# Timing of intervention in non ST-segment elevation acute coronary syndromes

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Within the past ten years, a number of clinical trials have been conducted to compare invasive and conservative strategies in the treatment of non ST-segment elevation (NSTE) acute coronary syndromes (ACS). These trials have demonstrated that an invasive strategy determines a better clinical outcome than a conservative strategy. However, the optimal timing of the interventions remains uncertain.

**Table 1** shows the median time of catheterization in 10 such randomized clinical trials. This demonstrates that the timing of an early invasive strategy varies from 3-96 h, whereas late catheterization ranges from 50-1464 h (2 to 61 days). Two recent trials sought to clarify this matter.

| **Timing of catheterization (h)** | | | |
|---|---|---|---|
| **Trial name** | **Year** | **Early invasive strategy** | **Delayed invasive strategy** |
| **FRISC II** | **1999** | 96 | 408 |
| **TRUCS** | **2000** | 48 | 120 |
| **TACTICS-TIMI 18** | **2001** | 22 | 79 |
| **VINO** | **2002** | 6 | 1464 |
| **RITA 3** | **2002** | 48 | 1020 |
| **ELISA** | **2003** | 6 | 50 |
| **ISAR-COOL** | **2003** | 3 | 86 |
| **ICTUS** | **2005** | 23 | 263 |
| **TIME-ACS** | **2008** | 14 | 50 |

**Table 1: Timing of catheterization in 10 randomized clinical trials comparing invasive and conservative intervention strategies in NSTE-ACS**

## *TIMACS*

The results of the first of these studies, the TIMing of intervention in Acute Coronary Syndrome (TIMACS) trial, were presented at the American Heart Association (AHA) Scientific Sessions 2008, in New Orleans, LA, and published in the *New England Journal of Medicine* [1].

The investigators enrolled 3031 patients who had ACS and who were undergoing either routine early intervention (coronary angiography = 24 h after symptom onset) or delayed intervention (coronary angiography = 36 h after symptom onset).

In the early intervention group, 99.7% of patients had a coronary angiography, performed at a median time of 14 h (interquartile range, 3-21 h). In the delayed intervention group, 95.7% of patients had a coronary angiography, performed at a median time of 50 h (interquartile range, 41-81 h).

At 6 months, the primary outcome of death, new myocardial infarction (MI), or stroke occurred in 9.6% of patients in the early intervention group, in comparison with 11.3% in the delayed intervention group (hazard ratio [HR] in the early intervention group, 0.85; 95% confidence interval [CI], 0.68-

1.06; $p=0.15$).

However, there was a significant difference ($p=0.003$) in the composite endpoint of death, MI or refractory ischemia, which was lower (9.5%) in the early intervention group than in the delayed intervention group (12.9%; HR, 0.72; 95% CI, 0.58-0.89). This benefit was already obvious for this latter composite endpoint at 30 days (6.6 % vs. 9.3%, respectively; HR, 0.70; 95% CI, 0.54-0.90; $p=0.006$).

The major bleeding rate was similar in both groups (3.1% vs. 3.5%, respectively). More importantly, early intervention significantly reduced the primary endpoint and also the composite of death, MI or refractory ischemia in high-risk patients (defined as those with a GRACE risk score of >140). In these particular patients, the primary outcome occurred in 13.9% in the early intervention group, in comparison with 21% in the delayed intervention group, a relative risk reduction of 35% (HR, 0.65; 95% CI, 0.48-0.89; $p=0.006$).

### *ABOARD*

The results of the second trial have not yet been published, but they were presented at the American College of Cardiology (ACC) Scientific Sessions 2009, in Orlando, FL [2]. This study, the Angioplasty to Blunt the rise Of troponin in Acute coronary syndromes Randomized for an immediate or Delayed intervention (ABOARD) trial, was performed to determine whether immediate intervention (a primary coronary intervention [PCI] strategy) was superior to delayed intervention (a 'next-day' strategy) in patients with moderate-to-high-risk NSTE-ACS.

The primary endpoint was the rate of MI, defined as the peak of troponin I levels during hospitalization. The secondary endpoints were a composite of death, MI and urgent revascularization, and a composite of death, MI, urgent revascularization and recurrent ischemia. Central randomization was performed, and the investigators calculated that a sample size of 352 patients (mean age of 65 years old; 28% female) would generate an 80% power of detecting an effect size equal to 0.3.

At baseline, ST-segment changes were observed in 69.7% of patients in the immediate intervention group, and in 76.8% of patients in the delayed intervention group; elevated troponin I levels were observed in 75.4% and 72.9% of patients in these respective groups. Catheterization was mainly performed via a radial access (in 87.4% vs. 81.8% of patients, respectively). Revascularization was mainly achieved by PCI, and by bypass operation in 11% and 11.3%, respectively.

The median time of intervention was 1.1 h in the immediate intervention group and 20.5 h in the delayed intervention group. The primary endpoint, the peak of troponin I levels, was similar between the two strategies ($p=0.70$). The clinical outcome was also similar, although the study was not powered to provide a significant answer to this question. The rate of major bleeding at 1 month was 4% in the immediate strategy group and 6.8% in the delayed strategy group ($p=0.25$).

Thus, for NSTE-ACS, a 'primary PCI strategy' - as opposed to a rapid intervention on the following day - is feasible but does not reduce the risk of MI, which was the primary endpoint. This immediate strategy is not associated with significant differences in other efficacy or safety outcomes and does not benefit a particular subgroup of patients. However, it significantly shortens hospital stay (median 55 h vs. 77 h, respectively; $p<0.001$).

## *Conclusions*

Although they were differently designed, these two trials show relatively consistent results.

First, a risk stratification of NSTE-ACS is mandatory. Second, an early invasive strategy (median of 14 h) is superior to a delayed intervention strategy, but it is not necessary to apply an immediate strategy as it is in STE-ACS, for which it is absolutely mandatory to re-open the occluded artery as soon as possible. In most cases of NSTE-ACS, the culprit artery is not totally occluded. Therefore, in high-risk NSTE-ACS patients, it is wise to postpone intervention until the following day. In addition, this strategy allows us to 'prepare' the culprit vessel with an optimal antiplatelet strategy (aspirin plus clopidogrel and GPIIb/IIIa inhibitor) and to perform the intervention with the full team, within daytime hours. It is interesting to remind ourselves that the results of PCI are much better when performed during the day than during the night.

Finally, the results of these two trials were consistent with the ESC guidelines for NSTE-ACS, which propose that a 'primary PCI strategy' is reserved for the real emergency situations - NSTE-ACS patients with pulmonary edema, and life-threatening arrhythmias (ventricular fibrillation or ventricular tachycardia) - and that the invasive intervention is performed within the next 72 h in high-risk NSTE-ACS patients.

## References


1. Mehta SR, Granger CB, Boden WE, *et al*.; TIMACS Investigators. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med* 2009;**360**:2165-2175.
2. Montalescot G; on behalf of the ABOARD investigators. A multicenter randomized trial of immediate versus delayed invasive strategy in patients with non-ST elevation ACS. Presented at: American College of Cardiology Session/i2 Summit. March 30, 2009; Orlando, FL.