ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy (2018) **4**, 131–132
doi:10.1093/ehjcvp/pvy007

EDITORIAL

2017 ESC guidelines focus on dual antiplatelet therapy

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Dual antiplatelet therapy (DAPT), or the combination of aspirin and an oral inhibitor of the platelet $P2Y_{12}$ receptor, is indicated in acute coronary syndromes (ACS) and after percutaneous interventions (PCIs). The first randomized trial demonstrating the superiority of DAPT over oral anticoagulant therapy in patients undergoing PCI was performed in 1996. Nowadays, in Europe, ~1 400 000 and 2 200 000 patients may have an indication for DAPT after PCI or ACS, respectively.

With >35 randomized clinical trials, DAPT is one of the most investigated therapies in the cardiovascular area. In the last years, the focus has been on the development of new $P2Y_{12}$ inhibitors and optimal treatment duration.

The first therapeutic implementation was based on safety, with the introduction of clopidogrel after ticlopidine, and then the formulation of more potent and predictable $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) that overcome the differences in antiplatelet activity of the different clopidogrel salts and of its generic preparations.

As regards DAPT duration, at first the need for longer therapy was related to the thrombotic risk of the first-generation drug-eluting stents (DES). However, with the advent of safer newer generation DES, the DAPT extension after 12 months no longer seemed justifiable. On the other hand, new evidence highlighted the importance of DAPT in long-term secondary prevention of cardiovascular non-stent-related risk, paving the way for therapy beyond 12 months. The 2017 ESC guidelines have integrated all this evidence and have come up with the recommendation of long-term DAPT, preferentially with ticagrelor 60 mg b.i.d., for the secondary prevention of events in patients at high risk after myocardial infarction (MI).

Therefore, 21 years after the first evidence on DAPT, the paradigm is shifting from a 'local' treatment (prevention of stent thrombosis) to a 'systemic' treatment strategy, for global cardiovascular protection.

Obviously, the decision on long-term DAPT duration requires a balance between the individual ischaemic and haemorrhagic risk. Therefore, the 2017 ESC guidelines introduce the possibility of using two specific risk scores to assist clinicians in the estimation. As for the choice between the three oral $P2Y_{12}$ inhibitors, clopidogrel is the drug of choice in some specific cases: patients with stable coroanry artery disease (CAD) in elective PCI, patients on concomitant oral anticoagulant therapy, and ACS patients who have contraindications for prasugrel and ticagrelor. The two more potent drugs, therefore, remain the recommended drugs for all other cases.

Therefore, the main novelties in the 2017 ESC guideline recommendations on DAPT include the recommendation of a pre-treatment with a $P2Y_{12}$ inhibitor, the possibility of switching a $P2Y_{12}$ inhibitor, and the duration of the therapy.[1]

First, the guidelines recommend pre-treatment with a $P2Y_{12}$ inhibitor in patients whose coronary anatomy is known and the decision to proceed to PCI has been made, as well as in patients with ST-segment elevation myocardial infarction (STEMI) (level of recommendation IA).

To assist the choice between the three oral $P2Y_{12}$ inhibitors, the guidelines clearly define the different patient targets. Clopidogrel remains the elective drug in some specific cases: patients with stable CAD in elective PCI, patients on concomitant oral anticoagulant therapy, and ACS patients who have contraindications for prasugrel and ticagrelor. The two more potent drugs, therefore, remain the recommended drugs for all other cases. In particular, in patient with ACS, ticagrelor (180 mg loading dose, 90 mg twice daily) on top of aspirin is recommended, regardless of the initial treatment strategy, including patients pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contraindications. In patients with ACS undergoing PCI, prasugrel (60 mg loading dose, 10 mg daily dose) on top of aspirin is recommended for $P2Y_{12}$ inhibitor-naive patients with NSTE-ACS or initially conservatively managed STEMI if an indication for PCI is established, or in STEMI patients undergoing immediate coronary catheterization unless there is a high risk of life-threatening bleeding or other contraindications. For both, the recommendation is IB.

For the first time, the 2017 ESC guidelines introduce the recommendation on $P2Y_{12}$ switching: in patients with ACS who were previously exposed to clopidogrel, switching from clopidogrel to ticagrelor is recommended early after hospital admission at a loading dose of 180 mg irrespective of timing and loading dose of clopidogrel, unless contraindications to ticagrelor exist (recommendation IB).

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The DAPT duration is the second main concept developed in the guidelines, and its evaluation requires a balance between the ischaemic and the haemorrhagic risk of the patient. In this sense, the 2017 ESC guidelines introduce the possibility of using two specific risk scores to assist clinicians in the estimation: the DAPT score and the PRECISE DAPT (use recommended as IIbA). As a general recommendation, in patients with ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding (e.g. PRECISE-DAPT >25) (recommendation IA). The use of a score is not mandatory and a clinical judgement could be more appropriate due to the modest ability to predict the events. Clinicians must be aware that risk scores, although useful to improve the accuracy of the prognostic assumptions affecting clinical decisions, cannot be considered a clear-cut decision rule or a substitute for case by case clinical judgement.

As for duration, however, the more remarkable innovation introduced by the 2017 ESC guidelines regards the recommendation (level IIbB) on DAPT beyond 12 months. In patients with MI and high ischaemic risk who have tolerated DAPT without a bleeding complication, ticagrelor 60 mg b.i.d for longer than 12 months on top of aspirin may be preferred over clopidogrel or prasugrel. Moreover, in patients with prior MI and high ischaemic risk, who are managed with medical therapy alone, DAPT with ticagrelor 60 mg b.i.d for longer than 12 months and for up to 36 months may be considered. The recommendations are based on the results of the clinical trial PEGASUS-TIMI 54,[2] which randomized 21 162 patients ≥50 years old who had an MI from 1 to 3 years earlier and at high ischaemic risk (≥65 years, diabetes, >1 previous MI, microvasular disease, and chronic kidney disease) 1:1:1 for ticagrelor 90 mg b.i.d, ticagrelor 60 mg b.i.d., and placebo, on top of aspirin. The study demonstrated that ticagrelor treatment significantly reduces the risk of cardiovascular death, MI, or stroke in these high-risk patients, with a significant increase in TIMI major bleeding but not in fatal bleeding or in haemorrhagic stroke. Importantly, the high ischaemic risk population identified in PEGASUS is the reference for the definition in the guidelines. Pre-specified subanalyses confirm the results in different subpopulations, identifying the greatest benefits in patients continuing on or restarting DAPT after a brief interruption of the $P2Y_{12}$ inhibitor (≤30 days), and in those closer to their index MI.[3,4] Taking this evidence together, the European Medicines Agency approved ticagrelor 60 mg for DAPT after 12 months[5] in a specific population setting (≤2 years from qualifying MI or ≤1 year from prior ADP receptor inhibitor treatment); the related PEGASUS post-hoc analysis, named EU label[6] and involving >75% of the study population, demonstrated a relative risk reduction (RRR) of 20% in the composite of cardiovascular death, MI, or stroke, 29% in cardiovascular death, and 20% in all-cause mortality, with a favourable risk–benefit ratio.

In conclusion, the 2017 ESC guidelines confirm the new paradigm of DAPT,[7–9] from treating stents to treating patients, for a global protection of cardiovascular patients.

Conflict of interest: none declared.

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