

MULTISTARS AMI. A New Constellation or Just Stardust?

MULTISTARS AMI. ¿Una nueva constelación o solo polvo estelar?

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The MULTISTARS AMI study was presented at the 2023 Congress of the European Society of Cardiology and simultaneously published in the *New England Journal of Medicine*. (1) It was an open-label, randomized study to evaluate an immediate multivessel coronary angioplasty strategy versus a staged multivessel coronary angioplasty strategy. All the patients had acute ST-elevation myocardial infarction (STEMI) and multivessel disease. The staged strategy consisted of performing culprit lesion angioplasty during the index procedure and completing angioplasty on the rest of lesions from 19 to 45 days later. Large previous studies documented the benefits of complete staged revascularization in this context, (2,3) with reduced incidence of infarction or death upon remote progression, and the study was designed to see whether immediate revascularization was a non-inferior or eventually superior alternative.

The authors concluded that in hemodynamically stable patients with STEMI and multivessel disease, *immediate multivessel coronary angioplasty was non-inferior versus staged angioplasty* for the primary endpoint i.e., the risk of a combination of all-cause death, non-fatal myocardial infarction, stroke, unplanned ischemic revascularization, or heart failure hospitalization at a 1 year.

Remarkably, as clearly shown in Figure 1, the combined primary event in the immediate group was half reduced, with statistical significance for both non-inferiority and superiority.

Why immediate angioplasty was never concluded to be superior to the staged strategy and only non-inferiority was claimed?

This is a mystery, as the results appear to be very strong in terms of the advantages of immediate angioplasty and no investigator would deny its superiority, unless there was some barrier or criticism, which is not explicit in this case. According to the protocol design, if the primary endpoint analysis via the log-rank test was significant for non-inferiority, a similar supe-

riority analysis would follow, (4) which is a common methodology aspect.

The table 1 below summarizes the events.

We believe that a possible rationale for the authors' (or reviewers') decision may be two major weaknesses of the trial design, which prevents a firm answer to the research question.

Sui Generis Non-Inferiority Study

The COMPLETE study, (2) which showed the advantage of multivessel angioplasty, rather than limiting to the culprit vessel during the acute stage of the ST segment elevation infarction, considered progression to death or myocardial infarction as long-term comparative events in 4,000 patients. The logical design of a non-inferiority trial is to compare a new procedure or strategy against those validated by the original studies to show that there is no loss of the advantage gained in those studies, which would require a trial with at least the same sample size maintaining the combined death/infarction endpoint. (5) The MULTISTARS AMI design did not consider the events taken into account in the COMPLETE study, but a combined outcome including infarction, death, and also the need for revascularization, stroke, and heart failure hospitalization. However, this combined endpoint was changed during the course of the trial due to challenging patient enrollment. Therefore, this is a non-inferiority study of two strategies on previously untested events, with a sui generis design, of just 840 patients. Showing that the immediate strategy was non-inferior or superior to the staged strategy across an endpoint designed for this trial does not ensure whether the benefit over mortality and infarction upon follow-up was maintained, which had been confirmed by the COMPLETE study. In other words, this trial shows that the immediate strategy is non-inferior and even superior to the staged strategy for evaluated events, but this is not applicable to events remote from the original study, given the low number of cases, the low rate of events, and the brief follow-up.

REV ARGENT CARDIOL 2024;92:151-154. <http://dx.doi.org/10.7775/rac.v92.i2.20749>

Received: 12/11/2023 – Accepted: 01/04/2024

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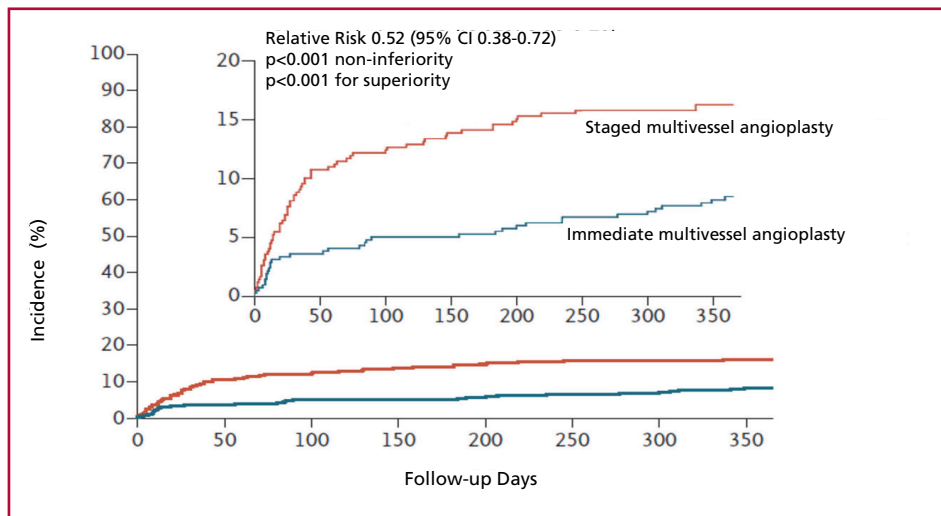


Fig. 1. Progress of cumulative incidence for the combined endpoint in MULTISTARS AMI study. The large difference between both groups was already present before 50 days, with few subsequent changes.

Modified from Stähli BE et al. *N Engl J Med.* 2023; 389:1368-1379.

Table 1.

Primary and secondary endpoints	Immediate Group (n=418)	Staged Group (n=422)	Relative Risk (95% CI)
Primary endpoint at 1 year			
	n (%)	n (%)	0.52 (0.38-0.72)
All-cause death, non-fatal myocardial infarction, stroke, unplanned ischemic revascularization, or heart failure hospitalization	35 (8.5)	68 (16.3)	
Secondary endpoints at 1 year			
	n (%)	n (%)	
All-cause death	12 (2.9)	11 (2.6)	1.10 (0.48-2.48)
Non-fatal myocardial infarction	8 (2.0)	22 (5.3)	0.36 (0.16-0.80)
Stroke	5 (1.2)	7 (1.7)	0.72 (0.23-2.26)
Unplanned ischemic revascularization	17 (4.1)	39 (9.3)	0.42 (0.24-0.74)
Heart failure hospitalization	5 (1.2)	6 (1.4)	0.84 (0.26-2.74)

What is a clinical trial relevant event?

The COMPLETE study considered two combined co-primary endpoints. The first combined endpoint considered as events related death or infarction during long-term follow-up. The second combined endpoint considered related death, infarction, or the need for long-term revascularization (Figure 2).

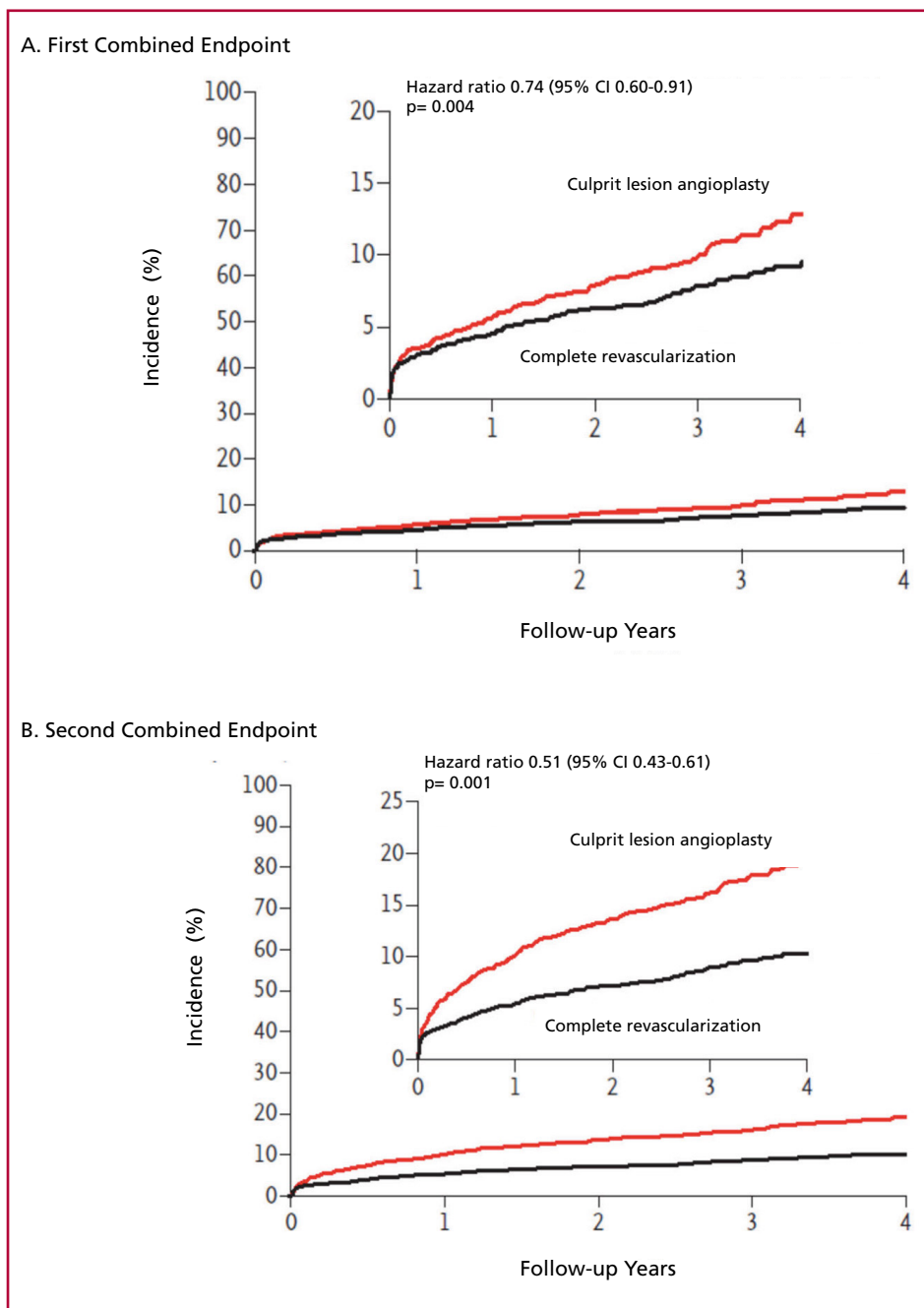
In the MULTISTARS AMI study, the curves are very different: every advantage is gained over the first few weeks, and then curves show parallel progression, which has a simple explanation.

Mortality in this trial was very low, and also the incidence of initial spontaneous infarction was very low during progression, with no differences between both strategies in the two cases. Nonfatal myocardial infarctions, excluding periprocedural ones, occurred in 5 patients (1.2%) in the immediate group and in 8 patients (1.9%) in the stage group (hazard ratio 0.62; 95% CI 0.20-1.89). The entire event difference was based on the rate of periprocedural infarctions and the revascularization indication.

Periprocedural myocardial infarction

The authors reported infarctions divided into 4a, overall post-angioplasty infarctions, and 4b, related to stent thrombosis. The incidence of stent thrombosis was similar in both groups (3 in the immediate and 2 in the staged group), but periprocedural infarction diagnosis was 0 in the immediate group and 12 in the staged group. The authors explain that it is difficult to diagnose a new enzyme elevation during the acute phase to be able to establish a procedure-related infarction, while, when angioplasty involves normalized enzyme levels, after several weeks, any elevated enzymes might induce the diagnostic assumption and be confirmed by minor clinical data, particularly infarctions with no new ST-segment elevation. The incidence of a new ST segment elevation infarction was 3 in the immediate group and 4 in the staged group, while the incidence of non-ST segment elevation infarction was 5 and 17, respectively. The periprocedural infarction diagnosis has been one of the most controversial and amended items in the proposed global definition of

Fig. 2. Cumulative incidence of events in the COMPLETE study.



2A. First combined co-primary endpoint of cardiovascular death or infarction. Divergence among curves is very slow in terms of infarction/death, with very little incidence in the first few months and increasing incidence upon progression.

2B. Second combined co-primary secondary endpoint of cardiovascular death, infarction, or need for deferred revascularization. Progression curves show an early separation that significantly increases over progression. Modified from Mehta SR et al. *N Engl J Med* 2019; 381: 1411-21.

infarction, (6) and the Society for Cardiovascular Angiography and Interventions (SCAI) (7) suggests that 7-fold enzyme elevation thresholds confirm this diagnosis. Previous studies of acute coronary syndrome with non-ST segment elevation showed that spontaneous infarctions were associated, as expected, with higher mortality and a 4- or 5-fold relative risk (RR), while, paradoxically, periprocedural infarctions in the

three classic studies (RITA 3, FRISC II and ICTUS) had HR 0.66 (95% CI 0.36-1.20), with a trend towards lower non-significant mortality. (8)

Different periprocedural infarction criteria affect the event rate reported by treating physicians versus central events evaluation committees, as observed in the PARAGON (9) and CHAMPION studies, (10) the latter showing three times the incidence of infarc-

tion. To summarize, periprocedural infarction, in this particular case, difficult to diagnose in the immediate group and overdiagnosed in the deferred staged group, may not be considered an adequate event for comparison. In addition, there is no pathophysiological hypothesis to explain that a deferred angioplasty might increase the rate of periprocedural infarction, which leads to the suspicion of a non-clinically relevant overdiagnosis, as commonly observed in intervention studies for acute coronary syndrome, as explained above. (11)

We ignore what led to "ischemia-guided" unplanned interventions

As this is an open-label study, a detailed description of the reasons leading to the decision of an unplanned ischemia-guided intervention would have been of much interest. Two reasons can be mentioned: angina recurrence, or ischemia findings upon stress tests. The revascularization rate was 17 (4.1%) in the immediate group versus 39 (9.3%) in the staged group. Unfortunately, the study has not provided any information in this sense, either in the original population or in the appendix. Had there been an indication for recurrent resting angina, it might be considered an event, but if findings of induced ischemia had been the indication in most cases, no event would be involved, but simply a logical and inevitable result of deferring the procedure, with no risks involved. Similar findings on this decision were reported by another non-inferiority trial with the same design. (12)

In summary:

COMPLETE, the original study, showing the benefits of complete revascularization versus limiting just to the culprit vessel in cases of ST-segment elevation infarction, deferred procedures at two different times, on the day after baseline and after several weeks, with similar benefits for both over remote progression of severe events, such as spontaneous infarction or death. This study, MULTISTARS AMI, does not provide any information on whether performing the procedure on the first day is non-inferior or superior to the staged approach in terms of relevant events, such as spontaneous infarction, death, or hospitalizations due to heart failure, as a result of the small sample size, the low rate of events similar to those in previous studies, the different combined endpoint composition, and the brief follow-up. It only shows that the immediate procedure will lead to fewer periprocedural infarction diagnoses and less common ischemia-induced revascularization, which are not relevant events to guide clinical behavior, as claimed above. Given these weaknesses, we believe that the authors (or reviewers) tried not to claim that the immediate strategy should be the standard-of-care for acute myocardial infarction and preferred eclectic "non inferiority" when it was clearly superior for their events. In other words, a study with a very limited contribution to the clinical decision.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Funding

No funding has been received for this paper.

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