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CLINICAL RESEARCH
Ischaemic heart disease

Effects of initial invasive vs. initial conservative treatment strategies on recurrent and total cardiovascular events in the ISCHEMIA trial

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See the editorial comment for this article 'First and Recurrent Events in the ISCHEMIA trial: Two sides of the Same Coin' by Roxana Mehran *et al.*, https://doi.org/10:1093/eurheartj/ehab603.

Aims The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial prespecified an analysis to determine whether accounting for recurrent cardiovascular events in addition to first events modified understanding of the treatment effects.

Methods and results Patients with stable coronary artery disease (CAD) and moderate or severe ischaemia on stress testing were randomized to either initial invasive (INV) or initial conservative (CON) management. The primary outcome was a composite of cardiovascular death, myocardial infarction (MI), and hospitalization for unstable angina, heart failure, or cardiac arrest. The Ghosh–Lin method was used to estimate mean cumulative incidence of total events with death as a competing risk. The 5179 ISCHEMIA patients experienced 670 index events (318 INV, 352 CON) and 203 recurrent events (102 INV, 101 CON). A single primary event was observed in 9.8% of INV and 10.8% of CON patients while ≥2 primary events were observed in 2.5% and 2.8%, respectively. Patients with recurrent events were older; had more frequent hypertension, diabetes, prior MI, or cerebrovascular disease; and had more multivessel CAD. The average number of primary endpoint events per 100 patients over 4 years was 18.2 in INV [95% confidence interval (CI) 15.8–20.9] and 19.7 in CON (95% CI 17.5–22.2), difference -1.5 (95% CI -5.0 to 2.0, $P = 0.398$). Comparable results were obtained when all-cause death was substituted for cardiovascular death and when stroke was added as an event.

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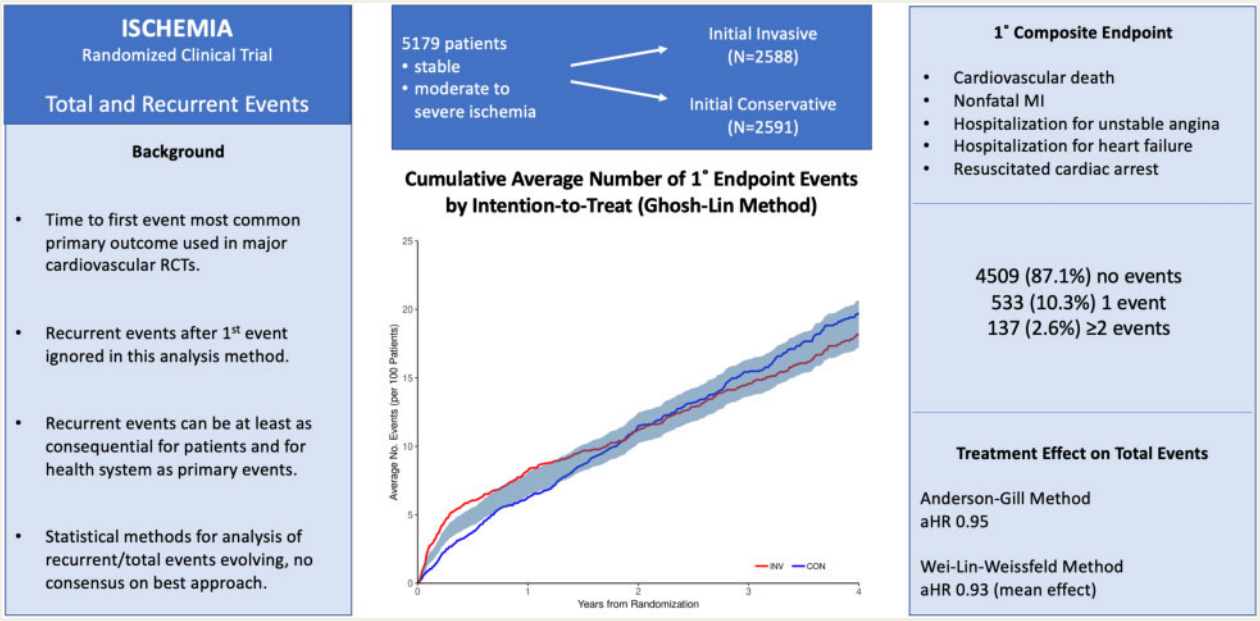
Conclusions In stable CAD patients with moderate or severe myocardial ischaemia enrolled in ISCHEMIA, an initial INV treatment strategy did not prevent either net recurrent events or net total events more effectively than an initial CON strategy.

Clinical trial registration ISCHEMIA ClinicalTrials.gov number, NCT01471522, https://clinicaltrials.gov/ct2/show/NCT01471522.

Graphical Abstract



Recurrent and Total Cardiovascular Events in the ISCHEMIA Trial.

Keywords Chronic ischaemic heart disease • Coronary revascularization • Optimal medical therapy • Stable angina

Introduction

Most large cardiovascular trials are interpreted based on treatment-induced differences in the time from randomization to a primary composite endpoint, which is typically comprised of several different types of adverse events (mortality, morbidity, hospitalizations).[1] This approach counts the first event experienced as signifying the failure of treatment for that patient and therefore intentionally ignores all subsequent events. However, the life course of patients with chronic cardiovascular disease is much more complex than this analysis strategy implies and is often characterized by long periods of disease stability interrupted by repeated episodes of disease progression of varying phenotypes. Recurrent episodes of disease activity can be at least as consequential for patients and for the health system as primary events, with effects on longevity, quality of life, and total cost of care. The prevalent practice of routinely regarding recurrent event information as unnecessary for an adequate understanding of treatment strategies is primarily pragmatic, rather than scientific or clinical. The statistical methods for analysing time-to-first event are very well established, whereas the methods for analysing total events are still evolving and no consensus on a comprehensive and fully satisfactory assessment has emerged.[2,3]

A number of trials of drug therapy in patients with coronary artery disease (CAD) have reported treatment benefits on recurrent events that equalled or exceeded the effects on first events.[4–10] These pharmacological interventions are presumed to produce their treatment benefits by reducing atherosclerotic disease progression and favourably altering plaque pathobiology. Coronary revascularization offers a very different mechanism of benefit from medical therapies that reduce the risk of clinical events. Whether improving coronary blood flow with coronary stenting or coronary artery bypass graft (CABG) surgery might alter the likelihood of repeat events in the setting of modern guideline-directed medical therapy is not clear. In the recently completed International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA), stable CAD patients with moderate or severe myocardial ischaemia were randomized to an initial invasive (INV) or conservative (CON) strategy, with angiography reserved for failure of medical therapy.[11] As part of the ISCHEMIA

research program, we report a prespecified examination of the impact of INV vs. CON on recurrent events and total events.

Methods

Study design and population

The study design and main results of the international ISCHEMIA trial have been published previously.[11,12] A total of 5179 stable patients with moderate or severe myocardial ischaemia were randomly assigned to an initial INV therapy with catheterization, angiography, and revascularization, if feasible, plus optimal medical therapy or to optimal medical therapy alone with cardiac catheterization reserved for patients in whom medical therapy failed. An initial coronary computed tomographic angiography (CCTA) study (with results blinded to site investigators) was performed at baseline in 3783 (73%) patients and was used to rule out significant left main disease and non-obstructive CAD. The median follow-up was 3.2 years.

Trial endpoints

The five-item primary composite endpoint comprised cardiovascular death, myocardial infarction (MI), and hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest. Secondary endpoints included the composite of cardiovascular death or MI; the six-item composite of cardiovascular death, MI, and hospitalization for unstable angina, heart failure, cardiac arrest, or stroke; and a six-item composite with all-cause death, MI, and hospitalization for unstable angina, heart failure, cardiac arrest, or stroke. Non-procedural infarction was defined based on the Third Universal Definition of MI types 1, 2, 4b, and 4c.[13] Procedural infarctions were defined with higher biomarker thresholds than have been previously published.[11] All components of the primary endpoint were adjudicated by an independent clinical events committee whose members were masked to treatment group assignment. For the purposes of the present analysis, when two or more non-fatal events were recorded on the case report form followed by death, each event was counted separately regardless of time between events.

Previously reported trial primary results

As reported previously, a primary outcome event occurred in 318 INV patients and 352 CON patients [time to primary outcome event adjusted hazard ratio (HR) by intention to treat 0.93; 95% confidence interval (CI) 0.80–1.08, $P = 0.34$].[11] The primary outcome Kaplan-Meier curves crossed at ~2.5 years; thus, the proportional hazards assumption of the Cox model was not met and additional comparisons were performed to clarify the time-varying treatment differences. At 6 months, the cumulative primary event rate was 5.3% for INV and 3.4% for CON (difference 1.9%; 95% CI 0.8–3.0%). At 5 years, the cumulative primary event rate was 16.4% for INV and 18.2% for CON (difference -1.8%; 95% CI -4.7% to 1.0%). For the secondary endpoint of cardiovascular death or MI, there were 276 events in INV and 314 in CON. All-cause death occurred in 145 INV and 144 CON patients (HR 1.05; 95% CI 0.83–1.32).

Data analysis overview and statistical methods

For descriptive purposes, patients were classified according to the number of primary outcome events experienced (none, one, two or more) and baseline characteristics were examined, including patient demographics, select medical history, medication use, and CCTA findings. Categorical variables are presented as counts (percentages), and continuous variables are presented as median (25th percentile, 75th percentile). The purpose of this exploratory analysis was to identify whether the multiple event patients had clinically distinctive phenotypic differences from single event and no event patients. Missing data were excluded from all denominators.

Given the lack of clear consensus regarding the best analytical approach to use in analysing multiple/recurrent time-dependent outcome events, we originally planned (before unblinding of the ISCHEMIA results) to employ several related methods based on the Cox model, each requiring different assumptions, with the intention of looking for concordance of results and treating the Andersen-Gill model as the reference case. However, when the primary ISCHEMIA analysis showed the proportional hazards assumption underlying the use of the Cox model was not met for the primary outcome, we altered our analysis plan to use the Ghosh–Lin cumulative incidence estimation approach as the reference case, with the Cox model approaches as supplemental[14] (Supplementary material online, *Table S1*). The Ghosh–Lin method is related to statistical methods used to estimate the cumulative probability of developing an event of interest by a certain time in follow-up. Standard 'cumulative incidence' methods, however, consider only first events and ignore all subsequent events. Ghosh and Lin[14] proposed a modification of the cumulative incidence methods that incorporates recurrent events while also accounting for death as a terminating (informative censoring) event. Their method, which does not require any parametric (i.e. distributional) assumptions, estimates the (marginal) mean cumulative number of events (first and recurrent) over time from randomization in each treatment group while accounting for the fact that patients who die cannot contribute any events after their death date. This is accomplished by keeping the patients who die in the risk set beyond their time of death but fixing their event rate after death to be zero. No assumptions are required about the relationship between recurrent events in the same patients. Using this approach, we estimated the cumulative average number of clinical primary endpoint events (first and recurrent) per 100 patients over a 4-year time horizon in the presence of a death by time *t*. These estimates were produced for the primary composite outcome event and each of the composite secondary endpoints described earlier.

The Andersen-Gill model is the method used most frequently to examine treatment differences in recurrent and total events.[15] This model is a generalization of the Cox model that models gap time (i.e. time from previous event to next event or from trial entry to first event if no previous event). Each subject contributes to the risk set for an event as long as she or he is under observation. The model assumes that every event is independent of every other event and that the order of events is not important. Because the Andersen-Gill model assumes that multiple events from an individual patient are independent (equivalent to each event being recorded from a different patient), which is clinically implausible, robust estimation is used to account for the correlation of events that occurs when individual patients contribute more than one event to the analysis.[16] The effects of the randomized treatment strategy on total clinical events were summarized using the HR and corresponding 95% CI and *P*-value. Model adjustment covariables included age, sex, randomized treatment strategy, estimated glomerular filtration rate, ejection fraction, and diabetes.

The Wei–Lin–Weissfeld[17] model is a stratified marginal Cox model, where the strata are defined by the number of events possible (up to three for the current analysis), and event time for each event is counted from the time of randomization (marginal approach). The objective of this model is to estimate the treatment effect on outcome (HR) for the first, second, and third events. This allows for examination of the possibility that the treatment effect size differs importantly for initial vs. recurrent events. All patients are included in the risk set for each event, regardless of their event history.[18] Like Anderson-Gill, this method assumes independence of events (first vs. second vs. third) when estimating model coefficients and uses robust standard errors to account for event interrelationships.

Forest plots were used to summarize Cox model-based results. Given that the proportional hazards assumption was not met for the primary ISCHEMIA intention-to-treat analysis, HRs are best understood as a weighted average of all the (time-varying) HRs over available follow-up.[19,20] Neither the Andersen-Gill model nor the Wei–Lin–Weissfeld model distinguish between censoring and terminating events and both therefore ignore the potential complexities created by competing risks.[21]

Analyses were performed using SAS software (version 9.4) and R (version 3.5.3).

Trial support and human subjects

The ISCHEMIA trial was supported by the National Heart, Lung, and Blood Institute with supplemental support from industry as reported previously.[11] The trial protocol was approved by institutional review boards or ethics committees at New York University Grossman School of Medicine, the Duke Clinical Research Institute, and at each participating clinical site. Every patient provided written informed consent to participate in the trial.

Results

Baseline characteristics of patients with and without recurrent primary endpoint events

Of the 5179 patients randomized in ISCHEMIA, 4509 (87.1%) had none of the events included in the primary composite endpoint (cardiovascular death, MI, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest), and 670 (12.9%) patients had one or more events: 533 (10.3%) had a single event and 137 (2.6%) had two or more events (*Table 1*).

The median age was lowest in the patients without an event (64 years) and highest in patients with 2 or more events (69 years). No consistent trend was present for sex (*Table 1*). The prevalence of hypertension and diabetes was higher in patients with recurrent events: hypertension was present in 71.7% of patients with no events and 89.8% of patients with 2 or more events; diabetes was present in 40.7% of patients with no events and 61.3% of patients with multiple events. Multiple event patients had a higher prevalence of peripheral vascular or cerebrovascular disease and a higher prevalence of prior CABG surgery (*Table 1*).

Patients with recurrent events also had a higher prevalence of multivessel disease (92.3%) determined by baseline CCTA relative to patients with 1 event (86.5%) or no events (77.9%). No consistent pattern was evident in the results of the qualifying stress test (data not shown). Patients with multiple events did not have more frequent or severe angina at trial entry relative to patients with a single event or with no events (*Table 1*).

Primary endpoint event distribution by treatment group

There were 873 primary endpoint events, with 670 occurring as index events (318 INV, 352 CON) and 203 as recurrent events (102 INV, 101 CON). The distribution of no, single, and two or more events did not differ by randomized treatment assignment: 9.8% of INV and 10.8% of CON had one event while 2.5% and 2.8%, respectively, had two or more events (*Table 2*). These findings did not depend on which primary events or combination of events the patients experienced except in the case of hospitalization for heart failure and for unstable angina. Patients in the INV arm had more hospitalizations for heart failure (one event: INV, 1.7% and CON, 0.7%; two or more events: INV, 0.3% and CON, 0.2%) and fewer hospitalizations for unstable angina (one event: INV, 0.6% and CON 1.1%; two or more events: INV, 0.0% and CON, 0.1%) (*Table 2*).

Cumulative incidence of events by treatment

The average number of primary endpoint events over 4 years was similar between patients randomized to the INV and CON strategies (*Table 3*). Specifically, the average number of events per 100 patients over 4 years was 18.2 (95% CI 15.8–20.9) among those randomized to INV and 19.7 (95% CI 17.5–22.2) among those randomized to CON [difference: -1.5 (95% CI -5.0 to 2.0), $P = 0.398$] (*Table 3* and *Figure 1*).

Comparable results were observed when the primary composite endpoint was varied to include all-cause death instead of cardiovascular death and to include stroke events (*Table 3*, *Figure 2*, and Supplementary material online, *Figures S1 and S2*). Similar findings were obtained for combinations of death and MI (*Table 3* and *Figure 3*). Examination of repeated non-fatal events of a single type (*Table 3* and *Figure 4*) showed that the average number of hospitalizations for heart failure per 100 patients over 4 years in the INV strategy was twice the average number in the CON strategy [2.6/100 patients vs. 1.3/100 patients, respectively; difference: 1.3 (95% CI 0.2–2.4), $P = 0.021$]. The INV arm had a lower average number of hospitalizations for unstable angina [0.7/100 patients vs. 1.5/100 patients in the CON arm, difference -0.8 (95% CI -1.5 to -0.1); $P = 0.020$].

Relative treatment effects on recurrent events

Using the Andersen-Gill model to examine the effect of treatment on recurrent events, the adjusted INV: CON HR for the primary composite event was 0.95 (95% CI 0.83–1.09; $P = 0.468$) (Supplementary material online, *Table S2* and *Figure S3*). Varying the composition of the composite endpoints did not materially alter the results. For single event types, hospitalization for heart failure was twice as likely for INV [HR 2.02 (95% CI 1.32–3.09); $P = 0.001$] and hospitalization for unstable angina was reduced by about half [HR 0.48 (95% CI 0.27–0.86); $P = 0.014$] (Supplementary material online, *Table S2*).

Using the Wei–Lin–Weissfeld model to compare the effects of treatment on recurrent events stratified by event sequence number (first, second, or third event) provided an average HR of 0.93 (95% CI 0.78–1.08; $P = 0.332$) with no consequential differences according to whether the event was the first or a recurrent event (Supplementary material online, *Table S3* and *Figure S4*).

Among the 540 ISCHEMIA patients with a qualifying (i.e. non-fatal) first event who were at risk for recurrent events (261 patients INV, 279 patients CON), the majority (80%) of initial events were MIs (Supplementary material online, *Table S4A*). After the first event, 37.8% of patients had a revascularization procedure [percutaneous coronary intervention (PCI) or CABG]: 28.4% of INV at a median of 12 days and 46.6% of CON at a median of 11 days (Supplementary materialonline, *Table S4B*). Second events were equally balanced in frequency between deaths and MIs and did not differ between the

Table 1 Baseline characteristics of randomized participants by frequency of primary endpoint events[a]

Characteristics	No events (*N* = 4509)	One event (*N* = 533)	Two or more (*N* = 137)	*P*-value
Demographics				
Age at randomization (years)				<0.001
Median (25th–75th)	64 (57–70)	66 (60–72)	69 (61–76)	
Male sex	3492/4509 (77.4%)	422/533 (79.2%)	97/137 (70.8%)	0.112
Race				<0.001
White	2908/4465 (65.1%)	389/528 (73.7%)	106/136 (77.9%)	
Black or African American	167/4465 (3.7%)	24/528 (4.5%)	13/136 (9.6%)	
Asian	1358/4465 (30.4%)	113/528 (21.4%)	14/136 (10.3%)	
Other	32/4465 (0.7%)	2/528 (0.4%)	3/136 (2.2%)	
Ethnicity				0.275
Hispanic or Latino	656/4185 (15.7%)	90/500 (18.0%)	17/130 (13.1%)	
Not Hispanic or Latino	3529/4185 (84.3%)	410/500 (82.0%)	113/130 (86.9%)	
Clinical history				
Hypertension	3219/4491 (71.7%)	447/533 (83.9%)	123/137 (89.8%)	<0.001
Diabetes	1835/4509 (40.7%)	245/533 (46.0%)	84/137 (61.3%)	<0.001
Prior myocardial infarction	841/4495 (18.7%)	117/531 (22.0%)	33/136 (24.3%)	0.058
Prior PCI	882/4506 (19.6%)	137/533 (25.7%)	31/136 (22.8%)	0.003
Prior CABG	152/4509 (3.4%)	35/533 (6.6%)	16/137 (11.7%)	<0.001
Atrial fibrillation/flutter	168/4505 (3.7%)	36/532 (6.8%)	17/136 (12.5%)	<0.001
Non-cardiac vascular				
Prior TIA	92/4499 (2.0%)	14/529 (2.6%)	8/137 (5.8%)	0.009
Prior stroke	124/4509 (2.8%)	16/532 (3.0%)	11/137 (8.0%)	0.001
Prior PAD	159/4499 (3.5%)	32/532 (6.0%)	13/137 (9.5%)	<0.001
Prior TIA, prior stroke, or prior PAD	340/4493 (7.6%)	56/531 (10.5%)	30/137 (21.9%)	<0.001
CCTA findings				
Any obstructive disease ≥50% stenosis by CCTA	3389/3393 (99.9%)	358/358 (100.0%)	85/85 (100.0%)	1.000
Multi-vessel disease ≥50% stenosis by CCTA	2325/2986 (77.9%)	282/326 (86.5%)	72/78 (92.3%)	<0.001
Vessels ≥50% stenosis by CCTA				<0.001
0	4/2630 (0.2%)	0/287 (0.0%)	0/69 (0.0%)	
1	649/2630 (24.7%)	42/287 (14.6%)	6/69 (8.7%)	
2	854/2630 (32.5%)	66/287 (23.0%)	18/69 (26.1%)	
3	1123/2630 (42.7%)	179/287 (62.4%)	45/69 (65.2%)	
Angina and heart failure history				
Participant has ever had angina	4051/4509 (89.8%)	472/533 (88.6%)	118/137 (86.1%)	0.262
Angina over the past month				0.187
None	881/4507 (19.5%)	114/533 (21.4%)	40/137 (29.2%)	
CCS angina Class I	1218/4507 (27.0%)	136/533 (25.5%)	35/137 (25.5%)	
CCS angina Class II	2213/4507 (49.1%)	254/533 (47.7%)	55/137 (40.1%)	
CCS angina Class III	194/4507 (4.3%)	29/533 (5.4%)	7/137 (5.1%)	
CCS angina Class IV	1/4507 (0.0%)	0/533 (0.0%)	0/137 (0.0%)	
New onset of angina over the past 3 months	765/4297 (17.8%)	67/493 (13.6%)	23/128 (18.0%)	0.064
Angina began or became more frequent over the past 3 months	1172/4040 (29.0%)	140/472 (29.7%)	43/116 (37.1%)	0.167
Prior heart failure	171/4509 (3.8%)	24/533 (4.5%)	11/137 (8.0%)	0.035
Ejection fraction[b]				<0.001
N	4031	481	125	
Median (25th–75th)	60 (55–65)	60 (52–65)	59 (51–63)	
Heart failure status over the past month				0.003
None	2765/4509 (61.3%)	311/533 (58.3%)	87/137 (63.5%)	

Continued

Table I *Continued*

Characteristics	No events (*N* = 4509)	One event (*N* = 533)	Two or more (*N* = 137)	*P*-value
NYHA Class I	892/4509 (19.8%)	90/533 (16.9%)	17/137 (12.4%)	
NYHA Class II	852/4509 (18.9%)	132/533 (24.8%)	33/137 (24.1%)	
Medications				
Anti-platelet medications	4257/4506 (94.5%)	489/532 (91.9%)	126/137 (92.0%)	0.033
Anticoagulant medications	162/4465 (3.6%)	27/529 (5.1%)	14/137 (10.2%)	<0.001
Anti-platelet or anticoagulant medications	4341/4505 (96.4%)	504/532 (94.7%)	133/137 (97.1%)	0.155
Statins	4277/4505 (94.9%)	501/532 (94.2%)	126/137 (92.0%)	0.245
High-intensity statin				0.013
Yes	1697/4505 (37.7%)	174/532 (32.7%)	40/137 (29.2%)	
No/unknown dose	2808/4505 (62.3%)	358/532 (67.3%)	97/137 (70.8%)	
Anti-hypertensive and anti-ischaemic/anginal medications	4362/4506 (96.8%)	520/532 (97.7%)	135/137 (98.5%)	0.269
Beta blocker	3623/4506 (80.4%)	429/532 (80.6%)	109/137 (79.6%)	0.961
Calcium channel blocker	1353/4506 (30.0%)	176/532 (33.1%)	49/137 (35.8%)	0.139
ACE inhibitor	1837/4506 (40.8%)	233/532 (43.8%)	71/137 (51.8%)	0.017
ARB	1132/4506 (25.1%)	141/532 (26.5%)	33/137 (24.1%)	0.748
ACE inhibitor or ARB	2940/4506 (65.2%)	372/532 (69.9%)	104/137 (75.9%)	0.005
Long-acting nitrate	1462/4506 (32.4%)	167/532 (31.4%)	46/137 (33.6%)	0.845

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CCS, Canadian Cardiac Society; CCTA, coronary computed tomographic angiography; NYHA, New York Heart Association; PAD, periferal artery disease; PCI, percutaneous coronary intervention; TIA, transient ischemic atack.
[a]Primary endpoint events: any of the following: death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest.
[b]Site-reported value, if available. If not available, then core-lab entered value.

treatment groups (Supplementary material online, *Table S4C*). The median time to death was short (9 days INV, 11 days CON) while the median time to recurrent MI was 101 days for INV and 203 days for CON. Procedure-related MIs were infrequent as repeat events (two events INV, three events CON).

A total of 26 second primary endpoint events occurred in the 7-day period following the first event. Death accounted for 22 (84.6%; 10 INV, 12 CON) of the events. The remaining four events consisted of two hospitalizations for cardiac arrest (7.7%, INV), one MI (3.9%, CON), and one hospitalization for heart failure (3.9%, INV).

Discussion

Two findings of our analysis deserve special emphasis. First, recurrent primary endpoint events were quite infrequent in the stable CAD patients enrolled in ISCHEMIA despite the fact that they had objective evidence of moderate or severe ischaemia at trial entry. Second, evaluation of treatment assignment on total events rather than first events did not substantively alter the patterns of treatment-related differences from that reported for the primary endpoint analysis of ISCHEMIA[11] (Graphical abstract).

Relevance of recurrent and total events in clinical trial interpretation

Three factors have increased interest in routinely examining treatment outcomes in clinical trials using total events.[22] First, a total event analysis strategy, including both first and recurrent events, seems to better serve the holistic patient-centric ideal of assessing treatment-related changes on the overall disease burden. Second, because the number of recurrent events may at times equal or exceed the number of initial events, including them in the analysis has the potential in some circumstances to substantially improve power/precision of the estimated treatment effect. Finally, some therapies may differ in the effectiveness of prevention of primary vs. recurrent events or in the type of primary events prevented, possibly reflecting clinically relevant differences in mechanisms of benefit.

Recurrent and total events proportions in ISCHEMIA

A number of medical therapy trials in stable CAD patients have reported that recurrent events comprised ~40% of total primary outcome events observed.[5–9] The explanation for the lower proportion of recurrent events in ISCHEMIA (~20% of total events) is likely multifactorial, with the type of events counted, effects of therapy on each event type, and follow-up duration having potentially important influences. Many of the trials reporting higher proportions of recurrent events included revascularization as a component outcome. Coronary artery disease trial reports of recurrent events that did not include revascularization appear more consistent with ISCHEMIA in terms of the ratio of recurrent to total events.[4,23] The Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial reported that when events counted included only

Table 2 Total number of primary endpoint events[a] by randomized treatment strategy

Event	INV (*N* = 2588)	CON (*N* = 2591)	*P*-value
CV death, myocardial infarction, and hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest			
Total events	420	453	
Participants with 1 event	253/2588 (9.8%)	280/2591 (10.8%)	0.222
Participants with ≥2 events	65/2588 (2.5%)	72/2591 (2.8%)	0.549
All-cause death, myocardial infarction, and hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest			
Total events	473	486	
Participants with 1 event	298/2588 (11.5%)	302/2591 (11.7%)	0.874
Participants with ≥2 events	69/2588 (2.7%)	77/2591 (3.0%)	0.506
CV death or myocardial infarction			
Total events	336	379	
Participants with 1 event	234/2588 (9.0%)	267/2591 (10.3%)	0.124
Participants with ≥2 events	42/2588 (1.6%)	47/2591 (1.8%)	0.597
All-cause death or myocardial infarction			
Total events	389	412	
Participants with 1 event	283/2588 (10.9%)	291/2591 (11.2%)	0.734
Participants with ≥2 events	44/2588 (1.7%)	51/2591 (2.0%)	0.472
CV death			
Total events	92/2588 (3.6%)	111/2591 (4.3%)	0.176
All-cause death			
Total events	145/2588 (5.6%)	144/2591 (5.6%)	0.944
Myocardial infarction			
Total events	244	268	
Participants with 1 event	186/2588 (7.2%)	208/2591 (8.0%)	0.254
Participants with ≥2 events	24/2588 (0.9%)	25/2591 (1.0%)	0.889
Hospitalization for unstable angina			
Total events	17	35	
Participants with 1 event	15/2588 (0.6%)	29/2591 (1.1%)	0.034
Participants with ≥2 events	1/2588 (0.0%)	3/2591 (0.1%)	0.625
Hospitalization for heart failure			
Total events	62	33	
Participants with 1 event	43/2588 (1.7%)	19/2591 (0.7%)	0.002
Participants with ≥2 events	8/2588 (0.3%)	6/2591 (0.2%)	0.591
Hospitalization for resuscitated cardiac arrest			
Total events	5	6	
Participants with 1 event	5/2588 (0.2%)	4/2591 (0.2%)	0.754
Participants with ≥2 events	0/2588 (0.0%)	1/2591 (0.0%)	1.000
Type 1 myocardial infarction			
Total events	88	163	
Participants with 1 event	76/2588 (2.9%)	142/2591 (5.5%)	<0.001
Participants with ≥2 events	5/2588 (0.2%)	10/2591 (0.4%)	0.197
Type 2 myocardial infarction			
Total events	48	44	
Participants with 1 event	30/2588 (1.2%)	38/2591 (1.5%)	0.331
Participants with ≥2 events	8/2588 (0.3%)	3/2591 (0.1%)	0.131

CV, cardiovascular; CON, conservative; INV, invasive.
[a]Including variations with all-cause death substituted for CV death.

cardiovascular death, MI, or stroke, recurrent events accounted for 20% of total events but when coronary revascularization and hospitalization for unstable angina were added, the recurrent event proportion increased to 41%.[7]

Treatment effects on recurrent and total events in ISCHEMIA

No prior large clinical trial of invasive vs. CON treatment strategies in stable CAD has compared the analysis of total events vs. first events

Table 3 Average number of clinical events per 100 patients over 4 years of follow-up by randomized treatment strategy[a]

Endpoint	Average number of events (95% CI)		Estimated difference (95% CI)	*P*-value
	Invasive strategy (*N* = 2588)	Conservative strategy (*N* = 2591)		
Cardiovascular death, myocardial infarction, and hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest	18.2 (15.8–20.9)	19.7 (17.5–22.2)	-1.5 (-5.0 to 2.0)	0.398
Cardiovascular death, myocardial infarction, hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest, or stroke	20.0 (17.5–22.9)	21.5 (19.1–24.1)	-1.5 (-5.2 to 2.2)	0.422
All-cause death, myocardial infarction, and hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest	20.6 (18.1–23.4)	21.1 (18.8–23.7)	-0.5 (-4.1 to 3.1)	0.785
All-cause death, myocardial infarction, hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest, or stroke	22.5 (19.9–25.5)	22.9 (20.5–25.6)	-0.4 (-4.2 to 3.4)	0.835
Cardiovascular death or myocardial infarction	14.7 (12.7–17.0)	16.6 (14.6–18.8)	-1.9 (-4.9 to 1.1)	0.212
All-cause death or myocardial infarction	17.2 (15.1–19.6)	18.0 (16.0–20.3)	-0.8 (-3.9 to 2.3)	0.615
Myocardial infarction	10.6 (9.0–12.5)	11.6 (10.1–13.4)	-1.0 (-3.4 to 1.4)	0.419
Hospitalization for heart failure	2.6 (1.9–3.6)	1.3 (0.8–2.2)	1.3 (0.2–2.4)	0.021
Hospitalization for unstable angina	0.7 (0.4–1.1)	1.5 (1.0–2.2)	-0.8 (-1.5 to -0.1)	0.020

CI, confidence interval.
[a]Cumulative incidence estimates using the Ghosh–Lin approach (see section Methods).

on estimated treatment effects. Therapies that affect atherosclerotic plaque biology or stability appear to have effects that are the same on first and recurrent events, which seems consistent with our general understanding of how these therapies provide benefit.[4–10] Whether such expectations extend to coronary revascularization is less clear. The INV arm in ISCHEMIA, as previously reported, reduced spontaneous MI rates progressively over time relative to the CON arm.[11] Whether that pattern will continue and will result in a late-emerging mortality difference is being assessed in the ongoing ISCHEMIA long-term follow-up study. Thus, an invasive management strategy complicated by a subsequent spontaneous MI may not provide any protective prognostic benefits over a CON-medical strategy. Also, noteworthy is the finding that very few of the second event MIs were procedure related (*Table 2*).

In the ISCHEMIA prespecified covariate-adjusted time to primary event Cox model-based analysis, the invasive: CON HR was 0.93 (95% CI 0.80–1.08, $P = 0.34$).[11] Cox model-based analysis of recurrent and total events in the present analysis were almost identical with these results: for the Andersen-Gill model HR 0.95 (95% CI 0.83–1.09, $P = 0.47$); Wei–Lin–Weissfeld model HR 0.93 (95% CI 0.78–1.08, $P = 0.33$). Since the proportional hazards assumption of the Cox model was not consistent with observed treatment-related data patterns, cumulative event rates were also estimated. As reported previously, at 6 months, the INV arm had an estimated cumulative primary (first) event rate of 5.3% vs. 3.4% for CON (difference of 1.9%).[11] At 5 years, the INV had an estimated cumulative (first) event rate of 16.4% vs. 18.2% for CON with a difference of -1.8%. In the present analysis, the estimated cumulative total mean event rate difference at 4 years was -1.5%, providing further evidence that consideration of total events did not materially alter the estimates of treatment effect size or the conclusion of no overall difference when examined several different ways.

Patient perspective, disease burden, and total events

The strong preference in most cardiovascular randomized clinical trials for using the time to the first occurrence of a composite event as the primary metric of therapeutic effect is more pragmatic than scientific since the methods for this are familiar and well worked out and are generally favoured by regulators.[24] However, conceptually clinicians want to be able to tell patients faced with a therapeutic choice what the impact of that choice is likely to be on their total disease burden and not simply on the first event they chance to have. 'Disease burden' is not easy to quantitate in chronic illnesses such as CAD, but it does convey an intuition that both number, type, and severity of events and their consequences over the remaining lifetime of the patient are relevant. When both fatal and non-fatal events are a critical part of defining the disease burden, a number of different analytic methods must be employed to explore different features of the treatment effect since no single method addresses all the complexities involved. No consensus yet exists on what set of methods is sufficient to fully uncover the relevant treatment information in a complex trial such as ISCHEMIA. Our approach looked at both absolute and relative differences of different combinations of events under a variety of assumptions (Supplementary material online, *Table S1*)

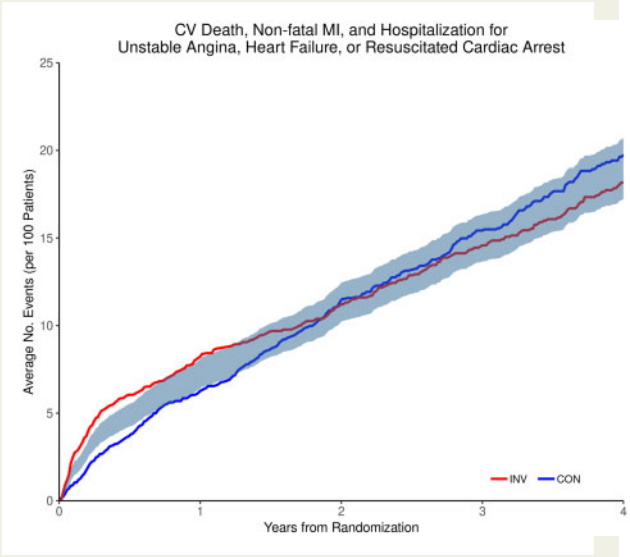


Figure 1 Cumulative average number of primary endpoint events by treatment. Plots of the mean frequency function of primary endpoint events (cardiovascular death, non-fatal myocardial infarction, or hospitalization for unstable angina, heart failure, or cardiac arrest) vs. time, stratified by randomized treatment strategy (Ghosh–Lin method). The grey-shaded region of the plot indicates regions where the null hypothesis of no difference between the curves can be rejected based on the 95% confidence interval for the difference. In other words, if the shading overlaps the two treatment curves, it is indicative of no significant difference. CON, conservative; CV, cardiovascular; INV, invasive; MI, myocardial infarction.

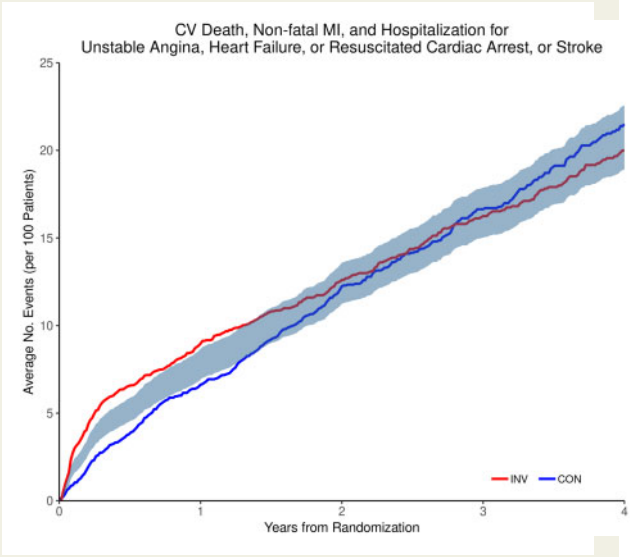


Figure 2 Cumulative average number of primary endpoint events plus stroke by treatment. Plots of the mean frequency function of primary endpoint events plus stroke (cardiovascular death, non-fatal myocardial infarction, or hospitalization for unstable angina, heart failure, cardiac arrest, or stroke) vs. time, stratified by randomized treatment strategy (Ghosh–Lin method). The grey-shaded region of the plot indicates regions where the null hypothesis of no difference between the curves can be rejected based on the 95% confidence interval for the difference. In other words, if the shading overlaps the two treatment curves, it is indicative of no significant difference. CON, conservative; CV, cardiovascular; INV, invasive; MI, myocardial infarction.

and found a high degree of consistency in the resulting treatment effect estimates. Thus, this report adds important new evidence to the ISCHEMIA primary publication that from a clinical events perspective, the two strategies tested provide equivalent outcomes for at least the first 4 years after randomization.

Importance of guideline-directed medical therapy

Secondary prevention was a core component of the treatment regimen provided to all ISCHEMIA patients, regardless of treatment assignment.[12] In prior work, prognostically effective medical therapies have been found to reduce repeat events at least as effectively as they reduce initial events.[4–10] What remains less clear is to what extent recurrent events that occur in the presence of guideline-directed medical therapy reflect either a lack of sufficient therapeutic intensity or a resistance to pharmacological therapy that cannot be overcome even at target doses. Since medical therapy intensity was not randomized in ISCHEMIA, we cannot distinguish these possibilities in the context of an intention-to-treat comparison.

Limitations

Several caveats should be considered in the interpretation of this report. First, as discussed above, of the 670 ISCHEMIA patients with at least one primary outcome event, only 20% had a repeat event. Five event types were included in the primary composite endpoint, some of which were very infrequent. Thus, even in this very large trial of CAD patients with moderate or severe ischaemia, our ability to identify all the relevant different patterns of recurrent events by treatment and according to specific event type with high precision was limited.

Second, combining the five different components of the primary ISCHEMIA composite event as a construct for analysis ignores the clear differences in importance that these events have for patients. Deaths, MIs, and hospitalizations carry very different implications for the patient and the healthcare system. Composite multicomponent endpoints have become increasingly common as primary outcomes for large clinical trials primarily because powering trials of chronic disease therapies to detect a mortality difference alone is often quite infeasible. In conjunction with the present recurrent events/total events analysis, the ISCHEMIA trial has prespecified a future analysis to examine the importance of differential weighting of different types of outcome events to the interpretation of the trial. These two investigations together, as well as the quality of life data reported by Spertus *et al.*,[25] should comprehensively describe the effect of the two ISCHEMIA treatment strategies on patient disease burden.

Third, since there is no single statistical analysis method that captures all the important aspects of recurrent event patterns without making problematic assumptions, we used several complementary methods to describe and compare different aspects of the recurrent

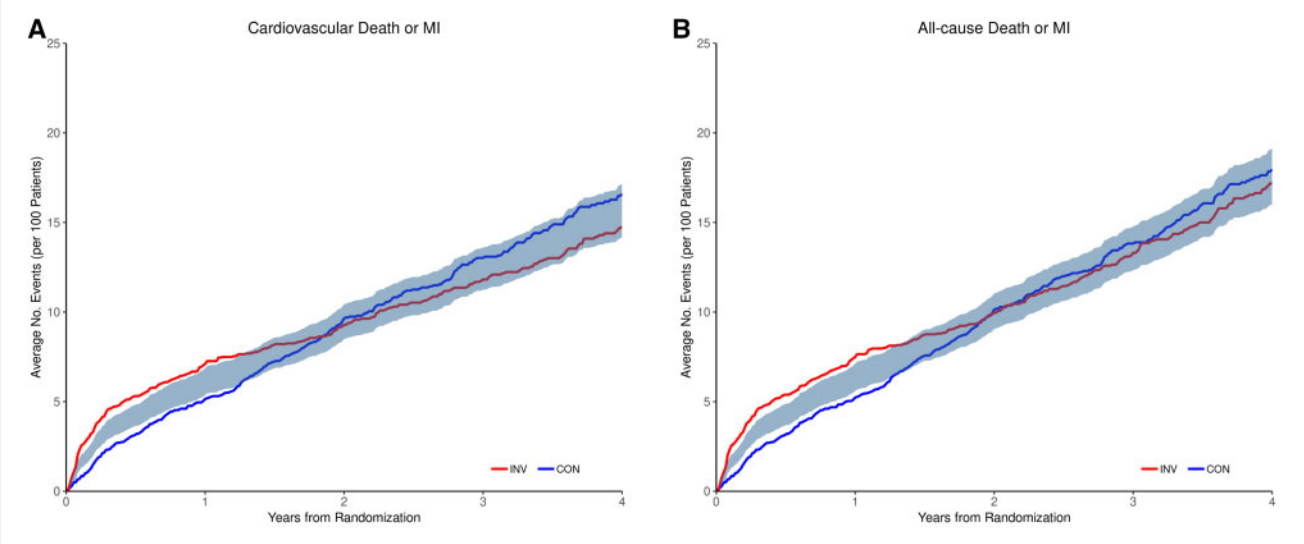


Figure 3 (*A*) Cumulative average number of cardiovascular death or myocardial infarction endpoints by treatment. Plots of the mean frequency function of the composite endpoint of cardiovascular death or myocardial infarction vs. time, stratified by randomized treatment strategy (Ghosh–Lin method). The grey-shaded region of the plot indicates regions where the null hypothesis of no difference between the curves can be rejected based on the 95% confidence interval for the difference. In other words, if the shading overlaps the two treatment curves, it is indicative of no significant difference. (*B*) Cumulative average number of all-cause death or myocardial infarction endpoints by treatment. Plots of the mean frequency function of the composite endpoint of all-cause death or myocardial infarction vs. time, stratified by randomized treatment strategy (Ghosh–Lin method). The grey-shaded region of the plot indicates regions where the null hypothesis of no difference between the curves can be rejected based on the 95% confidence interval for the difference. In other words, if the shading overlaps the two treatment curves, it is indicative of no significant difference. CON, conservative; INV, invasive; MI, myocardial infarction.

events that occurred in the trial. The concordance of these different approaches on a conclusion of no net difference by the treatment group provides important reassurance that our findings are not biased by a particular choice of analysis methods.

Fourth, ISCHEMIA tested an initial INV management strategy that comprised a mixture of 74% PCI and 26% CABG among the patients in this arm who received revascularization. The outcomes of the trial may have been affected in important ways by the composition of this mixture of PCI and CABG. In the context of stable ischaemic heart disease with evidence of ischaemia, PCI has not been shown to alter the probability of death or MI relative to medical therapy,[26,27] but CABG may reduce MI events.[28] Since assignment to PCI vs. CABG was not randomized, our data do not permit us to address whether a higher proportion of CABG use would have led to more favourable primary treatment effect estimates in ISCHEMIA.

Finally, our results are affected by the length of follow-up available for analysis, and longer-term follow-up could alter the findings and conclusions. The ISCHEMIA trial is currently collecting an additional 5 years of follow-up, and our conclusions about the impact of treatment on total events will be re-evaluated as part of that work.

Conclusions

In stable CAD patients with moderate or severe myocardial ischaemia enrolled in the ISCHEMIA trial, recurrent events were infrequent over 4 years of follow-up and comprised only ~20% of total events observed. An initial INV treatment strategy did not prevent either net recurrent events or net total events more effectively than an initial CON strategy.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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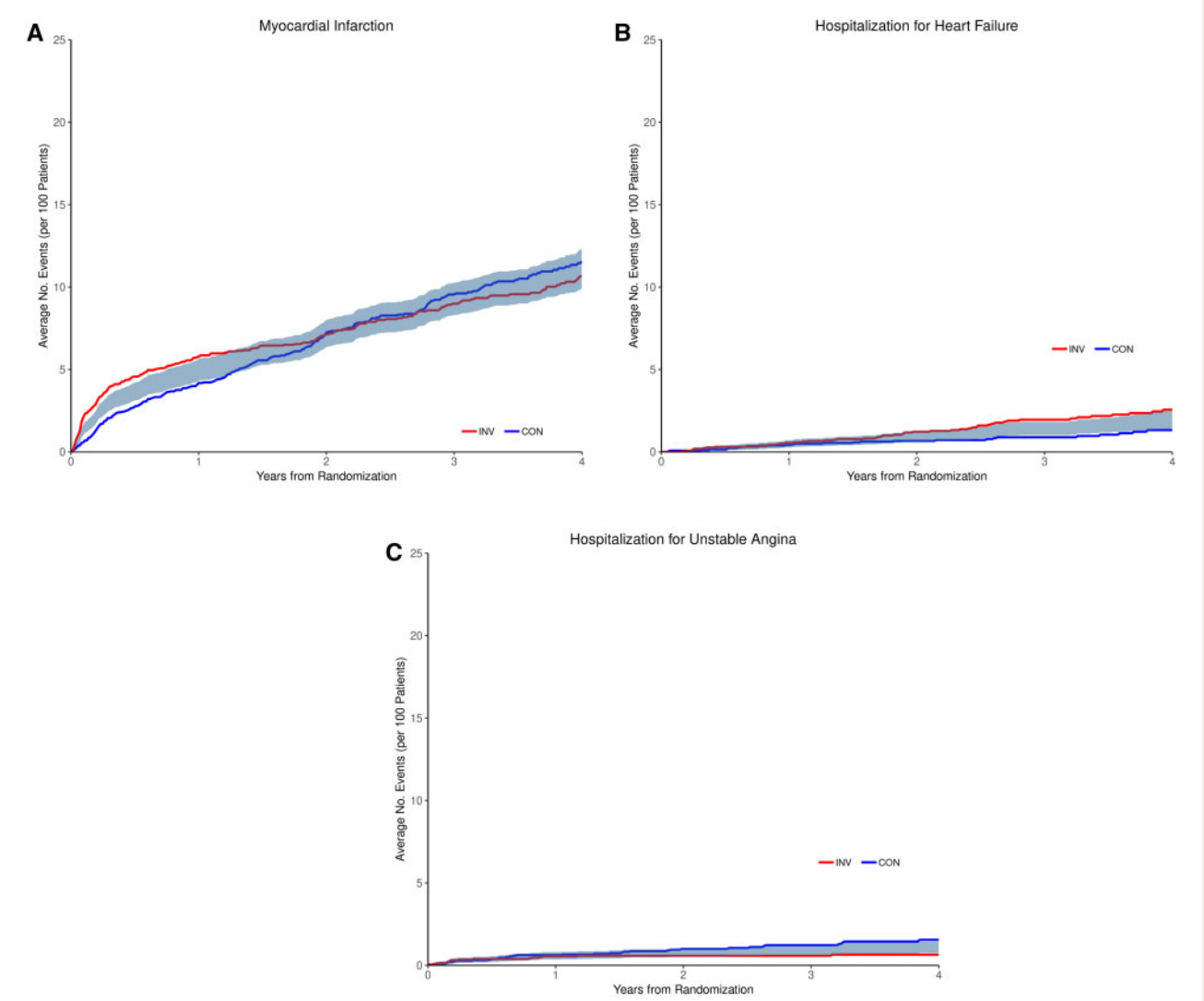

Figure 4 (*A*) Cumulative average number of myocardial infarction events by treatment. Plots of the mean frequency function of myocardial infarction vs. time, stratified by randomized treatment strategy (Ghosh–Lin method). The grey-shaded region of the plot indicates regions where the null hypothesis of no difference between the curves can be rejected based on the 95% confidence interval for the difference. In other words, if the shading overlaps the two treatment curves, it is indicative of no significant difference. (*B*) Cumulative average number of hospitalization for heart failure events by treatment. Plots of the mean frequency function of heart failure vs. time, stratified by randomized treatment strategy (Ghosh–Lin method). The grey-shaded region of the plot indicates regions where the null hypothesis of no difference between the curves can be rejected based on the 95% confidence interval for the difference. In other words, if the shading overlaps the two treatment curves, it is indicative of no significant difference. (*C*) Cumulative average number of hospitalization for unstable angina events by treatment. Plots of the mean frequency function of hospitalization for unstable angina vs. time, stratified by randomized treatment strategy (Ghosh–Lin method). The grey-shaded region of the plot indicates regions where the null hypothesis of no difference between the curves can be rejected based on the 95% confidence interval for the difference. In other words, if the shading overlaps the two treatment curves, it is indicative of no significant difference. CON, conservative; INV, invasive.

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Subcommittee,Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D; Trials & Registries Subcommittee,Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; ESC Committee for Practice Guidelines (CPG),Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Document R, Morais J, Aguiar C, Almahmeed W, Arnar DO, Barili F, Bloch KD, Bolger AF, Botker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E, Hlatky M, James S, Kern KB, Moliterno DJ, Mueller C, Neskovic AN, Pieske BM, Schulman SP, Storey RF, Taubert KA, Vranckx P, Wagner DR. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012;**60**:1581–1598.

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