Towards a reappraisal of the TACTICS TIMI 18 trial in the era of modern pharmacological and interventional therapies

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Making science appealing is quite a challenging task; and the scientific research industry is among the most sophisticated and promising. One important fact to keep in mind about science is that it never stands still, but is constantly changing. This may explain why we can never get too close to it, because it is like the mirage that recedes each time we approach it. Making good sense of this notion is never more relevant than in the realm of randomised controlled trials when comparing two alternative therapeutic strategies. A randomised controlled trial should be interpreted exclusively within the background of the population actually enrolled, and the therapeutic regimens received. Overextending the conclusions of a clinical trial beyond the specific population ultimately enrolled, and the context of pharmacological interventions eventually rendered, would be a grave prejudice. To underscore this viewpoint, let us review evidence from one of the landmark randomised controlled trials published a little more than a decade ago, that rigorously contributed to the standard-of-care approach in the management of patients presenting with non-ST-elevation acute coronary syndrome (ACS). The TACTICS TIMI 18 trial randomly assigned a little over 2200 patients with unstable angina, or non-ST-elevation acute myocardial infarction (MI), to either an early invasive strategy based on routine catheterisation within 48 h, and revascularisation as appropriate, or a conservative strategy in which catheterisation was performed only if the patient had objective evidence of recurrent ischaemia or an abnormal stress test.¹ At 6-month follow-up, the primary endpoint (a composite of death, non-fatal MI and rehospitalisation for ACS) occurred less frequently with the invasive, as compared with the conservative strategy (p=0.025), and so was the composite of death or non-fatal MI (p<0.05). The conclusion, accordingly, was that 'in patients with unstable angina and MI without ST-segment elevation who were treated with the glycoprotein IIb/IIIa inhibitor tirofiban, the use of an early invasive strategy significantly reduced the incidence of major cardiac events', and that 'these data support a policy involving broader use of the early inhibition of glycoprotein IIb/IIIa in combination with an early invasive strategy in such patients'.1

Although the conclusion was pretty convincing at that time, in-depth analysis of the details published from the TACTICS TIMI 18 trial would depict a largely different landscape. First, patients with unstable angina encompassed the whole spectrum of risk down to the lowest-risk patients without even the minimal (>0.05 mV) of ST-segment depression (62%), nor with elevation of cardiac markers (61%) had creatine kinase MB <5 ng/ml. 59% had troponin T \leq 0.1 ng/ml). Overall, patients with low TIMI risk score constituted 25% of the population. In a randomised controlled trial, patients must be equally eligible for both arms of the trial. One can wonder whether such low-risk patients with unstable angina were eligible for the early invasive strategy. Ongoing with this was the observation that the primary endpoint at 6 months was similar between the two arms in patients with prior aspirin use, in those without ST-segment changes, and in those without elevation of cardiac markers. Moreover, clinical outcome was slightly better in the conservative arm in the subset of patients with low TIMI risk score.

Second, adjunctive pharmacological interventions were far diverse from what constitutes current reallife clinical practice, and what is recommended by the most updated guidelines alike. Patients did not receive platelet receptor P2Y12 inhibitors, one of the cornerstones of the standard antithrombotic therapy in patients presenting with ACS (class I, level of evidence A, according to the 2011 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/ non-ST-elevation MI),² leave aside the degree of risk the intended management and strategy. did patients Furthermore, not receive low-molecular-weight heparins, with already proven reduction of major adverse cardiac events as compared with unfractionated heparin in the setting of non-ST-elevation ACS,³ not to mention the fact that unfractionated heparin was given in the trial without weight adjustment. Additionally, only 52% of patients received lipid-lowering agents. And, most importantly, whereas tirofiban was administered during 94% of percutaneous coronary intervention (PCI) procedures in the invasive-strategy group, this crucial drug was administered during only 59% of procedures in the conservative-strategy group. Given the fact that PCI was performed in 41% and 24% of patients in the invasive versus conservative arms, respectively, this would yield a differential in the use of tirofiban of 38.5% versus 14.2% (nearly 2.7-fold more frequent) of patients in the invasive versus the conservative arms, respectively. Finally, stents were used in no more than 83% and 86% of procedures in the invasive and conservative arms, respectively.

Third, strikingly, all the differences in adverse outcomes occurred in the early few weeks

following randomisation. This point is easily elucidated by careful review of clinical outcome data at the two time points of the trial: at 30 days and 6 months. The primary endpoint of the trial occurred at 30 days in 7.4% versus 10.5% of patients in the invasive versus conservative arms, respectively, p=0.009. Similarly, the composite of death or non-fatal MI occurred at 30 days in 4.7% versus 7.0% of patients, respectively, p=0.02. On the other hand, the cumulative incidence of the primary endpoint occurred at 6 months in 15.9% versus 19.4% of patients in the invasive versus conservative arms, respectively, p=0.025. Likewise, the cumulative incidence of the composite of death or non-fatal MI occurred at 6 months in 7.3% versus 9.5% of patients, respectively, p < 0.05. From the above data, it is evident that during the period of follow-up from 30 days to 6 months, the occurrence of major adverse cardiac events was quite similar between the two groups; the primary endpoint occurred in 8.5% versus 8.9%, and the composite of death or non-fatal MI occurred in 2.6% versus 2.5%, of patients in the invasive versus conservative arms, respectively. Further insight comes from analysis of the time-to-event curves of the two groups. If we imagine a landmark analysis of the two curves at 3-week time point, we would find that all the divergences of curves occurred well before this time point, whereas thereafter, the two curves continue almost exactly parallel to each other. This translates into the fact that all the benefits of the early invasive strategy occurred during the first 3 weeks of follow-up. Again, this may be viewed in light of the aforementioned substantially higher frequency of tirofiban use in the invasive-strategy group. This is further supported by the higher bleeding rates (protocol-defined) in the invasive versus the conservative arms (5.5% vs 3.3%, respectively, p < 0.01). To add more, the 30-day mortality rates after coronary bypass surgery and PCI were nominally higher in the invasive-strategy group (3.6% vs 1.9%), although it did not meet statistical significance.

Fourth, the primary endpoint of the trial included rehospitalisation for ACS. If this latter did not qualify to non-fatal MI, it should preferably be classified as recurrent ischaemia, rather than being assigned as a 'hard endpoint' equivalent to death and nonfatal MI. Consequently, if we again review the composite of death or non-fatal MI in patients with troponin T >0.01 ng/ml, we will find that at 30 days it was 5.3% versus 10.6% in the invasive versus the conservative arms, respectively, p=0.002. Surprisingly, however, the difference was no longer statistically significant at 6 months; 8.9% versus 12.3%, respectively, p=0.082. And even more interestingly, during the period of follow-up from 30 days to 6 months, the rate of occurrence of the composite of death or non-fatal MI was nearly 'two-fold higher' in the invasive versus the conservative arm; 3.6% versus 1.7%, of patients, respectively.

Finally, the conclusion drawn from available evidence is more than often manifold, depending on the weight ultimately given to the various facts. Hence, there is no single conclusion that can be drawn from the evidence. In light of the above discussion, one would eventually come up with the following conclusion from the TACTICS TIMI 18 trial: in patients presenting with non-ST-segment elevation ACS, who have ST-segment changes, elevated cardiac biomarkers, intermediate or high risk by TIMI risk score, who are not on prior aspirin, and who receive no clopidogrel, or low-molecular-weight heparins, the adoption of an early invasive strategy significantly reduced the incidence of major adverse cardiac events during the initial 3 weeks following the index ACS; the effect was most probably attributed to the differential in administration of the glycoprotein IIb/IIIa inhibitor tirofiban in favour of the invasive strategy.

Clearly, this reappraisal of the TACTICS TIMI 18 trial in view of the current pharmacological and interventional therapies would serve as hypothesis-generating, and therefore, should be further confirmed by the results of up-to-date prospective, randomised, controlled trials. The ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) trial compared early invasive versus selective invasive strategy (angiography only for refractory angina or recurrent ischaemia) in patients with non-ST-elevation ACS and elevated troponin T. The 5-year report of the trial did not demonstrate any reduction of death or MI with the former as compared with the later.⁴ Nevertheless, in the TIMACS (Timing of Intervention in Acute Coronary Syndrome) trial, early PCI reduced the composite of death, MI or refractory ischaemia at 6-month follow-up, versus delayed PCI in patients with 'highrisk' non-ST-elevation ACS.⁵ Finally, in the small randomised controlled ABOARD trial, there was no difference in outcome between immediate and delayed intervention in patients with non-ST-elevation ACS and TIMI risk score >3.6 Yet, quite often, the reporting of trial outcomes is not only incomplete but also biased and inconsistent with protocols. Hence, published articles that incorporate them might sometimes be rather unreliable, and overestimate the benefits of an intervention.

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