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How to manage prasugrel and ticagrelor in daily practice

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ABSTRACT

Prasugrel and ticagrelor are next-generation antiplatelet agents that provide a rapider and more potent inhibition of platelet P2Y12 receptor than clopidogrel. In combination with aspirin, these new P2Y12 inhibitors are now the first line treatments for patients with acute coronary syndrome. However, these potent antiplatelet agents introduce a new paradigm in the daily management of antithrombotic drugs, particularly when an invasive procedure is planned. The pharmacology of these antiplatelet agents, and the results of the main clinical trials, are reviewed with a special focus on good prescription practices (indications, contra-indications, drug interactions), and on peri-operative management. Strategies are proposed for safely reducing the bleeding risk in elderly patients, in patients requiring concomitant oral anticoagulant therapy, or in patients with an increased haemorrhagic risk.

1. Introduction

Antiplatelet agents (APA) are a cornerstone of atherothrombotic disease treatments [1]. Their main indications include coronary artery diseases (acute coronary syndrome ACS, myocardial revascularization, primary and secondary cardiovascular prevention), peripheral arterial diseases and cerebrovascular diseases including ischaemic stroke. In recent decades, APA were essentially limited to aspirin (a cyclooxygenase 1 inhibitor) and clopidogrel (a P2Y12 receptor blocker), which inhibit the thromboxane A2 and adenosine diphosphate (ADP) pathways, respectively—the two main platelet amplification pathways. Interestingly, there is variability in the pharmacodynamic response and thus in the level of platelet inhibition achieved by aspirin and clopidogrel. This phenomenon is particularly marked for clopidogrel and is responsible for a poor phenotype responsiveness also described as high on-treatment platelet reactivity (HPR). This in turn has been associated with recurrent thrombotic events and even cardiac death in the presence of a dual poor response to both aspirin and clopidogrel [2]. Clopidogrel is a prodrug that requires metabolism into an active metabolite by several hepatic cytochromes and through various mechanisms that can be altered in some patients. Recently, new antiplatelet drugs targeting the P2Y12 receptor, namely prasugrel and ticagrelor, have been introduced for the secondary prevention of thrombosis in patients with ACS [3–5]. These new drugs have been shown to inhibit the P2Y12 receptor more rapidly and more effectively than clopidogrel. The European Society of Cardiology now recommends that prasugrel or ticagrelor should be preferred to clopidogrel for dual antiplatelet therapy in ACS patients [6,7]: clopidogrel should be restricted to patients who are not eligible for prasugrel or ticagrelor treatment. Thus, physicians will be more and more frequently confronted with patients treated with these new agents along with aspirin. The present narrative review describes the pharmacology of these new antiplatelet agents, highlights the key points for good prescription practices and provides guidelines for peri-operative management when invasive procedures are needed.

2. Pharmacology of new antiplatelet agents

2.1. Pharmacokinetics

Prasugrel is an orally administered thienopyridine. Like clopidogrel, it is a prodrug that is metabolised to an active compound prior to binding irreversibly to platelet P2Y12 receptors, thus inhibiting platelet reactivity to ADP. The biotransformation pathways of clopidogrel and prasugrel are different, involving different hepatic cytochromes...
Ticagrelor is a non-thienopyridine oral P2Y12-inhibitor (cyclopentyl-triazolopyrimidine). It is rapidly absorbed in the intestine and does not require biotransformation for activation [12]. Contrary to thienopyridines, it binds to platelet P2Y12 receptors in a reversible fashion and at a different binding site than ADP, inducing an allosteric modification of the receptor [13,14]. After oral intake, plasma ticagrelor concentration reaches a peak within 1 h [15]. The major route of ticagrelor elimination is hepatic metabolism and biliary secretion, with a mean half-life of about 8 h for ticagrelor and 9 h for its active metabolites (Table 1). Although ticagrelor half-life is quite identical to that of prasugrel, ticagrelor has to be administered twice a day, due to its reversible P2Y12 binding.

The comparative pharmacokinetics of clopidogrel, prasugrel and ticagrelor are summarized in Fig. 1.

### 2.2. Pharmacodynamics

After administration of a prasugrel loading dose (60 mg), the inhibition of platelet aggregation to ADP is significantly faster (30 min vs 1.5 h) and more intense than after a clopidogrel loading dose [16]. In patients scheduled for percutaneous coronary intervention, inhibition of platelet aggregation is significantly greater in patients receiving prasugrel than those receiving clopidogrel, both at 6 h after a loading dose (mean ± SD, 75 ± 13% vs 32 ± 21%) and during maintenance doses (61 ± 18% vs 46 ± 21%) [17]. Although prasugrel metabolism is less influenced by known cytochrome genetic polymorphisms, a large variability in biological responsiveness is still present [8], and HPR can be present in up to 25% of ACS patients who in turn showed an increased incidence of ischaemic events at one month on from percutaneous coronary intervention (PCI) [18]. Therefore, platelet function testing, which has been shown to be useful for the prediction of both ischemic and bleeding events in clopidogrel-treated patients, could also be clinically relevant in prasugrel-treated patients [19].

As prasugrel binds irreversibly to platelet receptors, recovery of platelet function after discontinuation depends on platelet turnover. Due to the greater antiplatelet effect of prasugrel, normalization of platelet reactivity after discontinuation depends on platelet turnover.

When assessing platelet reactivity with the aggregation-based VerifyNow P2Y12 assay (Accumetrics, San Diego, California), a 7-day withdrawal of prasugrel provides the same degree of platelet function recovery as a 5-day withdrawal of clopidogrel [20], justifying a longer recommended waiting time for invasive procedure after prasugrel withdrawal.

Ticagrelor provides a more potent platelet inhibition than clopidogrel, with a more rapid onset of action. Two hours after a 180 mg loading dose of ticagrelor, inhibition of platelet aggregation is more pronounced (mean ± SD, 88 ± 15%) than after a 600 mg loading dose of clopidogrel (38 ± 33%); this difference persists during the maintenance therapy [21]. Since ticagrelor reversibly binds to the P2Y12 receptor, the recovery of platelet function after discontinuation is faster than that after cessation of clopidogrel. In the overall ONSET-OFFSET cohort [21], platelet reactivity at 3 days after ticagrelor withdrawal was similar to that observed at 5 days after clopidogrel withdrawal.

### 2.3. Phase III studies: TRITON TIMI 38 and PLATO

The clinical benefits of prasugrel over clopidogrel were assessed in the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction) study [22]. In this large prospective study on 13,608 patients with an ACS and percutaneous coronary intervention, prasugrel therapy resulted in a significant reduction in death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke, compared to clopidogrel (2.2% absolute risk reduction and 19% relative risk reduction). The price to pay was a significant increase of major bleeding events (2.4% vs 1.8%), life-threatening bleeding (1.4% vs 0.9%) and fatal bleeding (0.4% vs 0.1%). Overall, mortality was not significantly different between the two treatment groups. Among patients who underwent CABG in the TRITON-TIMI 38 trial, the excess of CABG-related major bleeding persisted up to 7 days after the last dose of prasugrel compared to 5 days after the last dose of clopidogrel.

In the prasugrel group, chest tube drainage was significantly greater, and a higher percentage of patients received platelet transfusions with a greater number of platelet units. The difference in platelet transfusion rates was more pronounced for patients who underwent CABG within 5 days of discontinuing clopidogrel or prasugrel [23].

It is of note that prasugrel, compared to clopidogrel, significantly reduces the risk of stent thrombosis for both bare metal stents (1.27% vs 2.4%, p = 0.0009, respectively) and drug-eluting stents (0.84% vs 2.31%, p = 0.0001, respectively), and significantly reduces early and late stage stent thrombosis [24]. In the TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) trial [25], prasugrel showed no benefits over clopidogrel in reducing death from cardiovascular causes, myocardial infarction or stroke among patients with ACS who were not undergoing PCI.

The Study of Platelet Inhibition and Patient Outcomes (PLATO) compared ticagrelor with clopidogrel in 18,624 patients with an ACS managed either with emergent PCI or medically without PCI [26]. Ticagrelor significantly reduced the rate of death from vascular causes, myocardial infarction or stroke (1.9% absolute risk reduction and 16% relative risk reduction), and also decreased the rate of all-cause mortality (1.4% absolute risk reduction). Ticagrelor increased neither trial-defined major bleeding nor the incidence of major bleeding events compared to clopidogrel, but did increase the rate of non-CABG-related bleeding and the rate of fatal intracranial bleeding. The rates of other types of fatal bleeding were lower in the ticagrelor group than in the

### Table 1

Comparison of the properties of oral P2Y12 receptors.

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading dose</td>
<td>300–600 mg</td>
<td>60 mg</td>
<td>180 mg</td>
</tr>
<tr>
<td>Time to peak inhibition</td>
<td>4–6 h</td>
<td>1–2 h</td>
<td>2 h</td>
</tr>
<tr>
<td>Binding</td>
<td>Irreversible</td>
<td>Irreversible</td>
<td>Reversible</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>75 mg</td>
<td>10 mg</td>
<td>90 mg</td>
</tr>
<tr>
<td>Frequency of administration</td>
<td>Once daily</td>
<td>Once daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Steady state</td>
<td>3–7 days</td>
<td>2–4 days</td>
<td>2–3 days</td>
</tr>
<tr>
<td>Half life</td>
<td>8 h</td>
<td>7 h (active metabolites)</td>
<td>9 h (active metabolites)</td>
</tr>
</tbody>
</table>
clopidogrel group. With respect to time from last dose before CAGB, there was no difference between ticagrelor and clopidogrel for fatal or life-threatening CAGB-related bleeding or GUSTO-study severe bleeding [27], and the perioperative bleeding and the decrease in haemoglobin concentration deemed less important when the interval between clopidogrel or ticagrelor and the CAGB was at least 5 days, with no differences between the two APA. Taking into account the different observations on pharmacodynamics and clinical bleeding events in these studies, the current consensus for an adequate haemostasis supports a 5-day withdrawal time frame for both clopidogrel and ticagrelor.

3. Prescriptions of new antiplatelet agents

3.1. Indications and guidelines on myocardial revascularization

The choice of antiplatelet agents and duration of antiplatelet therapy after ACS may be influenced by the presence of risk factors for stent thrombosis [28] and the type of management used (medical treatment with or without delayed angiography, acute or emergent PCI, CAGB) [29,30].

Prasugrel has been approved in association with aspirin for patients with ACS and percutaneous revascularization procedures, whereas ticagrelor is authorized in case of ACS with or without revascularization intervention, in association with aspirin.

No direct comparison between prasugrel and ticagrelor is available regarding clinical endpoints. After a loading dose, both drugs are similarly effective in providing platelet inhibition [31,32].

The European guidelines for patients presenting with ACS without persistent ST-segment elevation are (unless contraindicated) [6]:

- all patients must receive aspirin
- a P2Y12 inhibitor should be prescribed as soon as possible, and maintained for 12 months
- ticagrelor is recommended for patients at moderate-to-high risk of thrombotic events
- prasugrel is recommended for P2Y12-naïve patients, with known coronary anatomy and percutaneous revascularization.

In cases of acute myocardial infarction in patients presenting with ST-segment elevation [7]:

- aspirin should be used in all patients as long-term secondary prevention
- association with a P2Y12-blocker is recommended for up to 12 months:
  - prasugrel in clopidogrel-naïve patients (if no history of prior stroke/transient ischaemic attack, age less than 75 years, body weight more than 60 kg)

Irrespective of the indication, duration of dual antiplatelet therapy should not exceed 12 months, as it has not been proved that a longer period prevents ischaemic events beyond this period, and there remain concerns with the increased bleeding risk of dual antiplatelet therapy in stable cardiovascular patients [33–36].

3.2. Benefits and risks for specific subgroups

Subgroup analyses of TRITON-TIMI 38 and PLATO studies suggest that there might be greater benefits or risks for specific groups; such results have to be interpreted with caution, especially because of the increased risk of false positive results arising from multiple post-hoc analyses.

For prasugrel, the benefit-risk ratio was unfavourable for patients with a history of stroke or transient ischaemic attack, as they had got no benefit from prasugrel in terms of cardiovascular death or ischaemic events, but had a higher rate of bleeding. For patients ≥75 years old or with a body weight <60 kg, prasugrel showed no net clinical benefit over clopidogrel. A pharmacokinetic sub-study of TRITON-TIMI 38 [37] showed that patients <60 kg or ≥75 years old had higher levels of the active metabolite of prasugrel than other subjects. In these subjects, decreasing the maintenance dose of prasugrel to 5 mg reduced the levels of the active metabolite [38]. In medically-managed ACS patients older than 75 years, post-hoc analysis of the TRILOGY ACS trial showed that 5 mg of prasugrel daily had a similar risk-efficacy profile to 75 mg of clopidogrel daily [39]. However, this subgroup was not powered to be either an equivalence or a superiority trial.

In the TRITON-TIMI 38 cohort, the benefit of prasugrel was found to be greater in the subgroup of patients with diabetes, with a 30% relative risk reduction at the primary end point; this was essentially due to a lower incidence of myocardial infarction during the first few days after PCI and there were no differences in major bleeding compared to non-diabetic patients [40]. The lack of difference in major bleeding between the prasugrel and clopidogrel groups may be due to an unexpectedly higher rate of major bleeding among diabetics receiving clopidogrel compared to non-diabetics. Nevertheless, patients with diabetes mellitus have enhanced platelet reactivity, especially greater ADP-induced platelet aggregation, and thus they may benefit from more efficient anti-P2Y12 therapies [41]; this hypothesis remains to be demonstrated in prospective randomized studies.

In the subgroup of patients with chronic kidney disease included in the PLATO study [42] ticagrelor was found to be associated with a 4.7% absolute risk reduction of death from vascular causes, myocardial infarction or stroke, and a 4.0% absolute risk reduction in total mortality compared to clopidogrel. In patients with renal insufficiency, ticagrelor

![Fig. 1. Comparative pharmacokinetics of oral P2Y12 inhibitors. t\textsubscript{half-life}, time to peak platelet inhibition.](image-url)
may thus provide a greater reduction of ischaemic events, contrary to what has been shown with thienopyridines in major trials such CURE, CREDO and TRITON-TIMI38 [43].

3.3. Contraindications and cautions

Contraindications and cautions for prasugrel and ticagrelor are listed in Table 2.

The use of prasugrel or ticagrelor should be discouraged in patients with a high bleeding risk, especially in patients cumulating several risk factors for bleeding. Concomitant use of medications that increase the propensity to bleed, such as anticoagulants or fibrinolytics, should be used with great caution and only for a short time if necessary; they should be avoided as an association for long term therapy.

Ticagrelor has side effects, such as dyspnoea and bradyarrhythmia, which are seen with all P2Y12 inhibitors, but they seem more frequent than with clopidogrel or prasugrel. Thus, ticagrelor should be prescribed with caution in patients who have severe chronic obstructive pulmonary disease or bradyarrhythmias unprotected by a pacemaker.

3.4. Drug interactions

In the past years, concerns have been raised about the possibility that proton pump inhibitors attenuate the biological action of clopidogrel [44]. When associated with omeprazole, clopidogrel was shown in in vitro pharmacodynamic studies, to have a lower inhibitory effect. Some retrospective cohort studies performed in clopidogrel-treated patients suggested an increased risk of major cardiac events when patients were also treated with proton pump inhibitors. The only existing randomized controlled double-blind trial, the Clopidogrel and the Optimization of Gastrointestinal Events (COGENT), found similar rates of cardiovascular events in 3873 patients receiving aspirin plus clopidogrel with omeprazole or placebo [45]. However, because the recruitment was discontinued prematurely, the statistical power of this study is limited, and it does not exclude possible interactions between clopidogrel and omeprazole. A recent meta-analysis including 23 studies did not find significant evidence for adverse cardiovascular effects of proton pump inhibitors when associated with clopidogrel [46].

Up to now, there is no evidence that proton pump inhibitors decrease the efficacy of prasugrel or ticagrelor [47].

Drugs affecting cytochromes CYP3A and CYP2B6 (which are primarily responsible for prasugrel biotransformation) might interfere with prasugrel metabolism (Table 3). However, some studies showed that the platelet inhibition induced by prasugrel was not altered by ketoconazole (CYP3A inhibitor), statins or rifampicin (CYP3A and CYP2C19 inducer). However, drugs that inhibit CYP3A more strongly than ketoconazole, such as ritonavir, might significantly alter prasugrel pharmacokinetics and thus might decrease the action of prasugrel on platelets [48,49].

Ticagrelor is a substrate (and also a weak inhibitor) of both cytochrome CYP3A4 and P-glycoprotein. Due to the primary role of cytochrome CYP3A in ticagrelor degradation [50], inhibitors of CYP3A4 may increase ticagrelor concentrations. Strong inhibitors of CYP3A4 are thus contraindicated with ticagrelor (ketonazole, clarithromycin, nefazodone, ritonavir, atazanavir). Moderate inhibitors of CYP3A4 should be used with caution (diltiazem, verapamil, erythromycin, fluconazole, grapefruit juice). Conversely, CYP3A4 inducers, such as rifampicin, might reduce ticagrelor exposure. Ticagrelor administration may increase exposure to drugs that are metabolised by CYP3A4 (statins, especially simvastatin [51]): for lovastatin or simvastatin, the maximum recommended dosage when combined with ticagrelor is 40 mg once a day. As an inhibitor of P-glycoprotein, ticagrelor increases plasma levels of P-glycoprotein substrates, such as digoxin or cyclosporin.

4. Peri-interventional management

Peri-procedural management of APA is closely related to the evaluation of the individual’s thrombotic risk when the antithrombotic agent is withdrawn, and to the individual’s bleeding risk if the antithrombotic agent is continued during the procedure.

4.1. Risk factors for ischaemic events

Premature discontinuation of antiplatelet therapy may lead to major cardiovascular events, including stent thrombosis, myocardial

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### Table 2

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prasugrel</strong></td>
<td>Age &gt; 75 years</td>
</tr>
<tr>
<td>Hypersensitivity to prasugrel or excipients</td>
<td>Weight &lt; 60 kg</td>
</tr>
<tr>
<td>Active pathological bleeding</td>
<td>Hepatic impairment (Child–Pugh classes A and B)</td>
</tr>
<tr>
<td>Prior stroke or transient ischaemic attack</td>
<td>Propensity to bleed (recent trauma, surgery, gastrointestinal bleeding or active peptic disease, coagulation disorders)</td>
</tr>
<tr>
<td>Severe hepatic impairment (Child–Pugh class C)</td>
<td>Concomitant use of medications increasing bleeding risk (anticoagulants, fibrinolytics, chronic non-steroidal anti-inflammatory drugs)</td>
</tr>
<tr>
<td><strong>Ticagrelor</strong></td>
<td>Propensity to bleed (recent trauma, surgery, gastrointestinal bleeding or active peptic disease, coagulation disorders)</td>
</tr>
<tr>
<td>Hypersensitivity to ticagrelor or excipients</td>
<td>Concomitant use of medications increasing bleeding risk (anticoagulants, fibrinolytics, chronic non-steroidal anti-inflammatory drugs)</td>
</tr>
<tr>
<td>Active pathological bleeding</td>
<td>Risk of bradycardia (severe sinoatrial disease)</td>
</tr>
<tr>
<td>History of intracranial haemorrhage</td>
<td>Asthma/chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Moderate to severe hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>Concomitant use of strong CYP3A4 inhibitors</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3

Impact of drug–drug interactions on prasugrel and ticagrelor metabolism and efficacy.

<table>
<thead>
<tr>
<th>Strong inhibitors of CYP3A4</th>
<th>Moderate inhibitors of CYP3A</th>
<th>Strong inhibitors of P-gp</th>
<th>Substrats</th>
<th>Pharmacodynamic interaction</th>
<th>Co-medication</th>
<th>Pharmacodynamic interaction</th>
<th>Co-medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole, clarithromycin, nefazodone</td>
<td>Verapamil, diltiazem, quinidine, erythromycin, fluconazole, grapefruit juice</td>
<td>Verapamil, quinidine, cisaprid</td>
<td>No effect</td>
<td>Allowed</td>
<td>Ticagrelor exposure</td>
<td>With caution</td>
<td></td>
</tr>
<tr>
<td>Ritonavir, indinavir</td>
<td>Verapamil, diltiazem, quinidine, erythromycin, fluconazole, grapefruit juice</td>
<td></td>
<td>No effect</td>
<td>Allowed</td>
<td>Ticagrelor exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strong inhibitors of CYP3A</td>
<td>Statins</td>
<td>Statins</td>
<td>No effect</td>
<td>Allowed</td>
<td>Ticagrelor exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibitors of P-gp</td>
<td>Diclofenac, ciclosporin</td>
<td>Diclofenac, ciclosporin</td>
<td>No effect</td>
<td>Allowed</td>
<td>Exposure to substrats</td>
<td>Low dose statins</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T3 avoidance</td>
</tr>
</tbody>
</table>
infarction, non-fatal stroke and death. In a retrospective analysis, the incidence of ischaemic complications after the implantation of drug eluting stents (DES) was higher in the group of patients who stopped APA prematurely, with 28.6% of major adverse cardiac events and 7.6% of stent thrombosis [52]; mortality (13.4%) and cardiovascular death (5%) were also significantly greater among patients who discontinued early. The earlier the cessation, the higher the risk of major adverse cardiac events, stent thrombosis, and death (with greatest risk within the first 30 days) [53,54]. The thrombotic risk is of particular concern in the following situations [55]:

- any stent placement <6 weeks
- a DES placement <12 months
- non-ST-segment elevation myocardial infarction NSTEMI <6 weeks
- ST-segment elevation myocardial infarction STEMI <12 months.

Patients with coronary stents undergoing an invasive procedure are at high risk of peri-operative cardiovascular complications. The risk of major adverse cardiac and cerebrovascular events in the peri-operative period may be partially related to the prothrombotic and proinflammatory effects of surgery. Discontinuation of all antiplatelet drugs more than 5 days prior to an invasive procedure is an independent risk factor for cardiovascular complications [56,57]. Early discontinuation of low-dose aspirin for secondary prevention leads to a 40% increased risk of stroke [58], suggesting that discontinuation of aspirin in 40 patients would lead to one more stroke.

4.2. Risk factors for bleeding events

The main concern, when maintaining antithrombotic therapy during surgery or an invasive procedure, is the risk of haemorrhage due either to regional anaesthesia or to surgical procedure. Pre-operative aspirin intake has been associated with increased blood loss, especially with aspirin doses > 325 mg/day [59], although generally without any clinical significance [60]. Several studies showed that clopidogrel, when associated with aspirin, increases bleeding and transfusion requirements in patients undergoing CABG [61] or other invasive surgery [62,63]. Recent studies have tended to show that the more potent the platelet inhibition provided by P2Y12 inhibitors, the higher the risk of bleeding [22,23]. However, in a subgroup analysis of the PLATO trial, with similar delays between cessation of treatment and surgery, the risk of bleeding during CABG surgery was similar in patients taking ticagrelor and those taking clopidogrel [27], possibly owing to a faster offset effect with ticagrelor.

The peri-interventional risk of bleeding related to antiplatelet therapies varies with the type of procedure [64]:

- low bleeding risk: cutaneous surgery, anterior chamber ophthalmic surgery, dental extractions, endoscopy with small colonic polyp resection;
- moderate bleeding risk: orthopaedic surgery, intra-abdominal surgery, intra-thoracic surgery, large colonic polyp resection;
- high bleeding risk: cardiovascular surgery, prostatectomy or bladder surgery.

Although not having a high bleeding risk per se, neurosurgical procedures and ophthalmic surgery of the posterior chamber are classified as being of high haemorrhagic risk because any bleeding may compromise the vital or functional prognosis.

4.3. Current recommendations

To decide whether antithrombotic therapy should be discontinued during the peri-operative period, patients should be classified on the basis of their bleeding and thrombotic risks (Fig. 2).

For any surgery with a low bleeding risk, it is currently recommended to continue single and dual antiplatelet therapy [65–67], especially if the thrombotic risk is high.

For surgery with a moderate or high bleeding risk that requires the discontinuation of dual antiplatelet therapy, the strategy regarding the peri-procedural management of APA must be the result of a multidisciplinary consensus involving cardiologists or vascular specialists, anaesthesiologists, and surgeons or interventional physicians. All non-urgent surgery should be delayed until the anti-P2Y12 drug can be safely withdrawn. No randomized trials have yet assessed the optimal timing of APA cessation before an invasive procedure, with regard to bleeding and thrombotic events.

In the vast majority of surgery, with the sole exception of neurosurgical procedures, aspirin (given for secondary prevention) should be continued peri-operatively [68,69]. If aspirin discontinuation is deemed necessary, a delay of no more than 3–5 days is suggested [70]. Based on expert opinions, pharmacodynamics and clinical studies, the optimal duration for anti-P2Y12 discontinuation that leads to sufficient platelet function recovery should be 5 days for clopidogrel and ticagrelor, and 7 days for prasugrel [71–73].

Stopping anti-P2Y12 while continuing aspirin is the current guidelines for both European and American societies when only one antiplatelet agent is acceptable during the peri-operative period. Alternatively, since recent studies suggested that clopidogrel could lead to the same bleeding risk that aspirin, some authors propose to stop aspirin and keep clopidogrel alone for some surgeries with intermediate bleeding risk [74].

In case of interventions with high bleeding risk associated with a high thrombotic risk, bridging with short-acting intravenous glycoprotein IIb/IIIa inhibitors (anti-GP IIb/IIIa) should be considered [75–77] (Fig. 3). In the future, cangrelor—a direct and reversible inhibitor of the P2Y12 receptor, administered intravenously—could become an

![Fig. 2. Management of prasugrel and ticagrelor before an elective surgery.](image-url)
alternative to anti-GPIIb/IIa bridging [78]. Indeed, canegrelor has a very short lasting inhibitory action allowing a full recovery of P2Y12 activity 60 min after infusion is stopped.

After surgery, anti-P2Y12 therapies should be restarted as soon as the bleeding risk is deemed acceptable (depending of the type of surgery), and with a loading dose of a P2Y12 inhibitor such as 300 or 600 mg of clopidogrel. Some experts propose alternatives such as loading doses of ticagrelor or prasugrel in cases of high thrombotic risks [73], but these must be discussed on an individual basis. When the bleeding risk remains high it is unlikely that newer P2Y12 inhibitors will be represcribed (Table 2).

Various platelet function assays, including point-of-care testing, are available for evaluating the antplatelet effects of APA. The clinical usefulness of these tests during the peri-operative period has yet to be demonstrated [79,80]. A recent study aimed to evaluate the role of platelet function assessment using thromboelastography on clopidogrel-treated patients scheduled for CABG [81]: the delay between clopidogrel withdrawal and CABG was based on on-treatment platelet reactivity during treatment, as determined by ADP-induced platelet-fibrin clot strength. In that study, the pre-operative use of platelet function testing allowed the time before surgery to be reduced, with no excess bleeding in comparison with clopidogrel-naïve patients. To our knowledge, this is the only study that correlates platelet function testing with clinical outcomes in the pre-operative setting. Consequently, laboratory testing cannot be recommended for the peri-operative management of APA.

5. When to prefer older over newer APA

The association of prasugrel or ticagrelor with an oral anticoagulant (OAC) therapy, whether it is a vitamin-K antagonist or a new direct oral anticoagulant, increases the bleeding risk and should be discouraged. The reduction of stroke, stent thrombosis and myocardial infarction with a triple therapy (aspirin, P2Y12 inhibitors, OAC) must be balanced with the increased bleeding risk of such an association [82,83].

In patients treated with aspirin plus prasugrel or ticagrelor, and who secondarily require an OAC with a clear indication:
- prasugrel or ticagrelor should be switched to clopidogrel when an OAC is introduced during the early period following a DES implant, with continuation of aspirin
- prasugrel or ticagrelor should be stopped when an OAC is introduced after the early period following a DES implant; there is no consensus regarding which APA to continue—clopidogrel or aspirin [84]—when only one is needed.

The optimal antiplatelet regimen for patients on long-term OAC therapy, and requiring coronary stenting, is controversial and represents a significant problem, since close to 30% of patients with atrial fibrillation have concomitant coronary artery disease. In cases with high coronary-thrombotic risk, such as the early period following PCI with stenting, a triple therapy (OAC, aspirin, clopidogrel) might be proposed for the short term [85].

In patients with an increased haemorrhagic risk, new APA should be used with great caution. However, when the thrombotic risk is deemed high, ticagrelor should be preferred over clopidogrel, although it might increase the bleeding risk. The thrombotic risk is highest during the first 4 to 6 weeks after a DES implant, and antiplatelet inefficacy or withdrawal during this period can lead to major adverse cardiac events (stent thrombosis, myocardial infarction or death) [52,53,86].

In patients with both high thrombotic and high haemorrhagic risks, for whom DES may be a clear indication, we propose that the association of aspirin plus ticagrelor should be used for 1 to 2 months after a DES implant (when the thrombotic risk is highest). After this initial period, ticagrelor could be replaced with clopidogrel in order to lower the bleeding risk. This suggestion is not supported by specific trials addressing the issue of a balanced bleeding/ischaemic risk in the long term, but it is in line with the indications of the different anti-P2Y12 drugs and is aimed at a favourable net benefit, beyond acute ischaemic event management. Similarly, the latest generation of DES with a lower thrombotic risk should be favoured when it is anticipated that the dual therapy will have to be stopped a few weeks after stenting.

6. Conclusions

For patients with ACS, prasugrel and ticagrelor are now the antiplatelet drugs of choice, in combination with aspirin. However, in such acute settings, the high level of platelet inhibition induced by these APA increases the bleeding risk, and clopidogrel remains recommended for patients with contra-indications to both ticagrelor and prasugrel. In daily practice, the use of the new APA also requires knowledge of their specific features and interactions with other drugs. Treatments interfering with cytochromes (especially CYP3A) may lead to either prasugrel or ticagrelor inefficacy (increasing thrombotic risk), or to hyper-response (increasing bleeding risk).

Special attention should be paid to management of the peri-operative period since discontinuation of APA may lead to thrombotic events. In cases of minor surgery, with low bleeding risk, continuation of dual antiplatelet therapy is recommended. In cases involving moderate and high bleeding risk procedures, aspirin should be continued (with the sole exception of neurosurgery); ticagrelor and prasugrel should be stopped 5 days and 7 days before surgery, respectively. In a setting with a high risk of thrombosis, bridging with an intravenous antiplatelet drug with a short half-life may be considered.

The optimal peri-operative management of APA still remains to be defined, and the management of newer drugs have to be evaluated in this setting.
Learning points
- Prasugrel and ticagrelor provide a more rapid and more potent inhibition of platelet aggregation, which translates into a reduced risk of ischemic events after an ACS, when compared to clopidogrel.
- Close attention must be paid to drugs interfering with prasugrel or ticagrelor metabolism.
- In cases of elective surgery, with a moderate or high bleeding risk, prasugrel or ticagrelor should be stopped 5 days before, and prasugrel should be stopped 7 days before.
- Considering the strong antiplatelet effects of prasugrel and ticagrelor, their use in combination with an OAC should be avoided.

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