Bivalirudin and cangrelor are 2 intravenous drugs, 1 for anticoagulation and the other for antiplatelet therapy, with a rapid onset of action, thus in theory perfectly adapted to percutaneous coronary intervention (PCI) that requires simultaneous thrombin and platelet inhibition. These effects are especially needed for mechanical coronary reperfusion of acute patients such as those presenting with ST-segment elevation myocardial infarction (STEMI). The short half-lives and good tolerance of these 2 drugs add to the attractiveness of their profile in the contemporary era of expeditious and safety-oriented care.

Bivalirudin anticoagulation has been associated with a reduction of major bleeding complications, the magnitude of which varies based on whether glycoprotein IIb/IIIa inhibitors are used in the control arm with unfractionated heparin (1). There is no significant reduction of major bleeding when glycoprotein IIb/IIIa inhibitors are used provisionally with both anticoagulant strategies of unfractionated heparin and bivalirudin. Currently, glycoprotein IIb/IIIa inhibitors are mostly used provisionally. A bivalirudin-based regimen compared with a heparin-based regimen for PCI increases ischemic events and stent thrombosis (1). Any strategy that could reduce major thrombotic events after PCI would be welcome in bivalirudin-oriented catheterization laboratories. The use of the more potent P2Y12 receptor antagonists prasugrel and ticagrelor in patients receiving bivalirudin is an option but was not confirmed in the EUROMAX trial (European Ambulance Acute Coronary Syndrome [ACS] Angiography) (61% use of prasugrel or ticagrelor) and HEAT-PPCI study (How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention) (89% use of prasugrel or ticagrelor) studies, both of which showed a persistent excess of stent thrombosis (2,3). Cangrelor, more potent and more rapidly active than prasugrel and ticagrelor, is another option, considering the demonstrated reduction of ischemic events (~20%) and stent thrombosis (~40%) compared with clopidogrel in the CHAMPION-PHOENIX trial (A Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Required Percutaneous Coronary Intervention) and a meta-analysis (4,5). These attractive results were associated with no excess bleeding but also no reduction in mortality. The study reported in this issue of JACC: Cardiovascular Interventions examines this marriage of bivalirudin and cangrelor in the CHAMPION-PHOENIX trial (6).

In this subset analysis of patients receiving bivalirudin (9% of the CHAMPION-PHOENIX population), cangrelor compared with clopidogrel significantly reduced ischemic events as well as stent thrombosis to the same magnitude as in the main trial. This finding does not mean that cangrelor can eliminate the excess of stent thrombosis related to bivalirudin.

*Editorials published in JACC: Cardiovascular Interventions reflect the views of the authors and do not necessarily represent the views of JACC: Cardiovascular Interventions or the American College of Cardiology.
use. Indeed, a similar effect of cangrelor was reported with unfractionated heparin in the initial publication (p value for interaction = 0.51). Are these findings relevant? It is noteworthy that this subset analysis applies almost exclusively to patients from the United States (93%) when the global study recruited the majority of patients outside the United States (63%) where anticoagulants other than bivalirudin were generally used. So the findings are relevant to these catheterization laboratories using bivalirudin. The cangrelor effect is preserved but does not eliminate the excess risk of stent thrombosis related to bivalirudin itself. In the rest of the world where other anticoagulants are used, the cangrelor effect is similarly present. The survival curves show clearly the timing of the cangrelor effect, preventing stent thrombosis in the first 3 h after PCI, exactly as in the ATLANTIC study (A 30 Day Study to Evaluate Efficacy and Safety of Pre-hospital vs. In-hospital Initiation of Ticagrelor Therapy in STEMI Patients Planned for Percutaneous Coronary Intervention [PCI]) when using prehospital (rather than in-hospital) ticagrelor in primary PCI (7). The timing of P2Y12 inhibition appears to be a key modulator of stent thrombosis and is best obtained with an early oral load of ticagrelor or later intravenous administration of cangrelor. Neither strategy is associated with increased bleeding. Late administration of clopidogrel, particularly in STEMI, would be the least effective strategy for the prevention of post-procedural thrombotic events.

There are obvious regional differences in the use of bivalirudin, which has replaced unfractionated heparin in places where glycoprotein IIb/IIIa inhibitors were commonly used, but was seen as less useful and too expensive in places where glycoprotein IIb/IIIa inhibitors were not as popular. In addition to the stent thrombosis and cost issues, practicality was also seen as a limiting factor for bivalirudin (1 bolus, 2 infusion doses, prolonged infusion after PCI). The recent European Guidelines on Myocardial Revascularization give the same Class IIa recommendation to bivalirudin and enoxaparin, the latter being another alternative to unfractionated heparin, without the stent thrombosis, cost, and practicality concerns of bivalirudin (8-10).

In conclusion, the arranged marriage of bivalirudin and cangrelor presupposes that they are complementary and that the 2 are perfectly matched, but, as we indicate, nothing suggests such complementarity here. The same company selling both drugs may want to arrange this marriage but is fully aware that the physicians can always refuse this marriage and simply look for another choice. This arranged marriage may not be forced, especially when the cost is taken into account, knowing that effectiveness is not guaranteed. Finally, 1 reason for marrying bivalirudin and cangrelor may well be a cultural trademark in labs where the economic pressure is not too important and where bivalirudin adoption is so pervasive, there is reluctance to change. Elsewhere, tolerance of a different type of marriage will be necessary, accepting a selection of patients for cangrelor and routine anticoagulant strategies other than bivalirudin.

REFERENCES


KEY WORDS anticoagulation, antiplatelet therapy, P2Y12 antagonists, percutaneous coronary intervention, stent thrombosis