Optimal duration of dual anti-platelet therapy after percutaneous coronary intervention: 2016 consensus position of the Italian Society of Cardiology

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Definition of the optimal duration of dual anti-platelet therapy (DAPT) is an important clinical issue, given the large number of patients having percutaneous coronary intervention (PCI), the costs and risks of pharmacologic therapy, the consequences of stent thrombosis, and the potential benefits of DAPT in preventing ischaemic outcomes beyond stent thrombosis. Nowadays, the rationale for a prolonged duration of DAPT should be not only the prevention of stent thrombosis, but also the prevention of ischaemic events unrelated to the coronary stenosis treated with index PCI. A higher predisposition to atherothrombosis may persist for years after an acute myocardial infarction, and even stable patients with a history of prior myocardial infarction are at high risk for major adverse cardiovascular events. Recently, results of pre-specified post-hoc analyses of randomized clinical trials, including the PEGASUS-TIMI 54 trial, have shed light on strategies of DAPT in various clinical situations, and should impact the next rounds of international guidelines, and also routine practice. Accordingly, the 2015 to 2016 Directive Council of the Italian Society of Cardiology addressed newer recommendations on duration of DAPT based on most recent scientific information. The document states that physicians should decide duration of DAPT on an individual basis, taking into account ischaemic and bleeding risks of any given patient. Indeed, current controversy surrounding optimal duration of DAPT clearly reflects the fact that, nowadays, a one size fits all strategy cannot be reliably applied to patients treated with PCI. Indeed, patients usually have factors for both increased ischaemic and bleeding risks that must be carefully evaluated to assess the benefit/risk ratio of prolonged DAPT. Personalized management of DAPT must be seen as a dynamic prescription with regular re-evaluations of the risk/benefit to the patient according to changes in his/her clinical profile. Also, in order to derive more benefit than harm from new treatments, a multi-parametric approach using several risk scores of the ischaemic and bleeding risks might improve the process of risk factor characterization. In patients with high ischaemic risk, particularly those with a history of myocardial infarction, the benefits of extended DAPT (particularly with ticagrelor up to 3 years) are likely to outweigh the risks.

Keywords: drug-eluting stent, dual anti-platelet therapy, percutaneous coronary intervention, ticagrelor

J Cardiovasc Med 2016, 17:000–000

Preamble

Dual anti-platelet therapy (DAPT) with aspirin and a P2Y12 receptor inhibitor is of paramount importance after percutaneous coronary intervention (PCI) to prevent stent thrombosis. Two decades after its introduction, however, duration of DAPT after PCI remains a matter of debate. Indeed, long-term use of DAPT may reduce the risk of stent and non-stent-related ischaemic events, but may increase the risk of bleeding, which, in turn, counteracts the potential benefits of anti-platelet therapy. Definition of the optimal duration of DAPT is an important clinical issue, given the large number of patients treated with drug-eluting stent (DES), the costs and risks of anti-platelet therapy, the life-threatening consequences of stent thrombosis, and the potential benefits of anti-platelet therapy in preventing ischaemic outcomes beyond stent thrombosis.
Introduction

Duration of DAPT may have a major impact on the outcome of patients with cardiovascular disease, as several million patients around the world undergo PCI each year. One should, however, consider that newer pharmacologic options coupled with newer DES have significantly reduced in recent years the risk of patients treated with PCI to experience an ischaemic event after the procedure. Patients without any new event during the initial 12 months pass into a stable phase associated with a low risk of further events. The annual risks for these patients are 1.0−2.0% for non-fatal myocardial infarction, 1.0% for cardiovascular mortality, 0.5% for ischaemic stroke, and 0.5% for stent thrombosis. The low risk of the late post-revascularization setting, therefore, is an important factor affecting any attempt to assess the risk/benefit ratio of prolonged DAPT.

Trials on optimal duration of dual anti-platelet therapy

The pivotal studies evaluating clopidogrel, prasugrel, and ticagrelor showed continued divergence of the ischaemic event curves beyond the first month of treatment, suggesting that treatment should be for at least 12 months, and raised the possibility that treatment beyond 12 months might lead to further reductions in ischaemic events. However, all trials that have compared more than 1 year DAPT with standard DAPT have yielded conflicting results (Table 1). Initial trials were the DES-LATE (Optimal Duration of Clopidogrel Therapy with DES to Reduce Late Coronary Arterial Thrombotic Event) trial, the ARCTIC-Interruption (Assessment by a double Randomization of a Conventional anti-platelet therapy versus a monitoring-guided strategy for DES implantation and of Treatment Interruption versus Continuation 1 year after stenting) trial, and the OPTIDUAL (OPTimal DUAL Anti-platelet Therapy) trial. Despite not powered for mortality, the first trial that was adequately powered for safety and efficacy endpoints was the DAPT trial. In each of these trials, which included either stable patients or patients with prior myocardial infarction undergoing PCI, event-free patients on DAPT 1 year after stent placement were randomized to either aspirin monotherapy or to continue clopidogrel or prasugrel for a variable amount of time. Discrepant results were apparent in these four trials. Specifically, no significant difference in the rate of the primary endpoint was apparent between the two DAPT strategies in the DES-LATE trial, ARCTIC-Interruption trial, and the OPTIDUAL trial. In contrast, continuation of DAPT between 12 and 30 months in the DAPT trial was associated with significantly lower rates of definite/probable stent thrombosis and newer events compared with aspirin monotherapy, but at the expense of increased bleeding (2.9 vs. 5.6%; P < 0.001). Moreover, in the DAPT trial, there was a borderline difference in mortality between the two DAPT strategies, with a 0.5% absolute difference favouring shorter compared with extended DAPT (1.5 vs. 2.0%, respectively; P = 0.052). The largest study examining the role of DAPT in coronary patients beyond 1 year is the PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis In Myocardial Infarction 54) trial. This randomized double-blind trial, which included only patients with

Table 1 Randomized clinical trials of DAPT duration after PCI

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration of DAPT</th>
<th>Patients</th>
<th>Drug</th>
<th>Primary study endpoint</th>
<th>Trial outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES-LATE</td>
<td>12 vs. 36 months</td>
<td>N = 2701</td>
<td>Clopidogrel</td>
<td>Cardiac death, myocardial infarction, or stroke ≤ 24 h</td>
<td>At 2-year follow-up, rates of the primary endpoint were 2.4% with aspirin monotherapy vs. 2.7% with extended DAPT (P = 0.75)</td>
</tr>
<tr>
<td>ARCTIC-Interruption</td>
<td>12 vs. 18 months</td>
<td>N = 1259</td>
<td>Clopidogrel or prasugrel</td>
<td>Death, myocardial infarction, stent thrombosis, stroke, or urgent target vessel revascularization bleeding</td>
<td>After a median follow-up of 17 months, rates of the primary endpoint were 4.0% in both treatment groups (P = 0.58)</td>
</tr>
<tr>
<td>OPTIDUAL</td>
<td>12 vs. 48 months</td>
<td>N = 1385</td>
<td>Clopidogrel</td>
<td>Death, myocardial infarction, stroke, or major bleeding</td>
<td>At 3-year follow-up, rates of the primary endpoint were 7.5% with aspirin monotherapy vs. 5.8% with extended DAPT (P = 0.17)</td>
</tr>
<tr>
<td>DAPT</td>
<td>12 vs. 30 months</td>
<td>N = 9961</td>
<td>Clopidogrel or prasugrel</td>
<td>Co-primary: stent thrombosis and MACCE</td>
<td>At 2.5-year follow-up, rates of stent thrombosis and MACE were 1.4 and 4.1% with aspirin monotherapy vs. 0.4 and 2.1% with extended DAPT (P = 0.001 for both comparisons)</td>
</tr>
<tr>
<td>PEGASUS-TIMI 54</td>
<td>12 vs. 36 months</td>
<td>N = 21,162</td>
<td>Ticagrelor 90 or 60 mg b.i.d. (vs. placebo)</td>
<td>Cardiovascular death, myocardial infarction, or stroke</td>
<td>The two ticagrelor doses each reduced, as compared with placebo, the rate of the primary efficacy endpoint, with Kaplan–Meier rates at 3 years of 7.85% in the group that received 90 mg of ticagrelor twice daily, 7.77% in the group that received 60 mg of ticagrelor twice daily, and 9.04% in the placebo group</td>
</tr>
</tbody>
</table>
previous myocardial infarction, evaluated the efficacy and safety of ticagrelor in addition to low-dose aspirin for long-term treatment in 21,162 stable patients with a history of spontaneous non-ST-segment elevation or ST-segment elevation myocardial infarction 1–3 years before randomization. Noteworthy, PEGASUS-TIMI 54 evaluated the 90 mg twice-daily dose of ticagrelor previously studied, and also the 60 mg twice-daily dose, and followed up patients for a median of 33 months. Both doses of ticagrelor reduced the risk of cardiovascular death, myocardial infarction, or stroke compared with placebo, with a hazard ratio of 0.85 (7.85 vs. 9.04%; \( P = 0.008 \)) for the 90 mg dose and a hazard ratio of 0.84 (7.77 vs. 9.04%; \( P = 0.004 \)) for the 60 mg dose. Both doses increased the risk of Thrombolysis in Myocardial Infarction (TIMI) major bleeding (2.6, 2.3, and 1.1%, respectively), but the rates of fatal bleeding or non-fatal intracranial haemorrhage did not differ significantly between either ticagrelor dose group or placebo. The rates of bleeding and other side effects such as dyspnoea were numerically lower with the 60-mg dose of ticagrelor than with the 90-mg dose, resulting in a lower rate of discontinuation of the study drug and a better safety and tolerability profile with the 60-mg dose. Since publication of PEGASUS-TIMI 54, multiple meta-analyses have been performed on this topic, yielding conflicting results.\(^{13–16} \) Noteworthy, some authors have detected an increase in all-cause mortality and non-cardiovascular mortality associated with prolonged DAPT, thus raising concern on the risk/benefit ratio of extended duration of therapy.\(^{13–16} \)

In patients with high bleeding risk, the possibility exists to shorten DAPT duration when third-generation stents are implanted. Several trials published since 2011 have explored DAPT duration of 3 or 6 months compared with 1 year or longer. Indeed, REA Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation, Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice, Intracoronary Stenting and Antithrombotic Regimen: Safety And Efficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting, is There A Life for DES after Discontinuation of Clopidogrel, Second Generation Drug-Eluting Stent Implantation Followed by Six-Versus Twelve-Month Dual Antiplatelet Therapy, Efficacy of Xience/promus versus Cypher in rEducing Late Loss after stENTing, and PRODIGY trials have demonstrated that shorter DAPT is associated with lower all-cause mortality versus longer DAPT.\(^{17–23} \) Also, results from the Zotarolimus-eluting Endeavor sprint stent in Uncertain DES candidates and Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk trials have shown that some new-generation stents allow even 1-month course of DAPT only.\(^{24,25} \)

**Current European and American guidelines**

European guidelines (Table 2) have long recommended 1 year of DAPT in patients after PCI, based on expert consensus and observational studies, suggesting a delayed propensity for complete endothelialization and subsequent risk of late stent thrombosis after discontinuation of DAPT in patients treated with early-generation DES.\(^{26,27} \) Similarly, the most recent European Society of Cardiology guidelines on non-ST-segment elevation myocardial infarction recommend 12 months of DAPT after PCI.\(^{28} \) However, the risk of stable patients differs from the risk of acute coronary syndrome patients after stenting and hospital discharge.\(^{29} \) Also, stent type has emerged as an important risk factor for stent thrombosis. Several lines of evidence suggest that the newer-generation DES are associated with a risk of stent thrombosis approximately one half that of the first-generation DES.\(^{30} \) Accordingly, in stable patients undergoing PCI with the latest generation DES, treatment should be for 6 months. Longer courses of therapy may be reasonable in patients at low bleeding risk who are tolerating DAPT well. For patients with acute coronary syndrome, conversely, prolonged DAPT is beneficial and reasonable, if tolerated. Also, prolonged DAPT can be used when the diagnosis of obstructive coronary artery disease is manifest (i.e. documented spontaneous myocardial infarction, typically with confirmed coronary artery disease on angiography) and when there are no bleeding contraindications.\(^{2} \)

Updated US guidelines now support prescribing 6 months, rather than 12 months, of DAPT after DES implantation for patients with stable ischaemic heart disease.\(^{31} \) Specifically, therapy for at least 6 months is given a class I recommendation in stable patients, with class IIb caveats that physicians can prescribe for longer in patients at low bleeding risk and shorter in patients at high bleeding risk. As regards drugs, aspirin 81 mg should be preferred, and ticagrelor and prasugrel are now recommended as a class IIa indication over clopidogrel. American experts also introduced the so-called DAPT score (Table 3), which provides individualized assessment of the risks and benefits of prescribing DAPT beyond 1 year in patients who underwent PCI based on a patient’s specific risk factors.\(^{32} \) The new tool was developed from

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**Table 2 Duration of DAPT according to 2014 and 2015 ESC guidelines**

<table>
<thead>
<tr>
<th>PIs in stable patients</th>
<th>DAPT: 1 month after bare metal stent</th>
<th>Class I</th>
<th>Level A</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPT: 6 months after drug-eluting stent</td>
<td>Class I</td>
<td>Level B</td>
<td></td>
</tr>
<tr>
<td>DAPT: &gt;6 months if high ischaemic risk and low haemorrhagic risk</td>
<td>Class IIb</td>
<td>Level C</td>
<td></td>
</tr>
</tbody>
</table>

| PIs in STEMI or ACS/NSTEMI patients | DAPT: 12 months if not contraindicated | Class I | Level A |

ACS, acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.
DAPT trial of more than 11,000 patients undergoing PCI that demonstrated an overall lower risk of myocardial infarction and stent thrombosis, but a higher risk of bleeding when the therapy was extended beyond 1 year. Analysis of study data suggested that in patients treated for 1 year with DAPT without significant bleeding or ischaemic events, the benefit/risk ratio with prolonged DAPT may be favourable for those with a high DAPT score (≥2) because prolonged DAPT reduces net (ischaemic and bleeding) events when compared with non-prolonged DAPT. Conversely, in those with a low DAPT score (<2), the benefit/risk ratio with prolonged DAPT is not favourable (increased bleeding without a reduction in ischaemic events). The risk calculator, which is available at http://www.daptsstudy.org/for-clinicians/calchome.htm, assigns individual patients a numerical score (−2 to 10). Although the DAPT score represents a significant step forward in understanding benefits and risks of treatment, its major limitation lies on the lack of a prospective validation (Table 4).

### The rationale for prolonged dual anti-platelet therapy: a paradigm shift

Drug-eluting stents have substantially improved the outcomes of patients with coronary artery disease undergoing PCI. After implantation of a DES, patients are treated with DAPT in order to reduce the risk of stent thrombosis and minimize adverse cardiac outcomes. Prior to the DES era, physicians prescribed DAPT for 4 weeks after bare metal stent implantation. The duration of treatment was increased to 3 months after approval of a sirolimus-eluting stent in 2003 and then to 6 months after the approval of a paclitaxel-eluting stent in 2004. Duration of DAPT, however, was questioned when case reports of very late stent thrombosis were published. On December 7 and 8, 2006, the US Food and Drug Administration (FDA) convened an advisory panel meeting to discuss stent thrombosis and the overall safety of DES. Despite the lack of any scientific background, the advisory panel concurred with the joint clinical practice guideline recommendation for 12 months of DAPT after placement of a DES in patients who are not at high risk of bleeding.

Nowadays, stent thrombosis has become relatively rare with newer-generation DES, though it remains a life-threatening event. Indeed, the long-term risk of very late stent thrombosis is somewhat linear and low, particularly with the use of newer generations of stents. Consequently, if there is a benefit of extended DAPT in preventing late stent thrombosis, there is no particular reason to expect the risk to abate after 12 or 18 months. Although newer-generation metallic DES have further advanced the safety and efficacy profile compared with first-generation devices, the persistence of a metallic cage has been suggested to prevent complete arterial healing. A novel cause for concern comes from the bioabsorbable stents. Although fully bioresorbable scaffolds have been introduced into clinical practice for avoiding late adverse events including restenosis and thrombosis, very late scaffold thrombosis may occur at advanced stages of scaffold resorption. Potential mechanisms specific for very late scaffold thrombosis include scaffold discontinuity and restenosis during the resorption process, which appear delayed in humans. These findings suggest an extended period of vulnerability for thrombotic events and therefore constitute a pathophysiologic basis for an extended duration of DAPT.

The rationale for a prolonged duration of DAPT, however, should not only be the prevention of stent thrombosis, but also the prevention of ischaemic events unrelated to the coronary stenosis treated with index PCI. Patients with myocardial infarction have heightened platelet activation and aggregation resulting in atherothrombosis after the rupture or fissuring of an unstable atherosclerotic plaque compared with patients with stable ischaemic heart disease. A higher

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**Table 3** Factors used to calculate a ‘DAPT score’

<table>
<thead>
<tr>
<th>Variables</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 75 years</td>
<td>−2</td>
</tr>
<tr>
<td>Age &gt; 65 ≤ 75 years</td>
<td>−1</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
</tr>
<tr>
<td>Previous myocardial infarction or percutaneous coronary intervention</td>
<td>1</td>
</tr>
<tr>
<td>Stent diameter ≥3 mm</td>
<td>1</td>
</tr>
<tr>
<td>Paclitaxel-eluting stent</td>
<td>1</td>
</tr>
<tr>
<td>Heart failure and/or left ventricular ejection fraction ≤30%</td>
<td>2</td>
</tr>
<tr>
<td>Percutaneous coronary intervention on a saphenous vein graft</td>
<td>2</td>
</tr>
</tbody>
</table>


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**Table 4** Clinical and procedural factors associated with increased ischaemic risk (including stent thrombosis) or increased bleeding risk

<table>
<thead>
<tr>
<th>Factors associated with increased ischaemic risk (including stent thrombosis) or increased bleeding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
</tr>
<tr>
<td>Acute coronary syndrome presentation</td>
</tr>
<tr>
<td>Multiple prior myocardial infarctions</td>
</tr>
<tr>
<td>Extensive coronary artery disease</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Factors associated with increased risk of stent thrombosis</td>
</tr>
<tr>
<td>Acute coronary syndrome presentation</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Left ventricular ejection fraction ≤40%</td>
</tr>
<tr>
<td>First-generation drug-eluting stent</td>
</tr>
<tr>
<td>Stent characteristics (size, length, under-deployment)</td>
</tr>
<tr>
<td>Coronary anatomy of stented vessel (bifurcation, in-stent restenosis)</td>
</tr>
<tr>
<td>Factors associated with increased bleeding risk</td>
</tr>
<tr>
<td>History of previous bleeding</td>
</tr>
<tr>
<td>Oral anti-coagulant therapy</td>
</tr>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>Advanced age</td>
</tr>
<tr>
<td>Low body weight</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Anaemia</td>
</tr>
<tr>
<td>Steroids or non-steroidal anti-inflammatory drugs</td>
</tr>
</tbody>
</table>

predisposition to atherothrombosis may persist for years after an acute myocardial infarction,\textsuperscript{46–49} and even stable patients with a history of prior myocardial infarction are at high risk for major adverse cardiovascular events.\textsuperscript{50–52} Thus, after myocardial infarction, patients may have a persistent state that predisposes them to benefit more from DAPT.\textsuperscript{45}

**What’s new on dual anti-platelet therapy in 2016**

Recently, results of pre-specified post-hoc analyses of randomized clinical trials, including the PEGASUS-TIMI 54 trial, have shed light on strategies of DAPT in various clinical situations, and should impact the next rounds of international guidelines, and also routine practice.\textsuperscript{5} In PEGASUS-TIMI 54, ticagrelor reduced major adverse cardiovascular event by 15% in patients with prior myocardial infarction. Subsequently, investigators evaluated the possibility that the timing of P2Y12 inhibitor withdrawal prior to randomization would be associated with ischaemic risk and the benefit of ticagrelor.\textsuperscript{53} Bonaca et al. hypothesized that patients enrolled after recent P2Y12 inhibitor withdrawal would be at heightened ischaemic risk and therefore derive greater benefit from long-term ticagrelor therapy, whereas patients who had remained event-free on aspirin therapy alone for an extended period would be at relatively lower risk and derive a more modest benefit. Patients in PEGASUS-TIMI 54 were categorized by time from last P2Y12 inhibitor withdrawal (days: $\leq$30, 30–360, $>$360). In the placebo arm, patients who more recently stopped P2Y12 inhibitor therapy had a greater number of risk factors, but still had a higher risk of major adverse cardiovascular event compared with those who stopped 1 year before ($P$ trend $= 0.0097$). The benefit of ticagrelor for long-term secondary prevention in patients with prior myocardial infarction and at least one additional risk factor appeared more marked in patients continuing on or re-starting after only a brief interruption of P2Y12 inhibition, when compared with patients who had proved themselves stable more than 2 years from their myocardial infarction and off P2Y12 inhibitor therapy for more than a year. Specifically, in subgroup analysis, the greatest reduction in ischaemic events was in patients in whom P2Y12 inhibitor therapy either had not been discontinued or had been discontinued for 30 days or less before enrolment in the study (absolute reduction in Major adverse cardiovascular event: 1.9–2.5%), and no benefit was seen in patients in whom P2Y12 inhibitor therapy had been discontinued for more than 1 year before enrolment in the study. For clinicians considering a strategy of prolonged P2Y12 inhibitor therapy in high-risk patients, these data suggest greater benefit in the continuation of such therapy without interruption after myocardial infarction, rather than re-initiating such therapy in patients who have remained stable for an extended period. The benefit of extended DAPT has been shown also in ‘difficult’ patients, such as those with prior myocardial infarction and concomitant peripheral artery disease or diabetes. Results of recent subgroup analyses of the PEGASUS-TIMI 54 trial have shown that there was a very favourable net clinical benefit for ticagrelor in patients with peripheral artery disease, with a slightly better net clinical benefit risk profile for the lower 60-mg dose.\textsuperscript{54} Also, the relative efficacy of DAPT in the pre-specified diabetic subgroup was essentially identical to that of the cohort as whole, suggesting that the protective mechanism of anti-platelet therapy operates similarly in diabetic and in non-diabetic patients.\textsuperscript{55}

On the basis of these results, a new approval for the use of ticagrelor has been announced on February 19, 2016. The European Commission has followed the recommendation from its Committee for Medicinal Products for Human Use for an additional indication for ticagrelor in the treatment of post-myocardial infarction patients in the European Union. The new marketing authorization from the European Commission is for a dose of 60 mg. The efficacy endpoint was almost identical for the 60 and 90-mg twice-daily doses. However, there was a significantly higher risk of bleeding, transfusion, and dyspnoea in the ticagrelor group versus the placebo group. Therefore, it was concluded that the 60-mg dose would be the preferred dose in the long-term chronic phase. The European decision follows the approval on September 3, 2015 of ticagrelor 60 mg by the US FDA, to be used in patients with a history of heart attack beyond the first year. Thus, the 60 mg dose may now be started as continuation therapy after an initial 1-year treatment with ticagrelor 90 mg and aspirin or other DAPT.

**The 2016 recommendations of the Italian Society of Cardiology**

Current controversy surrounding optimal duration of DAPT clearly reflects the fact that, nowadays, a ‘one size fits all’ strategy cannot be reliably applied to patients treated with PCI. Indeed, multiple factors are associated with increased ischaemic risk (including increased risk of stent thrombosis) and increased bleeding risk (Table 4), and patients usually have factors for both increased ischaemic and bleeding risks that must be carefully evaluated to assess the benefit/risk ratio of prolonged DAPT. In patients with high ischaemic risk, particularly those with a history of myocardial infarction, the benefits of extended DAPT are more likely to outweigh the risks. In patients with lower ischaemic risks, particularly in case of a higher risk of bleeding, the benefits are less clear. Accordingly, based on the most recent scientific evidences, the Italian Society of Cardiology makes the following recommendations (Table 5):

**Personalized treatment**

Physicians should decide duration of DAPT on an individual basis, taking into account ischaemic and bleeding
risks of any given patient. Moreover, personalized management of DAPT must be seen as a dynamic prescription with regular re-evaluations of the risk/benefit to the patient according to changes in his/her clinical profile. Last, but not the least, the initial decision must be changed promptly as changes occur.

Use of tools for risk factor characterization
The use of the so-called DAPT score (Table 3), as currently recommended by American experts, is helpful. One should, however, consider that DAPT score has not been prospectively validated, yet. Furthermore, the score does not take into consideration some factors associated with increased bleeding risk. More recently, two newer scores have been derived from the Patterns of non-ST elevation myocardial infarction registry (PARIS) scores.\(^6^5\) The PARIS scores allow categorization into low, intermediate, and high risk for thrombotic and bleeding events, with two separate scales. The model performance of both scores, which have been validated in the Assessment of Dual Anti-Platelet Therapy With Drug-Eluting Stents registry, is moderate.\(^6^6\)

In order to derive more benefit than harm from new treatments, a multi-parametric approach using other risk scores might improve the process of risk factor characterization. Indeed, the possibility exists that tools currently used for assessing the ischaemic risk in other clinical conditions, that is, TIMI, \(^5^8^\) GRACE (Global Registry of Acute Coronary Events), \(^5^9\) SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery), \(^6^0\) and residual SYNTAX score (i.e. an index of incomplete revascularization), \(^6^1\) could be useful also in the PCI setting. Similarly, bleeding risk might be estimated through multiple indexes, such as HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly), \(^6^2\) OBRI (Outpatient Bleeding Risk Index), \(^6^3\) ORBIT (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), \(^6^4\) and CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) scores. In this regard, it has already been shown that the HAS-BLED score and the OBRI score can reliably identify bleeding risk in patients with heart failure with reduced ejection fraction in sinus rhythm treated with aspirin.\(^6^6\) Nevertheless, physicians, at present, are strongly recommended to make judicious use of the ischaemic and bleeding scores that were originally proposed to assess the in-hospital risk of patients with acute coronary syndrome, as information concerning their long-term performance in the post-PCI setting is scarce. Also, current tools do not allow estimation of the ischaemic/bleeding risk in patients requiring concomitant DAPT and oral anti-coagulation therapy.

Duration of dual anti-platelet therapy in stable patients
The 6-month duration of DAPT currently recommended by European and American guidelines should be personalized on the basis of patients’ characteristics and type of stents. Stable patients with a high coronary atherosclerotic burden are at increased risk of progression of coronary disease and occurrence of death, myocardial infarction, and stroke.\(^6^7^\) Thus, duration of DAPT longer than 6 months is appropriate particularly in those patients with high SYNTAX score.\(^6^0\) Also, stent thrombosis still has a profound impact on mortality and morbidity, given its significant association with sudden death and myocardial infarction. Whereas it has become a rare event in stable patients, small absolute differences in stent thrombosis are clinically significant in individual patients. Accordingly, although shorter-term DAPT lasting for 3 months or less may be safe with third-generation DES, longer duration of DAPT is mandatory in case of first and second-generation DES (i.e. paclitaxel-eluting stent), complex index PCI (i.e. bifurcation, multiple stents), and also with newer bioresorbable vascular scaffold systems.

Duration of dual anti-platelet therapy in post-myocardial infarction patients
The 12-month duration of DAPT currently recommended by European and American guidelines events in patients with previous non-ST elevation or ST-elevation myocardial infarction should be prolonged on an individual basis in light of the new information derived.
from PEGASUS-TIMI 54 trial. Specifically, at the end of the initial 12-month post-infarction period, DAPT with ticagrelor 60 mg twice daily (b.i.d.) should always be continued for up to 3 years in all patients with high ischaemic risk at time of presentation, as assessed by a multi-parametric approach using risk prediction scores (i.e. GRACE, TIMI, SYNTAX, PARIS scores). In those patients without high ischaemic risk at time of presentation, DAPT with ticagrelor 60 mg b.i.d. up to 3 years can be considered individually. However, DAPT should be withdrawn in all post-myocardial infarction patients after the initial 12 months of therapy in case of high bleeding risk, as assessed by a multi-parametric approach using prediction scores of the haemorrhagic risk (i.e. HAS-BLED, OBRI, ORBIT, CRUSADE, PARIS scores).

The future

Improvements in risk factor characterization should ideally be paralleled by improvement in therapeutic strategy (Table 6). All of the randomized controlled trials to date have investigated different durations of the adenosine diphosphate (ADP) antagonist after a mandatory period of DAPT after DES implantation, with aspirin continued indefinitely. There are no randomized data assessing the relative safety and efficacy of the opposite strategy in which aspirin is interrupted and the ADP antagonist required to prevent very late stent thrombosis. Sharma and Forrester tested a strategy of alternate day administration of clopidogrel 1 year after PCI with DES. They hypothesized that the degree of anti-platelet effect required to prevent very late stent thrombosis decreases with time as the stent undergoes endothelialization. Accordingly, the use of clopidogrel every other day or a lower dose of ticagrelor among patients receiving a DES was shown to be sufficient to cross the much reduced therapeutic threshold that is required to prevent very late stent thrombosis after 1 year and to avert recurrent coronary events from spontaneous plaque rupture without much bleeding risk. With this background, the large multicenter, international GLOBAL LEADERS trial is currently investigating the relative safety and efficacy of a strategy of aspirin and ticagrelor for 1 month, followed by ticagrelor for 23 months versus aspirin indefinitely, and either clopidogrel or ticagrelor for 12 months in 16,000 patients treated with DES. The study is powered for superiority for the 2-year composite endpoint of all-cause mortality or non-fatal Q-wave myocardial infarction.

Also, more information is needed on the optimal strategy in case of elective or urgent non-cardiac surgery. Non-cardiac surgery is often required in patients taking DAPT after PCI. Cessation of DAPT prior to the recommended duration of its use, and also the pro-thrombotic and pro-inflammatory state associated with surgery contribute to an increased risk of adverse cardiovascular events such as stent thrombosis, myocardial infarction, or death. On the contrary, the risk of bleeding attributable to DAPT may sometimes be greater than the risk of an adverse cardiovascular event off such therapy. Ticagrelor has a shorter clinical half-life than clopidogrel or prasugrel, and can be stopped 48–72 h before surgery. However, at present, its role as a substitute for these other P2Y12 receptor blockers in this setting has not been evaluated.

Acknowledgements

There are no conflicts of interest.

References


Table 6 Take-home messages

A ‘one size fits all’ strategy can not be reliable applied to patients treated with PCI. Physicians should decide duration of DAPT on an individual basis, taking into account ischaemic and bleeding risks of any given patient by means of a multi-parametric approach for risk factor stratification.

The use of the so-called DAPT score, as currently recommended by American experts, is helpful though it has not been prospectively validated, yet. Judicious use of additional scores already developed for assessing ischaemic and bleeding risk of any given patient by means of a multi-parametric approach for risk factor stratification is recommended.

Duration of DAPT in stable patients can be longer than 6 months in case of first and second-generation DES, complex index PCI, and newer bioresorbable vascular scaffold systems.

Duration of DAPT in post-myocardial infarction patients should be continued up to 3 years in all patients with high ischaemic risk, provided that the haemorrhagic risk is not high.

DAPT, dual anti-platelet therapy; DES, drug-eluting stent; PCI, percutaneous coronary intervention.

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randomized trial.


