

## Inglese

The combination of the irreversible cyclo-oxygenase (COX) inhibitor aspirin (acetylsalicylic acid) 75–100 mg once-daily (OD) and the P2Y<sub>12</sub> inhibitor ticagrelor 90 mg twice-daily (BD) represents a standard recommended regimen of dual antiplatelet therapy (DAPT) in acute coronary syndromes (ACS). The Platelet inhibition and patient Outcomes (PLATO) study showed that DAPT with aspirin and ticagrelor was superior to the previous standard regimen of aspirin and clopidogrel in ACS, reducing the incidence of major adverse cardiovascular events (MACE). Despite such potent antiplatelet therapy, the residual MACE risk remains around 10% at 1 year.

Continuing DAPT with aspirin and reduced-dose ticagrelor long-term in stable high-risk individuals further decreases the risk of MACE compared with aspirin alone. However, increasing the potency or duration of DAPT also leads to increased bleeding, which is associated not only with higher mortality but also patient distress, inconvenience, and premature discontinuation, even if events are considered minor or trivial by clinicians. Concern about bleeding risk may, therefore, dissuade clinicians from recommending DAPT, particularly in the long-term, to the potential detriment of high-risk patients.

Further subgroup analysis of the PLATO study suggested that doses of aspirin  $\geq 300$  mg were associated with reduced benefit of ticagrelor over clopidogrel and, as a result, daily aspirin doses  $>100$  mg are not recommended when used in DAPT.

Aspirin and ticagrelor have additive antithrombotic effects. Whilst ticagrelor inhibits the platelet adenosine diphosphate P2Y<sub>12</sub> receptor, aspirin's action relates to its ability to irreversibly inhibit platelet COX-1, thus reducing prothrombotic eicosanoid TXA<sub>2</sub> production. Aspirin can achieve almost-complete ( $\geq 95\%$ ) inhibition of TXA<sub>2</sub> biosynthesis in healthy subjects at repeated daily doses as low as 20–30 mg. At doses above 300 mg, aspirin also inhibits COX-2 in humans, a key enzyme in the pathway of constitutive, vascular-protective prostacyclin (PGI<sub>2</sub>) release by the endothelium. Inhibition of COX-2 and PGI<sub>2</sub> biosynthesis may be counterproductive in patients with ACS: both traditional and COX-2-selective nonsteroidal anti-inflammatory drugs are associated with an increased risk of MACE. There is also evidence from animal studies that ticagrelor may beneficially induce COX-2 and endothelial nitric oxide synthase through an adenosine-dependent mechanism, which may limit myocardial infarct size through synergistic antiplatelet and vasodilatory effects of PGI<sub>2</sub>, nitric oxide and P2Y<sub>12</sub> inhibition. Therefore, inhibition of COX-2 by high-dose aspirin may compromise the beneficial effects of ticagrelor on this pathway.

Aspirin dosing frequency may also influence pharmacodynamic efficacy: OD aspirin administration may be insufficient to maintain consistency of platelet inhibition over 24 h in patients with higher platelet turnover, including smokers and those with obesity or diabetes mellitus, or in individuals undergoing procedural intervention. Multiple daily-dosing regimens of aspirin have been shown to improve consistency of pharmacodynamic effect, not only in conditions with extreme acceleration of platelet turnover, such as essential thrombocythemia, but also in patients with ischemic heart disease when administered as single antiplatelet therapy. However, such regimens of aspirin have not been studied in those receiving dual antiplatelet therapy (DAPT) with ticagrelor, which is already given BD, in whom the overall pharmacodynamic profile of DAPT may potentially be improved by BD aspirin dosing.

An ideal regimen of aspirin and ticagrelor would be one that maintains the anti-ischemic benefit of DAPT through effective and steady inhibition of platelet COX-1 and P2Y<sub>12</sub>, ensures consistency of effect across the dosing interval, avoids inhibition of vasoprotective COX-2-dependent PGI<sub>2</sub> biosynthesis and has minimized effects on hemostatic capacity. We hypothesized that ticagrelor administered with a lower-than-standard, multiple-daily dose of aspirin establishes a beneficial hemostatic profile and so we investigated a novel regimen of aspirin 20 mg BD and ticagrelor 90 mg BD in patients treated for ACS.

1. What are the standard total daily doses for dual antiplatelet therapy in acute coronary syndromes?
  - A aspirin 75-100 mg and ticagrelor 90 mg
  - B aspirin 75-100 mg and ticagrelor 180 mg**
  - C aspirin 70 mg and clopidogrel 180 mg
  - D aspirin 20 mg and ticagrelor 90 mg
  - E aspirin 40 mg and ticagrelor 180 mg

2. Why do those treating high-risk patients sometimes choose not to propose extended DAPT treatment?

A the residual MACE risk remains around 10% at 1 year

**B the extended regime can increase bleeding**

C it reduces the benefits of ticagrelor over clopidogrel

D it is not appropriate for smokers and those with obesity or diabetes mellitus

E it may compromise the beneficial effects of ticagrelor

3. High doses of aspirin may prove deleterious because of

A potential detriment to high-risk patients

B reduced benefit of clopidogrel over ticagrelor

**C inhibition of COX-2 and thus PGI2 biosynthesis**

D inhibition of endothelial nitric oxide synthase through an adenosine-dependent mechanism

E extreme acceleration of platelet turnover

4. In which conditions have multiple daily doses of aspirin as single antiplatelet therapy been shown to be beneficial?

A patients with obesity or diabetes mellitus

**B patients with essential thrombocythemia and ischemic heart disease**

C smokers

D individuals undergoing procedural intervention

E patients receiving dual antiplatelet therapy (DAPT) with ticagrelor

5. What variation on the standard total daily doses did the authors undertake to study for dual antiplatelet therapy in acute coronary syndromes?

A aspirin 75-100 mg and ticagrelor 90 mg

B aspirin 75-100 mg and ticagrelor 180 mg

C aspirin 70 mg and clopidogrel 180 mg

D aspirin 20 mg and ticagrelor 90 mg

**E aspirin 40 mg and ticagrelor 180 mg**