There is considerable evidence supporting an aggressive approach to the management of non-ST-segment elevation (NSTE) acute coronary syndrome (ACS). This includes intensive medical therapy and an early invasive strategy. These tactics, alone or in combination, can reduce the rate of subsequent ischemic events but increase bleeding events. The challenge for clinicians is to efficiently identify those patients (from among the very large number of patients presenting to the hospital with chest pain) who will receive the greatest net benefit from an aggressive approach. Numerous methods for risk stratification of patients with NSTE-ACS have emerged. Clinical risk assessments, such as the thrombolysis in myocardial infarction risk score, have been shown to predict adverse outcomes and, perhaps more importantly, identify patients most likely to benefit from an early invasive strategy or intensive antithrombotics. Elevated levels of serum troponin have been found separately to predict adverse events and identify patients likely to benefit from intensive antiplatelet therapy. Other biomarkers, such as B-type natriuretic peptide (BNP) and N-terminal-proBNP, predict adverse outcomes in the setting of NSTE-ACS but have not consistently been shown to predict a response to a specific treatment regimen. In this issue of Circulation, Wallentin et al report their analysis of baseline levels of high-sensitivity troponin T (hs-TnT), N-terminal-proBNP, and growth differentiation factor-15 in patients with NSTE-ACS who were enrolled in the Platelet Inhibition and Patient Outcomes trial.

The Platelet Inhibition and Patient Outcomes trial randomly assigned 18,624 patients with ST-segment elevation acute coronary syndrome or NSTE-ACS to ticagrelor or clopidogrel, in addition to routine ACS medications including aspirin and antithrombin therapy, as appropriate. At 12-month follow-up, the occurrence of the primary composite end point—vascular death, myocardial infarction, and stroke—was reduced 16% with ticagrelor. To be enrolled, patients with NSTE-ACS had to be hospitalized for an ACS within the previous 24 hours and meet at least 2 of the following criteria: (1) ischemic electrocardiographic changes; (2) a positive biomarker indicative of myocardial necrosis; and (3) the presence of one or more cardiac risk factors. The present substudy included 9946 patients with NSTE-ACS who provided blood samples for biomarker analyses at baseline. In a post hoc fashion, these patients were divided into 2 groups; the in-hospital invasive group underwent revascularization (percutaneous coronary intervention or coronary artery bypass grafting) during the index hospitalization (n=5357), and the noninvasive group did not (n=4589). On average, the invasively managed patients were more likely men and habitual smokers. The noninvasively managed patients had more comorbid conditions such as hypertension, diabetes mellitus, a previous myocardial infarction, stroke, or heart failure.

Among patients who were managed noninvasively, there was a reduction in the composite ischemic end point for those assigned to ticagrelor (10.3% versus 12.2%; hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.71–1.01). Although this degree of benefit from ticagrelor was similar to that observed in the overall Platelet Inhibition and Patient Outcomes trial, a significant interaction (P=0.042) between hs-TnT levels and outcomes was detected. Specifically, the beneficial effect of ticagrelor was statistically evident at higher baseline levels of hs-TnT but not with low or normal hs-TnT levels. For patients with the lowest hs-TnT levels (<14 ng/L), the HR favored clopidogrel, although with CIs widely overlapping the line of identity with ticagrelor, in part because of a low total number of ischemic events (n=28) and a low event rate (2.8%). In contrast, for medically managed patients with the highest hs-TnT levels (≥495 ng/L), the relative reduction in events with ticagrelor appeared greatest (12.8% versus 19.3%; HR, 0.65; 95% CI, 0.49–0.87). As such, and as nicely displayed by the forest plots in Figure 1 of the article by Wallentin et al, there looks to be a consistently increasing benefit from ticagrelor with progressively abnormal troponin levels for patients managed noninvasively.

Among patients with NSTE-ACS who were managed with revascularization, ticagrelor likewise reduced the occurrence of the primary composite end point (8.8% versus 11.2%; HR, 0.77; 95% CI, 0.65–0.91), although no association between hs-TnT levels and the primary end point was detected (interaction P=0.41). In other words, a consistent benefit was observed with ticagrelor for patients undergoing revascularization irrespective of the baseline troponin level. However, as with patients with normal troponin levels who were managed noninvasively, for those with a normal baseline troponin...
undergoing revascularization, few ischemic events occurred (n=41) in this particularly small subset of patients (n=346), and no overt benefit of ticagrelor could be appreciated in isolation (Figure 4 in the article by Wallentin et al). No statistical interaction was noted between the relative superiority of ticagrelor over clopidogrel and baseline levels of N-terminal-proBNP or growth differentiation factor-15 for patients managed invasively or noninvasively.

Pulling these observations together, several points can be considered. First, baseline levels of hs-TnT but not N-terminal-proBNP or growth differentiation factor-15 provide some insight into the extent of benefit to be expected from ticagrelor over clopidogrel. Although inarguable benefit is seen among ticagrelor-treated patients with an elevated baseline hs-TnT level, the benefit appears muted or absent for those with a normal troponin level. For the 1359 substudy patients with hs-TnT levels <14 ng/L, managed either invasively or noninvasively, the rate of the primary composite end point appeared similar between ticagrelor- and clopidogrel-treated patients (5.4% and 4.7%, respectively), as seen in the top panels of the authors’ Figure 2. Moreover, patients with a hs-TnT level <14 ng/L who were able to be managed noninvasively had an impressively low and similar event rate regardless of study drug assignment, and this might have allowed physicians to take a less aggressive and less expensive approach to pharmacotherapy in these patients. Future studies will, no doubt, address this important topic prospectively and focus on other ways in which the care of patients with chest pain and a normal hs-TnT level can be further streamlined.

Second, whether managed invasively or noninvasively, patients with an elevated hs-TnT level at presentation had a relatively high ischemic event rate at 12-month follow-up, again as seen in the top panels of Figure 2 (dashed lines). Specifically, vascular death, myocardial infarction, or stroke occurred in 9.9% of such patients undergoing revascularization and, impressively, in 13.7% of patients managed noninvasively. In the present substudy data set, a remarkable proportion of patients (42%) with a frankly elevated baseline troponin were managed noninvasively. This may reflect differences in practice pattern related to the geographic locations from which patients were enrolled. In the main trial, enrollment was dominated by patients from Europe, the Middle East, and Africa (n=13859) as opposed to North America (n=1814). Clinicians may need to reconsider the decisions to manage patients noninvasively who have a particularly elevated hs-TnT level. Whether other factors were present among these patients to make an invasive approach unattractive or unavailable or whether this physician preference, the so-called treatment-risk paradox, was at play is unknown.

Third, the extent of benefit of ticagrelor over clopidogrel appears not only to be predicted by the extent of hs-TnT abnormality but also by the time interval considered. For invasively managed patients, the interval of greatest benefit may be in the early weeks to months, whereas in the noninvasively managed patients this interval may only become evident over a longer period. Both of these concepts can be related to the 2012 American College of Cardiology Foundation/American Heart Association Guidelines for NSTE-ACS Management and the Wallentin et al Kaplan-Meier event-rate curves according to hs-TnT and treatment strategies. On the basis of previous randomized trial data, the American College of Cardiology Foundation/American Heart Association Guideline writers state that dual antiplatelet therapy (ie, more potent antiplatelet therapy with aspirin and a P2Y12 antagonist) should be used for patients with definite ACS at medium or high risk and managed invasively. Considering the event rates in Figure 2, right panel A (invasive) by Wallentin et al, the curves representing ticagrelor- and clopidogrel-treated patients diverge most among those with an elevated hs-TnT (ie, definite ACS), and this separation occurred in the early weeks. Thereafter, the lines appear more parallel. The guideline writers also state that patients managed noninvasively should receive dual antiplatelet therapy for ≥1 month and ideally for 12 months. This also appears to be reinforced by the event-rate curves in Figure 2, left panel A (noninvasive) by Wallentin et al. Patients with a definite NSTE-ACS (dashed lines for hs-TnT levels >14 ng/L) who were managed noninvasively have a steadily increasing incidence of ischemic events during the first 12 months, with the benefit of more aggressive antiplatelet therapy manifest over time.

In summary, the Platelet Inhibition and Patient Outcomes investigators have added further evidence to support an aggressive approach for the management of definite NSTE-ACS. In addition, they have reminded us of the value of the baseline troponin level to guide our treatment decisions. Although there are a number of caveats with their biomarker substudy, these newest data again suggest that patients with a normal troponin level receive little to no value from aggressive antiplatelet strategies, whereas patients with an elevated troponin level receive substantial benefit from more potent antiplatelet therapy—in this case, ticagrelor. We are also reminded that patients with NSTE-ACS who have an elevated troponin level can have a poor outcome when managed without revascularization.

Disclosures

None.

References


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Value of High-Sensitivity Troponin in Assessing the Extent of Benefit Provided by Ticagrelor Versus Clopidogrel in Non–ST-Segment Elevation Acute Coronary Syndromes
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