Despite treatments for secondary prevention, patients with prior myocardial infarction (MI) remain at high risk for recurrent thrombotic events.\textsuperscript{1} The addition of a P2Y12 receptor antagonist to aspirin for the first year after an acute coronary syndrome (ACS) has been shown to reduce the risk of cardiovascular (CV) death, MI, or stroke.\textsuperscript{2–4} Based on this evidence, the current guidelines recommend dual antiplatelet therapy for up to 1 year after an ACS.\textsuperscript{5–8}

Several observations, however, had suggested that more prolonged therapy would be beneficial in patients with prior MI. Landmark analyses from the 1-year ACS trials of P2Y12 receptor antagonists showed a continued separation of the event curves over the entire year.\textsuperscript{4,9,10} Similarly, in landmark analyses from TRA 2\textsuperscript{°}P-Thrombolysis in myocardial infarction (TIMI) 50, more intensive antiplatelet therapy, achieved by adding the Protease-activated receptor (PAR)-1 inhibitor vorapaxar to standard antiplatelet treatment, significantly reduced the risk of ischaemic events over several years in patients with prior MI.\textsuperscript{11} Moreover, although overall the CHARISMA trial was neutral, in the subgroup of patients with prior MI, the addition of clopidogrel to aspirin significantly reduced the primary endpoint of CV death, MI, or stroke over a median of 27.6 months.\textsuperscript{12} Although these observations suggested that there was a benefit of more prolonged dual antiplatelet therapy in patients with MI, a definitive, prospective clinical trial was required to validate this hypothesis, which was the rationale for conducting the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS-TIMI 54) trial.\textsuperscript{13}

Ticagrelor is a potent, reversibly binding, direct-acting P2Y12 receptor blocker beyond the first year after an MI will significantly reduce the risk of CV death, MI, or stroke, with a directionally consistent benefit for cardiac death and from the recently reported subgroup of patients with MI from the DAPT trial. In that subgroup, continuation of a P2Y12 receptor treatment arm HRs (95% CI) vs. placebo of 0.85 (0.71–1.00) for CV death, 0.83 (0.72–0.95) for MI, and 0.78 (0.62–0.98) for stroke. The benefit of ticagrelor was consistent among major clinical subgroups, including region. The rate of the primary safety endpoint of TIMI major bleeding was higher with the two ticagrelor doses than with placebo (HR 2.69, 95% CI 1.96–3.70; \textit{P} < 0.001 for 90 mg; HR 2.32, 95% CI 1.68–3.21; \textit{P} < 0.001 for 60 mg); however, fatal bleeding or intracranial haemorrhage did not differ significantly. Thus, in terms of irreversible events of harm to the patient, a very favourable benefit–risk of prolonged ticagrelor is apparent (Figure 1). Dyspnoea was more frequent with the two ticagrelor doses; the majority of the cases were of mild or moderate intensity and did not lead to cessation of therapy. The similar efficacy and numerically lower rates of adverse events with the ticagrelor 60 mg bid dose make it appear to be the more attractive long-term option. The results of PEGASUS–TIMI 54 are highly consistent with data both from the CHARISMA MI subgroup, as noted earlier, and from the recently reported subgroup of patients with MI from the DAPT trial. In that subgroup, continuation of a P2Y12 receptor antagonist significantly reduced the risk of CV death, MI, or stroke, with a directionally consistent benefit for cardiac death and, unlike the still unexplained observation in patients without MI, no excess of non-CV death.\textsuperscript{15} Thus, taken together, we now have three randomized controlled trials that show that P2Y12 receptor blockade beyond the first year after an MI will significantly reduce the risk of future CV death, MI, or stroke. As expected, there was more bleeding, but no excess of intracranial haemorrhage (ICH) or fatal bleeding.

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

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The current practice of limiting P2Y12 receptor blockade after an ACS to 1 year is an artefact of the duration of the ACS trials; however, patients remain at high risk of platelet-mediated ischaemic events long-term. Given the PEGASUS-TIMI 54 results, as well as the data from the CHARISMA prior MI population and the DAPT MI population, long-term therapy for secondary prevention is logical. Of note, the benefit of adding ticagrelor 60 mg bid to aspirin is very similar to that of aspirin for secondary prevention after MI (Figure 2). In terms of safety, the 1.5- to 2-fold increased risk of major GI bleeding with aspirin post-MI is roughly comparable to the bleeding risk with adding ticagrelor 60 mg bid, and ticagrelor 60 mg bid did not increase ICH or fatal bleeding. Thus, the benefit–risk for ticagrelor 60 mg bid is generally as favourable as aspirin for secondary prevention. Consequently, consistent with what is recommended for aspirin, patients with ACS should be treated with dual antiplatelet therapy, and if they are at high ischaemic risk and tolerating such therapy well, it should be continued beyond 1 year.

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