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Editorial Comment
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Appropriate Use of Dual Antiplatelet Therapy

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Ischemic heart disease (IHD) is the leading cause of years of life lost globally.[1] Percutaneous coronary intervention (PCI) was developed in 1977 and the first coronary stent was introduced to the cardiology realm in 1986.[2] This art along with the evolution of the devices has revolutionized the cardiology practice ever since. Even though PCI effectively improves quality of life, when comparing to medical therapy, and reduces the need for revascularization, when using new-generation stents, this innovation often leverages the risks between restenosis and thrombosis. The rate of restenosis is reduced with more advanced stent technology probably at a cost of an increased risk of stent thrombosis. Beside restenosis, in patients with IHD, ischemic events can still occur beyond the stented lesion after PCI.[3] Therefore, the current guidelines recommend continuing the use of dual antiplatelet therapy (DAPT), combining aspirin with a P2Y12 receptor antagonist, at least for one month after PCI, depending on patient and disease characteristics.

DAPT is the bedrock of contemporary treatment for patients after PCI, it is, nevertheless, associated with a significant increase in bleeding, particularly gastrointestinal bleeding. In addition, diabetes mellitus (DM) is a growing public health challenge and a partially modifiable risk factor for worse outcomes in patients with an array of cardiovascular complications.[4-6] Patients with DM are at higher risk of stent thrombosis and are more susceptible to gastrointestinal bleeding. Randomized trials suggest that proton-pump inhibitors (PPIs) reduce the risk of recurrent gastrointestinal bleeding in patients requiring antiplatelet treatment.[7,8] Therefore, it is appealing to add PPIs to those who are at high risk of gastrointestinal bleeding and require long-term aspirin treatment.

Clopidogrel, the most common P2Y12 receptor antagonist used in the management of patients with IHD, is a prodrug that is metabolized by hepatic enzymes into its active form.[9] A number of observations presented conflicting data on whether the potential drug interactions between clopidogrel and PPIs would further attenuate clopidogrel actions clinically and lead to more thrombotic events.[10,11] The randomized trial comparing omeprazole with placebo in patients requiring DATP showed omeprazole reduced the rate of upper gastrointestinal bleeding. But it was unpowered to exclude the possibility that omeprazole may increase cardiovascular events.[12] In this issue of the Journal, Lee, et al., shed a light on this long debate.[13] Using the National Health Insurance research database, they identified 6757 patients with DM who received bare-metal stent implantation during the index PCI between 2001 and 2005. After statistical adjustments, the hospitalization rate for revascularization or acute coronary syndrome was similar between 514 patients who received clopidogrel and PPIs and 6243 patients who received clopidogrel alone. They, therefore, concluded that PPIs may not modify the protective effect of clopidogrel in patients with DM receiving bare-metal stent implantation.

Their study design was consistent with their prior work that was in the different setting (patients with DM receiving drug-eluting stent implantation). However, their conclusion was not.[14] In the previous study, they showed that the rate of acute coronary syndrome was higher in patients who received clopidogrel and PPIs than those who received clopidogrel alone. Before judging the different conclusions of these two observations, what should we keep in mind first? Firstly, the current study enrolled an earlier cohort receiving bare-metal stent implantation (between 2001 and 2005) than the previous cohort receiving drug-eluting stent implantation (between 2007 and 2010). In the more contemporary cohort, they probably enrolled sicker patients as ev-

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ident by greater proportions of patients with multiple comorbidities (a mean Charlson comorbidity index of 1.97) and a lower proportion of patients using any antiplatelet drugs during the follow-up. Secondly, we have no information on what type of PPIs were used. In addition, there was no information on the duration of either DAPT or PPIs in both studies. Thirdly, the key information regarding why PPIs were used is unknown. Lastly and most importantly, was the rate of gastrointestinal bleeding lower in those who received clopidogrel and PPIs compared with those received clopidogrel alone?

Is there a biological plausibility? It seems that the higher risk of acute coronary syndrome with clopidogrel and PPIs compared with clopidogrel alone occurred only in the early 3 to 6 months after PCI in patients receiving drug-eluting stent implantation.[14] Therefore, it might be related to the stent technology that was associated with stent thrombosis. Stent thrombosis is attributed to different mechanisms according to the time point of its occurrence.[15,16] Although being multifactorial in origin, late stent thrombosis, defined by 30 days after stent implantation, is more device-specific.[17] Thrombogenicity of the stent, the level of reendothelialization, and the development of neoatherosclerosis are important factors. These differences probably explained why they reported different results. Nevertheless, the key to the prevention of stent thrombosis is the appropriate use of DAPT after PCI.[18]

The post-PCI care, particularly in patients at high risk, often leverages the risk of thrombosis and the risk of bleeding. The advancement in pharmacotherapy has introduced the new, reversible, and more potent P2Y12 receptor antagonist that requires no hepatic activation.[19] In a subset of patients who need long-term anticoagulant treatment, two recent PCI trials recommended using PPIs that do not interact with the cytochrome P450 2C19 enzyme to reduce the risk of gastrointestinal bleeding.[20,21] Therefore, as a clinical cardiologist, according to patient and disease characteristics, we should individualize the treatment strategy when using DAPT and take a holistic approach when managing patients with IHD.[22-24]

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REFERENCES

1. Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet* 2018;392: 2052-90.
2. Serruys PW, Kutryk MJ, Ong AT. Coronary-artery stents. *N Engl J Med* 2006;354:483-95.
3. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011; 364:226-35.
4. Chen TY, Lin L, Hsieh MY, et al. Deficiency of endothelial progenitor cells associates with graft thrombosis in patients undergoing endovascular therapy of dysfunctional dialysis grafts. *Acta Cardiol Sin* 2017;33:81-91.
5. Chang HY, Wang CC, Wu YW, et al. One-year outcomes of acute decompensated systolic heart failure in Taiwan: lessons from TSOC-HFrEF Registry. *Acta Cardiol Sin* 2017;33:127-38.
6. Chu CY, Lin TH, Lai WT. The management and prognostic factors of acute coronary syndrome: evidence from the Taiwan Acute Coronary Syndrome Full Spectrum Registry. *Acta Cardiol Sin* 2017;33:329-38.
7. Chan FK, Ching JY, Hung LC, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med* 2005;352:238-44.
8. Lai KC, Lam SK, Chu KM, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N Engl J Med* 2002;346:2033-8.
9. Fernando H, Dart AM, Peter K, Shaw JA. Proton pump inhibitors, genetic polymorphisms and response to clopidogrel therapy. *Thromb Haemost* 2011;105:933-44.
10. O'Donoghue ML, Braunwald E, Antman EM, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet* 2009;374:989-97.
11. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009;301: 937-44.
12. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 2010;363: 1909-17.
13. Lee CW, Tsai FF, Su MI, et al. Effects of clopidogrel and proton

pump inhibitors on cardiovascular events in patients with type 2 diabetes mellitus after bare metal stent implantation: a nationwide cohort study. *Acta Cardiol Sin* 2019;35:402-11.
14. Hsieh CF, Huang WF, Chiang YT, Chen CY. Effects of clopidogrel and proton pump inhibitors on cardiovascular events in patients with type 2 diabetes mellitus after drug-eluting stent implantation: a nationwide cohort study. *PLoS One* 2015;10:e0135915.
15. Mak KH, Belli G, Ellis SG, Moliterno DJ. Subacute stent thrombosis: evolving issues and current concepts. *J Am Coll Cardiol* 1996;27:494-503.
16. Luscher TF, Steffel J, Eberli FR, et al. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. *Circulation* 2007;115:1051-8.
17. Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Gruntzig Lecture ESC 2014. *Eur Heart J* 2015;36:3320-31.
18. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2016;68:1082-115.
19. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045-57.
20. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;375:2423-34.
21. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med* 2017;377:1513-24.
22. Chiang CE, Wang TD, Lin TH, et al. The 2017 focused update of the guidelines of the Taiwan Society of Cardiology (TSOC) and the Taiwan Hypertension Society (THS) for the management of hypertension. *Acta Cardiol Sin* 2017;33:213-25.
23. Li YH, Fang CY, Hsieh IC, et al. 2018 expert consensus on the management of adverse effects of antiplatelet therapy for acute coronary syndrome in Taiwan. *Acta Cardiol Sin* 2018;34:201-10.
24. Chen KC, Yin WH, Wu CC, et al. In-hospital implementation of evidence-based medications is associated with improved survival in diabetic patients with acute coronary syndrome - data from TSOC ACS-DM Registry. *Acta Cardiol Sin* 2018;34:211-23.