VGHKS12-CT7-08

Institution/Department：Kaohsiung Veterans General Hospital
Principal Investigator (PI)：Prof. Ping-I Hsu
Research Project Title ： Pantoprazole versus famotidine for the prevention of recurrent peptic ulcers in thienopyridine users — a double-blind randomized controlled trial
NCT Number：NCT02551744
Date of the document：From 07 31 2018 （MM/DD/YYYY）

ABSTRACT

Background: Although proton pump inhibitor (PPI) can prevent recurrent peptic ulcer in clopidogrel users with a history of peptic ulcer, the interaction between PPIs and clopidogrel has drawn much attention recently. Several studies reported that certain PPIs could reduce clopidogrel's antiplatelet effects and increase cardiovascular events. These data suggested that PPIs may potentially inhibit the CYP2C19 pathway and interfere with the conversion of clopidogrel to active form. Therefore, searching for other gastroprotective agents such as histamine-2 receptor antagonist (H2RA) to prevent gastrointestinal events for clopipogrel users is urgently needed in clinical practice.

Aims: To compare the efficacy of PPI and H2RA for the prevention of recurrent peptic ulcers in thienopyridine users.

Methods: We plan to enroll 334 thienopyridine (clopidogrel or ticlopidine) users without baseline gastroduodenal ulcer at initial endoscopy. The patients will be randomly assigned to receive either (1) pantoprazole (40 mg qd) or (2) famotidine (40 mg qd) for 6 months. Blood sampling for genotyping of *CYP2C19* is carried out on enrollment. Follow-up endoscopy is carried out at the

end of the 6th month and whenever severe epigastric pain, hematemesis or melena occurs. The primary end point is the occurrence of gastric and/or duodenal ulcers during the 6-month study period.

INTRODUCTION

Platelet activation and aggregation play an important role in the pathogenesis of arterial thrombosis and lead to ischemic events. Thienopyridine (clopidogrel or ticlopidine) inhibits platelet function by selectively and irreversibly blocking the adenosine diphosphate (ADP) receptor on platelets, thereby affecting ADP-dependent activation of the GpIIb-IIIa complex, the major receptors for fibrinogen present on the platelet surface.[1,2] Alone or in association with aspirin, clopidogrel is a thienopyridine, which has successfully proved to be beneficial in the treatment of acute coronary syndrome[3] and prevention of ischemic events in patients with atherosclerotic diseases.[4,5]

The CAPRIE study showed that long-term administration of clopidogrel to patients with atherosclerotic vascular disease is more effective than aspirin in reducing the combined risk of ischemic events.[6] Additionally, Clopidogrel induced fewer episodes of gastrointestinal bleeding than aspirin.[6,7] The American College of Cardiology-American Heart Association guidelines therefore recommend clopidogrel as an alternative to aspirin for patients with unstable angina or non-ST-segment elevation myocardial infarction who have an aspirin intolerance.[8]

However, a recent study from our center demonstrated that 11% of the patients with a peptic ulcer history who took clopidogrel for the prevention of ischemic events had recurrent peptic ulcer during a 6-month follow-up period.[9] Another prospective study also showed 9% of patients with a history of peptic ulcer bleeding who took clopidogrel had recurrent ulcer bleeding within

one year.[10] The mechanisms leading to recurrent peptic ulcers and ulcer bleeding among patients receiving clopidogrel are unclear. Nonetheless, an animal study revealed that platelet ADP-receptor antagonists impair the healing of gastric ulcers by suppressing the release of platelet-derived growth factors.[11] Platelet aggregation plays an important role in ulcer healing through the release of platelet-derived growth factors that promote angiogenesis, which is important for ulcer healing. An endoscopic study revealed that a point prevalence of peptic ulcer was 1.3% in the adult general population.[12] Although clopidogrel might not be primarily responsible for the development of peptic ulcer, it may impair healing of background ulcers and convert silent ulcers to bleeding lesions.

Our previous study has proved that esomeprazole can effectively prevent recurrent peptic ulcers among clopidogrel users with a history of peptic ulcer.[9] Currently, very few studies have evaluated the efficacy of histamine-2 receptor antagonist (H2RA) in the prevention of GI injury with antiplatelet agents. Ng et al. showed that H2RA is inferior to proton pump inhibitor (PPI) in preventing recurrence of aspirin-related peptic ulcers or erosions in patients with aspirin-related peptic ulcers/erosions.[13] A recent case-control study by Lanas et al. revealed that, compared with patients undergoing antiplatelet therapy without protective co-therapy, H2RAs can significantly reduce the risk of upper GI bleeding in patients taking low-dose aspirin but not in those taking clopidogrel.[14] Another cohort study also reported that 22% of clopidogrel users taking concomitant H2RAs had recurrent upper GI bleeding after a 1-year follow up, whereas no patient taking clopidogrel plus a PPI had recurrent bleeding.[15]

Recently, the interaction of PPIs and thienopyridines has raised the concern for the safety of combination use of the two medicines.[16-18] Thienopyridines are prodrugs, which must be absorbed in the gastrointestinal tract, and metabolized in the liver to generate active metabolites and acquire their anti-platelet properties. The metabolism of thienopyridines involve CYP2C19 isoenzyme, which is also the key enzyme for the metabolism of most PPIs.[19] This has led to the assumption that some PPIs may potentially inhibit the CYP2C19 pathway and interfere with the conversion of thienopyridines to active form. Three large retrospective observation studies also reported that patients prescribed clopidogrel who also took PPIs had significant increases in cardiovascular events.[20-22] However, Bhatt et al.[23] recently conducted a double-blind, prospective randomized trial (COGENT; Clopidogrel and the Optimization of Gastrointestinal Events Trial) to investigate the effect of omeprazole in patients receiving both aspirin and clopidogrel. The data demonstrated that prophylactic use of omeprazole reduces the rate of upper GI bleeding among patients receiving aspirin and clopidogrel, and there were no differences in CV events between omeprazole and placebo groups.

Our recent study[9] demonstrated that esomeprazole does not influence the action of clopidogrel on platelet aggregation when doses of esomeprazole and clopidogrel are widely separated. However, whether H2RA may interfere with the conversion of thienopyridines to active form remain unclear. Therefore, we design the randomized double-blind comparison study to investigate whether proton pump inhibitor is superior to H2RA in the prevention of recurrent peptic ulcers in thienopyridine users.

References

1. Savi P, Nurden P, Nurden AP, Levy-Toledano S, Herbert JM. Clopidogrel: a review of its mechanism of action. Platelets 1998;9:251-255.
2. Boeynaems JM, van Giezen H, Savi P, Herbert JM. P2Y receptor antagonist in thrombosis. Curr Opin Investig Drugs 2005;6:257-282.
3. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndrome without ST-segment elevation. N Engl J Med 2001;345:494-502.
4. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J, Topol EJ; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006;354:1706-1717.
5. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA; Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527-533.
6. CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). Lancet 1996;348:1329-1339.
7. Fork FT, Lafolie P, Toth E, Lindgarde F. Gastroduodenal tolerance of 75 mg clopidogrel versus 325 mg aspirin in healthy volunteers: a gastroscopic study. Scand J Gastroenterol 2000;35:464-469.
8. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE

2nd, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. Circulation 2007;116:e138–304.

9. Hsu PI, Lai KH, Lau CP. Esomeprazole with clopidogrel reduces peptic ulcer recurrence, compared with clopidogrel alone, in patients with atherosclerosis. *Gastroenterology* 2011; **140**: 791-8.
10. Chan FKL, Ching JYL, Hung LCT, et al. Clopidogrel versus aspirin and esomeprazole for the prevention of recurrent ulcer bleeding. *N. Engl. J. Med.* 2005; **352**: 238-44.
11. Ma L, Elliott SN, Cirino G, Buret A, Ignarro LJ, Wallace JL. Platelets modulate gastric ulcer healing: role of edostatin and vascular endothelial growth factor release. *Proc. Natl. Acad. Sci. USA* 2001; **98**: 6470-5.
12. Laine L, Maller ES, Yu C, Quan H, Simon T. Ulcer formation with low-dose enteric-coated aspirin and the effect of COX-2 selective inhibition: a double-blind trial. *Gastroenterology* 2004; **127**: 395 - 402.
13. Ng FH, Wong SY, Lam KF, et al. Famotidine is inferior to pantoprazole in preventing recurrence of aspirin-related peptic ulcers or erosions. *Gastroenterology* 2010; **138**: 82-8.
14. Lanas A, Garcıa-Rodrıguez LA, Arroyo MT, et al. Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants. *Am. J. Gastroenterol.* 2007; **102**: 507–15.
15. Ng FH, Wong SY, Chang CM, et al. High incidence of clopidogrel-associated gastrointestinal bleeding in patients with previous peptic ulcer disease. *Aliment. Pharmacol. Ther.* 2003; 18: 443-9.
16. Laine L, Hennekens C. Proton pump inhibitor and clopidogrel interaction: Fact or fiction? Am J Gastroenterol 2010;105:34-41.

17. Sibbing D, Kastrati A. Risk of combining PPIs with thienopyridines: fact or fiction? Lancet 2009;374:952-954.
18. Norgard NB, Mathews KD, Wall GC. Drug-drug interaction between clopidogrel and proton pump inhibitors. *Ann. Pharmacotherapy* 2009; **43**: 1266-74.
19. Simon T, Mary-Krause M, Quteineh L, Drouet E, Méneveau N, Steg PG, Ferrières J, Danchin N, Becquemont L; French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) Investigators. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med 2009;360:363-375.
20. Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, Rumsfeld JS. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA 2009;301:937-944.
21. Juurlink D, Gomes T, Ko DT, Szmitko PE, Austin PC, Tu JV, Henry DA, Kopp A, Mamdani MM. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ 2009;180:713-718.
22. Stanek EJ, Aubert RE, Flockhart DA. A National Study of the Effect of Individual Proton Pump Inhibitors on Cardiovascular Outcomes in Patients Treated with Clopiodogrel Following Coronary Stenting: The Clopidogrel Medco Outcomes Study . http://www.scai.org/pdf/20090506Medcoabstract.pdf (Abstract).
23. 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.

PATIENTS AND METHODS

Study population

We will screen for eligible patients who have a past history of gastroduodenal ulcer and underwent endoscopy for dyspeptic symptoms or routine screening, while receiving thienopyridine(either clopidogrel or ticlopidine) therapy to prevent ischemic events. We enroll 334

patients in the study if they meet the following criteria: endoscopic examination reveals normal appearance or pictures of gastritis only; they have received thienopyridine for at least two weeks; they have an atherosclerotic disease such as ischemic heart disease or stroke; they require long-term anti-platelet therapy; and they are adult patients aged ≧ 20 years. Patients are excluded if they have a history of gastric or duodenal surgery other than oversewing of a perforation; if they are allergic to the study drugs; if they require long-term treatment with non-steroidal anti- inflammatory drugs (NSAIDs), corticosteroids, aspirin, or anticoagulant agents; if they are pregnant; if they have active cancer, acute serious medical illness or terminal illness; and if they have gastroesophageal reflux disease.

Study Protocol

Randomization and treatment

Eligible patients are randomly assigned to receive either (1) 40 mg of famotidine daily or (2) 40 mg of pantoprazole daily for 6 months. Randomization is carried out with the use of a computer-generated list of random numbers. An independent staff member assigns the treatments according to consecutive numbers that are kept in sealed envelopes. Anticoagulants, cyclooxygnease-2 inhibitors, conventional NSAIDs, aspirin, over-the-counter analgesics, corticosteroids, misoprostol, sucrafate are prohibited. The administration of an antacid (Iwell, Everest, Taiwan) is permitted for the control of dyspeptic symptoms. Compliance with the regimen is assessed by counting the pills that are returned. If *Helicobacter pylori* (*H pylori*) infection is documented on recruitment, a seven-day course of anti-*H pylori* therapy is administered. Urea breath test is performed at four weeks after the end of anti-*H pylori* therapy.

Blood sampling for genotyping of *CYP2C19* is carried out on enrollment. Platelet aggregation tests are performed in Day 1 and Day 28. The *CYP2C19* genotype is determined using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) as previous description.27,28 Genotypes are classified into three groups: homogeneous extensive metabolizer

(homEM; *CYP2C19**1/*CYP2C19**1); heterogeneous extensive metabolizer (hetEM; *CYP2C19**1/*CYP2C19**2 and *CYP2C19**1/*CYP2C19**3); poor metabolizer (PM; *CYP2C19**2/*CYP2C19**2, *CYP2C19**2/*CYP2C19**3, and *CYP2C19**3/*CYP2C19**3).

Follow-up

Patients are followed up as outpatients with visits every month. Upper gastrointestinal and cardiovascular symptoms are assessed at each visit. They are asked to return to the outpatient clinic if they have persistent dyspeptic symptoms (epigastric pain, fullness, nausea or vomiting) and to report to the emergency room if they have evidences of gastrointestinal bleeding (hematemesis, melena, or sudden onset of severe epigastric pain), cardiovascular events (chest pain, syncope, or sudden onset of severe palpitation) or cerebrovascular accidents (conscious disturbance, hemiparesis, or dysphagia). Follow-up endoscopy with biopsy for urease test is performed whenever persistent dyspepsia, severe epigastric pain, hematemesis or melena occurred and at the end of the 6th month. The endoscopists who performed follow-up endoscopy are unaware of the treatment group assignments. The events of acute coronary syndrome and cerebral vascular accidents during the study period are carefully monitored and assessed.

End points

The primary end point is the occurrence of gastric and/or duodenal ulcers, as determined by endoscopy, during the 6-month study period. An ulcer is defined as a circumscribed mucosal break at least 0.5 cm in diameter (measured using endoscopy forceps) and with a perceptible depth. Only events that are confirmed by the adjudication committee and that occurred during treatment are included in the analysis. Patients who do not have follow-up endoscopic examination are assumed to have had normal findings.