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Chapter

Dual Antiplatelet Therapy

Edidiong Orok, Funmilayo Adeniyi and Oluwole Akawa

Abstract

Antiplatelet agents have been utilized to enhance outcomes in patients with acute coronary syndrome for decades and are increasingly valued for their antithrombotic as well as anti-inflammatory characteristics. Dual antiplatelet therapy (DAPT) is a combination of aspirin and a P2Y12 inhibitor. Different modes of action are employed by these drugs. Aspirin is an anti-inflammatory medication that also has antioxidant characteristics, while P2Y12 inhibitors act by inhibiting thrombocytes activation/aggregation. There are two types of P2Y12 inhibitors: thienopyridines and nucleoside/nucleotide compounds. Nucleoside/nucleotide derivatives are reversible direct-acting P2Y12 receptor antagonists that do not need hepatic metabolism, whereas thienopyridines are competitive and irreversible P2Y12 inhibitors. In patients with acute coronary syndrome or undergoing percutaneous coronary intervention for stable coronary artery disease, dual antiplatelet therapy, which contains aspirin and a P2Y12 receptor inhibitor, has consistently been shown to reduce recurrent major adverse cardiovascular events compared to aspirin monotherapy, but at the cost of an increased risk of major bleeding. This chapter is meant to elaborate on dual antiplatelet therapy highlighting the current guidelines and recent evidences on the indications, dosing, and duration of treatment using dual antiplatelet therapy.

Keywords: dual antiplatelet therapy, aspirin, P2Y12 inhibitors, acute coronary syndrome, coronary artery disease

1. Introduction

Because of a global change in illness and death from infectious to noninfectious causes during the 20th century, life expectancy doubled and global population quadrupled [1]. Cardiovascular diseases (CVDs) have surpassed cancer as the main cause of mortality, with low- and middle-income countries bearing the brunt of the burden [2].

In 2015, the United States spent more than $200 billion on heart problems, including related medications and health-care services [3]. In 2017, the American Cardiology Association reported that more than 360,000 persons were diagnosed with coronary heart disease [4].

The principal therapy for preventing arterial thrombosis in CVD patients is platelet inhibitors [5, 6]. Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is the standard medical treatment for patients with acute coronary
syndrome (ACS) and those undergoing percutaneous coronary intervention (PCI) with an intracoronary stent [6].

Every year, about 1.2 million patients get DAPT after receiving a drug-eluting stent (DES). DAPT is used for a variety of cardiologic, neurologic, and surgical indications where the need to prevent thromboembolic events outweighs the risk of bleeding [7, 8]. DAPT is widely used to treat thrombotic stroke, coronary artery disease (CAD), peripheral vascular diseases, and transient ischemic attack (TIA). When compared to aspirin alone, DAPT with aspirin and clopidogrel has been shown to enhance clinical outcomes in patients with acute coronary syndrome or PCI [9, 10].

Despite the effectiveness of DAPT in preventing primary and subsequent myocardial infarction (MI) and stroke, there is an increased associated risk of spontaneous intracerebral hemorrhage (ICH) [11]. Interestingly, in-hospital mortality is greater in patients with ICH who are on DAPT compared to other antiplatelet agents [12, 13]. The goal of achieving efficient antiplatelet activity while avoiding gastrointestinal (GI) injury and bleeding has become a key focus in the management of thrombotic disease patients. This chapter is meant to explore on dual antiplatelet therapy highlighting the current guidelines and recent evidences on the indications, dosing, and duration of treatment using dual antiplatelet therapy.

2. Mechanisms of action of the components of DAPT

DAPT comprises of aspirin together with a P2Y12 inhibitor. These agents have different mechanisms of actions. This section will focus solely on the mechanism of action related to antithrombotic effects of dual antiplatelet therapy.

2.1 Mechanism of action of aspirin

Aspirin is an anti-inflammatory drug, which possesses both anti-inflammatory and antioxidant properties [14]. The primary mechanism of action of aspirin is centered on the irreversible inhibition of cyclooxygenase (COX 1) enzyme, thus preventing the conversion of arachidonic acid into prostaglandin G2 and prostaglandin H2, subsequently inhibiting thromboxane A2 synthesis. Aspirin acetylates and forms a covalent bond with serine residues in COX active site at position 529, thus inhibiting COX 1 enzyme [15, 16]. Other activities of aspirin include mitochondrial oxidative phosphorylation and modulation of NF-KB signals [14].

2.2 Mechanism of action of P2Y12 inhibitors

P2Y12 inhibitors, otherwise known as P2Y12 antagonists, act by blocking P2Y12 adenosine diphosphate (ADP) receptors on platelet surface membrane, subsequently inhibiting thrombocyte activation/aggregation [17]. P2Y12 inhibitors can be classified into two groups: thienopyridines and nucleoside/nucleotide derivatives [16].

Thienopyridines are competitive and irreversible P2Y12 inhibitors [16]. Drugs in this class can be further subdivided into three generations: first-, second-, and third-generation thienopyridines.

Ticlopidine is a first-generation thienopyridines that was withdrawn due to major side effects such as GI disorders, cytopenia, and allergies. Clopidogrel is a prodrug.
of second-generation thienopyridine derivatives, which is a drug of first choice in DAPT. Clopidogrel active metabolite binds to P2Y12 receptor to form an irreversible covalent bond, which inhibits ADP-dependent platelet activation and aggregation [18]. Dual antiplatelet therapy with aspirin and clopidogrel has been associated with more than 3% platelet reactivity [19] and 10% ischemic occurrences after 12 months of treatment.

Third-generation thienopyridine (prasugrel) was developed with rapid absorption and higher bioavailability than clopidogrel [16, 18]. Some drugs in this class are mainly reversible P2Y12 inhibitors such as ticagrelor and cangrelor. Ticagrelor is a more potent, efficacious, and fast acting P2Y12 inhibitor when compared with other P2Y12 inhibitors such as clopidogrel and prasugrel [20]. Ticagrelor acts by binding to P2Y12 receptor site other than the ADP binding site. In addition, ticagrelor binds to equilibrative nucleoside transporter 1 (ENT 1) in platelets and red blood cells to block the reuptake of adenosine [21].

The P2Y12 inhibitors have peculiar features, advantages and disadvantages, as well as adverse effects. These effects have been summarized in Table 1.

<table>
<thead>
<tr>
<th>P2Y12 inhibitor</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clopidogrel</strong></td>
<td>• First drug of choice among P2Y12 inhibitors</td>
<td>• Slow onset of antiplatelet effect.</td>
<td>• Jaundice</td>
</tr>
<tr>
<td></td>
<td>• DAPT with clopidogrel is efficient in preventing MACE</td>
<td>• High susceptibility to genetic variation and drug–drug interactions</td>
<td>• Seizures</td>
</tr>
<tr>
<td></td>
<td>• Prevents the risk of thrombotic complications in patients with AF that are undergoing PCI</td>
<td>• Variability of response with a poor response associated with increased risk of thrombosis.</td>
<td>• Gastric ulceration</td>
</tr>
<tr>
<td></td>
<td>• Highly effective in secondary prevention of cardiovascular and cerebrovascular events</td>
<td>• High platelet reactivity especially in diabetic patients subsequently leading to impaired antiplatelet response.</td>
<td>• Haematuria</td>
</tr>
<tr>
<td></td>
<td>• Greatest efficacy in patients undergoing thrombolysis</td>
<td>• High risk of MACE in patients with vascular risk factors receiving clopidogrel therapy.</td>
<td>• Slow or difficult speech</td>
</tr>
<tr>
<td></td>
<td>• Once-daily dosing</td>
<td></td>
<td>• Muscle weakness</td>
</tr>
<tr>
<td></td>
<td>• Quite affordable</td>
<td></td>
<td>• Dyspnea</td>
</tr>
<tr>
<td><strong>Ticagrelor</strong></td>
<td>• More potent, efficacious and fast acting P2Y12 inhibitor when compared with other P2Y12 inhibitors</td>
<td>• Low bioavailability.</td>
<td>• Dyspnea at rest, after exercise</td>
</tr>
<tr>
<td></td>
<td>• Reduction in ischemic event rates unlike clopidogrel</td>
<td>• Increased risk of non–CABG surgery bleeding when compared with clopidogrel</td>
<td>• Chest pain</td>
</tr>
<tr>
<td></td>
<td>• Rapid and extensive platelet inhibition</td>
<td>• Twice-daily dosing</td>
<td>• Bleeding risk</td>
</tr>
<tr>
<td></td>
<td>• Fast onset of effect and Reversible inhibition</td>
<td>• It is expensive</td>
<td>• Tachycardia, brady-cardia or irregular heartbeat</td>
</tr>
<tr>
<td></td>
<td>• Less susceptible to genetic variation and drug–drug interactions</td>
<td></td>
<td>• Edema of the face, throat, tongue, lips, and eyes</td>
</tr>
<tr>
<td></td>
<td>• Prevents non-fatal MI, ischaemic CVS events, stroke and other CVS related death</td>
<td></td>
<td>• Rashes</td>
</tr>
</tbody>
</table>
3. Indications for DAPT

3.1 Atrial fibrillation

About 40% of patients with atrial fibrillation have a high risk of having CAD. DAPT prevents the risk of thrombotic complications in patients with atrial fibrillation that are undergoing percutaneous coronary intervention [24]. DAPT is preferable to triple therapy with an oral anticoagulant (OAC) due to low risk of bleeding and other thrombotic complications [24–26]. Clopidogrel is a drug of first choice; however, prasugrel and ticagrelor have been recently approved for treating patients with high ischemic risk and high risk of hemorrhage and stent thrombosis associated with clopidogrel [27]. However, prasugrel is contraindicated in patients undergoing treatment with aspirin and OAC due to the risk of hemorrhage [28].

3.2 Acute coronary syndrome

DAPT can be prescribed for prevention of ACS and other adverse cardiovascular (CVS) events. A combination of aspirin and ticagrelor or prasugrel is commonly recommended for treating patients with ACS within 6–12 months [29, 30]. DAPT is recommended for treating patients with ACS and atrial fibrillation who are at a risk of developing coronary artery disease, which may necessitate PCI with stents [31]. Clopidogrel can be replaced with ticagrelor in rare cases [32, 33]. Cangrelor, a potent intravenous P2Y12 inhibitor with fast onset of action, can be indicated for treating unconscious ACS patients on emergency who are unable to absorb an oral P2Y12 inhibitor [34].

3.3 Coronary artery disease

DAPT with aspirin and clopidogrel is recommended for patients with CAD in order to avert atherothrombotic events. In patients undergoing elective stent
implantation, DAPT with aspirin and clopidogrel is usually recommended for 3–6 months [30, 35].

3.4 Myocardial infarction, ischemic events, and stroke

In previous years, DAPT with aspirin and clopidogrel or ticagrelor was formerly recommended for preventing recurrent stroke especially in patients with high risk of transient ischemic attack and noncardioembolic mild stroke [36]. However, DAPT has been found in previous studies to reduce the incidence of stroke and CVS-related death, thus making it effective for stroke prevention. Because DAPT reduces the risk of minor stroke and high transient ischemic attack in these patients, DAPT can be recommended in combination with aspirin and a P2Y12 inhibitor for acute treatment of patients with acute noncardioembolic minor ischemic stroke [37].

Novel and trending studies have compared the efficacy of other potent P2Y12 antagonist such as ticagrelor and prasugrel with clopidogrel especially in preventing nonfatal MI, ischemic CVS events, stroke, and other CVS-related death [38]. DAPT with aspirin and clopidogrel is also approved for treating patients with severe stenosis of the intracranial artery [39] and chronic symptomatic peripheral artery diseases (PADs) [40].

3.5 Transcatheter aortic valve implantation (TAVI), peripheral artery disease, atherosclerosis, and mechanical prosthesis

Dual antiplatelet therapy is indicated in patients on the line for transcatheter aortic valve implantation (TAVI) without high risk of hemorrhage for 3–6 months [17]. After revascularization, DAPT is usually indicated for 1–12 months in peripheral artery disease (PAD) patients [17]. It is worth to note that DAPT can be extended for more than 1 year in patients with atherosclerosis and mechanical prosthesis having high risk of coronary events [17].

3.6 Other indications of DAPT

DAPT can also be used in other nonconventional indications, which include diabetes, renal transplant, and carotid endarterectomy. In diabetes, DAPT consisting of aspirin and prasugrel or ticagrelor is indicated due to increased platelet reactivity [41]. DAPT administration reduces the risk of cardiovascular events in patients undergoing renal transplant. On the other hand, the risk of postoperative hemorrhage is increased with DAPT. Therefore, DAPT is strictly recommended for renal transplant patients with high risk of cardiovascular events [42]. DAPT can also be used for patients undergoing carotid endarterectomy [34].

4. Recent evidence and guidelines on DAPT use in patients

Antiplatelet therapy is an important pharmacological component in preventing atherothrombotic events. Aspirin, a widely used antiplatelet drug, has been found to reduce the risk of recurrent major adverse cardiovascular events (MACE) by around one-fifth [43]. However, the combination of antiplatelets has been reported to achieve better outcomes than the use of aspirin alone [10]. DAPT refers to a therapy that includes aspirin and a P2Y12 receptor inhibitor (clopidogrel, prasugrel, or ticagrelor). When compared to single antiplatelet medication, DAPT has been found to prevent
recurrent major ischemic episodes in patients with ACS or undergoing PCI at the cost of an unavoidable increased risk of major bleeding [10]. Below are guidelines on the effective use of DAPT across various indications.

4.1 Use of DAPT after undergoing percutaneous coronary intervention

Clinical trials have shown that all the patients receiving PCI require DAPT as it reduces risk of short- and long-term thrombotic events when compared to aspirin. Current guidelines recommend a 6-month DAPT for patients with stable symptoms and a 12-month DAPT for those who have had an ACS [29].

Except for patients who have received a bioabsorbable drug-eluting stent, the clinical setting in which it occurs—stable or unstable—and the patient’s bleeding risk are the two most important factors to consider when determining the DAPT duration following PCI. When feasible, extended (at least 12 months) and potent DAPT should be used for these individuals.

4.2 DAPT in stable coronary artery disease

Platelet inhibition is critical for the treatment and prevention of short- and long-term thrombotic events. The cyclooxygenase-1 inhibitor aspirin and the platelet adenosine diphosphate P2Y12 receptor inhibitors clopidogrel, prasugrel, and ticagrelor are all available as oral antiplatelet medicines for secondary prevention in patients with CAD. The more recent powerful P2Y12 platelet receptor inhibitors prasugrel and ticagrelor have been tested in individuals with ACS, whereas aspirin and clopidogrel have been studied across the entire range of CAD [44].

A 6-month DAPT time is advised for individuals with stable illness following PCI; however, this might be decreased based on the patient’s bleeding risk or for safety considerations. The guidelines go beyond specifics and advocate for the use of metallic stents as a first-line therapy, even in patients who are only given a 1-month antiplatelet regimen for safety reasons [45, 46]. DAPT should be continued for 6 months in individuals who have had angioplasty with a drug-coated balloon. This guideline is based on the results of many clinical trials that employed empirical antiplatelet methods.

4.3 DAPT in acute coronary syndrome

The use of DAPT to inhibit platelet function after an acute coronary syndrome aims to reduce short- and long-term thrombotic consequences [47]. The stent protective effect of DAPT in the first weeks after percutaneous revascularization reduces the risk of stent thrombosis, a potentially fatal event caused by inflammation and endothelial damage associated with mechanical insult during PCI [48]. Long-term therapy has been demonstrated to reduce the risk of subsequent ischemia episodes caused not only by the culprit lesions/vessels, but also by the advancement of atherosclerosis, a phenomenon described as the “patient protective effect” [48].

Several antithrombotic medications have been proposed over time with the goal of offering the best thrombotic protection while minimizing hemorrhagic hazards. However, recent European guidelines advise the use of the two most modern and strong P2Y12 inhibitors (prasugrel and ticagrelor) in patients with or without PCI [49, 50]. The default DAPT length for patients with ACS treated with coronary stenting should be 12 months, while it may be fair to cut it to 6 months in patients with
a high bleeding risk or to extend it to more than 12 months in certain cases. These choices should be made after a thorough assessment of the patients’ bleeding and ischemia risks. Although some criteria can aid in the identification of patients who will benefit the most, the requirement to validate surgical tools in clinical practice is well understood. This is especially essential if the DAPT is extended beyond 1 year. A longer dual antiplatelet duration may be considered for patients with this indication who have tolerated this length of DAPT without bleeding problems. In this sense, ticagrelor 60 mg twice daily is advised for patients with a history of myocardial infarction and a high ischemia risk.

4.4 DAPT immediately after transient ischemic attack (TIA) or minor stroke

According to recent BMJ Rapid Recommendations, patients with a mild ischemic stroke or a high-risk transient ischemic attack (TIA) should begin dual antiplatelet medication with aspirin and clopidogrel as soon as feasible after the incident, preferably within 24 hours [51]. Dual therapy is favored over aspirin alone, according to the guidelines, because there is a lower risk of recurrent stroke and functional disability with dual therapy. In addition, the guideline committee strongly recommends a shorter term of dual therapy (10–21 days, rather than 22–90 days). Most patients, however, should continue to take a single antiplatelet drug, such as aspirin, continuously. Patients with TIA or mild stroke may benefit from antiplatelet treatment with aspirin and clopidogrel. DAPT with clopidogrel and aspirin (acetylsalicylic acid) within the first 21 days after the index incident was observed to minimize the incidence of recurrent major ischemic events compared to aspirin alone [51]. The recommendations in this clinical practice guideline are based on a linked systematic review sparked by a randomized controlled trial published in August 2018 in the New England Journal of Medicine [52].

5. Management of bleeding associated with the use of DAPT

A higher reduction in thrombotic risk comes at the cost of an increase in significant bleedings, which occur in 1–8% of patients in the first year after starting DAPT [53–55]. Even less severe bleeding has been linked to an increased risk of death through indirect mechanisms such as unplanned hospitalization, the necessity for urgent operations, and the termination of DAPT [56]. Bleeding is reportedly linked to an increased risk of death and is also linked to the recurrence of ischemic events such myocardial infarction (MI) and stroke [57, 58].

5.1 Intracranial bleeding (ICB)

The most significant DAPT-related adverse event is intracranial bleeding (ICB). With recurrence rates of more than 15% and 3%, respectively, ICB is classed as lobar (affecting the cerebral cortex and underlying white matter) or deep (affecting the basal ganglia, thalamus, and brainstem). Antiplatelet therapy on admission was linked with a greater 24-hour in-hospital [59] and 3-month death rate compared to naive patients in a recent study on patients with ICB [60].

Patients with ICB should be observed and managed in an intensive care unit or a dedicated stroke unit with a high level of skill in the acute environment. All the anticoagulant and antiplatelet medications should be stopped immediately.
5.2 Gastrointestinal bleeding

GI hemorrhage is the most prevalent significant DAPT-related bleeding event following PCI [61, 62].

Owing to its direct suppression of cyclooxygenase-1, aspirin promotes GI bleeding by lowering the endothelium protective action of prostaglandins. P2Y12 inhibitors are thought to affect ulcer healing through limiting platelet aggregation, angiogenesis, and endothelial proliferation rather than being directly ulcerogenic. When compared to clopidogrel, ticagrelor and prasugrel have been linked to a greater incidence of GI bleeding [61].

Owing to its insidious nature, GI bleeding in patients with recent ACS and/or PCI poses a significant treatment challenge. The need to achieve hemostasis frequently necessitates the early termination of antithrombotic therapy. Furthermore, acute bleeding causes platelet activation, and the formation of a prothrombotic environment could explain why patients with GI bleeding who get DAPT after ACS have a higher risk of ischemic stroke [63].

Proton pump inhibitors (PPIs) should be prescribed alongside antiplatelet medication since gastrointestinal (GI) bleeding is the most prevalent major bleeding event [64]. PPIs are only recommended by the ACC/AHA for individuals who are at risk of bleeding (previous GI bleeding, advanced age, and concurrent use of warfarin, steroids, or nonsteroidal anti-inflammatory medicines); however, the ESC supports PPIs for all DAPT patients [7]. The disparity in recommendations stems from different interpretations of a big clinical research that found a pharmacokinetic interaction between clopidogrel and omeprazole, but no effect on cardiovascular events. Given the known cytochrome pharmacokinetic interaction, it is best to avoid co-prescribing clopidogrel with omeprazole/esomeprazole if at all possible [65]. However, there is no known interaction between PPIs and prasugrel.

5.3 Role of tranexamic acid (TXA) in management of DAPT-induced bleeding

Antiplatelet drugs commonly block glycoprotein receptors in ACS because they are required for platelet aggregation. Tranexamic acid (TXA) has been demonstrated to be an effective drug for reduce antiplatelet-related bleeding in a number of clinical scenarios, including trauma, and has a good safety profile [66]. TXA has specifically been shown to increase in vitro platelet activity among coronary artery bypass graft (CABG) patients taking antiplatelet medication as well as demonstrating a reduction in operational blood loss [67]. By enhancing platelet function, TXA can be regarded a potential strategy for reducing bleeding problems associated with antiplatelet monotherapy or DAPT.

5.4 Role of platelet infusions in the management of DAPT-induced bleeding

Platelet concentrates (PCs) are sometimes infused to patients with ICH who are on antiplatelet medications to enhance primary hemostasis before neurosurgery. Platelet concentrates (PCs) are frequently given to patients on APT who develop ICH to overcome platelet inhibition induced by antiplatelet medications [68]. Preoperative transfusion of at least two PCs can enhance primary hemostasis in individuals who require decompression neurosurgery owing to ICH while on APT. Rebleeding could still be a concern especially in individuals with chronic ICH and those using P2Y12 inhibitors. Other options can be explored in the control of bleeding in patients on antiplatelet
agents especially DAPT. The options include prothrombin complex concentrates [69] and fresh frozen plasma [70] although they are mostly used for bleeding associated with vitamin K antagonists and direct oral anticoagulants.

6. Conclusion

Antiplatelet agents have been widely utilized in patients with acute coronary syndrome for decades and are increasingly valued for their antithrombotic as well as anti-inflammatory characteristics. DAPT has been shown to be effective in improving the clinical outcomes of patients with ACS or PCI but is associated with high bleeding risk. Recent guidelines have been proposed not only to help reduce the tendency of bleeding in DAPT patients but also to ultimately improve patient overall quality of life.

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Conflict of interest

The authors declare no conflict of interest.

Author details

Edidiong Orok‡*, Funmilayo Adeniyi‡ and Oluwole Akawa³

1 Department of Clinical Pharmacy and Public Health, Afe Babalola University, Ado-Ekiti, Nigeria

2 Department of Pharmacology and Toxicology, Afe Babalola University, Ado-Ekiti, Nigeria

3 Department of Pharmaceutical and Medicinal Chemistry, Afe Babalola University, Ado-Ekiti, Nigeria

*Address all correspondence to: pharmorok@gmail.com
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