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Survival After Invasive or Conservative Management of Stable Coronary Disease

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BACKGROUND: The ISCHEMIA trial (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) compared an initial invasive versus an initial conservative management strategy for patients with chronic coronary disease and moderate or severe ischemia, with no major difference in most outcomes during a median of 3.2 years. Extended follow-up for mortality is ongoing.

METHODS: ISCHEMIA participants were randomized to an initial invasive strategy added to guideline-directed medical therapy or a conservative strategy. Patients with moderate or severe ischemia, ejection fraction ≥35%, and no recent acute coronary syndromes were included. Those with an unacceptable level of angina were excluded. Extended follow-up for vital status is being conducted by sites or through central death index search. Data obtained through December 2021 are included in this interim report. We analyzed all-cause, cardiovascular, and noncardiovascular mortality by randomized strategy, using nonparametric cumulative incidence estimators, Cox regression models, and Bayesian methods. Undetermined deaths were classified as cardiovascular as prespecified in the trial protocol.

RESULTS: Baseline characteristics for 5179 original ISCHEMIA trial participants included median age 65 years, 23% women, 16% Hispanic, 4% Black, 42% with diabetes, and median ejection fraction 0.60. A total of 557 deaths accrued during a median follow-up of 5.7 years, with 268 of these added in the extended follow-up phase. This included a total of 343 cardiovascular deaths, 192 noncardiovascular deaths, and 22 unclassified deaths. All-cause mortality was not different between randomized treatment groups (7-year rate, 12.7% in invasive strategy, 13.4% in conservative strategy; adjusted hazard ratio, 1.00 [95% CI, 0.85–1.18]). There was a lower 7-year rate cardiovascular mortality (6.4% versus 8.6%; adjusted hazard ratio, 0.78 [95% CI, 0.63–0.96]) with an initial invasive strategy but a higher 7-year rate of noncardiovascular mortality (5.6% versus 4.4%; adjusted hazard ratio, 1.44 [95% CI, 1.08–1.91]) compared with the conservative strategy. No heterogeneity of treatment effect was evident in prespecified subgroups, including multivessel coronary disease.

CONCLUSIONS: There was no difference in all-cause mortality with an initial invasive strategy compared with an initial conservative strategy, but there was lower risk of cardiovascular mortality and higher risk of noncardiovascular mortality with an initial invasive strategy during a median follow-up of 5.7 years.

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Key Words: catheterization ■ coronary artery bypass ■ medication therapy management ■ myocardial ischemia ■ percutaneous coronary intervention

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Clinical Perspective

What Is New?

- An initial invasive versus an initial conservative management strategy for patients with chronic coronary disease and moderate or severe ischemia resulted in lower cardiovascular mortality at median 5.7 years.
- The previously observed excess of noncardiovascular mortality with initial invasive strategy persisted.
- In this interim report of extended follow-up of ISCHEMIA, with a total of 557 deaths (nearly twice the number of deaths in the initial phase), the probability of a survival benefit at 7 years with either initial management strategy was not different.

What Are the Clinical Implications?

- These findings provide important evidence for patients with chronic coronary disease and their physicians as they decide whether to add invasive management to guideline-directed medical therapy.

Nonstandard Abbreviations and Acronyms

CAD	coronary artery disease
CCTA	coronary computed tomography angiography
MI	myocardial infarction
MVD	multivessel disease

The ISCHEMIA trial compared initial invasive versus conservative management strategies for patients with chronic coronary disease and moderate or severe ischemia on stress testing.[1] After a median follow-up of 3.2 years, there was no net benefit for the initial invasive strategy on the primary or major secondary clinical outcomes. Although there was no significant difference in the rate of total myocardial infarction (MI), the invasive strategy led to more periprocedural MIs, but fewer spontaneous MIs, all centrally adjudicated. MI events were associated with a higher risk of subsequent mortality,[2] with a stronger association for spontaneous MI than for periprocedural MI. There appeared to be a late divergence of the cardiovascular mortality curves in favor of the invasive strategy over the conservative strategy with 4-year rates of 4.1% versus 5.0% (hazard ratio, 0.87 [95% CI, 0.66–1.15]). In contrast, the 4-year rates of noncardiovascular mortality were higher in the invasive strategy (2.5% versus 1.4%; hazard ratio, 1.63 [95% CI, 1.06–2.52]),[3] and all-cause mortality was not different (6.5% versus 6.4%; hazard ratio, 1.05 [95% CI, 0.83–1.32]).[1] The severity of coronary artery disease (CAD) on coronary computed tomography angiography (CCTA) was strongly associated with primary and secondary outcome events.[4] Herein we report the interim 7-year all-cause, cardiovascular, and noncardiovascular mortality rates for the ongoing National Heart, Lung, and Blood Institute–funded ISCHEMIA Extended Follow-up (ISCHEMIA-EXTEND), including findings across subgroups.

METHODS

Study Design

ISCHEMIA and ISCHEMIA-EXTEND were sponsored by the National Institutes of Health/National Heart, Lung, and Blood Institute, and the trial data sets will be made available through the National Institutes of Health BioData Catalyst website (https://biodatacatalyst.nhlbi.nih.gov/). The ISCHEMIA trial and ISCHEMIA-EXTEND designs have been reported.[5,6] In brief, ISCHEMIA randomized patients with chronic coronary disease and moderate or severe ischemia to an initial invasive strategy of cardiac catheterization and revascularization, when feasible, added to guideline-directed medical therapy; or an initial conservative strategy of guideline-directed medical therapy alone, with catheterization and revascularization reserved for failure of medical therapy. Major exclusion criteria for the trial included left main stenosis ≥50%, ejection fraction <35%, acute coronary syndrome within 2 months, and angina that could not be managed with medical therapy alone. The trial protocol included long-term assessment with up to 20-year follow-up in the consent form.

All 5179 randomized trial participants' baseline and survival data are included in this report. ISCHEMIA-EXTEND is continuing to follow participants who survived the initial trial phase and had not withdrawn consent (referred to as EXTEND-eligible) for collection of vital status and cause of death data. Of the original 37 countries, 36 obtained vital status information: 33 contacted participants or their designated surrogate 1 or 2 times a year. One country is pending regulatory approval. Three of the 36 countries had central data available. One of these was not able to provide cause of death, and these deaths were "unclassified." Consistent with the ISCHEMIA trial phase in which deaths of undetermined cause after Clinical Events Committee adjudication were included in the protocol definition of cardiovascular death,[5] we grouped undetermined deaths during the extended follow-up period as cardiovascular deaths. Death dates including year, month, and day for the extended follow-up period were available for all but 1 participant, whose date included only the year. For this participant, we substituted the midpoint of the indicated year.

Information on whether death was coronavirus disease 2019 (COVID-19)–related was collected, when available, as of July 2020. Cause of death was not centrally adjudicated during extended follow-up. All sites had local ethics committee or institutional review board approval, and participants gave informed consent.

The findings from subgroups[1,5] of interest that were prespecified at trial inception, including those previously found to be independently associated with higher risk of mortality, are reported. For the subset of participants that had core lab–interpreted CCTA, severity of CAD was categorized as single or multivessel disease (MVD), by both ≥50% and ≥70% stenosis criteria, when possible.[4] MVD was assessed when either all key

segments required to determine the number of diseased vessels were evaluable, or when 2 of 3 major vessels were evaluable as diseased (MVD present) or not diseased (MVD absent).

Statistical Analysis

All analyses are performed according to intention-to-treat on the basis of initial randomized trial strategy assignment. We compared baseline characteristics of participants included in the ISCHEMIA-EXTEND eligible study population versus the original trial population and ineligible participants who withdrew from the trial with no database search allowable or who declined extended follow-up.

Intention-to-treat analysis was used to estimate the effect of an assigned management strategy on risk of all-cause, cardiovascular, and noncardiovascular mortality from the time of randomization. Using the Kaplan-Meier method, we estimated the cumulative event rate of mortality by assigned management strategy and used the log-rank test to assess differences in the survival distributions. We estimated yearly mortality differences through 7 years of follow-up. For the competing events of cardiovascular and noncardiovascular mortality, we used a nonparametric cumulative incidence function estimator and the Fine-Gray method to test for differences in the cumulative incidence functions by strategy.

Using separate Cox proportional hazards regression models for all-cause, cardiovascular, and noncardiovascular mortality, we estimated the adjusted hazard ratio for the invasive versus conservative strategy, after controlling for prespecified baseline participant characteristics as done in the initial ISCHEMIA trial phase,[1] namely, sex, age, diabetes status, estimated glomerular filtration rate, and ejection fraction. In randomized clinical trials, adjustment for a prespecified, parsimonious set of covariates is recommended to improve precision of the estimated treatment effect and safeguard against potential covariate imbalances between treatment groups.[7–11] For cardiovascular and noncardiovascular mortality, we estimated cause-specific Cox models to obtain cause-specific hazard ratios. We assessed the proportional hazards assumption with the score test of the null hypothesis of no association between the scaled Schoenfeld residuals for management strategy and log time. The null hypothesis was not rejected at the 5% significance level (all-cause mortality, P=0.27; cardiovascular mortality, P=0.06; noncardiovascular mortality, P=0.26).

To further characterize the effect of assigned management strategy, we used Bayesian piecewise exponential survival modeling.[12] For all-cause mortality, we estimated the posterior mean adjusted absolute percent difference for the invasive versus conservative strategy in the cumulative event rate at 7 years (controlling for the aforementioned baseline characteristics). We quantified the posterior probability that the difference was higher or lower than varying thresholds. For cardiovascular and noncardiovascular mortality, we modified the piecewise survival model to account for competing events in the spirit of the model for competing risk failure times in Andrinopoulou et al.[13] We extended the piecewise exponential survival model to jointly model the hazard of each event of interest (cardiovascular and noncardiovascular mortality). We used this model to estimate the posterior mean adjusted absolute percent difference for the invasive versus conservative strategy in the 7-year cumulative incidence of cardiovascular mortality and noncardiovascular mortality (accounting for the respective competing risk). Details about model specification, assignment of prior distributions, and model fitting, convergence, and diagnostics are available in the Supplemental Material.

To assess heterogeneity of treatment effect in prespecified subgroups of interest, we estimated the adjusted hazard ratio for the invasive versus conservative strategy in each prespecified subgroup. We tested the null hypothesis that the treatment effect did not differ by subgroup using the Wald test for interaction.

We conducted sensitivity analyses to examine whether the estimated effect of treatment strategy at 7 years of follow-up was robust to the classification of new undetermined deaths during the extended follow-up phase as cardiovascular deaths, and the proportional hazards assumption. To conduct sensitivity analysis about our assumption that new undetermined deaths during the extended follow-up phase have cardiovascular-related causes (as per the ISCHEMIA trial protocol definition),[5] we assumed that these new undetermined deaths were instead noncardiovascular deaths. For 1 country in which cause of death during the extended follow-up was unavailable, we ran models based on either censoring new deaths from the country at the end of the trial phase or treating these new deaths as undetermined deaths—as in countries collecting cause of death data. To evaluate the proportional hazards assumption, we extended the Bayesian piecewise exponential model to allow time-varying treatment effects (Supplemental Material).

All analyses were conducted using R statistical software,[14] with Bayesian modeling conducted using JAGS.[15]

RESULTS

Baseline Characteristics

Figure 1 presents the participant flow for long-term follow-up. In baseline data and survival analyses, all 5179 trial participants are included, with participants who withdrew or declined extended follow-up censored at their last known alive date. Among 5179 participants initially randomized, 289 (5.6%) had died by the end of the original trial follow-up in June 2019, 29 (0.6%) withdrew with no database search allowable, and 36 (0.7%) participants declined extended follow-up. Thus, 4825 participants were eligible for additional follow-up for mortality in ISCHEMIA-EXTEND, including 2407 in the invasive strategy and 2418 participants in the conservative strategy. Median follow-up among the 5179 participants was 5.7 years.

Baseline characteristics for the 5179 ISCHEMIA trial participants overall and by eligibility status are shown in Table S1. Among the 5179 trial participants, the median age was 65 years, 23% were women, 16% were Hispanic, 4% were Black, 42% had diabetes, and the median ejection fraction was 60%. There were no major differences in baseline characteristics between those who were eligible for extended follow-up and the original randomized cohort (Table S1). Compared with participants eligible for extended follow-up,

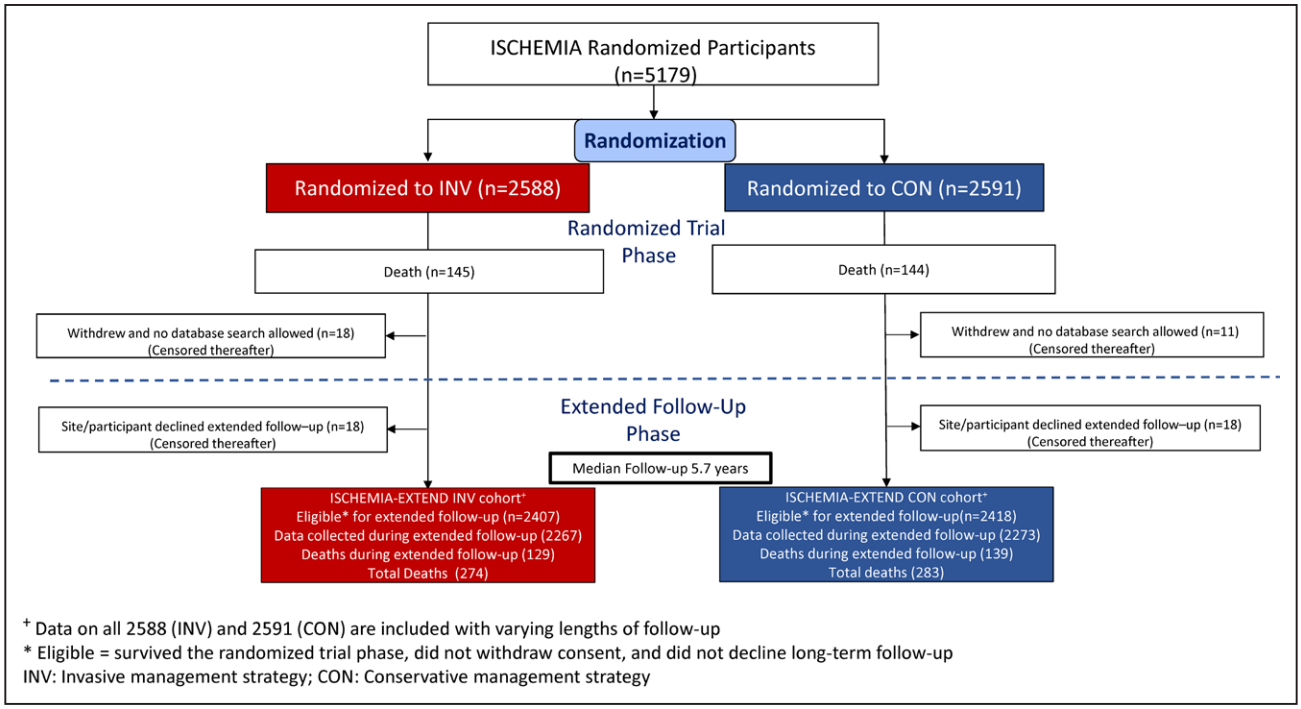

Figure 1. Participant flow.
The top portion, delineated by the dashed line and labeled Randomized Trial Phase, shows 5179 randomized to either invasive (red) or conservative (blue) strategy between 2011 and 2018. The original reported trial findings included follow-up through June 2019. Twenty-nine participants withdrew from follow-up during the trial phase with no database search allowable. In the bottom portion, labeled Extended Follow-Up Phase, 36 participants declined extended follow-up. The median follow-up was 5.7 years. In survival analyses, all 5179 trial participants are included, with participants who withdrew or declined extended follow-up censored at their last known alive date. ISCHEMIA indicates International Study of Comparative Health Effectiveness With Medical and Invasive Approaches.

participants who withdrew with no database search allowable during the initial trial phase or who declined extended follow-up were older and more likely to be of Asian race.

Clinical Outcomes

There were 268 additional deaths during the extended follow-up period, leading to a total of 557 deaths at a median of 5.7 years. This total included 343 cardiovascular deaths, 192 noncardiovascular deaths, and 22 deaths with cause not classified (from a country without cause of death data available at the time of this report). The cumulative all-cause mortality rate was not different between assigned management strategies (Figure 2A, log-rank *P*=0.74). A small early excess risk of mortality at 1 year in the invasive versus conservative strategy resolved by 2 years (Figure 2A, Table). The Cox adjusted all-cause mortality hazard ratio for invasive versus conservative management was 1.00 (95% CI, 0.85–1.18). In contrast, the cumulative incidence of cardiovascular mortality by management strategies diverged at approximately 2.5 years in favor of the invasive strategy (Figure 2B, Fine-Gray *P*=0.008), with an estimated 7-year difference in the cumulative incidence for invasive versus conservative management of −2.19% (95% CI, −3.85% to −0.53%) and adjusted hazard ratio of 0.78 (95% CI, 0.63–0.96) (Table). Noncardiovascular mortality cumulative incidence curves by assigned strategy diverged at ~2.5 to 3 years in favor of the conservative strategy (Figure 2C, Fine-Gray *P*=0.015). Between 4 and 6 years, the cumulative incidence of noncardiovascular mortality was significantly higher in the invasive versus conservative strategy (Table). At 7 years, the estimated difference in the cumulative incidence of noncardiovascular mortality for invasive versus conservative management was 1.20% with a 95% CI just covering the null (95% CI, −0.32% to 2.72%) (Table). Adjusting for baseline characteristics, the hazard ratio for noncardiovascular mortality was 1.44 for the invasive strategy compared with the conservative strategy (95% CI, 1.08–1.91) (Table). Twenty-one deaths were noted to have a proximate COVID-19 diagnosis.

The Bayesian posterior distributions of the adjusted absolute percent difference between the invasive versus conservative strategy in the cumulative all-cause mortality rate at 7 years, and the cumulative incidence of cardiovascular and noncardiovascular mortality at 7 years, are shown in Figure 3, with detailed posterior summaries presented in Table S2. The posterior mean adjusted absolute percent difference in the 7-year all-cause mortality rate was near null (absolute difference, 0.09% (95% credible interval, −1.85% to 1.99%). The

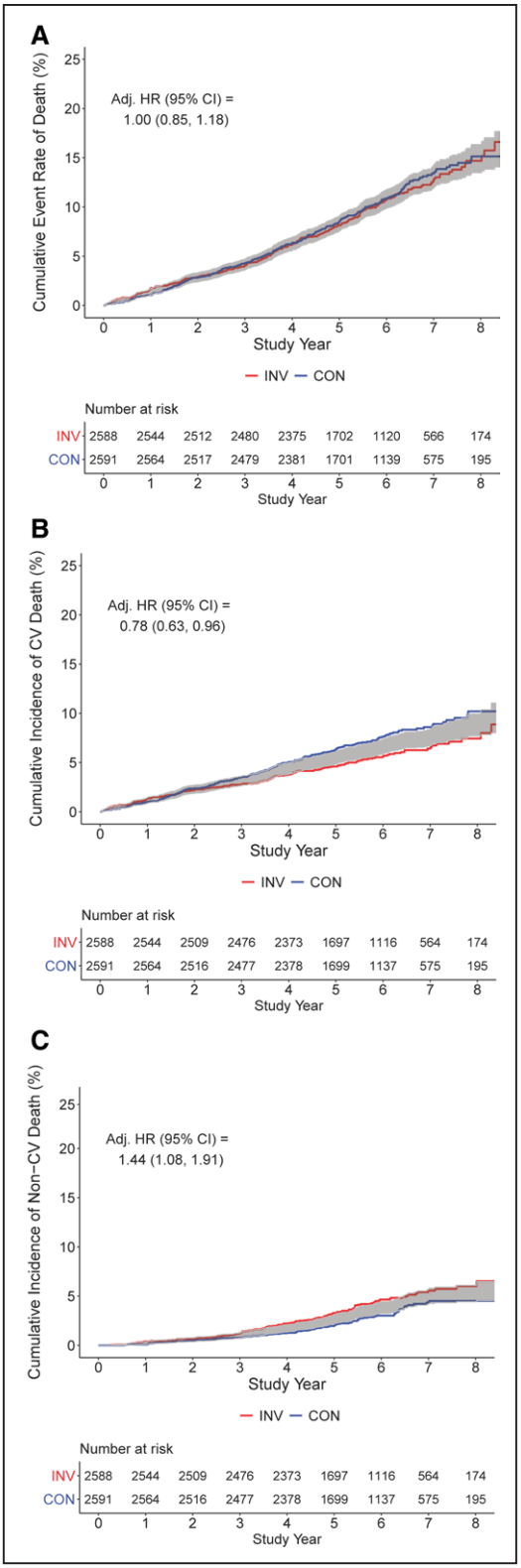

Figure 2. Cumulative incidence of mortality for invasive versus conservative strategy.
For each panel, cumulative mortality data are presented by initial randomized assignment to invasive (INV, red) versus conservative (CON, blue) management strategy. Shading indicates the half width of the 95% CI for the difference. Lack of overlap between the lines and shading indicates that the 95% CI for the difference excludes 0. (*Continued*)

Figure 2 Continued. For countries collecting cause of death data, cases with undetermined cause of death are included as cardiovascular (CV) death, as was prespecified in the trial CV death definition. In 1 country, where cause of death data were not available after the end of the trial phase on June 30, 2019, 22 deaths after June 30, 2019 were censored as of June 30, 2019. Numbers at risk for each group are below the x axis. **A**, All-cause mortality cumulative event rate by initial randomized assignment to invasive versus conservative management strategy. The adjusted hazard ratio (Adj. HR) is 1.00 (95% CI, 0.85–1.18). **B**, Cumulative incidence function for CV mortality by initial randomized assignment to invasive versus conservative management strategy, accounting for competing risks. The Adj. HR is 0.78 (95% CI, 0.63–0.96). **C**, Cumulative incidence function for noncardiovascular mortality by initial randomized assignment to invasive versus conservative management strategy, accounting for competing risks. The Adj. HR is 1.44 (95% CI, 1.08–1.91).

cumulative incidence of cardiovascular mortality at 7 years was 1.70% lower in the invasive versus conservative strategy (95% credible interval, −3.14% to −0.26%). The posterior probability that the 7-year difference in the incidence of cardiovascular mortality favored the invasive strategy by at least 1% compared with the conservative strategy was 82%. In contrast, the cumulative incidence of noncardiovascular mortality at 7 years was an estimated 1.65% higher in the invasive versus conservative strategy (95% credible interval, 0.37%–2.82%). There was an 85% posterior probability that the 7-year difference in the incidence of noncardiovascular mortality favored the conservative strategy by at least 1%.

Subgroup Analyses

Subgroup analyses for all-cause mortality, cardiovascular mortality, and noncardiovascular mortality are presented in Figure 4A through 4C, respectively. After adjusting for baseline characteristics, there were no significant differences between management strategies. Baseline CCTA was performed in 3913 (76%) of the 5179 randomized trial participants and was analyzable for MVD (using the ≥70% stenosis definition) in 3047 (78%) (Table S3). Figure 5 shows the cumulative event rate for all-cause mortality and the cumulative incidence of cardiovascular and noncardiovascular mortality for the invasive versus conservative strategy, stratified by whether or not MVD was present using the ≥70% stenosis definition (Figure 5).

Sensitivity Analyses

During the trial phase and extended follow-up, there were 267 cardiovascular deaths, 192 noncardiovascular deaths, and 98 undetermined deaths. This totals 557 deaths. Of the 98 undetermined deaths, 60 occurred during the extended follow-up period. Of the 60 undetermined deaths occurring during the extended follow-up

Table. Effect of an Invasive Versus Conservative Strategy on All-Cause Mortality, Cardiovascular Mortality, and Noncardiovascular Mortality

	INV	CON	Estimated % difference for INV vs CON* (95% CI)	Adjusted hazard ratio† (95% CI)
All-cause mortality				1.00 (0.85 to 1.18)
Number of participants with event	274	283		
1-year cumulative event rate	1.70%	1.04%	0.66% (0.02% to 1.29%)	
2-year cumulative event rate	2.90%	2.86%	0.04% (−0.87% to 0.95%)	
3-year cumulative event rate	4.06%	4.28%	−0.23% (−1.31% to 0.86%)	
4-year cumulative event rate	6.19%	6.29%	−0.11% (−1.42% to 1.21%)	
5-year cumulative event rate	8.15%	8.48%	−0.33% (−1.87% to 1.21%)	
6-year cumulative event rate	10.78%	10.88%	−0.10% (−1.96% to 1.76%)	
7-year cumulative event rate	12.70%	13.40%	−0.70% (−2.95% to 1.56%)	
Cardiovascular mortality				0.78 (0.63 to 0.96)
Number of participants with event	147	196		
1-year cumulative incidence	1.31%	0.96%	0.35% (−0.23% to 0.93%)	
2-year cumulative incidence	2.24%	2.39%	−0.15% (−0.97% to 0.67%)	
3-year cumulative incidence	2.78%	3.51%	−0.73% (−1.68% to 0.22%)	
4-year cumulative incidence	3.75%	5.02%	−1.27% (−2.38% to −0.15%)	
5-year cumulative incidence	4.60%	6.35%	−1.74% (−3.01% to −0.48%)	
6-year cumulative incidence	5.62%	7.64%	−2.02% (−3.48% to −0.56%)	
7-year cumulative incidence	6.41%	8.60%	−2.19% (−3.85% to −0.53%)	
Noncardiovascular mortality				1.44 (1.08 to 1.91)
Number of participants with event	112	80		
1-year cumulative incidence	0.39%	0.08%	0.31% (0.05% to 0.57%)	
2-year cumulative incidence	0.66%	0.46%	0.19% (−0.21% to 0.60%)	
3-year cumulative incidence	1.24%	0.77%	0.47% (−0.08% to 1.01%)	
4-year cumulative incidence	2.21%	1.24%	0.97% (0.26% to 1.68%)	
5-year cumulative incidence	3.29%	1.96%	1.32% (0.42% to 2.23%)	
6-year cumulative incidence	4.65%	3.02%	1.63% (0.46% to 2.81%)	
7-year cumulative incidence	5.56%	4.36%	1.20% (−0.32% to 2.72%)	

CON indicates conservative strategy; and INV, invasive strategy.

*For mortality, we estimated the Kaplan-Meier–based event rate at each time point. For the competing events of cardiovascular and noncardiovascular mortality, we used a nonparametric cumulative incidence function to estimate the cumulative incidence at each time point.

†Adjusted hazard ratios were estimated from separate multivariable Cox proportional hazards regression models for each outcome. Models were adjusted for prespecified participant baseline characteristics, namely, sex, age, diabetes, estimated glomerular filtration rate, and ejection fraction. For competing events cardiovascular and noncardiovascular mortality, we estimated cause-specific hazard ratios.

period, 22 were from the country that could not provide cause of death. We conducted sensitivity analyses with respect to the classification on new undetermined deaths from extended follow-up as cardiovascular deaths (Table S4, cardiovascular mortality; Table S5, noncardiovascular mortality). In the analyses of cardiovascular and noncardiovascular mortality, the estimated hazard ratio for an invasive versus conservative strategy was robust to grouping new undetermined deaths as noncardiovascular deaths, including grouping deaths from the 1 country without cause of death data available during extended follow-up.

For all-cause, cardiovascular, and noncardiovascular mortality, Tables S6 through S8 (respectively) compare the estimated effect of treatment strategy based on the proportional hazards assumption with nonproportional hazards specifications where the treatment effect is allowed to vary according to time intervals during the follow-up period. Estimated treatment effects do not appear sensitive to the proportional hazards assumption.

DISCUSSION

In this interim report of the extended follow-up of the ISCHEMIA trial, there was no difference in all-cause mortality out to 7 years, but there was a lower risk of 7-year cardiovascular mortality and a higher risk of noncardiovascular mortality with the initial invasive strategy as compared with the initial conservative strategy. Because these 2 mortality patterns were of

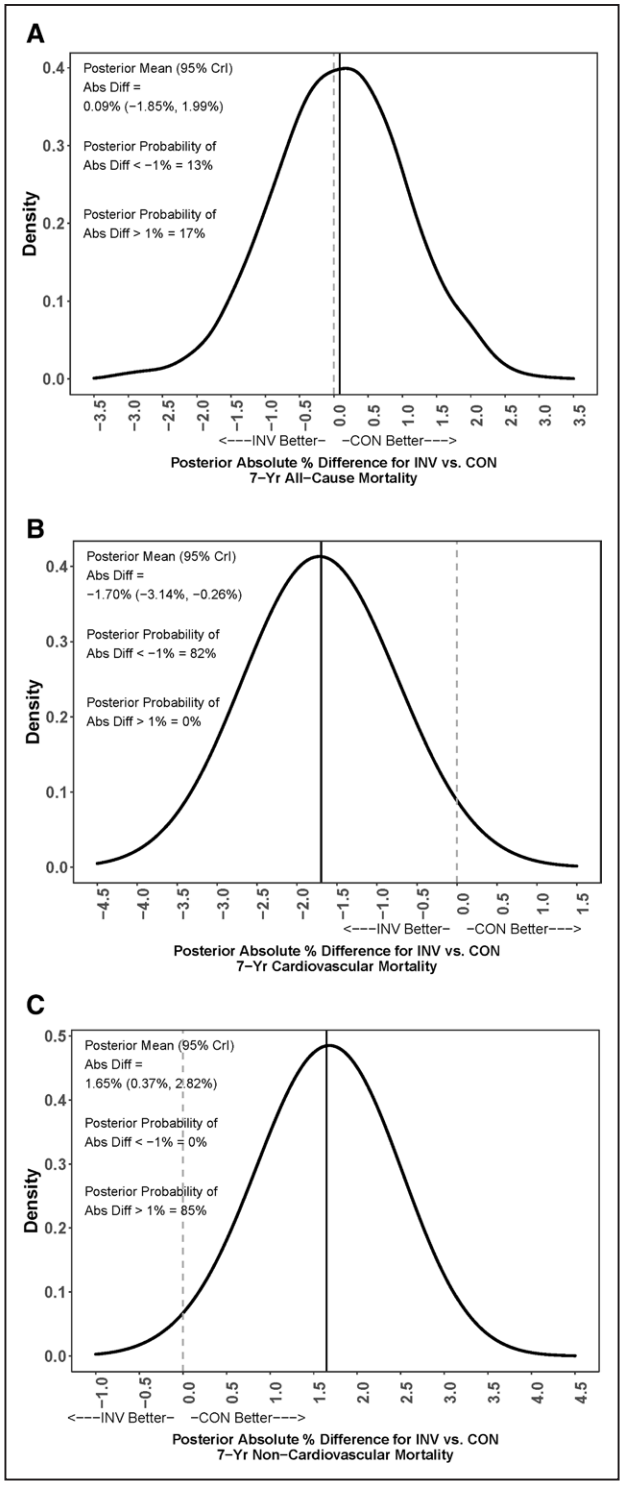

Figure 3. Probability that one strategy is better than another for 7-year all-cause mortality.
Posterior distribution of the adjusted absolute percent difference (Abs Diff) in risk of mortality at 7 years for an invasive (INV) versus conservative (CON) strategy. The gray dashed vertical bar is the null value indicating no difference. The solid black vertical bar is the posterior mean value of the difference. Positive values represent lower mortality for a conservative strategy, and negative values represent lower mortality for an invasive strategy. **A**, The posterior distribution of the Abs Diff in risk of all-cause mortality at 7 years for an INV versus CON strategy. The solid line is close to the gray dashed null value line, (*Continued*)

Figure 3 Continued. indicating no difference between the groups. **B**, The posterior distribution of the Abs Diff in risk of cardiovascular mortality at 7 years for an INV versus CON strategy. The concentration of values around −2 indicates a benefit to an invasive rather than conservative strategy by ~2 percentage points. In contrast, in **C** for noncardiovascular mortality, the posterior distribution of the Abs Diff in risk of noncardiovascular mortality at 7 years for an INV versus CON strategy shows a concentration of values around +2 and indicates a benefit to a conservative rather than invasive strategy by ~2 percentage points.

approximately equal magnitude, all-cause mortality rates showed no net treatment difference. This interim report of extended follow-up of participants adds almost twice as many deaths compared with that reported in the trial phase. Although not well-powered for all-cause mortality, these additional deaths afford greater precision around the estimated adjusted hazard ratio for invasive versus conservative management strategies (hazard ratio, 1.00 [95% CI, 0.85–1.18]). Using Bayesian analysis, there was a 82% probability that an invasive strategy was superior to a conservative strategy by at least 1 absolute percentage point for cardiovascular mortality, and a 85% probability that a conservative strategy was superior by at least 1 absolute percentage point for noncardiovascular mortality. The probability of near 50% for either a survival benefit with an invasive strategy or a conservative strategy suggests that there is no clinically meaningful difference in 7-year all-cause mortality between groups.

The incremental value of an initial invasive strategy was tested in the context of the population randomized, the procedures performed, and the use of guideline-directed medical therapy.[16] The strategy did not test routine revascularization for those with angiographic findings suitable for revascularization; rather, we tested routine cardiac catheterization compared with selective use of catheterization and revascularization on the basis of clinical need, eg, acute coronary syndrome or refractory angina. During the trial phase, there was greater use of revascularization in the invasive strategy group (mean 0.9 procedures per invasive strategy participant and 0.3 per conservative strategy participant),[1] consistent with the trial randomization. We did not collect information on revascularization during the extended follow-up phase. The 4-year cumulative rate of revascularization in the conservative group was 23%.[1] Dual antiplatelet therapy use was higher in the invasive strategy group throughout the trial phase.

Our results are consistent with previous randomized trials of revascularization versus medical therapy alone, which have reported similar rates of all-cause mortality between groups.[17–22] A meta-analysis of such randomized trials, including the initial trial phase of ISCHEMIA, has also reported similar all-cause mortality between groups (odds ratio, 0.99 [95% CI, 0.90–1.09).[23] When considering cardiovascular mortality, it has previously been suggested that longer term follow-up[24] will demonstrate a benefit of revascularization on all-cause mortality.

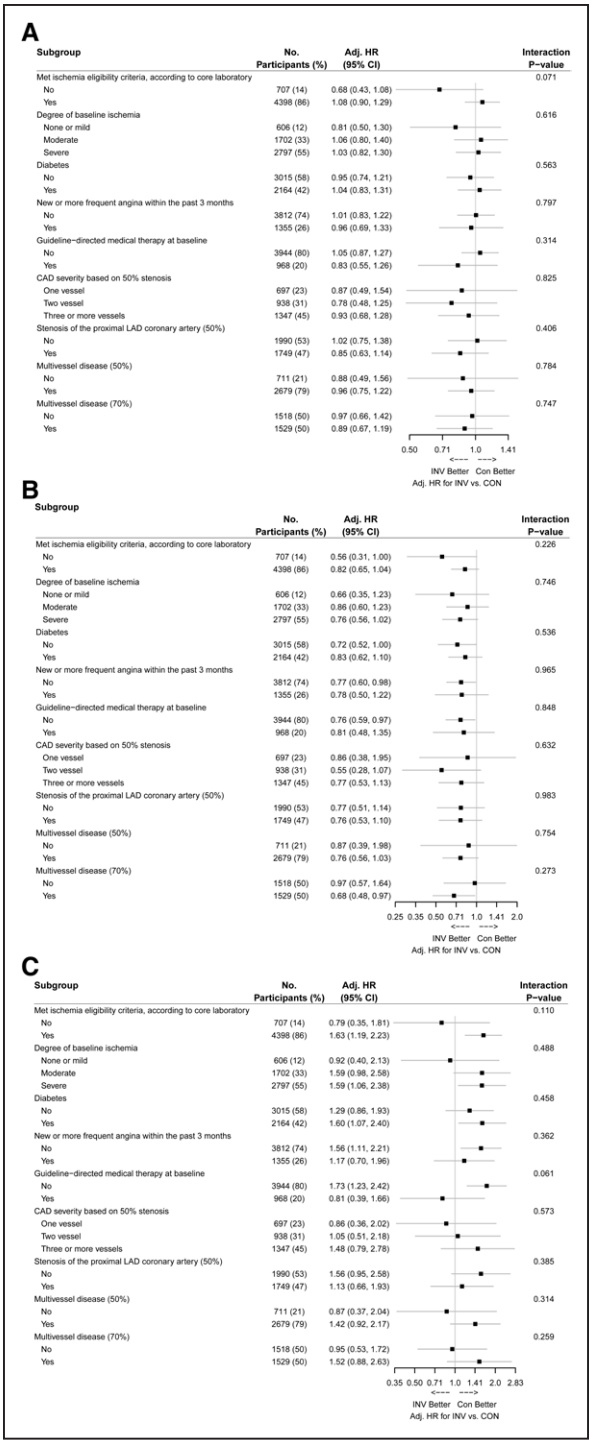

Figure 4. Forest plot for heterogeneity of treatment effect. A, All-cause mortality. B, Cardiovascular mortality. C, Noncardiovascular mortality.

Adjusted hazard ratios and associated 95% CIs for an invasive (INV) versus conservative (CON) strategy in prespecified subgroups are shown. The subgroup-specific treatment effects are adjusted for sex, age, diabetes status, estimated glomerular filtration rate, and ejection fraction. Denominators in a given subgroup may vary by data availability. MVD, multivessel disease; MVD (50, 70) indicates the stenosis threshold for determination of a diseased vessel was ≥50% or ≥70%, respectively. For coronary artery disease (CAD) severity on the basis of ≥50% stenosis, 4 participants with 0 vessel disease were excluded from the analysis. Adj. HR indicates adjusted hazard ratio; and LAD, left anterior descending artery.

Although not powered for all-cause mortality, the current analysis shows an effect size similar to the previously described meta-analysis with a hazard ratio of 1.00 and 95% CIs from 0.85 to 1.18. We estimated a probability of 13% that there was at least a 1% absolute percentage point difference in all-cause mortality at 7 years in favor of an invasive strategy, and a 17% probability of at least a 1% advantage in all-cause mortality in favor of a conservative strategy.

Accrual of additional deaths during extended follow-up allowed us to detect a lower rate of cardiovascular death with the invasive strategy. This is consistent with a previous meta-analysis reporting a 21% reduction in the odds of cardiovascular mortality associated with an invasive strategy whether ISCHEMIA was included (odds ratio, 0.79 [95% CI, 0.67–0.93]) or not.[24] The trial phase demonstrated an excess of periprocedural MI events and a reduction in spontaneous MI events with the invasive strategy.[12] Because spontaneous MI in this trial and other studies has been associated with greater risk of subsequent death compared with periprocedural MI, we postulated that these differences in the rates and effect of MI during the trial would translate to reduction in long-term all-cause and cardiovascular mortality.[2] We observed lower cardiovascular mortality with the invasive strategy, but that benefit was offset by higher noncardiovascular mortality of approximately equal magnitude with the invasive strategy, resulting in no difference in all-cause mortality.

The higher rate of noncardiovascular death in the invasive group was unexpected and remains unexplained. The low rate of all-cause death makes it unlikely that the observed excess risk of noncardiovascular death among invasive strategy participants is explained by the phenomenon of competing risks; the rate of noncardiovascular death would have to be substantially higher to explain the apparent observed difference in noncardiovascular death between the 2 treatment groups on the basis of competing risks alone. Common causes of noncardiovascular death in ISCHEMIA and other studies of chronic coronary disease are typically cancer and infection.[3,25] We previously reported that noncardiovascular death was higher with the invasive strategy and that there were more deaths from malignancy in the invasive strategy group despite equal baseline prevalence of cancer in the 2 groups. There was a significant association between the number of procedures with radiation exposure (ie, stress nuclear test, CCTA, cardiac catheterization, and percutaneous coronary intervention) and death from malignancy. The higher use of dual antiplatelet therapy in the invasive arm of ISCHEMIA was not associated with a higher rate of incident malignancy during the trial.[3] As noted previously, the timing of the association between radiation exposure, new malignancy, and malignancy-related death does not seem biologically plausible as

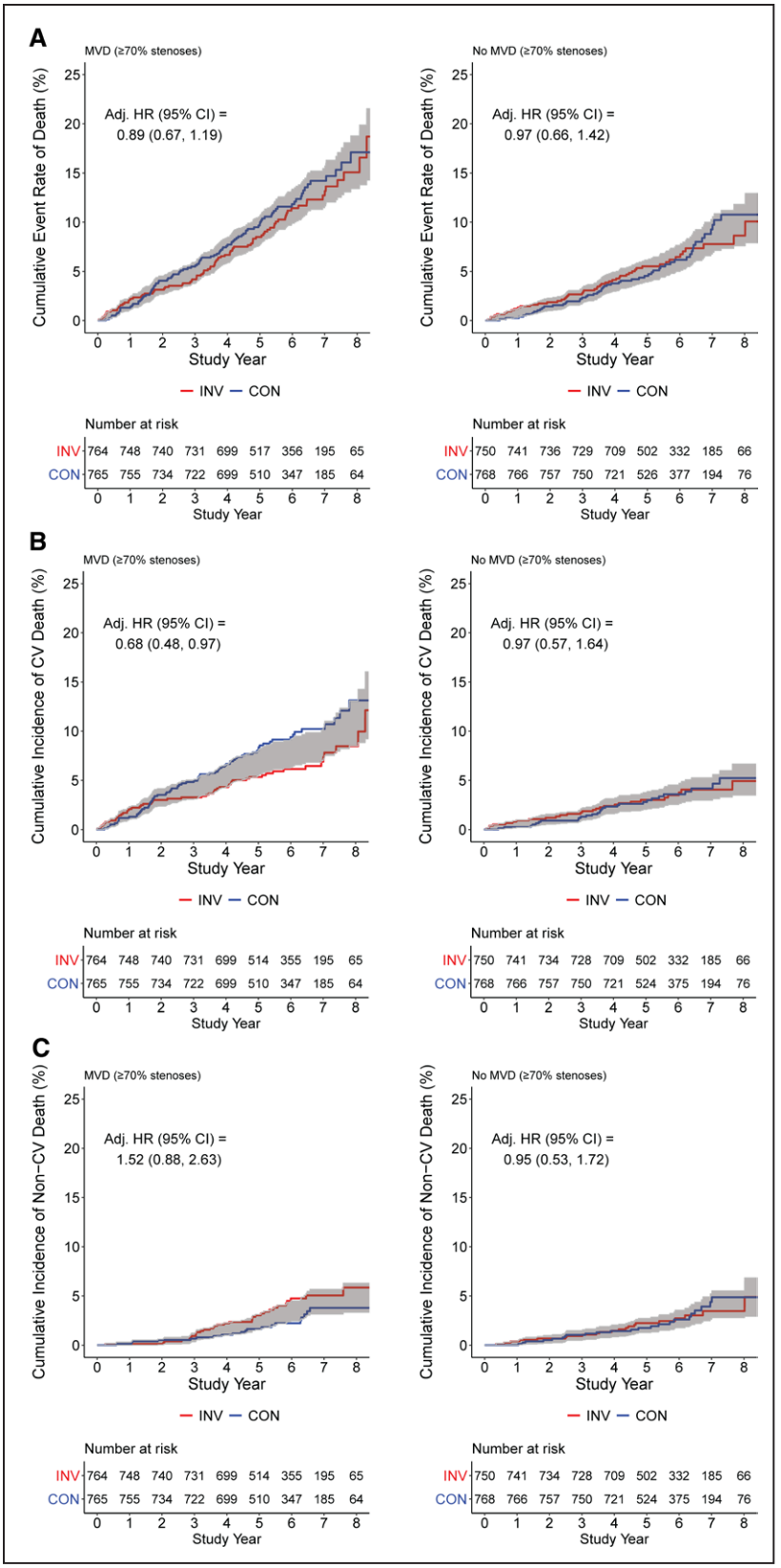

Figure 5. All-cause, cardiovascular, and noncardiovascular mortality among participants by presence of multivessel disease (N=3047).
For each of all-cause, cardiovascular, and noncardiovascular, the *P* values for interaction between the presence or absence of multivessel disease and treatment assignment were >0.05 (Figure 4). **A**, Cumulative all-cause mortality rate for participants with CCTA data evaluable for multivessel disease (MVD) (≥70% stenosis) by initial randomized assignment to invasive (INV, red) versus conservative (CON, blue) management strategy, stratified by participants with MVD on CCTA (**A**) and those without MVD on CCTA (**B**). **B**, Cumulative incidence of cardiovascular mortality for participants with CCTA data evaluable for MVD (≥70% stenosis) by initial randomized assignment to invasive (red) versus conservative (blue) management strategy, stratified by participants with MVD on CCTA (**A**) and those without MVD on CCTA (**B**). **C**, Cumulative incidence of noncardiovascular mortality for participants with CCTA data evaluable for MVD (≥70% stenosis) by initial randomized assignment to invasive (red) versus conservative (blue) management strategy, stratified by participants with MVD on CCTA (**A**) and those without MVD on CCTA (**B**). Adj. HR indicates adjusted hazard ratio; CCTA, coronary computed tomography angiography; and CV, cardiovascular.

the cause of an increase in noncardiovascular death because the latency period between radiation damage to a clinically diagnosable cancer and death is expected to be much longer than our trial follow-up period.

Cause of death is not being centrally adjudicated during extended follow-up. However, during the trial phase, when all deaths were centrally adjudicated for cause, the sensitivity of site-determined trial-defined

cardiovascular death was 91%, and when the site reported death as cardiovascular, it was confirmed as cardiovascular by the events committee in 96%.[6] Determination of cause of death is inherently limited on the basis of variation in the amount of information available from case to case, as well as intrinsic uncertainties about causal mechanisms of death in relation to chronic coronary disease and comorbidity.

The key finding remains that with 557 deaths, all-cause mortality was not different between groups. ISCHEMIA-EXTEND will continue to follow surviving participants into 2025 for a projected median of ~10 years to increase the precision around these mortality estimates. We note the absence of significant interaction on outcomes between the presence or absence of multivessel CAD on the basis of CCTA and the randomized initial strategy. This subgroup was selected for analysis on the basis of our previous publication demonstrating that CAD severity was strongly associated with mortality. A more detailed subgroup analysis related to ischemia severity was not performed because of its previously demonstrated lack of increased risk after adjustment for CAD severity.[4]

Studies of patient preferences demonstrate that quality of life, functional status, and survival rank highly.[26] We have previously shown that quality of life was improved with an initial invasive strategy, and the extent of benefit was related to the degree of angina on a medically tolerated regimen.[27] Those without angina did not experience quality-of-life benefits. We believe the data from this interim follow-up report demonstrating no difference in survival between groups at 7 years will add to the evidence base for shared decision-making between patients and their physicians.

Limitations

The ISCHEMIA trial tested 2 commonly used clinical management strategies—invasive versus conservative—and did not test revascularization versus no revascularization. ISCHEMIA-EXTEND was designed as a pragmatic long-term follow-up study of mortality, with limited data collection. Therefore, no data were collected on nonfatal events, use of medications or revascularization procedures, angina burden, or quality of life after the initial median 3.2-year follow-up. The cause of death (cardiovascular versus noncardiovascular) was adjudicated during the trial phase but not during the extended phase.

CONCLUSIONS

An initial invasive strategy of cardiac catheterization and revascularization, when feasible, added to guideline-directed medical therapy resulted in no difference in all-cause mortality, but a lower risk of cardiovascular mortality and a higher risk of noncardiovascular mortality as compared with an initial conservative strategy with catheterization and revascularization reserved for failure of medical therapy in patients with moderate or severe ischemia during a median follow-up of 5.7 years.

ARTICLE INFORMATION

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Supplemental Material

ISCHEMIA-EXTEND Study Organization

Bayesian Modeling of the Effect of Management Strategy on All-Cause, Cardiovascular, and Noncardiovascular Mortality

Tables S1–S8

Site Investigators

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