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Short Communication

Feasible Dual-Channel Therapy after PCI in Patients at Risk of Gastrointestinal Bleeding

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ABBREVIATIONS

ACS: Acute Coronary Syndrome; AF: Atrial Fibrillation; CHD: Coronary Heart Disease; DAPT: Dual Antiplatelet Therapy; GIB: Gastrointestinal Bleeding; GID: Gastrointestinal Disease; GRACE: Global Registry of Acute Coronary Events; NOAC: Novel Oral Anticoagulants; PCI: Percutaneous Coronary Intervention; PPI: Proton Pump Inhibitor

DESCRIPTION

Balancing the risks of bleeding and thrombosis associated with antithrombotic therapy following Percutaneous Coronary Intervention (PCI) remains a challenge, particularly in patients with Coexisting Gastrointestinal Disease (GID) and Coronary Heart Disease (CHD). Tienan Zhou et al. conducted a randomized controlled trial to compare the antithrombotic efficacy and bleeding risks of rivaroxaban plus clopidogrel versus aspirin plus clopidogrel in patients with CHD and GID undergoing PCI. [1]. the trial employed the more frequently utilized dosages of rivaroxaban at 10 mg/d, aspirin at 100 mg/d, and clopidogrel at 75 mg/d with a study duration of six months. To ensure patient safety, participants who had not previously taken or regularly taken clopidogrel or aspirin, or had stopped taking them for less than 5 days before inclusion, were given a loading dose of either medication (300 mg to 600 mg) within 12 hours prior to coronary angiography. The authors provide specific instructions for managing Gastrointestinal Bleeding (GIB) that may occur during the therapeutic process. In cases of hemodynamic stability, endoscopy is utilized for hemostasis and administration of a Proton Pump Inhibitor (PPI) drug treatment while discontinuing antiplatelet medication. Three days following complete hemostasis of gastric injury, clopidogrel 75 mg/d monotherapy may be administered promptly to reduce the risk of thrombosis in patients with no active bleeding recurrence and a hemoglobin level above 90 g/L. The authors aim to investigate a dual-channel therapy that achieves non-inferior anti-ischemic effects comparable to Dual Antiplatelet Therapy (DAPT) in CHD and GID patients undergoing PCI, while minimizing bleeding risk. The occurrence of ischemic events as well as bleeding events were assessed at 1 and 6 months following the initiation of treatment. Although DAPT may mitigate the risk of thromboembolic events, a pivotal concern with DAPT is its propensity to increase major bleeding events, particularly gastrointestinal mucosal injury such as ulcers and hemorrhage [2,3]. The OPT-PEACE trial monitored treatments involving aspirin plus placebo, clopidogrel plus placebo, or a combination of aspirin and clopidogrel for a duration of six months [4, 5]. Nearly all patients on antiplatelet therapy developed gastrointestinal injuries, but overt bleeding was rare. The combination of clopidogrel and aspirin caused more severe damage to the gastrointestinal tract [6]. Aspirin induces gastrointestinal injury by damaging the mucosa and activating antiplatelet mechanisms [6].

Although previous studies have shown that Proton Pump Inhibitors (PPIs) can protect against drug-induced gastrointestinal injury caused by aspirin and clopidogrel, combining PPI with clopidogrel significantly reduces gastrointestinal adverse effects without affecting cardiovascular events [3]. Pharmacokinetic studies have demonstrated that the concomitant use of antacids with certain PPIs may compromise the antiplatelet reactivity of clopidogrel, resulting in suboptimal therapeutic outcomes for some patients. Moreover, PPIs do not inherently mitigate the risk of bleeding associated with DAPT. The impact of DAPT-PPI interaction on clinical outcomes is uncertain due to conflicting evidence from non-randomized observational studies, especially in high-risk cardiovascular patients and *CYP2C19* loss-of-function allele carriers [7-9]. Notably, rivaroxaban circumvents the impact of genotype [10].

Patients with CHD and GID may not receive revascularization due to concerns about gastrointestinal damage from DAPT, which increases cardiovascular mortality risk in this population. Antiplatelet therapy is crucial in treating CHD and reducing ischemic events after PCI due to the important role of platelet activation and aggregation in atherothrombosis [11]. This clinical scenario presents a quandary when it comes to selecting antithrombotic strategies. While guidelines offer careful

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consideration and recommendations for antithrombotic agents, ongoing studies are exploring their efficacy after PCI. Research indicates that patient adherence to antithrombotic treatments is compromised in the presence of GIB. Discontinuing antithrombotic drugs significantly increases the incidence of ischemic events following PCI. Therefore, a positive strategy is to minimize gastrointestinal bleeding during antithrombotic therapy. In terms of GIB reduction strategies in antithrombotic therapy, researchers have explored the possibility of an aspirin-free regimen [12]. The Gemini ACS-1 study demonstrated that low-dose rivaroxaban in combination with either clopidogrel or ticagrelor did not result in an increase of clinically significant bleeding when compared to dual antiplatelet therapy. Therefore, the aspirin-free strategy may be considered a safe approach for acute coronary syndrome, as no evidence of thrombotic events due to aspirin discontinuation was observed [12]. In the PIONEER AF-PCI trial, both groups receiving rivaroxaban had lower rates of significant bleeding, but no statistically significant differences were found between the two groups in terms of stroke, myocardial infarction, or cardiovascular death [13]. Studies have shown that NOAC (rivaroxaban) can achieve comparable anti-ischemic effects to DAPT, offering an alternative option.

Rivaroxaban is the first oral direct factor Xa inhibitor approved for stroke prevention in Atrial Fibrillation (AF) patients, based on Phase III results from the ROCKET AF trial [14]. In diseases with high thrombotic risk, including Acute Coronary Syndrome (ACS), rivaroxaban demonstrates superior efficacy and safety compared to warfarin and other vitamin K antagonists. Moreover, low-dose rivaroxaban inhibition may improve cardiovascular outcomes for patients with recent ACS due to the crucial role of factor Xa in thrombotic disease. It also offers advantages in terms of onset speed, efficacy prediction, coagulation monitoring and dose adjustment [15,16].

In Tienan Zhou et al.'s study, patients aged 18-75 with stable CHD or non-ST segment elevation ACS and GID, and GRACE scores below 140 were included. Additionally, patients with a history of gastrointestinal bleeding or healed ulcers for over 12 months, as well as those taking aspirin accompanied by tolerable yet uncomfortable symptoms were included. The aim of this investigation is to explore the effectiveness and safety of rivaroxaban in conjunction with clopidogrel among Chinese patients suffering from CHD and GID who have undergone PCI. Additionally, aim to determine whether this treatment regimen can achieve a comparable anti-ischemic effect as standard DAPT, while minimizing the risk of gastrointestinal bleeding in patients with pre-existing gastrointestinal injury.

Although Asian populations have a lower risk of ischemia and a higher risk of bleeding, Lin et al.'s study found that low-dose rivaroxaban (10 mg once daily) had similar risks of stroke, embolism, and clinically relevant bleeding compared to standard doses (15 mg or 20 mg once daily) in Asian AF patients [17]. In this study, clopidogrel and rivaroxaban (10 mg once daily) were administered to non-AF patients undergoing PCI with regard to both efficacy and safety. Previous studies have confirmed the safety and effectiveness of NOACs combined with antiplatelet agents for patients with CHD and AF, but further investigation is needed to assess their safety and efficacy when used in combination with clopidogrel for patients with CHD and GID.

CONCLUSION

Dual-channel therapy utilizing bivalirudin and clopidogrel for antithrombotic management is a viable option for patients with CHD and GID undergoing PCI. In this study, clopidogrel and rivaroxaban (10 mg once daily) were administered to non-AF patients undergoing PCI with regard to both efficacy and safety. Previous studies have confirmed the safety and effectiveness of NOACs combined with antiplatelet agents for patients with CHD and AF, but further investigation is needed to assess their safety and efficacy when used in combination with clopidogrel for patients with CHD and GID.

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