

Aspirin vs. P2Y12 Inhibitor Rivalry: Which One Should be Continued During Gastrointestinal Bleeding

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ABSTRAK

Dual antiplatelet therapy (DAPT) adalah tatalaksana utama dalam pencegahan sekunder untuk Sindrom koroner akut, stroke iskemik, terutama setelah intervensi koroner. DAPT terdiri dari dua obat yaitu Aspirin dan golongan P2Y12 reseptor inhibitor (contohnya clopidogrel), yang penggunaannya meningkat seiring waktu. Efek samping yang paling serius yang paling sering dijumpai adalah pendarahan pada saluran cerna. Panduan klinis dalam menangani keadaan tersebut dapat dijumpai pada Panduan Perhimpunan Gastroenterologi dan Perhimpunan Kardiolog. Hampir semua setuju untuk melanjutkan aspirin dan menghentikan P2Y12 reseptor inhibitor. Namun demikian, European Society of Cardiologist (ESC) pada panduannya di tahun 2017 merekomendasikan inhibitor P2Y12 sebagai anti platelet pilihan pada pasien dengan pendarahan saluran cerna atas. Artikel ini akan membandingkan panduan klinis dan bukti-bukti penelitian yang mendasari pilihan anti platelet.

Kata kunci: antiplatelet, aspirin, clopidogrel, gastrointestinal, pendarahan

ABSTRACT

Dual antiplatelet therapy (DAPT) is the mainstay of secondary prevention treatment for acute coronary syndrome (ACS) and ischemic stroke, especially after coronary intervention. DAPT consists of aspirin and P2Y12 receptor inhibitor (e.g. clopidogrel), and the use of DAPT has been increased over time. The most serious and common adverse effect is gastrointestinal bleeding. Guidelines in managing such condition are available among Gastroenterologist Societies and Cardiologist Societies. Most guidelines are consistent with each other to continue the use of aspirin while withholding P2Y12. However, European Society of Cardiologist (ESC) guideline in 2017 recommended P2Y12 receptor inhibitor as the preferred antiplatelet for patient with upper gastrointestinal bleeding. This review will look on the guidelines and other supporting evidence for the justification on the antiplatelet of choice.

Keywords: antiplatelet, aspirin, clopidogrel, gastrointestinal, bleeding.

INTRODUCTION

Currently antiplatelet therapy is the standard treatment and care for secondary prevention of acute coronary syndrome, especially after interventional therapy. A patient may be indicated for double antiplatelet therapy (DAPT) after a

myocardial infarction (MI) or after percutaneous coronary intervention (PCI). DAPT consists of aspirin and platelet P2Y12 receptor inhibitor for Adenosine 5'-Diphosphate (ADP) (e.g. Clopidogrel, Prasugrel, ticagrelor).^{1,2}

The prevalence of using DAPT has increased

over time. During 2015, in Europe, there were estimated 1,400,000 - 2,200,000 subjects to DAPT.³ Gastrointestinal bleeding (GIB) is the most common serious complication from long term use of DAPT, and has adverse effect on survival. A meta-analysis showed that low dose of Aspirin (75-325 mg per day) was associated with increased risk for major gastrointestinal bleeding (OR = 1.55; 95%CI:1.27-1.90), and data regarding clopidogrel was greater or similar compared to aspirin.^{1,4} The data regarding DAPT is not commonly reported, but has been reported to be around 1.3 - 2.7%.⁵⁻⁸

The GIB, especially in patient using DAPT, should be investigated and treated; therefore, endoscopic related procedure and the risk and benefit of discontinuing either both or one antiplatelet agent should be considered. In our previous paper, we reviewed the comparison of guidelines between Digestive societies such as: i) European Society of Gastrointestinal Endoscopy (ESGE), ii) American Society of Gastrointestinal Endoscopy (ASGE), and iii) Asian Pacific Association of Gastroenterology – Asian Pacific Society for Digestive Endoscopy (APAGE-APSDE) guidelines.⁹ This paper will review and compare the guidelines between Digestive societies and European Society of Cardiology (ESC) standpoint in managing patient using DAPT with gastrointestinal bleeding especially regarding discontinuation of antiplatelet agent.

DIGESTIVE SOCIETIES STANDPOINT

In comparing ESGE, ASGE, and APAGE-APSDE guidelines, all guidelines show consistency on continuing aspirin and prompt consult to cardiologist. Furthermore, ASGE recommends that endoscopic procedures should be performed after 5-7 days after the cessation

of thienopyridine (P2Y12 receptor inhibitor). APAGE-APSDE limits the withholding of the second antiplatelet agent for up to 5 days after hemostasis (**Table 1**).¹⁰⁻¹³

ESC STANDPOINT

In 2017, ESC published expert consensus paper stated that in GIB with high risk stigmata restarting single treatment with low dose aspirin was recommended.¹⁴ Interestingly, in 2018 ESC in collaboration with European Association for Cardio-Thoracic Surgery (EACTS) published focused update on dual antiplatelet therapy in coronary artery diseases stated that patient with moderate, severe, and life-threatening bleeding especially for Upper GIB should be considered to switch to single antiplatelet therapy with P2Y12 inhibitor (**Figure 1 and Figure 2**).² There is a shift in recommendation by the ESC from continuing aspirin as recommended by Gastroenterology society guidelines to P2Y12 inhibitor.

SUPPORTING STUDIES

ESGE recommendation did not provide any justification for continuing aspirin without interruption and consultation with a cardiologist. ASGE recommendation is summarized in the American College of Cardiology Foundation and American College of Gastroenterology consensus statement.¹⁵ APAGE practice guidelines justify its recommendation of continuing aspirin based on two reasons.¹³ First, there is evidence that aspirin alone delays the onset of coronary events. The study stated that patient treated with DAPT cessation of both would result in thrombosis formation with the median time of only 7 days from cessation of treatment, as compared to 122 days with only clopidogrel withheld.¹⁶ Second, high dose of PPI will be used in the treatment

Table 1. The choice of antiplatelet in gastrointestinal bleeding patient using DAPT based on ESGE, ASGE, and APAGE-APSDE guidelines

ESGE	ASGE	APAGE-APSDE
Continue low dose aspirin therapy with early cardiology consultation regarding the timing of resuming the second antiplatelet.	ASA should be continued. Perform endoscopic procedures, especially for patients associated with bleeding risk, 5-7 days after thienopyridine drug cessation.	Aspirin should be continued and withhold second antiplatelet agent for up to 5 days after endoscopic hemostasis.

ASA = acetylsalicylic acid (Aspirin)

of acute bleeding. Clopidogrel, an example of P2Y₁₂ receptor inhibitor, and PPI are drugs that highly affected by hepatic metabolism of CYP2C19. As reported by some studies regarding the prevalence of slow metabolizer of CYP2C19 among Asians, some studies focused on the genetic variation of CYP2C19*17 allele which influenced transcriptional expression and activity was found relatively low (<5%) in East Asian countries especially among Japanese and Chinese population and 30% found in European and African.¹⁷⁻²¹ Food and Drug Administration (FDA) has issued a warning label against using clopidogrel with PPI that are extensively metabolized by CYP2C19. However, the interaction of PPI and clopidogrel remains controversial.^{22,23}

The continuation of aspirin is also reported to have more benefit despite the risk as reported by Sung, et al.²⁴ in 2010 stating that the

discontinuation of aspirin led to higher mortality rates. Furthermore, The APAGE consensus has also stated that when only one antiplatelet agent is used, aspirin is preferred as it is associated with a lower risk for causing recurrent bleeding.¹²

The change of recommendation from ESC expert consensus in 2017 to the newer ESC 2017 focused update on DAPT in coronary artery disease did not mention any justification for its change to prefer P2Y₁₂ inhibitor during gastrointestinal bleeding.^{14,2} It is worth mentioning that the earlier ESC expert consensus had similar recommendation and cited ESGE recommendation.

CONCLUSION

DAPT increases the risk of gastrointestinal bleeding. When such condition occurs, maintaining the balance between hemorrhage and thrombosis becomes challenging. Based

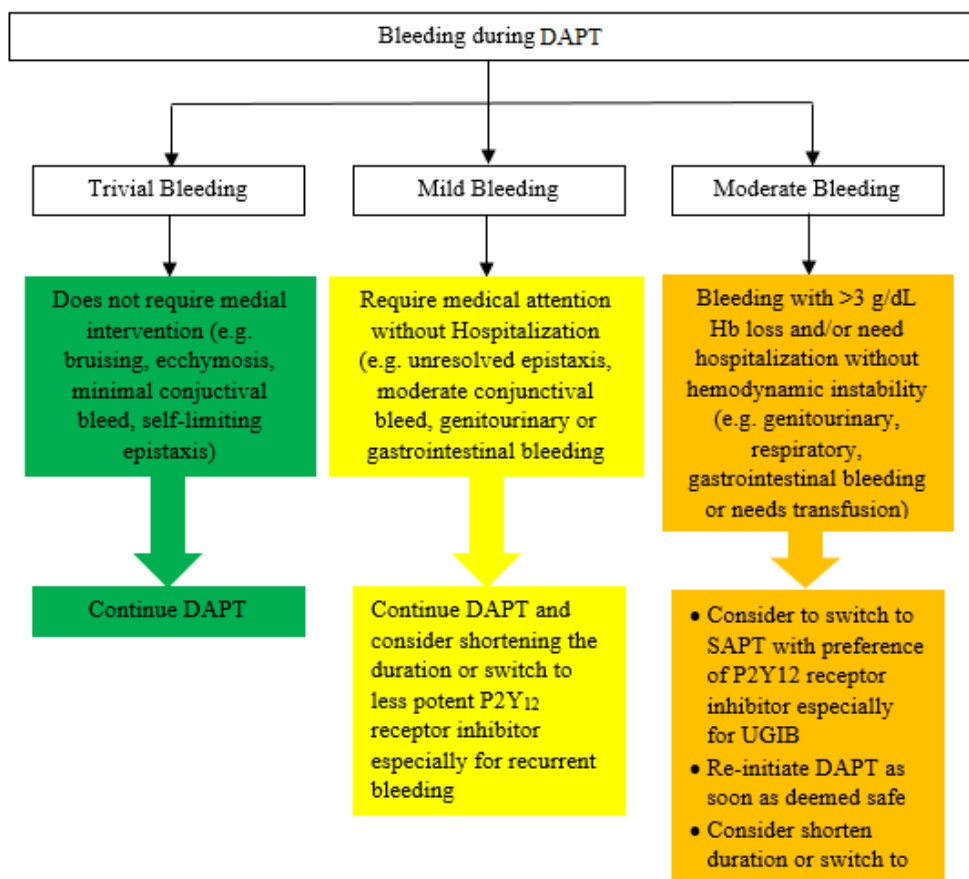


Figure 1. Practical recommendations for the management of bleeding in patients treated with dual antiplatelet therapy. DAPT = dual antiplatelet therapy; SAPT = single antiplatelet therapy; UGIB = upper gastrointestinal bleeding.

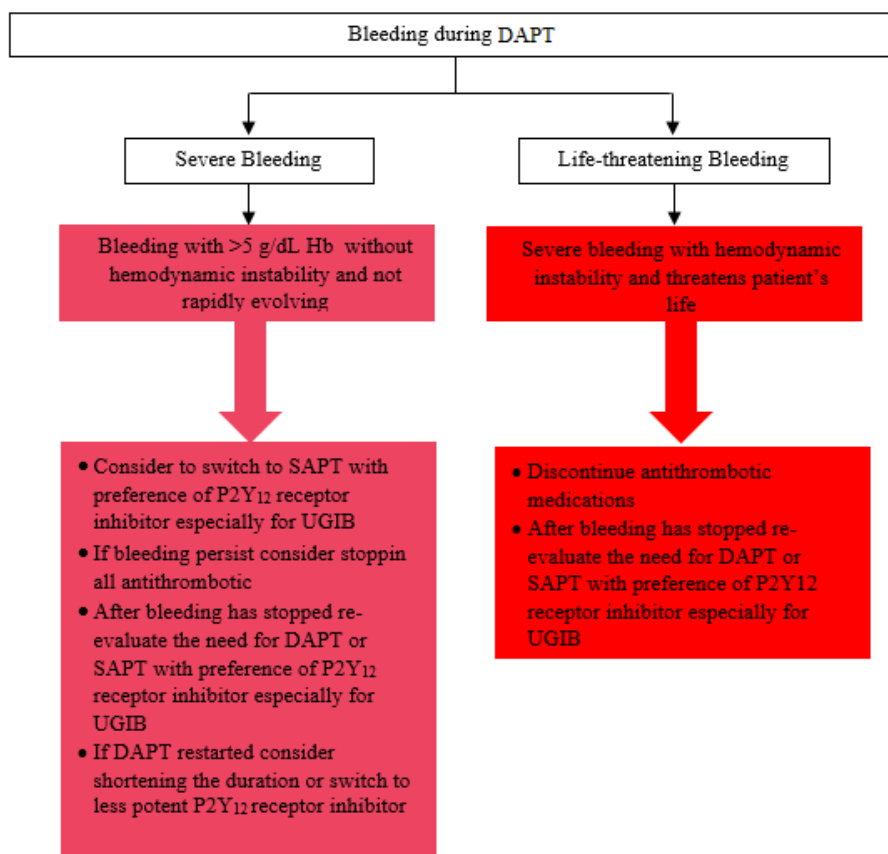


Figure 2. Continuation

on the majority of guidelines and supporting evidence, the appropriate course of action to manage patient using DAPT with gastrointestinal bleeding is to continue aspirin while withholding clopidogrel. Early consultation with cardiologist and individualized management based on patient's condition is very important to ensure safety and achieve the balance of hemorrhage and thrombosis.

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