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VIEWPOINT
Clinical trials

Interpreting myocardial infarction analyses in ISCHEMIA: separating facts from fallacy

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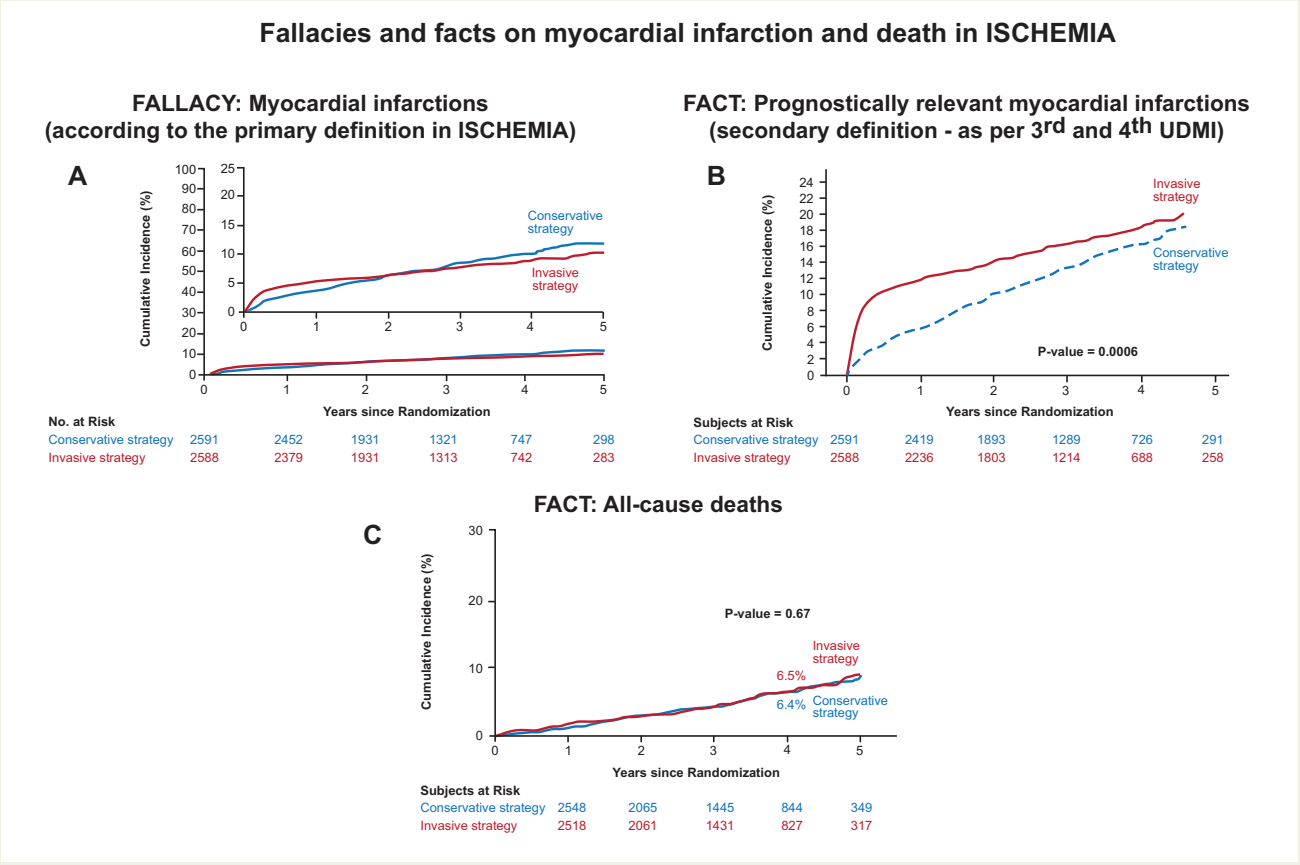

Graphical Abstract Hard endpoints in the ISCHEMIA trial. (*A*) Myocardial infarction according to the primary definition in the trial. (*B*) Prognostically relevant myocardial infarctions according to the criteria of the third and fourth Universal Definition of Myocardial Infarction. (*C*) All-cause deaths. CON, conservative arm; INV, invasive arm. From refs.[1,15]

After a decade of planning and execution, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial was published in April 2020.[1] This landmark study found that in patients with chronic coronary syndromes (CCS) both the composite primary endpoint [cardiovascular death, myocardial infarction (MI), hospitalization for unstable angina

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or heart failure, or resuscitated cardiac arrest] and secondary endpoint (cardiovascular death and MI) did not differ between invasive and conservative strategies, refuting the long-held belief in a prognostic benefit from revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery among patients with CCS who had significant inducible myocardial ischaemia at baseline.[1] In the invasive group of ISCHEMIA, 79% of patients underwent revascularization (PCI in 74%; CABG in 26%), whereas 21% did not. Periprocedural (Types 4a and 5) and late procedure-related MIs (Types 4b and 4c) were more frequent in the invasive arm, whereas late, spontaneous MIs were more common in the conservative arm. Although periprocedural MI was not associated with increased all-cause or cardiovascular mortality, late procedure-related MI was associated with a nearly four- and seven-fold increased risk in death and cardiovascular death, respectively. Type 1 MI was associated with a 2.4- and 3.3-fold increase in all-cause and cardiovascular death. On this basis, some have concluded that early revascularization should be offered to patients with CCS to prevent 'prognostically important' infarctions, i.e. spontaneous MIs while ignoring periprocedural and late procedure-related MIs (*Graphical abstract*). This commentary seeks to provide a rebuttal to this speculative conclusion by considering both biological plausibility and alternative evidence-based explanations, namely that (i) 'procedural' MIs are not innocuous and (ii) the higher mortality associated with revascularization-related (Types 4a, 4b, 4c, and 5) MI completely counterbalances the alleged mortality reduction attributed to a lower rate of Type 1 MI, resulting in net neutrality of total death rates.

Relevant background

Decades of accumulated dogma have suggested not just an association, but a *causal* relationship, between epicardial obstructive coronary artery stenoses, myocardial ischaemia, and adverse outcomes—including mortality and MI—thus leading to the prevalent belief that reduction of ischaemia by revascularization improves clinical outcomes. However, since 2003, a number of randomized controlled trials (RCTs)[2–4] and meta-analyses[5] have failed to demonstrate an interaction between ischaemia, revascularization, and mortality. However, in those studies, the extent and severity of ischaemia was not well characterized. ISCHEMIA was unique because it was the first RCT of an invasive strategy with state-of-the-art revascularization techniques plus optimal medical therapy (OMT) vs. OMT alone in patients with moderate-to-severe ischaemia. It also addressed other methodological weaknesses of prior studies, including randomization before delineating coronary anatomy, a goal of revascularization of all ischaemic areas (total ischaemic revascularization), and use of second-generation drug-eluting stents.

Reduction of future myocardial infarction by an invasive strategy—biologically plausible?

Pathological observations over the past 40 years have consistently demonstrated that culprit plaques responsible for most spontaneous MIs share common histological characteristics,[6] including inflammation, a thin fibrous cap, positive remodelling, and a large necrotic core, often found together in the so-called thin-capped fibroatheromas. These adverse plaque characteristics are demonstrable prospectively by advanced imaging techniques, including intravascular ultrasound with virtual histology, optical coherence tomography, or coronary computed tomography (CT) angiography. Even with advanced techniques, however, these imaging-based plaque characteristics have remarkably poor positive predictive value for clinical events. In the PROSPECT trial, 596 thin-cap fibroatheromas were identified using intravascular ultrasound, but only 6 patients had an MI within 3.4 years.[7] In the SCOT-HEART trial, 1376 plaques with adverse characteristics were identified on CT, yet across the entire cohort only 41 patients had an MI after 4.7 years.[8] Similarly, in the PROMISE trial, 1019 coronary plaques with adverse characteristics were observed on CT, yet only 24 subsequent non-fatal MIs occurred.[9] It strains credulity that less sophisticated angiographic selection of a lesion based simply on the degree of stenosis or physiologic lesion selection for PCI based on an inducible trans-stenotic pressure gradient would outperform advanced imaging techniques, identify plaques at the risk of rupture, and by intervening on them, avert downstream MIs. More likely, stenosis reduction by PCI ameliorates the trans-stenotic gradient, thus preventing the development of Type 2 MIs that are easily confused with Type 1 MIs based on clinical and angiographic criteria. Conversely, CABG may prevent future Type 1 MIs because bypass grafts to the mid-coronary arteries not only treat culprit lesions (even anatomically complex ones) but also provide prophylaxis against new proximal lesions, whereas stents treat only identified stenotic segments with no effect on remote native coronary artery disease (CAD) progression.[10]

Problems in downplaying periprocedural myocardial infarction

An advancing narrative in the aftermath of ISCHEMIA is that, compared to 'spontaneous' MI, periprocedural MI events are inconsequential and prognostically unimportant. ISCHEMIA, for unknown reasons, used a primary definition of periprocedural MI that required, for PCI, an increase of creatine kinase (CK)-MB >5 times the upper reference limit (URL) (preferred) or an increase in cardiac troponin (cTn) >35 times the URL with either new electrocardiographic changes or angiographic evidence of reduced flow or coronary dissection. In the absence of ancillary findings, CK-MB and cTn had to be >10 times and >70 times the URL, respectively. For CABG-related MI, definitions were even more stringent.[1] Thus, the frequent patient with 'only' an increase in troponin T (URL: 14 ng/mL)—say, from 6 to 910 ng/mL (= URL × 65)—would not be classified as having suffered an MI.

ISCHEMIA also considered alternative 'secondary' definitions of MI, consistent with the Third Universal Definition of Myocardial Infarction (UDMI)[11]: in patients with normal baseline cTn (as in most patients with CCS), elevations of cTn >5 and >10 times the URL occurring within 48 h of PCI or CABG, respectively—plus ancillary findings—would be defined as a Type 4a or 5 MI, respectively—not just 'myocardial injury'. These 'secondary' definitions, recently

reiterated in the 4th UDMI[12] based on expert consensus in the absence of definitive trial-based data, have now been corroborated by a recent analysis from the SYNTAX trial[13] and a meta-analysis of all PCI trials reporting on cardiac biomarkers in patients with CCS,[14] both concluding that such post-procedural troponin elevations are indeed associated with mortality. When the UDMI-consistent secondary ISCHEMIA definition is adopted, Type 4a MIs in the invasive arm in ISCHEMIA would more than *triple*, from 26 to 98.[1] Using the secondary MI definition, there would be overall 106 Type 1 and Type 2 spontaneous MIs in the invasive arm and 186 in the conservative arm, but this would be counterbalanced by far many more periprocedural (Types 4a and 5) and late procedure-related (Types 4b and 4c) MIs in the invasive arm (224 vs. 44): in aggregate, 330 MIs in the invasive strategy vs. 230 MIs in the conservative strategy[1] (*Graphical abstract*). The occurrence of some procedural MIs in the conservative arm was due to some cross-over from the conservative to the invasive arm during the course of the trial. In any case, in reality, according to current UDMI definitions, *more* MIs with adverse downstream effects on mortality occurred in the invasive than in the conservative arm.

Prognostic implications of myocardial infarctions in ISCHEMIA

For an MI to be clinically and prognostically significant, its prevention by revascularization should result in a mortality reduction. There has been much commentary regarding the greater impact on late mortality for spontaneous compared with periprocedural MIs (with little consideration of the excess mortality associated with late procedure-related MIs), yet in ISCHEMIA there was absolutely no differential effect of treatment strategy on all-cause and cardiovascular mortality at 5 years[1] (*Graphical abstract*). The only reasonable explanation for this observation is that the carry-over effects on mortality of the excess periprocedural (Types 4a and 5) and late procedure-related (Types 4b and 4c) MIs in the invasive arm (224 - 44 = 180) perfectly balanced the carry-over effects of the 80 (186 - 106) excess spontaneous MIs in the conservative arm. The finding that periprocedural MI according either to primary or secondary definitions in ISCHEMIA would not be associated with later mortality[15] is counterintuitive based on the above considerations, and likely the result of a type II statistical error—claiming the absence of an effect because of the inability to show it in statistical terms.

Implications of the myocardial infarction narrative in ISCHEMIA for routine cardiology practice

The findings of ISCHEMIA placed in appropriate context with prior randomized trials demonstrate that patients with CCS with moderate-to-severe ischaemia due to obstructive CAD in whom left main CAD is excluded should be initiated on a robust medical regimen of anti-anginal therapies, disease-modifying therapies, risk factor treatment and lifestyle interventions, including smoking cessation, weight loss where indicated, and regular aerobic exercise. Since the ISCHEMIA quality-of-life analysis showed a reduction in angina with the invasive strategy, patients with persistent and unacceptable angina should be referred for invasive angiography and considered for revascularization. For patients with infrequent (i.e. monthly) angina, which characterized ~80% of ISCHEMIA patients, there would seem to be a much less compelling justification for revascularization, and cardiologists should no longer refer patients for revascularization solely based on the results of ischaemia testing.

In summary, interpretations of presumed revascularization benefit predicated on a reduction in spontaneous MI in ISCHEMIA that dismiss the consequences of periprocedural and late procedure-related MI may lead to fallacious conclusions that are neither balanced nor fact-based. Thus, caution and circumspection should guide both discussions with patients with CCS and any decision-making about the risks and benefits of revascularization, while emphasizing that OMT remains the preferred initial approach to management.

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