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VIEWPOINT

Timing of invasive coronary angiography in non-ST-elevation acute coronary syndrome: can we wait?

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Strategies to optimise the care of acute coronary syndrome (ACS) remain critical given the burden of the disease, its morbimortality and related health costs. One main challenge regarding the best treatment of patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is the optimal timing for an invasive strategy.

The European Society of Cardiology (ESC) Guidelines for the management of ACS have recently modified the recommended delays for intervention[1]. According to these updated guidelines, an inpatient invasive strategy is recommended for patients with a working diagnosis of NSTE-ACS, which makes clinical sense regarding the potential risk of early severe complications and death.

Immediate coronary angiography (i.e., <2 hours) should be performed in some clinical scenarios (e.g., patients classified at very high risk). However, this has poor scientific background (no dedicated study) and should be amended. Considering persistent chest pain certainly makes sense, since some NSTE-ACS are related to a complete coronary occlusion, as in ST-elevation myocardial infarction (STEMI) patients (in up to one-third of the cases in a recent meta-analysis[2]). However, differential diagnoses including aortic dissection should be ruled out beforehand. By contrast, the idea that cardiac arrest or acute heart failure requires urgent coronary angiography should be tempered, since firstly, recent scientific evidence does not support such a strategy[3], and secondly, in our opinion, most patients would benefit from acute heart failure management in the first place.

Apart from these limited cases, the guidelines support early (i.e., <24 hours) management for non-STEMI (NSTEMI) patients. This is nevertheless based on weak evidence. In fact, most trials performed in the field did not show any clinical benefit for an early intervention compared to a delayed intervention. This shorter timing (compared to previous guidelines) is therefore rather based on recent meta-analyses suggesting that the main benefits for an early invasive strategy were a reduction in recurrent ischaemia (pending intervention) and in the length of hospital stay[4,5]. These are noteworthy benefits for patients and health systems. Avoiding recurrent ischaemia may lead to smaller infarct size and better long-term prognosis, but this remains to be demonstrated, since no trial in the field has provided long-term data on the risk of heart failure occurrence and/or on left ventricular ejection fraction. Accordingly, it is unlikely for studies to observe an in-hospital mortality benefit regarding a difference in delays for intervention in these patients under close scrutiny in the intensive care unit. In a recent meta-analysis focusing on high-risk NSTE-ACS patients, lower long-term mortality was suggested in patients with elevated cardiac biomarkers at baseline, diabetes and/or a Global Registry of Acute Coronary Events (GRACE) risk score above 140[6].

Of note, the timings of both early (from 2 to 24 hours) and delayed (from 20 to 90 hours) treatment substantially varied across studies in the field, $P2Y_{12}$ pretreatment was commonly used, the GRACE score was rarely provided at inclusion, and NSTE-ACS was not diagnosed based on the most recent ESC guideline algorithms. Indeed, aside from the previous considerations, it is important to note that recent modifications in NSTE-ACS management may also impact the timing of an invasive strategy.

First, since the publication of the first trials in the field, it is noteworthy that the delayed strategy has lost its only rationale, which was to enable antithrombotic therapies to be active at the time of percutaneous coronary intervention (PCI). Indeed, pretreatment is now discouraged by the most recent guidelines[1]. Without pretreatment, it no longer makes

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sense to delay the invasive strategy, and recurrent ischaemia pending intervention may be more frequent than it was in the past. So far, the EARLY trial[7] has been the only trial to assess optimal timing without pretreatment. It suggested that a very early strategy should be preferred with this new antithrombotic regimen. These results have been taken into account ever since the strategy of delaying up until 48 to 72 hours was banned from the last version of the guidelines, and to date, the optimal timing is within 24 hours[1].

Second, the use of the most recent high-sensitivity troponin has certainly largely improved sensitivity but has also reduced specificity as compared to dosages in the past. Accordingly, there is no doubt that it is faster to rule out NSTE-ACS in emergency departments today (based on the most recent ESC guideline algorithms), but it is also much more difficult to identify "true" ACS related to unstable coronary artery disease. In recent registries and studies, one-quarter to one-third of ACS patients selected for an invasive strategy have had neither an underlying significant coronary artery disease nor subsequent PCI. Importantly, a very early strategy may only be beneficial if very early coronary revascularisation is performed.

To conclude, while 2 hours may be too short for diagnosis confirmation and logistics, 24 hours may still be too long for high-risk NSTE-ACS patients, especially in the absence of pretreatment. In the EARLY trial, the delayed group had a mean timing of intervention of 24 hours which led to a worse outcome than the very early strategy. Therefore, the optimal timing is probably shorter than 24 hours. A further reduction to 6 or 12 hours would not only take into account the network delay but also reflect that sooner is better, as long as differential diagnoses were ruled out to avoid unnecessary invasive coronary angiography. The implications for the network would be to reduce the transfer time for non-PCI centres and to adapt logistics in order to enable such delays at PCI centres. Patients and healthcare systems would benefit from such improvements. Of importance, in the EARLY trial, although very high-risk NSTE-ACS patients were excluded, it was observed that the culprit coronary artery was totally occluded in 4.7% of patients in the delayed group as compared to 0.6% in the very early group, thus supporting a reduction in delays. However, no protocol is monolithic. In fact, based on patient symptoms, clinical scenarios, repeated troponin levels, echocardiographic and electrocardiogram findings, the optimal timing could be reduced or prolonged. In NSTEMI patients, there is a benefit in performing coronary angiography early.

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Conflict of interest statement

L. Bonello and G. Lemesle have no conflicts of interest to declare.

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