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Assessment of Nonfatal Myocardial Infarction as a Surrogate for All-Cause and Cardiovascular Mortality in Treatment or Prevention of Coronary Artery Disease
A Meta-analysis of Randomized Clinical Trials

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+ **Supplemental content**

IMPORTANCE Although nonfatal myocardial infarction (MI) is associated with an increased risk of mortality, evidence validating nonfatal MI as a surrogate end point for all-cause or cardiovascular (CV) mortality is lacking.

OBJECTIVE To examine whether nonfatal MI may be a surrogate for all-cause or CV mortality in patients with or at risk for coronary artery disease.

DATA SOURCES In this meta-analysis, PubMed was searched from inception until December 31, 2020, for randomized clinical trials of interventions to treat or prevent coronary artery disease reporting mortality and nonfatal MI published in 3 leading journals.

STUDY SELECTION Randomized clinical trials including at least 1000 patients with 24 months of follow-up.

DATA EXTRACTION AND SYNTHESIS Trial-level correlations between nonfatal MI and all-cause or CV mortality were assessed for surrogacy using the coefficient of determination (R^2). The criterion for surrogacy was set at 0.8. Subgroup analyses based on study subject (primary prevention, secondary prevention, mixed primary and secondary prevention, and revascularization), era of trial (before 2000, 2000-2009, and 2010 and after), and follow-up duration (2.0-3.9, 4.0-5.9, and $\geq$6.0 years) were performed.

MAIN OUTCOMES AND MEASURES All-cause or CV mortality and nonfatal MI.

RESULTS A total of 144 articles randomizing 1 211 897 patients met the criteria for inclusion. Nonfatal MI did not meet the threshold for surrogacy for all-cause (R^2 = 0.02; 95% CI, 0.00-0.08) or CV (R^2 = 0.11; 95% CI, 0.02-0.27) mortality. Nonfatal MI was not a surrogate for all-cause mortality in primary (R^2 = 0.01; 95% CI, 0.001-0.26), secondary (R^2 = 0.03; 95% CI, 0.00-0.20), mixed primary and secondary prevention (R^2 = 0.001; 95% CI, 0.00-0.08), or revascularization trials (R^2 = 0.21; 95% CI, 0.002-0.50). For trials enrolling patients before 2000 (R^2 = 0.22; 95% CI, 0.08-0.36), between 2000 and 2009 (R^2 = 0.02; 95% CI, 0.00-0.17), and from 2010 and after (R^2 = 0.01; 95% CI, 0.00-0.09), nonfatal MI was not a surrogate for all-cause mortality. Nonfatal MI was not a surrogate for all-cause mortality in randomized clinical trials with 2.0 to 3.9 (R^2 = 0.004; 95% CI, 0.00-0.08), 4.0 to 5.9 (R^2 = 0.06; 95% CI, 0.001-0.16), or 6.0 or more years of follow-up (R^2 = 0.30; 95% CI, 0.01-0.55).

CONCLUSIONS AND RELEVANCE The findings of this meta-analysis do not appear to establish nonfatal MI as a surrogate for all-cause or CV mortality in randomized clinical trials of interventions to treat or prevent coronary artery disease.

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n the 19th century, acute myocardial infarction (MI) resulting from coronary thrombosis was believed to be universally fatal. However, by the beginning of the next century, it was recognized that survival from acute MI was possible although still associated with significant mortality.[1] However, as mortality rates decreased with advances in acute MI management in the second half of the 20th century, the evaluation of new therapies required a different standard.[2] However, as mortality rates decreased with advances in acute MI management in the second half of the 20th century, the evaluation of new therapies became necessary using a different standard.[2] In the early 1990s, Braunwald and colleagues[3] suggested that combining mortality with nonfatal complications might better inform the overall outcomes of experimental therapies, accelerate the pace of evaluating proposed innovations, and minimize the number of patients exposed to ineffective therapies. Nonfatal MI was subsequently incorporated as an end point in landmark studies of acute coronary syndromes and ultimately in almost all studies of treatment or prevention of coronary artery disease based on the assumption that nonfatal MI was a surrogate for mortality and that preventing nonfatal MI would reduce mortality—a belief that endures.[4-10] However, the use of nonfatal MI as a surrogate for mortality has been questioned for not meeting accepted standards for surrogacy.[10-14]

The assertion of surrogacy of one end point for another requires 3 levels of evidence.[15] First, there must be biological plausibility. Although biological plausibility is necessary, it is not sufficient to establish surrogacy.[16] Second, observational or epidemiologic studies demonstrating a consistent association between the surrogate and the final outcome are required. The highest level of proof is trial-level surrogacy in which, across many trials, treatments that improve the surrogate end point also improve the ultimate end point of interest. Establishing trial-level surrogacy requires an analysis of all randomized clinical trials (RCTs), with each trial serving as a unique data point. There is abundant evidence demonstrating that the association between nonfatal MI and all-cause or cardiovascular (CV) mortality meets the first 2 levels of evidence but, to our knowledge, the third and most stringent level of proof has never been assessed. We therefore performed an analysis of RCTs reported over the past approximately 50 years to test the null hypothesis that nonfatal MI is not a surrogate for all-cause or CV mortality by assessing the correlation between the treatment effect of an intervention on nonfatal MI and the treatment effect of the same intervention on all-cause or CV mortality.

Methods

PubMed was searched from inception until December 31, 2020, for RCTs of interventions to treat or prevent the clinical manifestations of coronary artery disease published in *The New England Journal of Medicine*, *JAMA*, or *The Lancet* that reported all-cause mortality and nonfatal MI outcomes (eAppendix in the Supplement). The search was limited to these journals because trials published in the highest-impact journals have higher methodological quality, larger sample sizes, and lower risk of bias.[17] This report follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses protocol (PRISMA-P) and was registered with PROSPERO (CRD42020172341).[18]

Included studies required randomization to an investigational treatment or treatment strategy or a placebo or active control. Investigational treatments or strategies included any pharmacological, imaging, revascularization, or lifestyle intervention aimed at the primary or secondary prevention of coronary artery disease. To maximize precision of the reported treatment effects and the number of events, the inclusion criteria required a minimum sample size of at least 1000 patients with at least 24 months of follow-up.

Two independent investigators (K.O. and D.L.B.) screened trials and determined eligibility for inclusion. Risk of bias was also assessed using the Cochrane Collaboration tool. Trial-level data were then extracted from primary publications. Trial-level data have been previously demonstrated as the highest level of evidence for establishing the validity of surrogate end points.[19,20] Extracted variables included study subject, year of the first patient enrollment, total number of randomized participants, intervention type, control type, median follow-up time, and definition of MI used for outcome adjudication. Outcomes extracted included nonfatal MI, all-cause mortality, and CV mortality. Nonfatal MI data reflected the number of adjudicated MI events based on the definition of MI used in each trial. Most trials used the World Health Organization definition or a universal definition of MI; however, trial-specific definitions were also used.[21-25] If any outcomes data or the definition of nonfatal MI used for adjudication were unavailable in the primary publication, associated publications, or a published protocol, corresponding authors were contacted by email to request the missing data. Trials with missing data and negative response after 60 days (n = 74) were excluded. Negative responses included refusal by investigators (n = 3), no response to request (n = 55), or data declared no longer available (n = 16). The definition of CV mortality was that used in individual RCTs and was generally defined as a composite of sudden cardiac death or death from acute MI, heart failure, stroke, CV procedures, or other CV causes.

Key Points

Question Can nonfatal myocardial infarction be validated as a surrogate end point for all-cause or cardiovascular mortality in the treatment and prevention of coronary artery disease?

Findings In this meta-analysis of 144 randomized clinical trials with data from 1 211 897 patients, surrogacy between nonfatal myocardial infarction and all-cause or cardiovascular mortality was not noted.

Meaning Results of this meta-analysis suggest that treatments that reduce nonfatal myocardial infarction cannot be assumed to reduce all-cause or cardiovascular mortality.
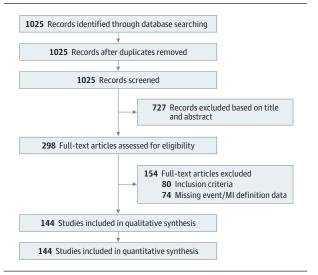
Statistical Analysis

A meta-analysis of summary statistics from each article was performed using Comprehensive Meta-Analysis, version 2.0 (Biostat Inc) software. Estimates of effect for all-cause mortality, CV mortality, and nonfatal MI were calculated from crude event rates with a random-effects model using inverse variance weighting, expressed as odds ratios (ORs) with 95% CIs and presented in forest plots. Data were analyzed according to the intention-to-treat principle. The presence of between-study heterogeneity was determined by the I^2 value (ranging from 0% to 100%) and graded as follows: values less than 25% (low heterogeneity), between 25% and 50% (moderate heterogeneity), and 50% or higher (high heterogeneity).[26] Funnel plots for mortality and nonfatal MI were constructed to assess for publication bias. The Egger test was used to identify asymmetry of funnel plots. The Egger test regresses the standardized effect sizes on their precisions; in the absence of publication bias, the regression intercept is expected to be 0.

To generate a graphic representation of the association between nonfatal MI and all-cause or CV mortality, the log-transformed ORs or hazard ratios (HRs) for nonfatal MI (the putative surrogate) were graphed on the x coordinate with the ORs and HRs for all-cause or CV mortality (the true end point) graphed on the y coordinate, with each trial serving as a unique data point. A horizontal line with slope = 0 indicates no association; a positive slope indicates some degree of positive association, whereas a negative slope indicates a negative association between nonfatal MI and all-cause or CV mortality. We attempted to determine the surrogate treatment effect, defined as the maximum value of the OR for nonfatal MI that needs to be observed in a trial to conclude a significant effect on all-cause or CV mortality. The surrogate treatment effect is determined by the intersection of the upper prediction limit and the horizonal line indicating log OR mortality = 0.

Because positive correlation does not necessarily meet the more stringent criteria for surrogacy, trial-level surrogacy of nonfatal MI for all-cause or CV mortality was assessed by generating a coefficient of determination, R^2 (with 95% CI), between the natural logarithm of the ORs or HRs for nonfatal MI and all-cause and CV mortality using a weighted linear regression in which each study was weighted by the number of observations. The R^2 values (corresponding to the explained variation) fall between 0 and 1.00, with 0 indicating the absence of surrogacy and 1.00 indicating perfect surrogacy. The CI for R^2 was obtained from bootstrap resampling. The threshold for validating nonfatal MI as a surrogate for all-cause or CV mortality was set at 0.8 with the 95% CI excluding 0.6. This predefined threshold was arbitrary but has been used elsewhere.[27] It was determined prospectively to limit post hoc biases. All statistical analyses other than the meta-analysis were performed in R, version 4.0 (R Foundation for Statistical Computing).

Four prespecified subgroup analyses based on study subject, era of the trial, duration of follow-up, and type of control group treatment were performed to investigate their associations with surrogacy. Study subjects included primary prevention, secondary prevention, mixed primary and second-

Figure 1. Preferred Reporting Items for Systematic Review and Meta-analysis Diagram

MI indicates myocardial infarction.

ary prevention, and revascularization trials. The time period was based on the year the first patient was enrolled and divided into 3 eras: before 2000, from 2000 to 2010, and after 2010, corresponding to the adoption of troponin in the universal definition of MI in 2000 and the widespread adoption of commercially available high-sensitive troponins in 2010.[22,28] Duration of follow-up was categorized as 2.0 to 3.9 years, 4.0 to 5.9 years, and 6.0 or more years. Control groups receiving either active or placebo treatments were analyzed separately. For sensitivity analysis, we analyzed only trials that reported time-to-event data presented as HRs.
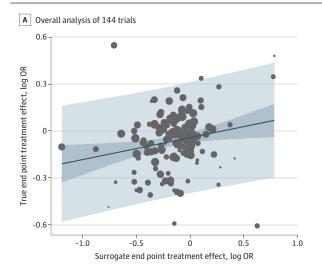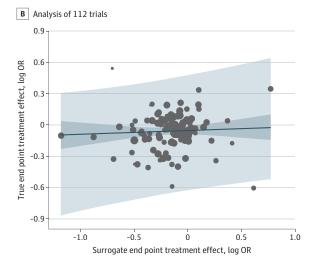
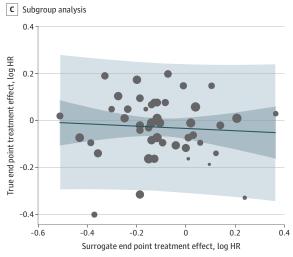## Results

Description of Trials

As illustrated in **Figure 1**, 1025 RCTs were identified for screening, with 298 meeting inclusion criteria. Data extraction was completed for 144 RCTs reflecting 5 726 395 patient-years of follow-up in 1 211 897 patients.[25,29-171] eTable 1 in the Supplement presents the trial-level characteristics of the 144 studies. eTable 2 in the Supplement provides an assessment of risk of bias, and eTable 3 in the Supplement provides the full study names. By study subject, there were 24 primary prevention, 57 mixed primary/secondary prevention, 46 secondary prevention, and 17 revascularization RCTs. By intervention, there were 117 trials of pharmacological agents, 3 trials of imaging strategies, 7 trials of lifestyle interventions, and 17 trials of interventional therapies. By time period, there were 62 trials with first patient enrollment before 2000, 44 trials that began enrollment between 2000 and 2009, and 38 trials that initiated enrollment in 2010 and after. Follow-up duration was between 2.0 and 3.9 years in 66 trials, between 4.0 and 5.9 years in 57 trials, and 6.0 or more years in 21 trials. The earliest included trial was published in May 1972, and the

Figure 2. Correlations of Treatment Effects on Nonfatal Myocardial Infarction (MI) and All-Cause or Cardiovascular Mortality

A, Overall analysis of 144 trials for the association between the logarithm of the odds ratio (log OR) for the surrogate end point of nonfatal MI and the true end point of all-cause mortality. B, Analysis of 112 trials for the association between the log OR for the surrogate end point of nonfatal MI and the true end point of cardiovascular mortality. C, Subgroup analysis of trials reporting hazard ratios (HRs) for the association between the log HR for the surrogate end point of nonfatal MI and the true end point of all-cause mortality. The dark blue area represents the 95% CI for the regression line (solid blue), light blue area represents the 95% prediction interval, and circle sizes are proportionate to the number of observations.

most recent trial was published in November 2020. Cardiovascular mortality was reported in 112 RCTs enrolling 1 023 852 patients. Hazard ratios were reported in 48 trials with 367 531 participants.

In the pooled analysis of the 144 trials, randomized assignment to an investigational treatment reduced the rate of nonfatal MI from 4.2% to 3.7% (OR, 0.87; 95% CI, 0.85-0.90; overall $P < .001$; $I^2 = 58\%$; $P < .001$) and reduced all-cause mortality from 7.3% to 7.0% (OR, 0.95; 95% CI, 0.93-0.97; overall $P < .001$; $I^2 = 53\%$; $P < .001$). Funnel plots were symmetrical for both end points, indicating lack of publication bias. The Egger test did not identify asymmetry for the funnel plot for nonfatal MI (intercept, −0.16; 95% CI, −0.80 to 0.49; $P = .31$) or mortality (intercept, −0.44; 95% CI, −1.02 to 0.14; $P = .07$) (eFigure 1 in the Supplement). eFigure 2 in the Supplement

demonstrates the outcomes of randomized interventions on nonfatal MI and mortality for the 144 RCTs grouped by study subject in ascending chronological order from the date of the first patient enrollment.

Correlations of Treatment Effects
Figure 2A illustrates the log-transformed graphical representation of the OR for nonfatal MI and the OR for all-cause mortality for all 144 trials. Overall, the slope of the regression line was not significantly different than the horizontal (0.09; 95% CI, −0.01 to 0.19), and the coefficient of determination confirmed that the trial-level treatment effect on nonfatal MI did not predict treatment effect on all-cause mortality ($R^2 = 0.02$; 95% CI, 0.00-0.08) (Table). Because the upper bound of the prediction interval never crossed the log

Table. Overall and Subgroup Analyses of the Correlation of Treatment Effects and Coefficient of Determination
of MI for All-Cause and Cardiovascular Mortality

Analysis	Trials	Patients, No.	Regression formula	Slope (95% CI)	P value	R^2 (95% CI)
All-cause mortality	144	1 211 897	−0.02 + 0.09 × log (OR_MI)	0.09 (−0.01 to 0.19)	.07	0.02 (0.00 to 0.08)
Study subject						
Primary prevention	24	352 897	0.001 + 0.12 × log (OR_MI)	0.12 (−0.05 to 0.29)	.14	0.01 (0.001 to 0.26)
Primary-secondary prevention	57	461 329	−0.04 + 0.02 × log (OR_MI)	0.02 (−0.14 to 0.18)	.80	0.001 (0.00 to 0.08)
Secondary prevention	46	351 823	−0.02 + 0.14 × log (OR_MI)	0.14 (−0.11 to 0.40)	.27	0.03 (0.00 to 0.20)
Revascularization	17	45 848	0.04 + 0.28 × log (OR_MI)	0.28 (−0.02 to 0.60)	.07	0.21 (0.002 to 0.50)
Era of first patient enrollment						
<2000	62	461 103	−0.02 + 0.27 × log (OR_MI)	0.27 (0.14 to 0.41)	<.001	0.22 (0.08 to 0.36)
2000-2009	44	397 766	−0.005 + −0.08 × log (OR_MI)	−0.08 (−0.26 to 0.10)	.38	0.02 (0.00 to 0.17)
≥2010	38	353 028	−0.05 + −0.05 × log (OR_MI)	−0.05 (−0.27 to 0.17)	.67	0.01 (0.00 to 0.09)
Length of follow-up, y						
2.0-3.9	66	484 978	−0.02 + 0.04 × log (OR_MI)	0.04 (−0.12 to 0.20)	.61	0.004 (0.00 to 0.08)
4.0-5.9	57	486 054	−0.009 + 0.14 × log (OR_MI)	0.14 (−0.01 to 0.29)	.07	0.06 (0.001 to 0.16)
≥6.0	21	240 865	−0.023 + 0.466 × log (OR_MI)	0.47 (0.12 to 0.81)	.01	0.30 (0.01 to 0.55)
Control arm						
Placebo	86	827 461	−0.02 + 0.09 × log (OR_MI)	0.09 (−0.06 to 0.25)	.23	0.02 (0.00 to 0.10)
Active	58	384 436	−0.03 + 0.10 × log (OR_MI)	0.10 (−0.04 to 0.23)	.16	0.03 (0.00 to 0.13)
Studies reporting time-to-event outcomes	48	367 531	−0.02 + −0.05 × log (HR_MI)	−0.05 (−0.16 to 0.26)	.63	0.01 (0.00 to 0.06)
Studies reporting cardiovascular mortality	112	1 023 852	−0.03 + 0.29 × log (OR_MI)	0.29 (0.13 to 0.44)	.0003	0.11 (0.02 to 0.27)

Abbreviations: HR, hazard ratio; MI, myocardial infarction; OR, odds ratio.

OR_mortality = 0 horizontal, the surrogate treatment effect cannot be calculated, indicating there is no OR achievable by an intervention for nonfatal MI that would predict a significant reduction in the OR for all-cause mortality. Figure 2B shows the log-transformed representation of the OR for nonfatal MI and the OR for CV mortality in 112 trials. The slope of the regression line indicates a positive correlation between nonfatal MI and CV mortality. However, at R^2 = 0.11 (95% CI, 0.02-0.27), the coefficient of determination does not validate nonfatal MI as a surrogate for CV mortality (Table). Because the upper bound of the prediction interval never crosses the log OR_mortality = 0 horizontal, the surrogate treatment effect cannot be calculated, indicating there is no OR achievable by an intervention for nonfatal MI that would predict a significant reduction in the OR for CV mortality. Limiting the analysis to the 48 RCTs that reported HRs, there was no significant difference between the slope of the regression line from the horizontal (−0.05; 95% CI, −0.27 to 0.17) and no evidence of surrogacy (R^2 = 0.005; 95% CI, 0.00 to 0.06) (Figure 2C) (Table).

By study subject, nonfatal MI did not meet the threshold for surrogacy of all-cause mortality in primary prevention (R^2 = 0.01; 95% CI, 0.001-0.26), secondary prevention (R^2 = 0.03; 95% CI, 0.00-0.20), mixed primary and secondary prevention (R^2 = 0.001; 95% CI, 0.00-0.08), and revascularization trials (R^2 = 0.21; 95% CI, 0.002-0.50) (Figure 3) (Table). By time period of the RCT in trials with the first patient enrollment before 2000, the slope of the regression line was significantly greater than the horizontal (0.27; 95% CI, 0.14-0.41), but despite the positive association, nonfatal MI did not meet the threshold for surrogacy of all-cause mortality (R^2 = 0.22; 95% CI, 0.08-0.36). There was no significant

difference in the regression lines from the horizontal and even weaker evidence of surrogacy for periods 2000-2009 (R^2 = 0.02; 95% CI, 0.00-0.17) and 2010 and beyond (R^2 = 0.01; 95% CI, 0.00-0.09) (Figure 4) (Table).
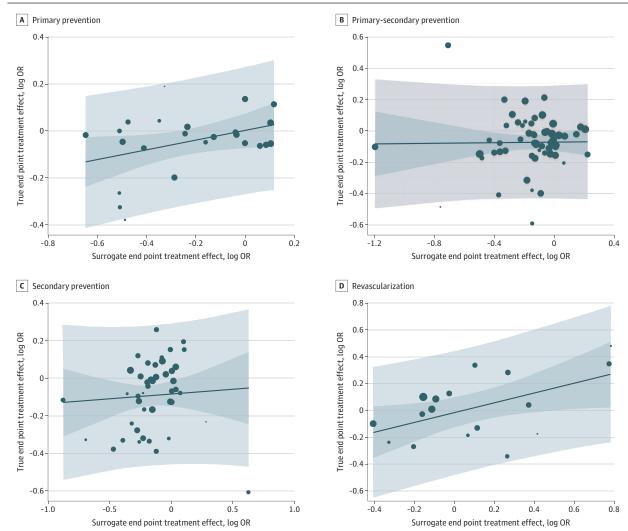
The regression lines were not significantly different from the horizontal line with no evidence of surrogacy of nonfatal MI for all-cause mortality for follow-up length of 2.0 to 3.9 years (R^2 = 0.004; 95% CI, 0.00-0.08) and 4.0-5.9 years (R^2 = 0.06; 95% CI, 0.001-0.16). For follow-up length of 6.0 or more years, there was a significant difference in the slope of the regression line from the horizontal (0.47; 95% CI, 0.12-0.81), but the coefficient of determination did not achieve the threshold for surrogacy (R^2 = 0.30; 95% CI, 0.01-0.55) (eFigure 3 in the Supplement) (Table).

eFigure 4 in the Supplement shows the subgroup analysis based on the type of treatment in the control group (placebo or active therapy). In neither case was the slope of the regression line significantly different than the horizontal, indicating no correlation. Furthermore, R^2 values were 0.02 for placebo and 0.03 for active control, indicating the absence of surrogacy of nonfatal MI for all-cause mortality (Table).

Discussion

Surrogate end points in clinical trials are biological markers or clinical events (eg, nonfatal MI) that may be observed earlier than the clinical end points (eg, death) that are of primary interest to patients and clinicians.[10] Since the earliest descriptions, it has been recognized that the natural history of acute MI includes mortality.[1] It has been assumed, therefore, that interventions to prevent nonfatal MI would reduce all-cause

Figure 3. Subgroup Analysis by Study Subject for the Association Between the Logarithm of the Odds Ratios (Log ORs) for the End Points
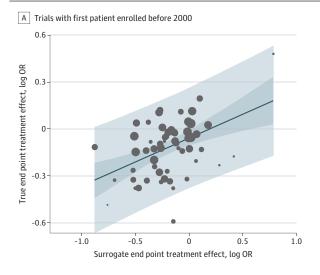

Surrogate end point of nonfatal myocardial infarction and the true end points of all-cause mortality primary prevention (A), mixed primary-secondary prevention (B), secondary prevent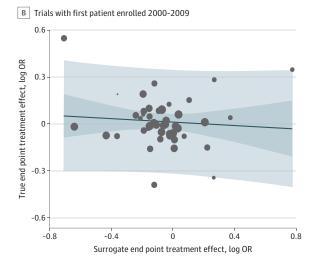ion (C), and revascularization (D). The dark blue area represents the 95% CI for the regression line (solid blue), light blue area represents the 95% prediction interval, and circle size is proportionate to the number of observations.
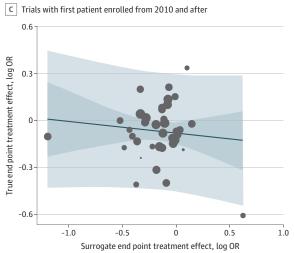
or CV mortality, supporting the notion that nonfatal MI is a surrogate for mortality. However, in this meta-analytic assessment of nonfatal MI surrogacy including 144 RCTs that randomized 1.2 million patients with 5.7 million years of follow-up to interventions to treat or prevent coronary artery disease, we found no trial-level correlation between nonfatal MI and all-cause or CV mortality. The I^2 values for the 144 RCTs included in the meta-analysis revealed significant heterogeneity, which is an advantage in this setting because between-trial differences provide opportunities in subgroup analyses to find more specific settings in which surrogacy exists. However, even in subgroups divided by study subject, study era, duration of follow-up, and control arm treatment, we were unable to detect any evidence of surrogacy. We also found no evidence of surrogacy when limiting the analysis to studies that reported time-to-event data.

There are at least 3 potential explanations for the lack of trial-level surrogacy between nonfatal MI and all-cause or CV mortality. First, over the time course of this study, the extent of myocardial injury required to diagnose nonfatal MI has decreased with the introduction of progressively more sensitive biomarkers. At the same time, background primary and secondary treatments have improved. Thus, more recently detected nonfatal MIs may be so small and secondary prevention treatments so successful that nonfatal MIs are no longer on the causal pathway of mortality. However, even in the earliest era of RCTs prior to 2000 and before the widespread introduction of troponin assays to detect myocardial injury, the R^2 value was only 0.27, which does not meet the threshold for surrogacy. In subsequent eras, from 2000 to 2010 before the introduction of high-sensitivity troponin assays and from 2011 to 2020 after the introduction

Figure 4. Subgroup Analysis by Era of Trial Enrollment for the Association Between the Logarithm of the Odds Ratios (OR) for End Points

Surrogate end point of myocardial infarction (MI) and true end point of all-cause mortality in trials with first patient enrolled before 2000 (A) from 2000 to 2009 (B), and in 2010 and after (C). The dark blue area area represents the 95% CI for the regression line (solid blue). Light blue area represents the 95% prediction interval. Circle size is proportionate to trial size.

of high-sensitivity troponin assays, there was no correlation between the treatment effects on nonfatal MI and all-cause mortality.

Second, it is plausible that the failure to demonstrate surrogacy between nonfatal MI and all-cause mortality relates to the competing risk of non-CV death that CV interventions would not be expected to reduce. In a post hoc analysis of the IMPROVE-IT trial (included in this analysis), the relative incidence of CV and non-CV death following an acute coronary syndrome was investigated.[172] For patients who presented with an ST-segment-elevation MI, the incidence of CV death was higher than non-CV death for 4 years following the index event after which non-CV death predominated. For unstable angina or non–ST-segment elevation MI, the cumulative incidence of CV death remained higher than non-CV death for the entire duration of follow-up (median, 6.0 years). Although similar data for RCTs performed in different settings are lacking,

our subgroup analysis showing no significant surrogacy at 2.0 to 3.9, 4.0 to 5.9, and 6.0 or more years suggests that an increasing risk of non-CV death over time is not a likely explanation for the overall lack of surrogacy. Furthermore, the lack of surrogacy of nonfatal MI for CV mortality further weakens this potential explanation.

The third potential explanation for the lack of surrogacy of nonfatal MI for all-cause or CV mortality relates to the heterogeneous nature of MI. Although the earliest descriptions attributed all acute MIs to coronary thrombosis, by 1939 it was recognized that there were both thrombotic and nonthrombotic causes of acute MI.[1,173] However, it was not until 2007 that an international consensus classification of acute MI subtypes, the universal definition of MI, was published.[23] By the time this classification was revised in 2012[24] and updated in 2018,[174] 5 clinical subtypes of acute MI in addition to the non-MI diagnosis of acute nonischemic

myocardial injury were recognized, each with different pathophysiologic mechanisms and different mortality rates and causes.

The 2 most common MI subtypes are type 1, attributed to atherosclerotic plaque rupture or erosion and secondary thrombosis, and type 2, resulting from an acute imbalance in myocardial oxygen supply and demand without thrombosis. The reported proportion of adjudicated type 2 MI ranges from 2% to 58% of all MI presentations.[175] Physician accuracy in differentiating type 1 from type 2 MI is poor.[176] However, distinction of the 2 categories is important because, in addition to different pathophysiologic characteristics, type 1 and type 2 MIs require different management and have different outcomes.

For type 1 MI, treatment focuses on restoring or maintaining coronary arterial patency pharmacologically or with revascularization. Treatment of type 2 MI focuses on reversing the underlying cause of supply and demand mismatch. In most studies, both short- and long-term mortality are higher in patients with type 2 MI.[176] The increased mortality in patients with nonfatal type 2 MI is associated with their greater burden of comorbidities rather than their underlying coronary disease. Thus, treatments that reduce nonfatal type 2 MI, which is a marker for comorbidities, would not be expected to reduce all-cause or CV mortality and would blunt any potential surrogacy of nonfatal type 1 MI for mortality.

Since its earliest recognition, most treatment and prevention strategies have focused on type 1 MI. Although the development of increasingly sensitive troponin assays over the past decade has increased the diagnosis of acute MI by approximately 50% and allowed the elucidation of the various MI phenotypes, it is unlikely their existence is new.[177] Thus, the application of type 1 MI treatment and prevention strategies to the other MI subtypes is likely an important contributor to the lack of correlation between the effects of treatment for nonfatal MI with the treatment effect for all-cause or CV mortality.

Limitations

There are limitations to this analysis. First, by confining our search strategy to 3 journals, we did not include all potentially relevant RCTs. Second, not all trials identified by our search strategy were included because of the lack of availability of relevant data. However, unlike traditional meta-analyses, the use of nonexhaustive sets of trials are less of a concern as long as the included trials reflect a wide range of heterogeneity of treatment effects.[178] Third, the specific threshold we used to grade the presence of surrogacy has not been externally validated. Others have recommended a threshold of 0.65 for coefficients of determination (R^2).[16] However, it is unlikely that the overall R^2 of 0.02 or even the highest R^2 of 0.30 identified in studies with a follow-up of 6.0 or more years would be interpreted as representing significant surrogacy by any standard.[179] Fourth, the patients enrolled in RCTs may not be representative of the overall population of patients with or at risk for coronary artery disease. Fifth, it is possible that with longer follow-up, especially in primary prevention trials, the R^2 values may have approached the surrogacy thresholds. Sixth, only 3 RCTs provided data on the MI subtypes, which prevented us from evaluating surrogacy as a function of MI subtype.

Conclusions

In this meta-analysis, nonfatal MI, as defined in RCTs of treatment and prevention of coronary artery disease, could not be validated as a surrogate end point for all-cause or CV mortality. Thus, interventions that reduce nonfatal MI cannot be assumed to reduce mortality. Inclusion of nonfatal MI as an end point in RCTs may still be justified based on its association with impaired quality of life and increased use of health care resources, but not based on its surrogacy for mortality.[10]

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