a pilot test evaluating a subset of trials was conducted, during which each bias judgment was discussed in depth. This training was structured to be consistent with the intensive risk of bias training of da Costa et al. [30,31], which was found to improve inter-rater reliability over other training methods. Following these training sessions, 3 additional trials were independently evaluated by CM and AB. Results were compared and discrepancies were resolved by consensus. All trials were independently evaluated by both CM and AB, after which the 2 investigators met to resolve discrepancies. MV was available for third-party adjudication.

2.5. Data analysis

Descriptive statistics, including medians, interquartile ranges, and correlations were calculated using Microsoft Excel. Before we analyzed the FI of each study, we recalculated the p-values of the included dichotomous outcomes using Fisher's exact test to ensure that the outcome was in fact statistically significant. Since the FI calculator uses Fisher's exact test in its calculation, a nonsignificant outcome by Fisher's exact test would result in an FI of zero. The FI for each study was calculated using the FI calculator located at https://clincalc.com/Stats/FragilityIndex.aspx. The calculator sequentially changes one "event" to a "nonevent" until the calculated statistical significance is lost. The FI is represented by the smallest number of changed events needed to raise the p-value above 0.05. We performed our power analysis of all eligible studies by choosing an exact test family, Fisher's exact test as our statistical test of proportions, and achieved power given each individual studies α, sample size, and effects size *post-hoc* using the G*Power™ software [32]. We calculated effect sizes when necessary, using the event rates of the intervention and control groups of the individual studies.

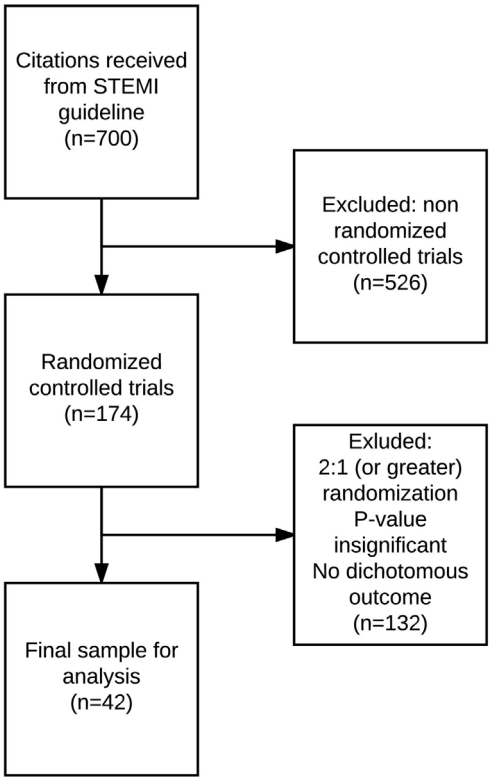

Fig. 1. Flow chart for selection of RCTs.

3. Theory

This is the only study looking at ST elevated myocardial infarction clinical practice guidelines, and only the second study known to date, that has applied both the fragility index and fragility quotient to assess the strength of individual trial outcomes. Future studies using these methods to analyze the soundness of randomized control trials underpinning clinical practice guidelines are warranted.

4. Results

4.1. Study selection

Our search of the STEMI guidelines returned 700 trials supporting the evidence-based guidelines. Trials were then screened for inclusion. Of the 700 trials, 42 met the inclusion criteria (Fig. 1).

4.2. Characteristics of trials and risk of bias

The median sample size of RCTs was 664 (interquartile range [IQR] 500 to 4413), and the median lost to follow-up was 5 (IQR 0 to 18). The median Web of Science Citation Index was 532 (IQR 174 to 1328). All 42 outcomes were listed as the primary outcome for their respective RCTs. For the 42 trials, 10 (23.8%) were at a low risk of bias, 25 (59.5%) had some concerns for bias, and 7 (16.7%) were at a high risk of bias (Table 1). High risk of bias was due to bias in domain 1 (risk of bias from the randomization process) all seven times. Additionally, two studies were also flagged for high risk of bias in domain 2 (risk of bias due to deviations from the intended interventions). Full risk of bias results can be found in Table 1.

4.3. Fragility index and fragility quotient

The median FI for the 42 trials was 10 events (IQR 4 to 21) (Fig. 2). The median FQ for included trials was 0.0055 (IQR 0.0023 to 0.0139) (Fig. 3). Applying the Fisher's exact test nullified statistical significance in 3 trials (7.1%), resulting in an FI of 0. The Science Citation Index values of the 5 most cited studies were 4969 (FI = 21, Power = 0.91), 4282 (FI = 8, Power = 0.75), 2951 (FI = 68, Power = 0.99), 2718 (FI = 0, Power = 0.57), and 2651 (FI = 27, Power = 0.90). The number lost to follow-up was greater than or equal to the FI in 16 (32.2%) trials. Full FI and FQ results can be found in Table 2.

4.4. Power analysis

The median power for our sample was 0.88 (IQR 0.74 to 0.94). Of the 42 studies in our sample, 15 (34.9%) were underpowered (Table 2).

4.5. Fragility and power

Our study found differences between adequately powered trials (defined as $\beta \geq 0.80$) and underpowered trials (defined as $\beta < 0.80$). A Mann Whitney *U* test indicated that adequately powered studies had higher FIs (Median = 17) than underpowered studies (Median = 2) ($Z = -4.54$, $p < 0.001$). Adequately powered studies also had higher FQs (Median = 0.0065) than underpowered studies (Median = 0.0020) ($Z = -3.37$, $p < 0.001$).

5. Discussion

Our analysis of the 42 RCTs that underpin recommendations in the ACA/AHA/SCAI guidelines found a median FI of 10. This result indicates that, on average, if only 10 patients in each trial had experienced a different outcome than recorded, the statistical significance of these trials would be nullified. With a median sample size of 1330 across these trials, this warrants concern. 7.1% (3 of 42) of RCTs had a FI of 0, meaning the statistical significance might be due to choice of statistical test rather than the effect of the chosen intervention. Our study identified the number lost to follow up was greater than or equal to the FI in 16 (32.2%) trials, further highlighting the fragility of these specific outcomes. The participants lost to follow up may have provided enough data to have changed the significance of the outcome.

Compared to previous studies, the FI of trials underlying STEMI guidelines are more robust. Walsh et al. evaluated approximately 399 RCTs from *NEJM*, *The Lancet*, *JAMA*, *BMJ*, and *Annals of Internal Medicine* with their results demonstrated a median FI of 8 [25]. Additionally, a FI of 2 has been reported for studies compromising the literature for spine surgery, sports surgery, critical care, and intracranial hemorrhage [33-36]. The RCT's underlying the STEMI guideline only fall short to studies comprising the literature of diabetes management which had a FI of 16 [37]. Kruse et al. [37] is currently the only literature to report a FQ alongside their FI value. When comparing FQ's, the trials underlying STEMI guidelines are less robust with a FQ of 0.0055 versus a FQ of 0.007 for trials underlying diabetes management.

These trial outcomes, which are the foundation for the ACA/AHA/SCAI guidelines, directly affect clinical practice and evidence-based medicine. While recommendations within guidelines are intended to improve patient care, if they are based on poor evidence, they can possibly lead to adverse patient outcomes. The median citation index of the 42 RCTs is 497 with the top 5 studies having indices of 4969 (FI = 21), 4282 (FI = 8), 2951 (FI = 68), 2718 (FI = 0), and 2651 (FI = 27) times. Concern

Table 1
Risk of bias assessments.

Study title	Risk of bias arising from the randomization process	Risk of bias due to deviations from intended interventions	Risk of bias due to missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall risk of bias
A clinical trial of the angiotensin-converting-enzyme inhibitor Trandolapril in patients with left ventricular dysfunction after myocardial infarction	Some concern	Low risk	Low risk	Low risk	Low risk	Some concerns
Addition of Clopidogrel to Aspirin and Fibrinolytic Therapy for Myocardial Infarction with ST-Segment Elevation	Some concern	Low risk	Low risk	Low risk	Some concerns	Some concerns
Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Beneficial Effects of Immediate Stenting After Thrombolysis in Acute Myocardial Infarction	Some concern	Low risk	Low risk	Low risk	Low risk	Low risk
Clopidogrel with or without Omeprazole in Coronary Artery Disease	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
Combined Angioplasty and Pharmacological Intervention Versus Thrombolysis Alone in Acute Myocardial Infarction (CAPITAL AMI Study)	Some concern	Low risk	Low risk	Low risk	Low risk	Low risk
Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation	Some concern	Low risk	Low risk	Low risk	Low risk	Low risk
Effect of Early, Pre-Hospital Initiation of High Bolus Dose Tirofiban in Patients With ST-Segment Elevation Myocardial Infarction on Short- and Long-Term Clinical Outcome	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
Effects of Fondaparinux on Mortality and Reinfarction in Patients With Acute ST-Segment Elevation Myocardial Infarction	Some concern	Low risk	Low risk	Low risk	Some concerns	Some concerns
Enoxaparin versus Unfractionated Heparin with Fibrinolysis for ST-Elevation Myocardial Infarction	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction	Some concern	Low risk	Low risk	Low risk	Low risk	Some concerns
Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomized, multicentre trial	High risk	Low risk	Low risk	Low risk	Low risk	High risk
Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes	Some concern	Low risk	Low risk	Low risk	Low risk	Some concerns
Percutaneous Coronary Intervention in Patients Receiving Enoxaparin or Unfractionated Heparin After Fibrinolytic Therapy for ST-Segment Elevation Myocardial Infarction in the ExTRACT-TIMI 25 Trial	Some concern	Low risk	Low risk	Low risk	Low risk	Some concerns
Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomized controlled trial	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Routine Early Angioplasty after Fibrinolysis for Acute Myocardial Infarction	High risk	Low risk	Low risk	Low risk	Low risk	High risk
Routine invasive strategy within 24 h of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomized controlled trial	Some concern	Low risk	Low risk	Low risk	Some concerns	Some concerns
Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes	Some concern	Low risk	Low risk	Low risk	Some concerns	Some concerns
A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias.	High risk	Low risk	Low risk	Low risk	Some concerns	High risk
A Randomized Comparison of Antiplatelet and Anticoagulant Therapy after the Placement of Coronary-Artery Stents	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bivalirudin during Primary PCI in Acute Myocardial Infarction	Some concern	Low risk	Low risk	Low risk	Low risk	Some concerns
Comparison of AngioJet rheolytic thrombectomy before direct infarct artery stenting with direct stenting alone in patients with acute myocardial infarction. The JETSTENT trial.	Some concern	Low risk	Low risk	Low risk	Low risk	Some concerns

Complete revascularization versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomized controlled trial.	Some concern	Low risk	Low risk	Low risk	Low risk	Some concerns
Early Intensive vs a Delayed Conservative Simvastatin Strategy in Patients With Acute Coronary Syndromes Phase Z of the A to Z Trial	High risk	Low risk	Low risk	Low risk	Some concerns	High risk
Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial.	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: the SWISSI II randomized controlled trial.	Some concern	Low risk	Low risk	Low risk	Low risk	Some concerns
Intensive versus Conventional Glucose Control in Critically Ill Patients	Some concern	Low risk	Low risk	Low risk	Some concerns	Some concerns
Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial–PRAGUE-2.	Some concern	Low risk	Low risk	Low risk	Low risk	Some concerns
Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction.	High risk	High risk	Low risk	Low risk	Some concerns	High risk
Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest.	High risk	Low risk	Low risk	Low risk	Some concerns	High risk
Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction.	Some concern	Low risk	Low risk	Low risk	Some concerns	Some concerns
Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes	Some concern	Low risk	Low risk	Low risk	Some concerns	Some concerns
Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomized trial. Lancet	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Randomized trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group	Low risk	Some concern	Low risk	Low risk	Some concerns	Some concerns
Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial.	Some concern	Low risk	Low risk	Low risk	Some concerns	Some concerns
Randomized Trial of Preventive Angioplasty in Myocardial Infarction	Some concern	Low risk	Low risk	Low risk	Some concerns	Some concerns
The care transitions intervention: results of a randomized controlled trial.	Some concern	Low risk	Low risk	Low risk	Low risk	Some concerns
The Effect of Pravastatin on Coronary Events after Myocardial Infarction in Patients with Average Cholesterol Levels	Some concern	Low risk	Low risk	Low risk	Some concerns	Some concerns
Thrombus aspiration during primary percutaneous coronary intervention improves myocardial reperfusion and reduces infarct size: the EXPIRA (thrombectomy with export catheter in infarct-related artery during primary percutaneous coronary intervention) prospective, randomized trial	Some concern	Low risk	Low risk	Low risk	Some concerns	Some concerns
Thrombus aspiration during primary percutaneous coronary intervention.	Low risk	High risk	Low risk	Low risk	Some concerns	Some concerns
Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia.	High risk	Some concern	Low risk	Low risk	Some concerns	High risk

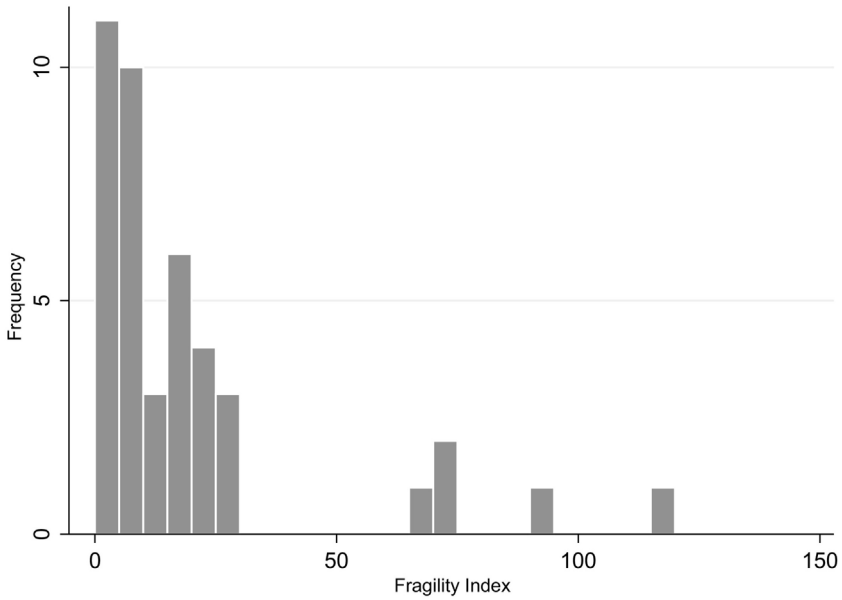

Fig. 2. FI stratified by frequency.

arises when highly cited studies have low FIs, especially an FI of 0, as found in the 4th highest cited study in the guideline. This study provides supporting evidence for the recommendation to begin therapeutic hypothermia as soon as possible in comatose patients with STEMI and out-of-hospital cardiac arrest. The large influence of the studies comprising the ACA/AHA/SCAI guidelines magnifies the need for FI reporting to be implemented on future trials when able.

Currently, there is no widely accepted FI. One reason is the FI must be interpreted using the study's sample size. To address this, we included the FQ that standardizes the FI allowing for greater comparability between trials. The FQ may confirm caution raised by a low FI or show that a small FI is robust when compared to its sample size. For example, a comparison of one study with a FI of 21 and a FQ of 0.10 with a second study which had a FI of 71 and a FQ of 0.0015 shows that the first study, with a smaller FI may be more robust than the second. This example illustrates the need to interpret these metrics together. Therefore, we suggest that the FQ always be reported with the FI for adequate interpretation.

To complement our FI and FQ analysis, we assessed the risk of bias associated with each trial. Flaws in the design, conduct, analysis, and reporting of RCTs can cause underestimation or overestimation of results [29]. Our analysis found 16.7% (7 of 42) trials were at a high risk of bias. The most common bias was baseline imbalances between groups during the randomization process. Baseline imbalances can occur due to problems with the randomization process, chance, or deliberate actions, therefore calling into question the validity of study results [38,39]. Randomization serves the purpose of minimizing bias, balancing the treatment

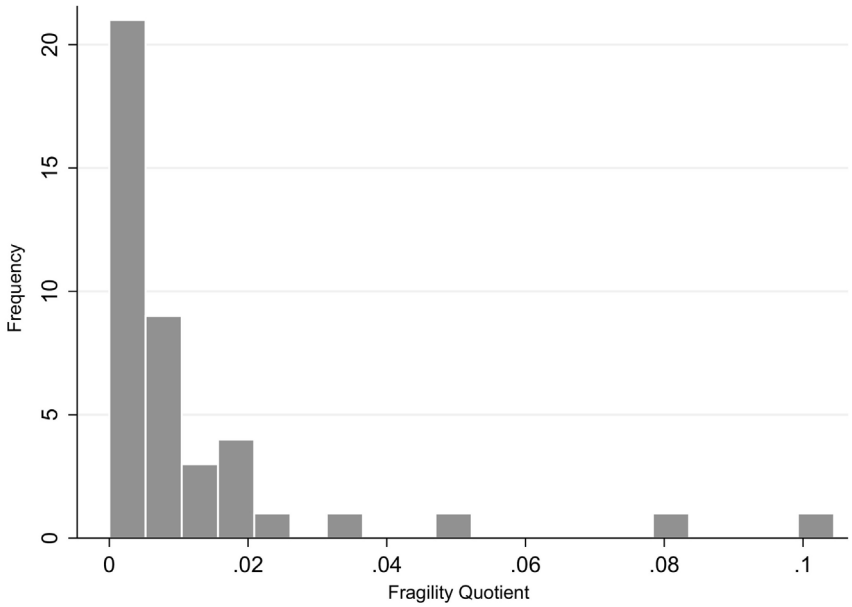

Fig. 3. FQ stratified by frequency.

Table 2
Trial outcome, fragility index, fragility quotient, and power.

Trial	Outcome	Fragility index	Fragility quotient	Power
A clinical trial of the angiotensin-converting-enzyme inhibitor Trandolapril in patients with left ventricular dysfunction after myocardial infarction	Mortality	26	0.0149	0.94
A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias.	Mortality	16	0.0157	0.941
A Randomized Comparison of Antiplatelet and Anticoagulant Therapy after the Placement of Coronary-Artery Stents	The primary cardiac endpoint was a composite measure reflecting death from cardiac causes or the occurrence of myocardial infarction, aortocoronary bypass surgery, or repeated angioplasty	3	0.0058	0.836
Addition of Clopidogrel to Aspirin and Fibrinolytic Therapy for Myocardial Infarction with ST-Segment Elevation	Composite of an occluded infarct-related artery (defined by a Thrombolysis in Myocardial Infarction flow grade of 0 or 1) on angiography or death or recurrent myocardial infarction before angiography.	70	0.0201	0.999
Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial	Composite of death, reinfarction, or stroke;	71	0.0015	0.924
Beneficial Effects of Immediate Stenting After Thrombolysis in Acute Myocardial Infarction	Composite of ischemic events, death, reinfarction, target lesion revascularization	8	0.0491	0.943
Bivalirudin during Primary PCI in Acute Myocardial Infarction	Combination of major bleeding or major adverse cardiovascular events, including death, reinfarction, target-vessel revascularization for ischemia, and stroke (hereinafter referred to as net adverse clinical events) within 30 days.	15	0.0042	0.865
Clopidogrel with or without Omeprazole in Coronary Artery Disease	Composite of overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction, or perforation	9	0.0024	0.967
Combined Angioplasty and Pharmacological Intervention Versus Thrombolysis Alone in Acute Myocardial Infarction (CAPITAL AMI Study)	Composite of death, reinfarction, recurrent unstable ischemia, or stroke at six months.	1	0.0059	0.672
Comparison of AngioJet rheolytic thrombectomy before direct infarct artery stenting with direct stenting alone in patients with acute myocardial infarction. The JETSTENT trial.	ST-segment resolution	1	0.0020	0.636
Complete revascularization versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomized controlled trial.	Composite of all-cause mortality, non-fatal reinfarction, and ischaemia-driven revascularization of lesions in non-infarct-related arteries	9	0.0144	0.895
Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial.	Composite of cardiovascular death, nonfatal myocardial infarction, readmission for ACS, and stroke.	20	0.0044	0.918
Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators	Mortality	8	0.0036	0.751
Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation	Composite of stroke, myocardial infarction, non–central nervous system systemic embolism, or death from vascular causes	17	0.0023	0.7809
Effect of Early, Pre-Hospital Initiation of High Bolus Dose Tirofiban in Patients With ST-Segment Elevation Myocardial Infarction on Short- and Long-Term Clinical Outcome	Major adverse cardiac events at 30 days	1	0.0007	0.61
Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial.	Composite of death, nonfatal acute myocardial infarction, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency rehospitalization	0	0.0000	0.594
Effects of Fondaparinux on Mortality and Reinfarction in Patients With Acute ST-Segment Elevation Myocardial Infarction	Composite of death or reinfarction at 30 day	24	0.0020	0.841
Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: the SWISSI II randomized controlled trial.	Survival free of major adverse cardiac events defined as cardiac death, nonfatal MI, and/or symptom-driven revascularization	21	0.1045	0.999
Enoxaparin versus Unfractionated Heparin with Fibrinolysis for ST-Elevation Myocardial Infarction	Death or nonfatal recurrent myocardial infarction through 30 days	120	0.0059	0.999
Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction	Mortality	17	0.0026	0.807
Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomized, multicentre trial	Composite of death, reinfarction, or refractory ischaemia at 30 days	5	0.0084	0.88
Intensive versus Conventional Glucose Control in Critically Ill Patients	The primary outcome measure was death from any cause within 90 days after randomization	9	0.0015	0.718
Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes	Composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke.	27	0.0065	0.9
Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction: final results of the randomized national multicentre trial: PRAGUE-2.	30-day Mortality	2	0.0025	0.683
Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction.	All-cause mortality	5	0.0127	0.824

(*continued on next page*)

Table 2 (*continued*)

Trial	Outcome	Fragility index	Fragility quotient	Power
Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest.	Favorable Neurologic outcome	5	0.0183	0.79
Percutaneous Coronary Intervention in Patients Receiving Enoxaparin or Unfractionated Heparin After Fibrinolytic Therapy for ST-Segment Elevation Myocardial Infarction in the ExTRACT-TIMI 25 Trial	Mortality	28	0.0060	0.942
Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction.	Composite of death, reinfarction, or urgent revascularization of the target vessel	2	0.0067	0.74
Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomized controlled trial	Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke	5	0.0014	0.704
Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes	Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.	68	0.0050	0.988
Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomized trial. Lancet	In-hospital mortality	5	0.0038	0.812
Randomized trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group	Mortality	3	0.0002	0.668
Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial.	Composite of all-cause death, recurrent myocardial infarction (MI), heart failure, and ischemia-driven revascularization within 12 months.	3	0.0101	0.755
Randomized Trial of Preventive Angioplasty in Myocardial Infarction	Composite of death from cardiac causes, nonfatal myocardial infarction, or refractory angina.	15	0.0323	0.99
Routine Early Angioplasty after Fibrinolysis for Acute Myocardial Infarction	Composite of death, reinfarction, recurrent ischemia, new or worsening congestive heart failure, or cardiogenic shock within 30 days.	10	0.0094	0.883
Routine invasive strategy within 24 h of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomized controlled trial	Combined rate of death, reinfarction, or revascularization at 12 months	11	0.0220	0.998
The care transitions intervention: results of a randomized controlled trial.	Nonelective rehospitalization	0	0.0000	0.6
The Effect of Pravastatin on Coronary Events after Myocardial Infarction in Patients with Average Cholesterol Levels	Death from CVD	21	0.0050	0.907
Thrombus aspiration during primary percutaneous coronary intervention improves myocardial reperfusion and reduces infarct size: the EXPIRA (thrombectomy with export catheter in infarct-related artery during primary percutaneous coronary intervention) prospective, randomized trial	The occurrence of myocardial blush grade $\geq$2	14	0.0800	0.993
Thrombus aspiration during primary percutaneous coronary intervention.	Blush score of 0 or 1	18	0.0168	0.96
Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes	Composite of death from vascular causes, myocardial infarction, or stroke	92	0.0049	0.934
Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia.	Survival till discharge	0	0.0000	0.566

groups on known and unknown prognostic factors, and forming the basis for statistical analysis. Without a proper randomization process, possible confounding factors will likely muddle the true effect of the intervention [40]. Risk of bias in selection of the reported result was the second most common risk of bias identified in our study, mostly due to the failure to specify statistical analysis methods. For example, some authors reported the use of both Fisher's exact test and chi square for dichotomous outcomes but failed to indicate which test was selected a priori to conduct these analyses. Therefore, selection of statistical test based on statistical significance is a concern in such cases.

Our study found a positive correlation between FI and FQ with trial power, further supporting that a fragile trial outcome may be the result of an underpowered study. Studies with sufficient power (>0.8) had a median FI of 17 and FQ of 0.0065, whereas underpowered studies had a median FI of 2 and a FQ of 0.0019. In these underpowered studies, had 2 patient "events" been "nonevents" the study outcome's statistical significance would have been lost. This data is supported by the median FQ illustrating the relatively small median FI of 2 compared to the median sample size.

Although FI and FQ analyses serve as important tools to aid clinicians in interpreting the robustness of randomized trials, however, they, like other metrics, are not without limitations. The FI and FQ can only be used to evaluate RCTs that are randomized in a 1:1 ratio, with two parallel groups, and a statistically significant dichotomous outcome. Additionally, there is no accepted threshold for FI or FQ score that classifies a trial as fragile or robust, thus introducing subjective interpretation of trial results. Future research is warranted to generate a standardized threshold for applying FI and FQ analyses to randomized trials. FI is heavily reliant on Fisher's exact test for statistical significance preventing the use of FI and FQ to analyze continuous variables and tends to provide more conservative calculations than other metrics. Being more prone to Type II errors can result in a trial with a FI of 0, despite exhibiting statistically significant results, as seen in trials where FI exceeds the number of participants lost to follow up indicating a less robust (fragile) trial [40].

6. Conclusion

Our findings support the use of FI and FQ analyses with power analyses in future methodology of RCTs. With understanding and reporting of FI and FQ, evidence of studies can be readily available and quickly eliminate some readers' concern for possible study limitations. Clinicians who turn to evidenced based medicine often have difficulty deciphering statistical significance of trials, which leads to limitations in interpretation of p-values and confidence intervals. Having an easy, understandable way to assess for treatment effectiveness such as FI and FQ, will allow physicians to have more confidence in a trial's results and application to clinical practice. We do caution that this analysis is limited to a restricted set of randomized trials for which dichotomous outcomes were used and for which only 2 groups were randomized. Thus, we do not suggest that our studies accounts for the robustness of all the evidence underpinning guideline recommendations. Nor are we implying that the evidence underpinning these recommendations have poor methodological quality. Thus, we did not intend to evaluate the robustness of the guideline recommendations, only the fragility of statistically significant endpoints of a subset of trials underpinning the STEMI guideline recommendations.

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