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EDITORIAL

Ticagrelor-based antiplatelet therapy after percutaneous coronary intervention in chronic coronary syndrome

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Unlike patients with acute coronary syndrome (ACS), in whom relatively urgent invasive treatment is favoured, lifestyle guidance and optimal drug treatment are prioritised in patients with chronic coronary syndrome (CCS), and the decision to proceed to coronary revascularisation is more dependent on symptom status and patient preference[1]. Current guidelines recommend a default antithrombotic strategy of 6-month clopidogrel-based dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) for CCS patients without high bleeding risk; the use of potent $P2Y_{12}$ inhibitors, such as prasugrel and ticagrelor, is recommended only for patients with high ischaemic risk. Nevertheless, compared with patients with ACS, those with CCS more often have high-risk demographics or clinical features, such as advanced age, multivessel disease, or chronic total occlusion, and complex PCI procedures are often required in CCS patients[2]. The appropriate antithrombotic management for CCS patients undergoing PCI is still under discussion.

The TWILIGHT trial enrolled 7,119 patients with either ACS or CCS, who had trial-defined high-risk features and experienced no significant clinical events during the initial 3-month DAPT following PCI[3]. These patients were randomly assigned to receive aspirin or matching placebo, while both groups received open-label ticagrelor for 12 months. The placebo-controlled, double-blind design was a strength of this trial compared to other trials comparing $P2Y_{12}$ inhibitor monotherapy and continued DAPT.

In this issue of EuroIntervention, Gitto et al present the results of a *post hoc* analysis specific to CCS patients in the TWILIGHT trial[4]. There were 2,503 CCS patients who were classified into two groups by the criterion of high ischaemic risk (HIR) stated in the 2019 European Society of Cardiology (ESC) guidelines. The definition of HIR included multivessel disease plus at least one feature of diabetes, prior myocardial infarction, peripheral artery disease, or chronic kidney disease. The observed incidence of major adverse cardiac and cerebrovascular events (MACCE) was significantly higher in patients with HIR than in those without (3.9% vs 2.3% at 1 year; p=0.015). Ticagrelor monotherapy and ticagrelor-based DAPT were associated with similar risks of MACCE (HIR: 4.0% vs 3.8%, hazard ratio [HR] 1.06, 95% confidence interval [CI]: 0.60-1.85; non-HIR: 2.1% vs 2.6%, HR 0.80, 95% CI: 0.38-1.66; p for interaction=0.553) and bleeding (HIR: 4.7% vs 5.7%, HR 0.82, 95% CI: 0.50-1.33; non-HIR: 4.9% vs 6.7%, HR 0.71, 95% CI: 0.44-1,14; p for interaction=0.684) in both HIR and non-HIR subgroups. The authors concluded that these findings suggest the potential to expand guideline recommendations for ticagrelor monotherapy in CCS patients. The authors should be commended for demonstrating that there was no concern regarding the application of ticagrelor monotherapy instead of ticagrelor-based DAPT even in patients with HIR CCS.

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Conventionally, the distinction between ACS and CCS has been an important stratification of patients with coronary artery disease; however, risk stratification within CCS has not been well established. In the latest ESC 2024 CCS guidelines, adding a second antithrombotic agent ($P2Y_{12}$ inhibitors or low-dose rivaroxaban) to aspirin for extended long-term secondary prevention in patients at enhanced ischaemic risk

without high bleeding risk is a Class IIa recommendation[1]. Here, enhanced ischaemic risk was defined by risk enhancers such as diabetes, and procedural or stent-related aspects. However, among the recent subgroup analyses of trials evaluating $P2Y_{12}$ inhibitors monotherapy after short-term DAPT, no study suggested a benefit of continued DAPT over $P2Y_{12}$ inhibitor monotherapy following a short period of DAPT, even in patients with high-risk features such as complex PCI or diabetes[5,6].

Therefore, should ticagrelor monotherapy after a short period of DAPT be applied for CCS patients? The principal issue in the present study is that the reference arm of ticagrelor-based DAPT was also experimental in nature among CCS patients. In the subgroup analysis of CCS patients in the GLOBAL LEADERS trial, ticagrelor monotherapy, compared with 12-month clopidogrel-based DAPT followed by aspirin monotherapy, was associated with similar cardiovascular outcomes but a numerically higher risk of Bleeding Academic Research Consortium 3 or 5 bleeding at 2 years (HR 1.32, 95% CI: 0.97-1.81)[7]. On the other hand, in STOPDAPT-2, clopidogrel monotherapy, compared with clopidogrel-based DAPT, in patients with CCS was associated with a significant reduction in Thrombolysis in Myocardial Infarction major or minor bleeding at 1 year (HR 0.26, 95% CI: 0.09-0.79) without an increased risk of cardiovascular events (HR 0.74, 95% CI: 0.38-1.45)[8]. Based on the currently available data, clopidogrel monotherapy, rather than ticagrelor monotherapy, might still be an appropriate therapy for CCS patients after a short duration of DAPT following PCI. Moreover, in STOPDAPT-3, which included both ACS and CCS patients, aspirin monotherapy, compared with clopidogrel monotherapy, was associated with similar cardiovascular and bleeding outcomes beyond 1 month and up to 1 year after PCI[9]. The appropriate monotherapy and lifetime management after PCI, including the choice of aspirin monotherapy, should be further discussed. In CCS patients with HIR features, ticagrelor monotherapy could be a treatment option. However, randomised trial data comparing ticagrelor monotherapy and clopidogrel or aspirin monotherapy are needed to expand guideline recommendations for ticagrelor monotherapy in CCS.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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