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Long-term follow-up after invasive or conservative management of stable coronary disease: the ISCHEMIA-EXTEND study

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The ISCHEMIA trial found no statistical difference in the primary endpoint between initial invasive and conservative management of patients with chronic coronary disease and moderate-to-severe ischaemia on stress testing. However, an invasive strategy increased peri-procedural myocardial infarction (MI) but decreased spontaneous MI with continued separation of curves over time. Thus, in order to assess the long-term effect of invasive management strategy on mortality, the ISCHEMIA-EXTEND observational study was planned including surviving participants from the initial phase of the ISCHEMIA trial with a projected median follow-up of nearly 10 years. Recently, an interim report of 7-year all-cause, cardiovascular (CV), and non-CV mortality rates has been published showing no difference in all-cause mortality between the two strategies, but with a lower risk of CV mortality and higher risk of non-CV mortality with an initial invasive strategy over a median follow-up of 5.7 years. The trade-offs in CV and non-CV mortality observed in ISCHEMIA-EXTEND raise many important questions regarding the heterogeneity of treatment effect, the drivers of mortality, and the relative importance and reliability of CV vs. all-cause mortality. Overall, findings from ISCHEMIA and ISCHEMIA-EXTEND trials might help physicians in shared decision-making as to whether to add invasive management to guideline-directed medical management in selected patients with chronic coronary artery disease and moderate or severe ischaemia.

Introduction

The aim of the ISCHEMIA trial was to determine whether routine cardiac catheterization and revascularization in patients with chronic coronary disease (CCD) reduce the likelihood of major adverse cardiac events when added to guideline-directed medical therapy (GDMT).[1] In ISCHEMIA, 5179 participants with moderate or severe stress-induced ischaemia were randomized to either initial invasive management with angiography, revascularization when feasible, and GDMT or initial conservative management with GDMT alone and angiography reserved for failure of medical therapy. Unlike previous trials,[2–4] ISCHEMIA participants required at least moderate ischaemia to qualify for the trial, and they were randomized before cardiac catheterization. The primary five-component outcome was cardiovascular (CV) mortality, myocardial infarction (MI), or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest. Major secondary outcomes were the composite of CV mortality or MI and angina-related quality of life. Over a median follow-up of 3.2 years, the ISCHEMIA trial found no statistical difference in the primary clinical endpoint between initial invasive management and initial conservative management.[1] Hazards comparing the treatment strategies were non-proportional, with crossing of the event curves just before 2 years. An invasive strategy exhibited early excess risk, driven by a higher risk of peri-procedural MI, relative to a conservative strategy. Conversely, a lower risk of spontaneous MI in the invasive strategy emerged over time.[5] Cardiovascular mortality curves by treatment

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strategy were suggestive of a late divergence in favour of the invasive strategy over the conservative strategy.[6] In contrast, non-CV mortality rates were higher in the invasive strategy as well as all-cause mortality.[6] Given the stronger association between spontaneous MI and subsequent CV mortality,[5,7] an initial invasive strategy might prove favourable over a longer period of time. An extended follow-up of participants from the ISCHEMIA trial may, therefore, inform whether an initial invasive strategy affects the long-term fate of patients with stable ischaemic heart disease. Thus, in order to assess the long-term effect of invasive management strategy on mortality, the ISCHEMIA-EXTEND observational study was planned by including surviving participants from the initial phase of the ISCHEMIA trial with a projected median follow-up of nearly 10 years. Recently, an interim report of 7-year all-cause, CV, and non-CV mortality rates for the ongoing NHLBI-funded ISCHEMIA-EXTEND study has been published.[8]

In contrast to the primary trial results, patients treated with an initial invasive strategy experienced an estimated 2.2% absolute reduction in CV mortality at 7 years (estimated number needed to treat 45). This is consistent with a prior meta-analysis reporting a 21% reduction in the odds of CV mortality associated with an invasive strategy.[9] This benefit was offset by an estimated 1.2% absolute increase in non-CV mortality over the same timeframe (estimated number needed to harm 83). The authors conclude that the probability of nearly 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 the groups. Limitations acknowledged by the authors include a lack of central event adjudication and limited data collection. In particular, no data were collected on non-fatal events, use of medications or revascularization procedures, angina burden, or quality of life after the initial median 3.2 years of follow-up.

A lot of lingering issues remain to be addressed. Are these findings from ISCHEMIA-EXTEND likely to change clinical practice? Can we identify patients with CCD treated with an initial invasive strategy for whom the CV mortality benefit meaningfully exceeds the risk of non-CV death? Cause of death in clinical research and clinical practice: which does matter?

Heterogeneity of treatment effect

The concept of heterogeneity of treatment effect becomes relevant whenever we try to apply trial results to individual patients. It might be expected that an initial invasive strategy would have a larger impact on CV mortality among patients with a higher CV risk. For example, previous analyses of the ISCHEMIA trial showed that coronary artery disease severity was strongly associated with mortality.[10] Unfortunately, heterogeneity of treatment effect does not appear to inform the interim findings of the ISCHEMIA-EXTEND study. In fact, no treatment heterogeneity for all-cause mortality was identified in subgroup analyses that would favour an early invasive strategy, including those with multi-vessel coronary artery disease. Possible explanations include insufficient power to identify this heterogeneity and the potential need for an even longer follow-up to identify subgroups for whom an invasive strategy results in an overall mortality benefit. The investigators plan to further follow-up for a maximum of 10 years to continue to monitor for a signal of a mortality difference.

Drivers of mortality in patients with chronic coronary disease

The higher rate of non-CV death in the invasive group was unexpected and remains unexplained. Understanding what drives non-CV mortality following an invasive strategy has important implications. ISCHEMIA investigators previously reported that common causes of non-CV death in the trial were typically cancer and infection.[6] Unfortunately, the ISCHEMIA-EXTEND study cannot provide more detailed data on the specific causes of death, preventing additional inference into a still unknown mechanism through which percutaneous coronary intervention would increase non-cardiac death.

ISCHEMIA investigators previously reported an increase in mortality from malignancy in the invasive group despite equal baseline prevalence of cancer in the two groups.[6] Furthermore, there was a significant association between the number of procedures with radiation exposure (i.e. stress nuclear test, computed tomography, cardiac catheterization, and coronary angioplasty) and death from malignancy. However, the timing of the association between radiation exposure, new malignancy, and malignancy-related death does not seem biologically plausible as the cause of an increase in non-CV death because the latency period between radiation damage to a clinically diagnosable cancer and death is expected to be much longer than the trial follow-up period.[11] While antiplatelet therapy increases the potential for bleeding, which could potentially unmask an unrecognized malignancy, the higher use of DAPT in the invasive arm of ISCHEMIA was not associated with a higher rate of incident malignancy during the trial. On the other hand, DAPT has been linked to non-cardiac-related deaths in a large trial,[12] but not in an individual data meta-analysis.[13] Evidence suggests that a longer duration of dual antiplatelet therapy is associated with an increased risk of non-cardiac mortality.[13] The reasons for these associations have not been fully understood, but may include deaths due to major bleeding events (that are often coded as non-cardiac) or a higher bleeding-related mortality in case of trauma or other acute events in patients receiving dual anti-platelet therapy. Despite these potential explanations, the relationship between invasive procedures and non-CV mortality deserves further investigation.

What should be the primary endpoint in revascularization trials?

Findings from the ISCHEMIA-EXTEND study raise the issue of what should be the primary endpoint in revascularization trials and meta-analyses. Total mortality has been advocated to be the best endpoint in clinical trials as it embraces both benefits and harms of treatments. However, for drawing precise treatment effect estimates, primary endpoints should be more specific than total mortality. The use of all-cause mortality in myocardial revascularization trials remains controversial,[14] as highlighted by the fact that most trials, including the ISCHEMIA trial,

used cause-specific rather than all-cause mortality in their primary composite outcome.

Long-term mortality tends to be biased towards the null, based on competing risks that cannot be influenced by the intervention, as well as the uncontrolled effects of care after the study intervention.[15] The competing risk of non-CV modes of death, which may blunt the effect of revascularization on all-cause mortality, becomes amplified with a longer follow-up, limiting the reliability of all-cause mortality as a main endpoint.[16] The longer the follow-up, the more likely non-CV deaths will occur, diluting the impact of a randomized treatment on total mortality even if there is an effect on cardiac mortality. ISCHEMIA-EXTEND investigators stated that due to the low rate of all-cause death, it is unlikely that the observed excess risk of non-CV death among patients of the invasive group is explained by the phenomenon of competing risks; the rate of CV death would have to be substantially higher to explain the apparent observed difference in non-CV death between the two treatment groups based on competing risks alone. However, a potential issue limiting the analysis of non-CV mortality is the above-mentioned inadequate data collection for the assessment of non-CV risk.

On a research level, it is easier to ascertain all-cause death than CV death, constituting a less biased and more reliable endpoint. Additionally, the effects of a coronary revascularization intervention are not mitigated if we include all-cause death as a component of the primary outcome (rather than CV death).

On a clinical/population level, the main utility of death surveillance is to plan risk mitigation strategies, aiming to reduce the most responsible specific components of all-cause death. Applied to the post-coronary revascularization setting, these data reinforce the importance of secondary prevention in preventing new CV events particularly in coronary artery disease patients, a population at a greater risk of having an MI-related death.

Conclusions

The interim report of the ISCHEMIA-EXTEND study shows that there was no difference in all-cause mortality in 7 years, but there was a lower risk of 7-year CV mortality and a higher risk of non-CV mortality with the initial invasive strategy when compared with the initial conservative strategy. The higher rate of non-CV death in the invasive group was unexpected and remains unexplained, deserving further investigation. Overall, the trial's extended follow-up provides much more robust evidence for the neutral effect on survival of the two strategies. Actually, when the ISCHEMIA trial was first designed, the goal of the trial was to determine whether a catheter-based strategy could ultimately reduce CV events like CV mortality and MI, and this seems to be the case: spontaneous MI at the earlier and CV death at the later time point being reduced by this strategy.

These findings might help physicians in shared decision-making as to whether to add invasive management to guideline-directed medical management in selected patients with chronic coronary artery disease and moderate or severe ischaemia.

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Data availability

No new data were generated or analysed in support of this research.

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