Antiplatelet agents and heart surgery: new drugs, new challenges?

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In this issue of the European Journal of Cardiothoracic Surgery, Schotola and associates present the result of an interesting study. They analysed the outcomes of patients undergoing isolated or associated coronary operations without discontinuation of double antiplatelet therapy, comparing patients under clopidogrel vs ticagrelor treatment. They could demonstrate that patients pretreated with ticagrelor had a higher postoperative blood loss, required more blood transfusions and more prothrombin complex concentrate and fibrinogen concentrate and had a tendency towards a higher rate of surgical re-exploration [1].

The problem of double antiplatelet therapy discontinuation before cardiac surgery and the risks associated with surgery in patients with ongoing double antiplatelet therapy (bleeding, transfusion, surgical re-exploration) is not new, but is recently becoming multifaceted, due to the availability of new-generation drugs.

The existing guidelines suggest discontinuation of clopidogrel, prasugrel and ticagrelor before heart surgery. However, the exact timing of discontinuation is still a matter of debate, with suggestions that range from 3 to 7 days in different documents released in different years [2–5]. As a matter of fact, this changing scenario depends on the different nature of the different antiplatelet agents.

Clopidogrel and prasugrel are thienopyridines and share the same mechanism of action (irreversible inhibition of the platelet receptor P2Y12). However, clopidogrel is a prodrug that requires hepatic conversion into its active form, and many studies have highlighted the variable and unpredictable response of platelets to clopidogrel treatment, with rates of non-responsiveness around 20%. Prasugrel is not affected by genetic variations of the CYP2C19 enzyme and its use has been suggested in clopidogrel non-responsive patients. However, high on-treatment platelet reactivity has been reported in prasugrel-treated patients, even if at a lower rate (around 5%) [6].

Getting rid of thienopyridines effects requires new platelet generation, and the time to recovery of platelet function depends on the rate of platelet turn-over.

Even if acting on the P2Y12 receptor, ticagrelor is not a thienopyridine; the inhibition of the P2Y12 is reversible, faster and more
Effective than with clopidogrel [7]. Offset of ticagrelor effects after discontinuation is faster than after clopidogrel discontinuation, but given the higher efficacy while on-treatment, 3 days of discontinuation are required to obtain a platelet function recovery significantly higher in ticagrelor vs clopidogrel-treated patients [7].

Recently, a novel antiplatelet agent has been tested in clinical practice. Vorapaxar has been shown to reduce cardiovascular events and mortality [8].

Coronary artery bypass graft (CABG) surgery in patients under the effects of the above-mentioned drugs is a matter of concern. CABG-related major bleeding in prasugrel vs clopidogrel-treated patients has a hazard ratio of 4.73 [9]; the study of Schotola and associates reports a 50% higher use of red blood cell transfusions in ticagrelor-treated vs clopidogrel-treated patients undergoing CABG; comparative studies of vorapaxar vs clopidogrel or prasugrel in terms of CABG-related bleeding are presently lacking. However, the present scenario, not surprisingly, highlights that the more these antiplatelet agents are effective in terms of platelet inhibition, the higher is the major bleeding risk in case of CABG surgery in patients with ongoing therapy or residual effects of the drug after discontinuation.

In a recent study [10], we investigated the recovery of platelet function after discontinuation from P2Y12 inhibitors in patients undergoing CABG surgery. We used multiple electrode aggregometry to assess platelet function before the operation (adenosine diphosphate test) in 344 patients. According to our definition, 28% of the patients were thienopyridine-resistant, and the remaining patients demonstrated a huge individual variation in the rate of platelet function recovery, with a daily percentage recovery ranging from 10 to 200% of the platelet function. We could not identify any predictor of this pattern, but the analysis of the whole population led us to establish that at least 3 days of discontinuation are required to reach an acceptable level of platelet function (60% of the lower limit of normal range) and up to 8 days may be required to reach a full recovery of platelet function. Finally, values of platelet function below 60% of the lower limit of normal range were associated with a significant higher postoperative bleeding.

In summary, it is very difficult to provide universal suggestions about the timing of major antiplatelet discontinuation in patients undergoing CABG surgery. There is a consistent rate of patients under clopidogrel or prasugrel treatment that are actually poor-responsive: in this patient population, postponing the operation for 3–5 days is probably an unnecessary measure. Within responsive patients, the rate of recovery of platelet function is highly unpredictable. Finally, ticagrelor-treated patients form a different patient population, where the recovery of platelet function after discontinuation is faster and more predictable, but where the high effectiveness of the drug places the patient at high risk of major bleeding in case of surgery without drug discontinuation or within 2 days of discontinuation.

In the present scenario, it is likely that a direct measurement of platelet function with the available point-of-care tests may offer a useful tool for an individualized decision-making process about timing of CABG surgery in patients treated with major antiplatelet drugs.

REFERENCES