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# Opioids and oral P2Y12 receptor inhibitors: A drug–drug interaction

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As recommended in the European Society of Cardiology guidelines, titrated intravenous opioids should be considered to relieve pain in patients presenting with ST-segment elevation myocardial infarction (STEMI) (class of recommendation IIa, level of evidence C) [1]. The class of recommendation for morphine use in STEMI has been lowered from I to IIa (i.e., from "it is indicated" to "should be considered") as compared to previous guidelines, due to the unfavorable impact of morphine on P2Y12 receptor inhibitors bioavailability and their antiplatelet effect [2–4].

The CRUSADE registry was the first to suggest drug–drug interaction between morphine and a P2Y12 receptor inhibitor, as it reported an increased prevalence of adverse clinical outcome in acute coronary syndrome (ACS) patients receiving morphine and clopidogrel [5]. This suggestion was then proven in a randomized, placebo-controlled trial in patients with acute myocardial infarction (AMI) [2] and was confirmed in several other studies [3, 4, 6–8]. According to ticagrelor pharmacokinetic and pharmacodynamic studies, compared with healthy volunteers, patients with uncomplicated AMI appear to have similar plasma concentrations of ticagrelor and its active metabolite — AR-C124910XX after loading dose administration. Co-administration of morphine results in a decrease in ticagrelor bioavailability to a degree similar in both groups. However, while platelet inhibition in healthy volunteers is largely independent of morphine, in AMI patients the antiplatelet effect of ticagrelor is significantly less pronounced with co-administration of morphine [4, 9]. The greater susceptibility to the P2Y12 receptor inhibitor-morphine interaction seen in AMI patients is probably due to enhanced platelet activation in this subset of patients. In a meta-analysis by Gue et al. [10], patients pretreated with morphine were shown to have a higher rate of reinfarction than those not receiving morphine. Several approaches to overcome the "morphine effect" in patients with ACS have been proposed, showing some, but unsatisfactory effects [11–16]. Iglesias et al. [17] reported results of the PERSEUS study — a randomized trial comparing the impact of fentanyl versus morphine on ticagrelor pharmacokinetics and pharmacodynamics in STEMI patients undergoing primary percutaneous coronary intervention (PCI). Previously, reduced bioavailability of ticagrelor had been demonstrated when co-administered with fentanyl in stable patients [17], however the influence of fentanyl on ticagrelor absorption and platelet inhibition in AMI patients had not been established. The PERSEUS study was prematurely terminated after the inclusion of 68% of originally designed study population due to a slower than anticipated patient enrolment rate resulting in loss of statistical power. Nevertheless, the study brought consistent pharmacodynamic and pharmacokinetic evidence that fentanyl may be associated with a more favourable ticagrelor absorption profile

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than morphine, while exerting a similar analgesic effect. Indeed, these results do provide a strong premise supporting the preferential use of fentanyl over morphine in symptomatic STEMI patients undergoing primary PCI. The PERSEUS study, however, does not provide a comparison with any non-opioid treatment strategy, making it impossible to truly assess the effects of fentanyl on the pharmacokinetics and pharmacodynamics of ticagrelor in AMI patients. In this specific clinical setting, despite opioid-induced decreased bioavailability of P2Y12 receptor inhibitors, some additional factors, including enhanced platelet activation and reduced gastrointestinal perfusion as well as impact of mild therapeutic hypothermia applied in cardiac arrest survivors, may also impede the effect of oral antiplatelet drugs [18–24].

Further research enriches the knowledge on the possibility of reducing the clinical significance of the opioid-P2Y12 receptor inhibitor interactions, however, without bringing any breakthroughs to date. Therefore, for the time being, ensuring immediate inhibition of platelets by using the bridging therapy with cangrelor, seems to be the best solution of all [25, 26]. Nevertheless, the limited availability of this intravenous P2Y12 receptor inhibitor is a serious obstacle to widespread implementation of this approach.

**Conflict of interest:** None declared

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