Ischaemic Events and Stent Thrombosis following Planned Discontinuation of Study Treatment with Ticagrelor or Clopidogrel in the PLATO Study

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Dual-antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor antagonist is recommended as routine treatment for at least 1 year following acute coronary syndromes (ACSs).[1,2] However, the risk of ischaemic events and, for patients treated with percutaneous coronary intervention (PCI), stent thrombosis persists beyond this time period and discontinuation of the $P2Y_{12}$ receptor antagonist has been associated with an increase in adverse clinical outcomes.[3–6] In the PLATelet inhibition and patient Outcomes (PLATO) trial (www.ClinicalTrials.gov NCT00391872), 18,624 patients with non-ST elevation and ST elevation ACS were randomized to treatment with either ticagrelor or clopidogrel with a planned duration of 12 months, scaled down to 9 or 6 months as the target number of events was accrued.[7,8] Following discontinuation of study medication, patients were followed up for 1 month. Although no evidence exists of any rebound increase in platelet reactivity following discontinuation of platelet $P2Y_{12}$ inhibitors,[9,10] it is unknown whether the differences in receptor binding and mechanisms of recovery of platelet function with clopidogrel and ticagrelor might lead to any difference in clinical outcomes after their discontinuation. We therefore assessed clinical outcomes in patients who discontinued study medication after completing their planned course of treatment in the PLATO study.

The study design and results of PLATO have been previously reported (see Online Supplement for brief details).[7,8] The primary endpoint of the study was the composite of nonfatal myocardial infarction, nonfatal stroke and cardiovascular death. In this subanalysis of PLATO, we first assessed the rates of the primary endpoint occurring from 24 hours after planned discontinuation of study medication (at the end of the trial period) up to 31 days after discontinuation in patients who had not had a primary endpoint event up to 1 day after discontinuation. Patients who discontinued study medication prior to planned completion of their course of study medication were also excluded. Second, for comparison with event rates during the trial period, we assessed the rates of the primary endpoint occurring between the date of the last scheduled study visit prior to discontinuation of study medication and up to 30 days later. Individual components of the primary endpoint and definite, probable or possible stent thrombosis rates, according to Academic Research Consortium criteria, were also determined. Baseline clinical characteristics of the populations

Table 1 Event rates from 1 to 31 days after planned discontinuation of study medication in patients who were free of events up to 24 hours after discontinuation

Event	Total N	Ticagrelor	K-M rate (%)	Total N	Clopidogrel	K-M rate (%)	HR (95% CI)	p
		Number (%) with event			Number (%) with event			
Primary endpoint (CV death, MI or stroke)	6,215	3 (0.05)	0.05	6,272	3 (0.05)	0.05	1.01 (0.20–5.00)	0.991
CV death	6,215	1 (0.02)	0.02	6,272	3 (0.05)	0.05	0.34 (0.03–3.23)	0.345
MI	6,215	2 (0.03)	0.03	6,272	0 (0.00)	0.00	–	–
Stroke	6,215	0 (0.00)	0.00	6,272	0 (0.00)	0.00	–	–
Definite stent thrombosis	4,461	1 (0.02)	0.02	4,481	0 (0.00)	0.00	–	–
Definite/probable stent thrombosis	4,461	1 (0.02)	0.02	4,479	0 (0.00)	0.00	–	–
Definite/probable/possible stent thrombosis	4,461	1 (0.02)	0.02	4,479	0 (0.00)	0.00	–	–

Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction (excluding silent myocardial infarction).

included in the analyses were determined to ensure matching of the assessed treatment groups. Details of the statistical methods are in the ►**Online Supplement**.

A total of 6,215 patients in the ticagrelor group and 6,272 patients in the clopidogrel group completed study medication as planned without a primary endpoint event up to 24 hours after discontinuation of study medication. Patients were well matched in their baseline characteristics and durations of study medication (►**Online Supplementary Table S1**). There were very few events during the follow-up period after planned discontinuation of study medication with no significant differences in the 30-day rates of either the composite primary endpoint (0.05 vs. 0.05%; equivalent to 6 events/1,000 patient years) or any of its individual components (►**Table 1**). There was only one definite, probable or possible stent thrombosis event in the ticagrelor group and none in the clopidogrel group (►**Table 1**). One-third of the patients transitioned to open-label dual-antiplatelet therapy with aspirin and clopidogrel after planned discontinuation of study medication with slightly higher rates in the subgroup of patients who had had PCI for the index ACS (37% in both treatment groups). There was no signal of higher event rates in those who discontinued dual-antiplatelet therapy compared with those who transitioned to open-label clopidogrel in addition to aspirin (►**Online Supplementary Table S2**). Event rates were actually lower than during treatment with study medication (►**Online Supplement**).

Results of recent studies highlight the risks of discontinuation of dual-antiplatelet therapy in patients with previous PCI and/or myocardial infarction, indicating a particularly increased risk of ischaemic events in the 3 months following discontinuation.[3–6] While the PLATO study did not provide the opportunity to assess events over this time period, it did allow an assessment of the early hazard that might occur as soon as the antiplatelet effects of clopidogrel or ticagrelor had worn off. We found no differences between the clopidogrel and ticagrelor groups in the rates of ischaemic events and stent thrombosis in the month after planned discontinuation of study medication. There was no differ-

ence in event rates between those who did and did not transition to open-label clopidogrel. These findings provide reassurance that the different mechanisms of action of clopidogrel and ticagrelor do not translate into any differential effect on thrombotic risk in the first few weeks after predicted recovery of platelet reactivity.

All patients in our analysis had completed at least 6 months of study medication and so were beyond the phase of increased vulnerability to stent thrombosis that is particularly marked in the first month after PCI.[11] Our findings are consistent with those of the PARIS registry, which showed no adverse impact of planned discontinuation of dual-antiplatelet therapy, in contrast to the adverse risk associated with treatment interruption or disruption.[3] Other large studies have not demonstrated an immediate spike in events in the 2 weeks following discontinuation of dual-antiplatelet therapy but a steadily higher event rate over the longer period of 3 months.[4,5] This suggests that, in this population of patients with previous ACS, recovery of platelet reactivity is a risk factor for subsequent events, likely related to new plaque rupture and evolution of disease within stented coronary artery segments, rather than a driving force for new events related to an existing thrombogenic substrate. It is clear that more than 1 month of follow-up is necessary to detect significantly increased rates of ischaemic events following discontinuation of dual-antiplatelet therapy. Furthermore, the power of our study was likely reduced by the fact that some patients transitioned from study medication to open-label clopidogrel and therefore continued dual-antiplatelet therapy during the follow-up period, which is particularly likely to have been the case in patients at higher risk of ischaemic events and stent thrombosis.

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