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Abstract

Triple antiplatelet therapy (TAPT, or triple therapy), is an oral medication regimen designed to reduce the risk of major cardiovascular events. It consists of aspirin, clopidogrel or an alternative, and an oral anticoagulant (OAC). It differs from dual antiplatelet therapy (DAPT) due to inclusion of an OAC. Multiple clinical studies have indicated that triple therapy is more effective at clot prevention, when compared to aspirin monotherapy and DAPT, but is associated with a higher risk of major bleeding. Pharmacists have a key role in determining candidates for DAPT and TAPT regimens. Other opportunities for pharmacists include patient monitoring, counseling and medication review throughout treatment with antithrombotic therapy.

Key Terms

Acute Coronary Syndrome; Anticoagulants; Antiplatelet Drugs; Aspirin; Cardiovascular Diseases; Dabigatran; Factor Xa Inhibitors; Percutaneous Coronary Intervention; Platelet Aggregation Inhibitors; Thrombosis, Warfarin

Introduction

Dual antiplatelet therapy (DAPT) consists of aspirin and clopidogrel (or an alternative). It is used to prevent thrombosis and inhibit platelet function for patients with coronary artery disease (CAD), atherosclerotic ischemic stroke, atrial fibrillation (AF) or acute coronary syndrome (ACS) with or without percutaneous coronary intervention (PCI).[1] However, the introduction of an additional antiplatelet agent to the regimen leads to an increased risk of bleeding when compared to aspirin monotherapy. In a study comparing the effectiveness of aspirin alone to a DAPT (aspirin-clopidogrel) regimen, there was a statistically significant decrease (95 percent confidence interval (CI): 0.59-0.82, $p < 0.05$) in the incidence of stroke among those on DAPT.[2]

Development of triple antiplatelet therapy (TAPT, or triple therapy) has led to controversy over the ideal number of antiplatelet/anticoagulant agents to provide the best efficacy for clot prevention while maintaining safety. The components of TAPT are aspirin, clopidogrel or an alternative, and warfarin.[3] Alternative antiplatelets to clopidogrel in either therapy include prasugrel and ticagrelor. Clopidogrel is a thienopyridine antiplatelet agent that acts by irreversibly blocking the $P2Y_{12}$ adenosine diphosphate (ADP) receptors on the platelet surface.[4] This prevents activation of certain complexes that cause platelet aggregation. Since this action is irreversible, platelet aggregation is reduced.

Prasugrel has a similar mechanism of action to clopidogrel.[5] A clinical trial assessed therapeutic outcomes using prasugrel in comparison to clopidogrel in patients with myocardial infarction (MI). The primary endpoints were death from cardiovascular (CV) causes, nonfatal MI and nonfatal stroke. The secondary outcomes were stent thrombosis and planned PCI for patients enrolled in the study with acute coronary syndrome. The results of this study showed that there was a reduced death rate from MI for subjects taking prasugrel compared to those taking clopidogrel. However, the prasugrel group experienced increased bleeding (1.4 percent in the prasugrel group versus 0.9 percent in the clopidogrel group, $p=0.01$).[5] Prasugrel is a more potent inhibitor of platelet aggregation than clopidogrel due to higher exposure of the metabolite to the receptor. It is well-absorbed and metabolized by the body and inhibits platelet aggregation within 30 minutes of administration. In comparison, clopidogrel has a median onset of inhibition of 1.5 hours.[6] It is suggested to weigh the benefits of prasugrel as an antiplatelet agent against its risks for bleeding as compared to clopidogrel.

Another antiplatelet agent used in place of clopidogrel is ticagrelor which acts via reversible inhibition of the $P2Y_{12}$ ADP receptor.[7] Ticagrelor has been shown to have greater inhibition of the receptor than clopidogrel. In a study comparing the efficacy and safety of ticagrelor and clopidogrel in patients hospitalized for ACS, ticagrelor decreased rates of death due to vascular MI and stroke more than clopidogrel, with a hazard ratio of 0.84 ($p < 0.001$, 95 percent CI [0.77-0.92]).[7] Clopidogrel and ticagrelor did not differ in risk of bleeding, while prasugrel showed more intracranial and gastrointestinal bleeding than ticagrelor.[5] This indicates that ticagrelor may be more effective as an antiplatelet agent, without the adverse effect of increased bleeding, as compared to clopidogrel and prasugrel.

An oral anticoagulant (OAC) is added to prevent stroke and other CV events. Despite the added benefits, traditional OACs introduce risks to the regimen, including an increased risk for bleeding, which can lead to worse health outcomes and decreased compliance.[3] However, an OAC exhibits greater anticoagulation than aspirin and clopidogrel combined.[8]

Novel oral anticoagulants (NOACs) may serve as alternatives to warfarin in the TAPT regimen.[9] Several NOACs have been investigated in TAPT, including dabigatran, apixaban and rivaroxaban. Dabigatran is a factor IIa (thrombin) inhibitor, and apixaban and rivaroxaban are factor Xa inhibitors. Using NOACs over warfarin may be beneficial because NOACs are not vitamin K antagonists and have fewer side effects. There is also a lower risk of bleeding associated with some NOACs when compared with warfarin. In a study comparing warfarin to dabigatran, rate of major bleeding was 3.57 percent per year in the warfarin group and 2.78 percent per year in

the dabigatran group (p=0.003).[9] The more traditional vitamin K antagonists do have a reversal option as vitamin K can be administered in the event of a bleed.[10] While there is a reversal agent for dabigatran (idarucizumab), there is currently no reversal agent for rivaroxaban or apixaban. Another risk associated with NOACs is liver injury, with reports that 1.8 to 3.9 percent of patients taking these medications experience unpredictable and severe liver injury or liver failure.[11]

Therapy Selection

Appropriate candidates for TAPT are PCI patients with stents implanted either electively or to treat ACS.[3] A patient with stent implantation requires DAPT because monotherapy with aspirin is insufficient to prevent thrombosis. Triple antiplatelet therapy may be suitable for these patients if they have a low risk of bleeding. Other candidates for TAPT include those with conditions that require stroke prevention as well as antiplatelet therapy, such as AF patients with ACS or mechanical valve patients with severe CAD.[12,13]

Percutaneous coronary intervention with stent implantation (PCI-s) has become a routine procedure for many individuals with myocardial ischemia.[14] In patients with AF who have undergone PCI-s, the decision to recommend TAPT is based on prevention of cardioembolic events associated with AF and stent thrombosis after PCI-s in addition to an assessment of bleeding risk. Combined aspirin-clopidogrel therapy is less effective in preventing stroke than OAC alone, but OAC alone is insufficient to prevent stent thrombosis.[8] Thus, TAPT is often recommended. In 2010, the European Society of Cardiology (ESC) published a consensus document with the recommendation that all patients with AF who undergo PCI-s should receive TAPT for at least one month and up to 12 months, depending on the type of stent used, the clinical indication (elective stent implantation versus ACS) and the patient's risk of hemorrhage.[14] After bare metal stent (BMS) implantation, triple therapy should be utilized for two to four weeks followed by OAC monotherapy.[8] Drug-eluting stents (DES), on the other hand, require three to six months of triple therapy followed by OAC monotherapy. Second-generation and third-generation DES may be preferred as they might be associated with shorter re-endothelialization times and shorter duration of triple therapy. However, the use of BMS is the ultimate preference in this population as the recommended duration of triple antithrombotic therapy is considerably shorter.[14]

Individually, antiplatelet and anticoagulant agents increase a patient's risk of bleeding, and, when used in combination, they further worsen this risk. A meta-analysis consisting of nine clinical trials that included 1,996 participants found that TAPT is associated with a twofold increase in major bleeding complications after PCI-s compared to DAPT in patients with an indication for long-term OAC.[14] Major bleeding was defined as an absolute decrease in hematocrit of more than 15 percent, the need for transfusion of two or more units of blood, the need for corrective surgery, the occurrence of an intracranial or retroperitoneal hemorrhage or any combination of the aforementioned events.[8] Almost all reported major bleeding events occurred in the first six months of follow up and were often associated with supratherapeutic international normalized ratio (INR) levels. Additionally, most bleeding events occurred in the gastrointestinal (GI) system of patients with baseline anemia. Another study that examined 4,959 patients over the age of 65 with acute MI and AF who underwent coronary stenting found that incidence of bleeding requiring hospitalization within two years post-discharge as well as incidence of intracranial hemorrhage, were significantly higher for patients discharged on TAPT compared to DAPT.[15]

Specific mechanisms contributing to increased bleeding associated with triple therapy have not yet been studied but are likely affected by various clinical and therapeutic factors such as advanced age, female gender, peri-interventional administration of glycoprotein IIb/IIIa inhibitors, smoking and high prevalence of comorbidities including renal dysfunction and previous major bleeding.[8] In the event that a major bleeding event should occur while a patient is on TAPT, treatment should be aggressive. If minor bleeding events occur (defined as observed blood loss and 9 to 15 percent decrease in hematocrit or decrease in hemoglobin level≥40 g/L if no bleeding is identified), antithrombotic therapy should not be discontinued because of the patient's increased risk of developing stent thrombosis or vascular thromboembolism.

For patients in whom a NOAC is used in place of warfarin in TAPT therapy, the lowest dose effective for stroke prevention in AF should be considered.[16] A meta-analysis involving 30,866 patients with recent ACS concluded that the inclusion of a NOAC in a triple therapy regimen increased the bleeding risk by 79 to 134 percent while minimally decreasing recurrent ischemic events in patients without AF. Several other studies were conducted that evaluated triple therapy with rivaroxaban, apixaban or dabigatran combined with aspirin and clopidogrel in patients with ACS. Rivaroxaban was tested using subtherapeutic doses (2.5 mg twice daily or 5 mg daily) for complete anticoagulation because higher doses were found to produce a dose-dependent increase of bleeding risk.[17,18] For this reason, use of rivaroxaban may not be preferred in triple therapy.[16] Unlike rivaroxaban, apixaban in triple therapy was studied in doses recommended for complete anticoagulation.[19] The study was stopped prematurely because there was a significant 2.5-fold increase in risk of bleeding among the apixaban group compared to the placebo group with no indication of benefit in preventing MI, stroke or CV death.[13] Thus, triple therapy with apixaban may not be preferred. Dabigatran in triple therapy was also found to be associated with dose-dependent increase of bleeding risk in patients with ACS.[20] A substudy analysis of the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study was conducted to further assess the bleeding risk of dabigatran in TAPT by comparing dabigatran 110 mg, dabigatran 150 mg, and warfarin.[21] This study determined that dabigatran 110 mg twice daily is noninferior to warfarin, with fewer bleeding incidents regardless of concomitant an-

tiplatelet use in patients with AF. While the relative risk of bleeding was found to be similar with dabigatran 110 mg, dabigatran 150 mg, and warfarin, the absolute risk was lowest with dabigatran 110 mg. Overall, bleeding risk must be assessed and monitored with all NOACs.

Despite the risks, TAPT is a viable option to consider for many patients, especially those with a higher risk of thrombotic events and a lower risk of bleeding events.[8] Conducting a risk assessment of bleeding and ischemic complications is highly advised for all patients who are candidates for TAPT. Triple therapy should not be continued long-term after PCI-s in patients with a high bleeding risk profile as even mild to moderate bleeding events are associated with poorer long-term prognosis. However, lowering the dosage of aspirin to less than or equal to 100 mg/day in the triple therapy regimen may reduce the occurrence of major or minor bleeding events.[22] In patients with low risk of bleeding complications, TAPT should be highly considered as the elective antithrombotic drug treatment approach.[8]

In spite of being associated with increased risk of bleeding, TAPT has been found to be more efficacious in lowering mortality in patients with AF and PCI compared to DAPT in addition to reducing major adverse CV events, including death or hospital readmission for MI, ischemic stroke or hemorrhagic stroke.[15] The meta-analysis discussed previously consisting of nine clinical trials demonstrated a 40 percent relative reduction in major adverse cardiac events and a 41 percent relative reduction in all-cause mortality.[14] Reduction in major adverse CV events is due to the lower occurrence of thrombotic and embolic events in the TAPT group.[8] Furthermore, reduction in all-cause mortality occurs as a direct result of significant reduction in major adverse CV events in the triple therapy group. One retrospective study conducted in Spain by Ruiz-Nodar et al. supports this conclusion.[23] The study included a cohort of 426 patients with AF who underwent PCI-s, 50 percent of whom were discharged on TAPT and 40.8 percent of whom were discharged on DAPT. Upon completion of a multivariate analysis, it was found that patients who received TAPT had a lower all-cause mortality rate (17.8 percent versus 27.8 percent, p=0.002) and lower major adverse cardiac event rate (26.5 percent versus 38.7 percent, p=0.001) compared to patients receiving DAPT.

Therapy Considerations and the Role of the Pharmacist

Due to the high risk of bleeding, the 2014 American College of Cardiology and the American Heart Association Task Force on Practice Guidelines recommends refraining from the long-term use of TAPT due to exponential increase in bleeding risk.[24] Additionally, DAPT is recommended to be utilized after PCI. However, the 2016 ESC Guidelines recommend the use of an OAC after stenting in patients with a history of deep vein thrombosis and pulmonary embolism and in AF patients with a stroke risk. This expert-based consensus suggests that TAPT should be used in these patients but only for a short duration.[16] Based on the ESC guidelines, clinical judgment influenced by thrombotic risk should be used to determine whether or not therapy should be supplemented by an OAC.

When the TAPT regimen is selected, regular monitoring for bleeding risk is advised upon discharge. Pharmacists play a critical role in the monitoring process, especially when the OAC of choice is warfarin. Upon discharge, patients on warfarin should be referred for anticoagulation monitoring so that the INR can be assessed regularly. INR is a key indicator of bleeding risk in those patients who are receiving warfarin.[8] Because of this increased bleeding risk with TAPT, the target range is lower and narrower than a typical warfarin treatment plan. The recommended goal INR for these patients is 2.0 to 2.5 as compared to the typical therapeutic INR range of 2.0 to 3.0.[16,24-25] This narrower INR range for TAPT patients is recommended but with low evidence since this target INR range has not been evaluated in many patient populations and is based solely on expert opinion.[24] Pharmacists may also utilize the HAS-BLED method for assessment of other disease states and lifestyle factors to monitor risk of bleeding in select patients. The HAS-BLED method is based on seven factors: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly and drugs/alcohol concomitantly which all contribute to the risk of bleeding for an AF patient.[14]

Discussion with TAPT patients is necessary so that health care providers can identify potential drug interactions, adverse effects, effective ways to educate and other drug therapies a patient is using. This necessary information is obtained best by addressing patient concerns, asking open-ended questions, listening to patient responses in their entirety and assessing patient adherence based on previous medical history.[14] In particular, warfarin is known to have many drug interactions that can be identified by talking to patients. All patients should be educated regarding warfarin's potential to react with specific medications, which could result in altered effects of warfarin. A common list of medications that interact with warfarin should be provided to patients. Additionally, the patient should receive education on how to identify bleeding risks with the biggest identifier as bruising.[14] In order to prevent GI bleeds, the use of proton pump inhibitors (PPIs), H_2 antagonists and antacids is common in TAPT patients and is recommended in patients with a history of GI bleeding.[16,24,26] However, close monitoring is advised to ensure efficacy because clopidogrel and PPIs are metabolized by CYP2C19 which can decrease the effects of clopidogrel due to competitive binding. While being treated with TAPT that includes clopidogrel, patients should only be on PPIs if there is a specific indication to treat a disease state such as chronic heartburn or if it will benefit the patient by protection from GI bleeding.[26] These discussions can happen in anticoagulation clinics, in community pharmacies and prior to discharge at the hospital.

Pharmacists must work with other health care providers to promote the continuum of care for each patient, especially while in the hospital. Pharmacists have a role in the medication reconciliation process before and after PCI to ensure

that TAPT candidates will receive the best and safest outcomes while on the therapy. Even though pharmacists in anticoagulation clinics will be assessing the INR of patients on warfarin after discharge, assessment of $CHADS_2$ scores for stroke risk in AF patients, INR monitoring and HAS-BLED are critical while in the hospital.[14] For those patients on NOACs, HAS-BLED remains an effective monitoring tool. All of this information should be communicated with all health care providers involved with the care of each patient.

Conclusion

Overall, when choosing a treatment regimen for a patient in need of anticoagulation therapy, it is important to evaluate the benefits of using TAPT as well as its risks in comparison to DAPT. While TAPT has shown to be more effective at preventing thrombosis, the increased risk of bleeding may cause harm in patients who are already at high risk to develop bleeds. However, TAPT is recommended for specific patient populations such as patients with ACS undergoing PCI-s or patients with a mechanical heart valve with severe CAD as these patients require more aggressive anticoagulation therapy. This recommendation is based on expert opinion. In order to obtain evidence-based recommendations, further research needs to be done comparing long-term outcomes of TAPT and DAPT in various patient populations. The safety of patients on TAPT is dependent on careful monitoring of treatment by health care professionals and thorough patient education about medication adherence, proper medication usage and the warning signs of bleeding.

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