Switching antiplatelet therapies is a common occurrence in clinical practice (1). The current availability of different oral P2Y<sub>12</sub> receptor antagonists allows for multiple treatment options and has raised questions on the optimal approach if switching among these therapies is needed or desired. Despite the evidence for sustained efficacy and safety of ticagrelor with long-term treatment, many physicians limit treatment duration with ticagrelor to the early phases (weeks or months) following an acute coronary syndrome (ACS) (1). The reduced costs associated with a generic formulation of clopidogrel, as well as concerns of increased risk of bleeding or the presence of dyspnea with ticagrelor therapy, remain important reasons for switching to clopidogrel (1). Discontinuation of ticagrelor treatment for adverse events is in fact common, primarily driven by dyspnea and non-major bleeding, with rates of dyspnea occurring in 13.8 to 19% of patients and leading to discontinuation in 0.9 to 6.5% of patients (2, 3). Overall, registry data indicate that the prevalence of in-hospital switching from a new-generation P2Y<sub>12</sub> receptor inhibitor to clopidogrel ranges from 5.0% to 13.6% (1, 4). Indeed, the rate of switching after hospital discharge, where patients are faced with costs of medications, may be at least as high (5).

The pharmacodynamic (PD) profiles after discontinuation of ticagrelor indicate faster recovery of platelet-inhibitory effects than clopidogrel (1), suggesting the need for early overlap of treatment among ticagrelor-treated patients in case of switching antiplatelet therapy. In the SWAP (Switching AntiPlatelet)-2 study, in which patients were switched from ticagrelor to prasugrel, a rebound in platelet reactivity with increased high on-treatment platelet reactivity (HPR) rates was observed, suggesting a drug-drug interaction when switching from ticagrelor to a thienopyridine (6). In this study, a loading dose (LD) of prasugrel appeared to be essential to mitigate the increase in platelet reactivity after switching (6). Of note, this drug interaction with increased platelet reactivity was not seen when switching from prasugrel to ticagrelor in the SWAP-3 study (7), or when switching from clopidogrel to either prasugrel or ticagrelor (8, 9). These observations, along with studies of transitioning from intravenous P2Y<sub>12</sub> receptor inhibitors to different classes of oral P2Y<sub>12</sub> receptor inhibitors, lead to strongly suggest that drug interactions may occur when switching from a non-thienopyridine to a thienopyridine P2Y<sub>12</sub> receptor inhibitor (1). However, to date, there has not been any study assessing the PD profiles of switching from ticagrelor to clopidogrel.

In this issue of *Thrombosis and Haemostasis*, Pourdjabbar et al. report the results of the CAPITAL OPTI-CROSS study, investigating the PD effects of switching from ticagrelor to clopidogrel with or without a LD (10). Patients (n=60) treated with ticagrelor after an ACS and with a clinical indication for in-hospital switching, mainly high risk of bleeding, were randomized to switch to clopidogrel with or without a 600-mg LD. Platelet function was assessed by VerifyNow P2Y12 before the first clopidogrel dose and 12, 24, 48, 54, 60 and 72 hours (h) after. The authors found that, although a LD strategy was not associated with improved platelet inhibition 72 h after switching (primary end point), at the 48-h time point platelet inhibition was significantly higher in the LD group with reduced incidence of HPR (10). The authors should be congratulated for their study, as for the first time they investigated the PD effects of transitioning from ticagrelor to clopidogrel and the differential profiles according to the administration of a LD, providing new and important information to clinicians who decide to switch. The major strengths of this well-conducted PD investigation are indeed the randomized prospective design, the high number of time points, and the fact that it has been conducted in a real setting of ACS patients deemed to require such switching option. In addition, they confirmed that switching from ticagrelor to clopidogrel is common in real world, as it occurred in-hospital in 11% of their population.

Some details should, however, be considered to fully interpret the study results. The authors measured platelet reactivity only with one assay. Although VerifyNow is a commonly used test, the use of additional assays would have added further strength to study findings. At the 24, 48 and 72-h time points, blood samples were collected either before or after the scheduled dose of clopidogrel. Indeed, the lack of consistency in measuring trough or peak levels of PRU might have affected the study results, as it is well-known that these methodological aspects can significantly influence PD measures (11). The authors administered the clopidogrel dose 12 h after the last dose of ticagrelor. In the SWAP-2 study it has had been hypothesised that the potential drug-drug interaction in switching from ticagrelor to prasugrel could have been attributed to the presence of ticagrelor or its major metabolite on the P2Y<sub>12</sub> recep-
tor when prasugrel was administered after 12 h from the last maintenance dose of ticagrelor. This also suggested that switching should occur after a later time frame post-maintenance dose to enable more time for the receptor to be unbonded by ticagrelor or its metabolite (6). Therefore, a third group randomized to clopidogrel administered 24 h after the last ticagrelor dose would have provided further important insights. The results of this study seem to rule out the presence of a drug-drug interaction. However, drug interactions may be difficult to assess when switching from a more potent to a less potent agent. The presence of a control group of patients receiving clopidogrel from the beginning would have allowed to better explore this issue. Finally, at each time point HPR rates were numerically higher in patients not receiving the LD. In particular, at 72-h the number of patients with HPR was more than two-fold higher in patients switched without a LD. However, the difference did not reach statistical significance as the study was not powered for this. Given the well-known association between HPR and thrombotic events, larger numbers would have potentially unravelled further insights with important clinical implications. In addition, because of the rising in PRU values from 60 to 72 h, it is unknown whether a further increase in PRU and HPR rates would have been observed after the 72 h. The ongoing SWAP-4 investigation (NCT02287909) will indeed provide further insights into the PD profiles associated with switching from ticagrelor to clopidogrel.

Overall, the results of CAPITAL OPTI-CROSS underline that switching strategies should be tailored based on the clinical scenario and patients’ risk profile. The study identifies a critical period between 24 and 72 h after switching, where the use of a LD may help to mitigate the recovery in platelet reactivity associated with switching from ticagrelor to clopidogrel. Although this should be interpreted with caution in the setting of a study which did not reach its primary end point, the potential clinical implications may be noteworthy in the acute phase after stent implantation for an ACS, when the risk of thrombotic complications is the highest. It may be argued that if switching occurs because of high risk of bleeding as in this study, having higher levels of platelet reactivity may be preferable. However, the risk of bleeding events associated with potent platelet inhibition accrues over time, while the thrombotic risk associated with lack of protection is a short-term event, as highlighted in studies investigating intravenous antithrombotic agents (12). On the other hand, when the transition occurs in the maintenance phase of treatment it seems reasonable to switch directly to a maintenance dose of clopidogrel. Indeed, the clinical implications of these findings should be explored in larger studies.

Conflicts of interest
None declared.

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References


