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Invasive management of acute coronary syndromes

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Invasive versus non-invasive treatment in patients with non-ST-elevation acute coronary syndromes has been shown to reduce fatal and non-fatal events in the FRISC-II,¹ RITA-3,² and TACTICS-TIMI 18³ trials, and in meta-analyses,^{4,5} with positive results extending to 5 years.⁶ In *The Lancet*, the FRISC-II investigators present the 15 year outcomes of their study.⁷ In FRISC-II, 2457 patients with non-ST-elevation acute coronary syndromes were randomly assigned between 1996 and 1998 to receive an early invasive strategy with revascularisation within 7 days or a non-invasive strategy with invasive procedures for recurrent symptoms or exercise-induced ischaemia. Revascularisation was done during the hospital admission for the index event in 76% of patients in the invasive group and 13% of patients in the non-invasive group. By 2 years, 46% of the non-invasive group underwent revascularisation. The primary endpoint was a composite of death or myocardial infarction. Data for survival were available for 2421 (99%) of the originally enrolled patients, and for other events for 2182 (89%) patients. Because of the long-term nature of the follow-up, the statistical approach was relatively unusual (differences were assessed by use of the area between mean cumulative count-of-event curves).

The invasive strategy provided a mean of 549 days' (95% CI 204–888) postponement of death or myocardial infarction ($p=0.002$). However, most of the effectiveness of the invasive strategy was in the first 3–4 years after the procedure. The investigators reported larger effects in non-smokers (mean gain 809 days, 95% CI 402–1175; $p_{\text{interaction}}=0.0182$), patients with elevated troponin (778 days, 357–1165; $p_{\text{interaction}}=0.0241$), and patients with high concentrations of growth differentiation factor-15 (1356 days, 507–1650; $p_{\text{interaction}}=0.0210$). The effectiveness of the invasive strategy was largely driven by postponement of a new myocardial infarction, whereas the difference in mortality shown in shorter term studies was not sustained for the full follow-up period. During 15 year follow-up, almost half the patients died and most had a non-fatal event. The investigators rightfully suggest that this study provides a lifetime perspective, especially for a group of patients with a median age of 66 at the time of randomisation. The only other study with survival analysis beyond 5 years in this patient population was RITA-3,⁸ which similarly noted a survival benefit in the first 3 years, which was likewise gradually lost over time.

These findings confirm and extend the results of trials and meta-analyses of patients with acute coronary syndromes allocated to invasive and non-invasive strategies. The findings are generally supportive of prevention of subsequent myocardial infarction, with a smaller effect on mortality, which has not been sustained over time. Notably, non-ST-elevation acute

coronary syndrome includes both patients with and without an acute myocardial infarction, and the present study reports an interaction by troponin concentration. Thus, the benefit is mainly in patients with non-ST-elevation myocardial infarction, with little benefit if any in patients with troponin-negative acute coronary syndromes. This outcome is entirely consistent with the TACTICS-TIMI 18 trial.³

Substantial advances in care have been made since the time of the first FRISC-II study. In developed countries, time to an invasive approach in patients with non-ST-elevation acute coronary syndrome has been greatly shortened, such that a wait of 7 days would be unusual, perhaps limited to patients with serious comorbidities. The shortened time to an invasive strategy was reflected in the TACTIC-TIMI 18 trial, which was done several years after FRISC-II. Patients who are biomarker-negative, have not had a myocardial infarction, and are stable and asymptomatic might well be evaluated by non-invasive testing, with only patients with inducible ischaemia undergoing catheterisation.^{9,10} Important changes have also been made in interventional therapies, with drug-eluting stents (now in second-generation form) used in nearly all patients.¹¹ Advances have been made in antiplatelet therapy, with better defined use of dual antiplatelet therapy and the availability of newer and better P2Y₁₂ blockers.¹² Finally, the efficacy of statins in patients who have had a cardiovascular event has been shown, and will now be essentially uniformly prescribed.⁹ The importance of cessation of smoking tobacco cannot be overestimated.¹³ In FRISC-II, effectiveness of the invasive approach was not apparent in smokers.

Much has been learned about the role of an invasive strategy in patients with acute coronary syndromes in the past 20 years, and the approach has become routine and safer. Coupled with appropriate secondary prevention with pharmacotherapy and a therapeutic lifestyle, patients can be offered a high probability of a good outcome. The high rate of events noted during follow-up in FRISC-II would almost certainly be lower in a contemporary cohort.

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