

Letters

TO THE EDITOR

Escalating Loading Dose Regimens of Ticagrelor in Primary Percutaneous Intervention



A Second Opportunity for IIB/IIIa Inhibitors?

We have read with great interest the report by Franchi et al. (1) on escalating loading-dose regimens of ticagrelor in primary percutaneous intervention (PPCI), and the investigators should be praised for their significant contribution to this important field. In the initial years of PPCI, IIB/IIIa inhibitors, especially abciximab in combination with unfractionated heparin, aspirin, and clopidogrel, were considered an indispensable component of the procedure. However, with the emergence of the new antiplatelet agents prasugrel and ticagrelor, which offer a more rapid onset of action and more powerful platelet inhibition than clopidogrel, the use of IIB/IIIa inhibitors has suffered a dramatic decline. In our opinion, the paper by Franchi et al. may represent a second opportunity for a revival of these intravenous agents. Although in stable disease and in non-ST-segment elevation myocardial infarction, the increase in the loading dose from 300 to 600 mg of clopidogrel was beneficial, Franchi et al. have now elegantly demonstrated that in ST-segment elevation myocardial infarction, in which the thrombus is already present, increasing the loading dose of ticagrelor beyond the current recommended dose of 180 mg does not provide any additional benefits. These findings could indicate that the administration of oral agents, such as ticagrelor and prasugrel, may not be sufficient and that therefore intravenous agents would be necessary in high-risk patients; as some investigators have shown, there may be sub-optimal platelet inhibition in the early hours. The American College of Cardiology and American Heart Association guidelines confer the same IB level of recommendation in PPCI to clopidogrel, prasugrel, and ticagrelor because of the limited benefit of ticagrelor in ST-segment elevation myocardial

infarction, without statistical significance in PLATO (Platelet Inhibition and Patient Outcomes) (2) after the inclusion of 7,544 patients and also because the benefit of prasugrel was due mainly to patients undergoing secondary percutaneous coronary intervention (3). As is explained in the introduction of its publication, the ATLANTIC (Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery) trial based its design on the concept of pre-hospital administration of IIB/IIIa inhibitors, but ticagrelor administered in the ambulance to patients in the first 6 h after ST-segment elevation myocardial infarction failed to meet the primary endpoint of the study. It seems that prasugrel and ticagrelor, which have stronger antiplatelet action, could offer a benefit over clopidogrel, mainly in patients with more organized thrombi, as demonstrated in the TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel) trial, in which patients who underwent percutaneous coronary intervention between 12 h and 14 days benefited the most, but in some cases, both agents might not be enough in the first hours, when a thrombus is already present and there is need for very rapid platelet inhibition. This could explain the aforementioned lack of benefit of an earlier pre-loading dose of ticagrelor in ATLANTIC in those patients randomized in the first 6 h. Some investigators have already defended the benefits of IIB/IIIa inhibitors even in the presence of prasugrel and ticagrelor (4,5).

To conclude, in some patients, there may be insufficient platelet inhibition in the first hours after PPCI, and this deficiency could be covered by using IIB/IIIa inhibitors, especially bearing in mind that the utility of thrombectomy after TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) and TOTAL (Trial of Routine Aspiration Thrombectomy With Percutaneous Coronary Intervention [PCI] Versus PCI Alone in Patients With ST-Segment Elevation Myocardial Infarction [STEMI] Undergoing Primary PCI) has been seriously questioned.

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Role of CVP to Guide Fluid Therapy in Chronic Heart Failure

Lessons From Cardiac Intensive Care



We read with great interest the article by Qian et al. (1) on central venous pressure (CVP)-guided fluid administration for the prevention of contrast-induced nephropathy (CIN). The authors used the initial and subsequent change in CVP to guide fluid administration before elective coronary angiography in heart failure (HF), calling CVP “a safe and accurate assessment of intravascular volume status.” Higher volumes of administered fluid were associated with greater urine output and lower CIN risk, without an increase in HF exacerbation. Irrespective of CVP-guided hydration, patients with a baseline CVP >12 cm H₂O received the same amount of fluids and had the highest CIN rates, implying that pre-existing congestion promotes CIN and that fluid volume, rather than CVP monitoring per se, produces the

benefit. This leaves uncertainty as to whether patients in both groups would have done equally well if they had received equal amounts of fluids, independent of the CVP, which could have served to encourage a fluid-liberal strategy.

Use of CVP to guide fluid resuscitation is fraught with inconsistencies, with accumulating data suggesting that CVP is a poor reflection of volume status, fluid responsiveness, and pre-load in cardiac intensive care patients (2,3). CVP, a reflection of right atrial pressure (RAP), is subject to variability from intrathoracic structures, valvular abnormalities, and pulmonary vascular disorders (2,3). Physiological studies have demonstrated that RAP actually opposes venous return (the difference between mean systemic filling pressure and RAP). Although the CVP generally correlates with the pulmonary capillary wedge pressure and/or left ventricular end-diastolic pressure in HF, this relationship requires normal biventricular compliance, integrity of atrioventricular valve function, and normal pulmonary hemodynamics (4). Pulmonary hypertension and severe mitral and tricuspid regurgitation are noted in nearly 60% to 90%, 50%, and 30%, respectively, of patients with HF with reduced ejection fraction (5). HF patients frequently have dilated right atria with abnormal chamber compliance affecting the pressure-volume relationship (3). The present study does not comment on these confounding factors to the assumption of volume status or fluid responsiveness using the CVP.

There are no standardized cutoffs for static CVP measurements in patient management, as noted in a meta-analysis of studies evaluating CVP in different settings (2). The classic “5-2 rule” using CVP to predict fluid responsiveness has been challenged over the years. Therefore, the use of arbitrary CVP cutoff values of 6 and 12 cm H₂O by the authors needs further definition of the strategy and rationale to arrive at these numbers.

Given these considerations, we believe that the conclusions of the authors (1) that CVP predicts fluid status and guides strategies to prevent acute decompensation of HF need further elaboration and investigation before establishing causation. In critically ill patients, the role of static measures of fluid status and/or responsiveness (such as CVP and pulmonary capillary wedge pressure) are increasingly being replaced by dynamic measures. Importantly, given the risk associated with invasive CVP measurement, we wonder whether a noninvasive measure such as echocardiography could have yielded similar results without the potential for vascular access complications.