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CURRENT OPINION

Expert position paper on the use of proton pump inhibitors in patients with cardiovascular disease and antithrombotic therapy

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Introduction

The ESC NSTEMI and STEMI guidelines[1,2] and an ACCF/ACG/AHA consensus document[3] recommend treatment with proton pump inhibitors (PPIs) in patients treated with dual antiplatelet treatment (DAPT) during the initial phase of an acute coronary syndrome (ACS) (ESC Class 1A recommendation), particularly in patients with a history of GI bleeding or peptic ulcer. Several studies have raised concerns that many PPIs, especially omeprazole, might diminish the antiplatelet effects of clopidogrel, most likely through inhibition of CYP2C19 and, consequently, the conversion of clopidogrel into its active metabolite.[4,5]

The aim of this position paper is to review the pharmacokinetic background of the interactions between these drugs, and their consequences on clinical outcomes, and to present suggestions for management of this important issue.

Acetylsalicylic acid and proton pump inhibitors

Several agents widely used in patients on acetylsalicylic acid (ASA) may interact with the antiplatelet effects of ASA, but none through the CYP2C9 pathway by which ASA is metabolized. Recently, it has been reported that concomitant use of PPIs reduces the protective efficacy of ASA in patients with ischaemic heart disease.[6,7] A case–control study investigated the antiplatelet effect of ASA in 418 ASA-treated CVD patients, 54 of whom were also treated with PPIs.[7] Patients receiving PPIs had reduced antiplatelet effect of ASA, as shown by greater residual platelet aggregation responses. However, interaction between PPI and ASA is controversial.[8] Potential clinical implications of these findings were explored by a registry study in a large population of ASA-treated patients with first time myocardial infarction.[6] Even after adjusting for baseline variables with multivariate analysis and propensity score matching, PPI use was still significantly associated with ~50% more ischaemic cardiovascular events. A sensitivity analysis showed no increase in risk related to the use of H2 receptor blockers.[6]

Suggested explanations for the observed interaction of PPIs with ASA in cardiovascular patients are (i) the reduced gastric acidity inhibiting the uptake of the weakly acidic ASA, (ii) the worse baseline characteristics of patients with concomitant GI disorders, and (iii) the play of chance. The studies on ASA uptake in relation to gastric acidity show negative findings.[8,9] Even with multivariate and propensity score matching analyses, the existence of unrecognized confounding variables can never be excluded in the absence of randomized controlled trials.

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Conclusion: acetylsalicylic acid and proton pump inhibitors

So far, there are insufficient data to suggest a clinical interaction between PPI use and the protective efficacy of ASA in patients with CVD. Use of PPIs is recommended for the prevention of gastric ulceration in ASA-treated patients at high risk of GI bleeding.

Clopidogrel and proton pump inhibitors

Clopidogrel is a pro-drug that is metabolized in a two-step oxidative process[10] (*Figure 1*). In the first step, the CYP isozymes CYP1A2, CYP2B6, and CYP2C19 form 2-oxo-clopidogrel that is then oxidized to the clopidogrel active metabolite by CYP2B6, CYP2C19, and CYP3A4. CYP2C19 contributes to 40% of the hepatic conversion of clopidogrel into the short half-life active metabolite that irreversibly binds to the platelet $P2Y_{12}$ receptor.[11]

The activity of CYP2C19 may be altered by xenobiotics such as PPIs, which are CYP2C19 substrates and interact with clopidogrel metabolism as a result of competitive antagonism. The interaction between PPIs and clopidogrel depends on the potency of each PPI to inhibit CYP2C19, ranging from stronger inhibitors such as lansoprazole (Ki: 0.4–1.5 μM), omeprazole (Ki: 2–6 μM), and esomeprazole (Ki: 8 μM) down to weaker ones such as rabeprazole (Ki: 17–21 μM) and pantoprazole (Ki: 14–69 μM).[12] A PPI with less CYP2C19 inhibitory capacity (e.g. pantoprazole) may represent a more optimal treatment option than a PPI with high CYP2C19 inhibitory capacity (e.g. omeprazole) in patients who require both clopidogrel and a PPI (*Figures 2* and *3*).[13]

Studies showing no effect of proton pump inhibitors on clinical outcome

Several publications show no clear impact of PPIs on the clinical outcome.[14–16] An analysis of the TRITON-TIMI 38 study showed that clopidogrel-treated patients on omeprazole had similar outcomes compared with patients treated with pantoprazole or other PPIs.[5] Moreover, the prospective randomized COGENT trial,[17] the only RCT that had been designed to test the hypothesis of PPI–clopidogrel interaction on MACE, demonstrated that omeprazole reduces GI events in patients on clopidogrel and ASA without any apparent impact on cardiovascular events, although rates of ischaemic events were low and the study was not powered to exclude a relevant interaction in higher-risk patients. The product was purposefully formulated to retard the dissolution and absorption of omeprazole, thereby reducing the risk of interaction with clopidogrel.

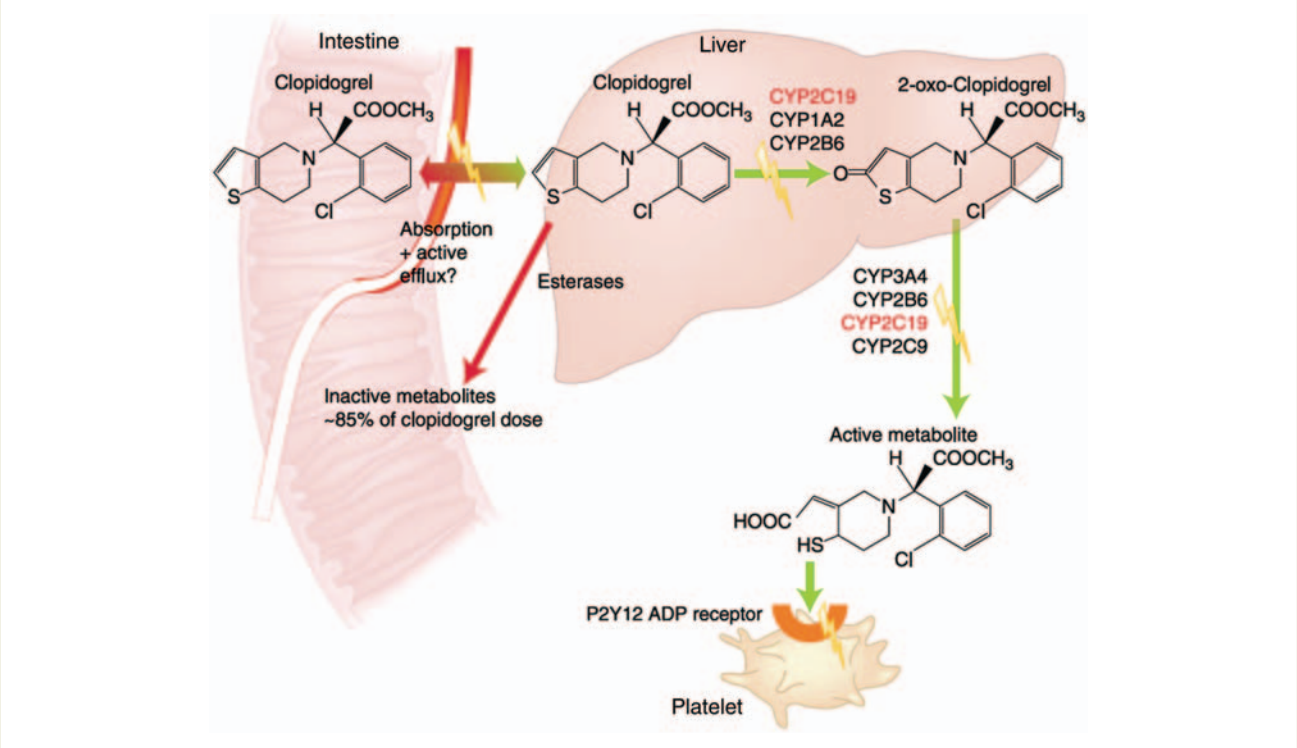

Figure 1 Two-step metabolic activation of clopidogrel. Bioavailability of the pro-drug is determined by intestinal absorption, which might be limited by the efflux pump MDR1 (encoded by *ABCB1*). Subsequently, 85% of the pro-drug is converted into inactive metabolites by ubiquitous esterases. The remaining 15% is converted into a thiol-containing active metabolite through two-step oxidations that involve several cytochrome P450 enzymes. The first oxidative step is catalysed by CYP2C19, CYP1A2 and CYP2B6 isoenzymes, producing the intermediate 2-oxo-clopidogrel. The second step is mediated by CYP3A4, CYP2B6, CYP2C19, and CYP2C9 and yield the bioactive metabolite, the cis-thiol isomer which irreversibly binds to platelet $P2Y_{12}$ receptors inhibits ADP-induced platelet activation.

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Similarly, in a recent study,[15] concomitant use of a PPI in patients receiving DAPT after coronary stenting was not an independent predictor of stent thrombosis although PPI-treated patients had higher mortality. This was explained by the higher risk profile of PPI-treated patients at baseline. Moreover, the worse clinical outcome of PPI-treated patients in large registry studies might be explained by confounding, because the sicker patients more frequently received gastric protection with PPIs. Analysis of a registry of consecutive patients undergoing coronary stenting did not demonstrate an association between the use of PPIs and an increased risk of adverse clinical outcomes after adjusting for potential confounders and a propensity score analysis. Importantly, there was no significant difference between pantoprazole and other PPIs, including omeprazole, on clinical endpoints.[16]

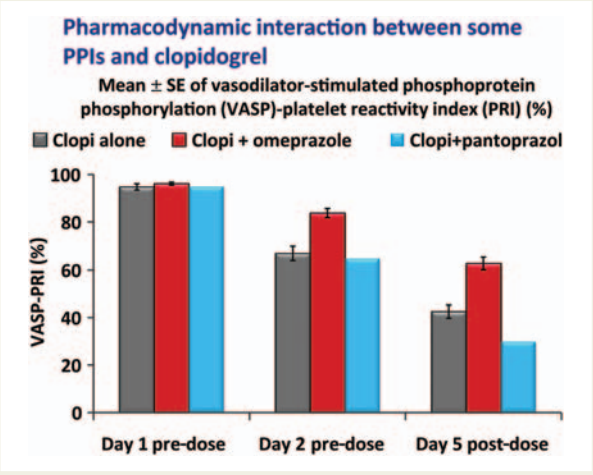

Figure 2 Pharmacodynamic interactions between proton pump inhibitors and clopidogrel: a metabolic drug–drug interaction exists between clopidogrel and omeprazole but not between clopidogrel and pantoprazole.[37]

Studies indicating potential effects of proton pump inhibitors on clinical outcome

Post hoc analyses from large registries suggested an increased rate of MACE when DAPT and PPIs were combined.[18–20] In a meta-analysis, concomitant PPI and DAPT use was associated with an increased risk of cardiovascular events but had no influence on mortality.[21] Another meta-analysis demonstrated that patients on PPIs and DAPT had an increased MACE event rate and mortality. This finding was observed only in high-risk patients.[22] Ho *et al.*[23] demonstrated that concomitant use of clopidogrel and PPIs was associated with an increased risk for recurrent ACS but not for all-cause mortality, while Juurlink *et al.*[19] demonstrated in a population-based nested case–control study that PPIs, except pantoprazole, are associated with re-infarction after treatment for acute myocardial infarction. Furthermore, patients receiving PPIs frequently represent a high-risk co-morbid population: Indeed, patients on concomitant PPI treatment in studies showing adverse effects of PPIs had more frequently co-morbidities including diabetes, renal dysfunction, hypertension, a history of myocardial infarction, and heart failure.[23] Such co-morbidities are obviously associated with worse clinical outcome. In the recent Trilogy study,[24] examining patients with unstable angina or myocardial infarction without ST-segment elevation who were not planned to undergo revascularization, prasugrel did not significantly reduce the frequency of the primary endpoint, when compared with clopidogrel. However, in the subgroup treated with PPI at randomization, the event rate was significantly lower in the prasugrel group

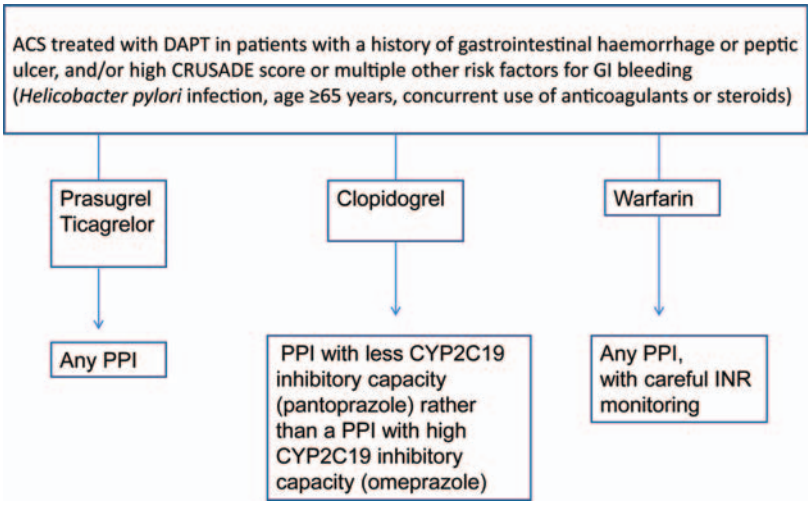

Figure 3 The proton pump inhibitor treatment algorithm in patients with acute coronary syndrome. ACS, acute coronary syndrome; GI, gastrointestinal; PPI, proton pump inhibitor.

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compared with the clopidogrel group (14.6 and 23.8%, respectively, $P < 0.02$).

The study entitled 'Double the Dose of Clopidogrel or Switch to Prasugrel to Antagonize Proton Pump Inhibitor Interaction'(DOSAPI) aimed to determine the optimal therapeutic strategy for patients with CVD chronically treated with clopidogrel 75 mg/day requiring co-administration of a PPI for treatment/prevention of GI ulceration (NCT01175200). The results were recently presented as an abstract. In summary, the effect of a double clopidogrel maintenance dose on platelet inhibition was significantly attenuated by the co-administration of lansoprazole as opposed to prasugrel 10 mg.

Conclusion: clopidogrel and proton pump inhibitors

In the absence of large prospective randomized trials powered for clinical outcome, there is concern that the higher event rates observed for PPI-treated patients in observational studies and meta-analyses might in part be explained by differences in baseline confounding variables.[19,23] In summary, potential negative clinical impacts of some PPIs on the therapeutic efficacy of clopidogrel are still controversial. In view of the pharmacokinetic data and inconclusive clinical evidence, PPIs with weaker inhibition of CYP2C19 are preferred in combination with clopidogrel compared with those with stronger inhibition such as omeprazole.

Prasugrel and proton pump inhibitors

In an open-label, four-period crossover study, the effects of lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel were assessed in healthy subjects given single doses of prasugrel 60 mg and clopidogrel 300 mg with and without concurrent lansoprazole 30 mg q.d. Lansoprazole did not significantly affect the inhibition of platelet aggregation induced by prasugrel, but tended to decrease platelet aggregation by clopidogrel.[25] In another study, the co-administration of lansoprazole with prasugrel decreased the area-under-the-curve (AUC) and peak plasma levels of prasugrel by 25 and 52%, respectively, suggesting an effect of PPI on prasugrel absorption.[26] In a study of 104 high-risk patients with ACS on treatment with prasugrel, the prevalence of high on-treatment platelet reactivity was not significantly affected by the co-administration of PPI with prasugrel.[27]

A retrospective analysis of two trials comparing prasugrel with clopidogrel, the PRINCIPLE-TIMI 44 trial and the TRITON TIMI-38 trial, revealed that: (i) the co-administration of PPI with prasugrel was associated with only a modest reduction in platelet aggregation after one loading dose (60 mg), while co-administration with clopidogrel was associated with reduced platelet aggregation; (ii) no association existed between PPI use and risk of the primary endpoint for patients with ACS treated with clopidogrel [adjusted hazard ratio (HR) 0.94, 95% CI: 0.80–1.11] or prasugrel (1.00, 0.84–1.20).[5] As discussed above, the event rate was significantly lower in the prasugrel group compared with the clopidogrel group in the Trilogy study,[24] in the subgroup treated with PPI at randomization, whereas the main study showed no significant benefit of prasugrel.

Conclusion: prasugrel and proton pump inhibitors

Current data do not support the need to avoid concomitant use of PPIs, when clinically indicated, in patients receiving prasugrel.

Ticagrelor and proton pump inhibitors

CYP2C enzymes are not known to be involved in the metabolism of ticagrelor and clearance is predominantly through CYP3A4.[28] Consequently, it is not expected that PPIs will have any significant pharmacokinetic interaction with ticagrelor.

In the PLATO PLATELET substudy, patients treated with a variety of PPIs in combination with ticagrelor had similar platelet reactivity to patients receiving ticagrelor without PPIs.[29] A *post hoc* analysis of the PLATO study was performed to assess clinical outcomes of patients who did or did not receive a PPI in the two treatment groups.[30] A total of 6539 patients were treated with PPIs at randomization compared with 12 060 patients who were not. Patients treated with a PPI at randomization had higher rates of ischaemic and bleeding events in both the ticagrelor and clopidogrel groups but the treatment effect of ticagrelor compared with clopidogrel was not influenced by PPI use. These data suggest that most likely there were unidentified confounding variables responsible for the increased event rates in PPI-treated patients rather than any adverse effect of PPIs *per se* on the therapeutic efficacy of ticagrelor.[30]

Conclusion: ticagrelor and proton pump inhibitors

There is no evidence of any adverse interaction between ticagrelor and PPIs. The use of PPIs is recommended in ticagrelor-treated patients who are at an increased risk of GI haemorrhage.

Warfarin and proton pump inhibitors: pharmacokinetics and clinical evidence

Proton pump inhibitors have been shown to reduce warfarin metabolism and clearance leading to increased prothrombin time prolongation induced by warfarin.[31,32] In studies of rats, a neutral or basic gastric pH was associated with faster warfarin absorption from the stomach into the plasma pool compared with an acidic pH, whereas low pH was associated with warfarin precipitation on the gastric wall mucosa and with slower plasma absorption.[33] Proton pump inhibitors may thus accelerate warfarin absorption. Proton pump inhibitors and warfarin are both metabolized by hepatic CYP enzymes. Warfarin, acenocoumarol, and phenprocoumon are largely metabolized by CYP2C9.[34,35] In addition to inhibiting CYP2C19, PPIs may also induce CYP2C9 activity.[36] Omeprazole, the oldest drug in the class of PPIs, is reported to have greater potential to alter CYP activity than the newer PPIs, such as pantoprazole.[37,38] Drug interaction studies in humans indicate that pantoprazole does not affect the pharmacokinetics or pharmacodynamics of

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phenprocoumon or warfarin and that the latter does not have relevant pharmacological effects on pantoprazole.[37]

Clinical evidence

In healthy volunteers, a double-blinded randomized cross-over 10-day administration of dexlansoprazole once daily, compared with placebo, did not influence the peak plasma concentration or AUC of warfarin nor INR values following a single dose of warfarin.[35] In 2755 Dutch patients receiving acenocoumarol maintenance treatment, an observational follow-up found a significant hazard of excessive anticoagulation (INR $\geq$6) in those receiving concomitant esomeprazole (HR: 1.99) or lansoprazole (HR: 1.49), and a non-significant hazard for other PPIs, with no detectable effect of the CYP2C19*2 genotype.[39]

Conclusion: warfarin and proton pump inhibitors

Proton pump inhibitors may accelerate absorption of warfarin, and omeprazole may influence vitamin K antagonists (VKAs)' pharmacokinetics more than newer PPIs. In clinical randomized studies, the administration of a single dose of warfarin may have reduced the chance to detect potential PPI effects on INR values. On the other hand, the observational studies that suggest enhanced bleeding risk when PPIs are co-administered with VKAs may be subject to selection biases. At present it is appropriate to monitor cautiously patients on VKA and PPI co-medication.

Dabigatran and proton pump inhibitors: pharmacokinetics and clinical evidence

Dyspepsia is more common during treatment with dabigatran compared with warfarin treatment.[40,41] Dyspepsia-like symptoms were not associated with an increased risk of major bleeding for dabigatran-treated subjects; however, the probability of any bleeding increased slightly.[42] Patients with dyspepsia related to dabigatran can alleviate symptoms by taking the drug with food or a large glass of water or by taking a PPI.[43] Limited data are available on the detailed pharmacokinetics of dabigatran when a PPI is also taken. Co-prescription with a PPI such as pantoprazole may mildly reduce dabigatran exposure and peak concentrations, although these effects do not have any appreciable impact on the efficacy of dabigatran.[44] In the RE-LY trial, concomitant use of PPIs reduced drug exposure by 15%, but no significant impact on efficacy outcomes was observed.[45]

Conclusion: dabigatran and proton pump inhibitors

Proton pump inhibitors may be useful to alleviate dyspepsia related to dabigatran as well as reduce GI bleeding risk. Current evidence indicates that the mild reduction in dabigatran exposure related to PPI usage does not warrant any dose adjustment.

Oral factor Xa inhibitors and proton pump inhibitors

Only potent inhibitors and inducers of CYP3A4 and P-glycoprotein influence the pharmacokinetics of rivaoxaban and apixaban and thus not PPIs.[46–49] Data from the ROCKET-AF trial, comparing rivaoxaban and warfarin in patients with atrial fibrillation, demonstrate the same rate of major bleeding in patients on rivaroxaban treatment compared with warfarin (target INR: 2–3), but a significantly higher rate of GI bleeding was seen with rivaroxaban.[46] At baseline, ~13% of patients were treated with a PPI, and the efficacy and safety of rivaroxaban compared with warfarin were not significantly influenced by this co-medication. In the ARISTOTLE study,[49] apixaban reduced both the primary outcome of stroke or systemic embolism (by 21%) and major bleeding (by 31%) compared with warfarin (with target INR: 2–3) in patients with atrial fibrillation. There was no difference in the risk of GI bleeding. At baseline, ~18.5% of patients received gastric antacid drugs, but no specific data are available for this subpopulation of patients.

Conclusion: oral factor Xa inhibitors and proton pump inhibitors

The administration of PPIs to patients receiving oral FXa inhibitory drugs is unlikely to influence the pharmacokinetics of the drugs and is warranted if an increased risk of GI bleeding is expected.

Summary and clinical implications

Several mechanisms may explain why co-administration of PPIs might reduce the cardiovascular benefits of antithrombotic drugs. Most importantly, PPIs interact with key metabolic enzymes in the liver, such as CYP2C19, which is the principal enzyme responsible for converting clopidogrel into its active metabolite. Another mechanism may be related to the reduced efficacy of ASA and other drugs whose absorption depend on gastric pH. Importantly, such an effect is likely to represent a class effect of PPIs, since all PPIs affect gastric pH to approximately the same extent.[50]

Another scarcely investigated issue is the fact that PPIs, in addition to reducing GI complications, may actually improve cardiovascular outcome by optimizing compliance with antiplatelet therapy.[51] This is important, because even short-term discontinuation of antiplatelet therapy may have ominous prognostic implications.[52]

Although all PPIs are extensively metabolized by hepatic CYP enzymes, there is some variation in the potential for drug interactions because of differences in enzyme inhibition.[50] Omeprazole, the first PPI on the market, may have greater potential to alter CYP activity than newer PPIs, such as pantoprazole,[37,38] yet no major differences between PPIs have been documented with respect to the cardiovascular outcomes.[6,16]

Still, potential interactions between clopidogrel and PPIs are controversial with less firm conclusions on clinical efficacy compared with measurements of platelet function. Pharmacodynamic, but not clinical, studies supports the use of newer PPIs, such as pantoprazole, instead of omeprazole.[13] On the other hand, PPIs may *potentiate* VKA-induced anticoagulation, resulting in increased

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INR values and bleeding risk, most likely due to facilitated gastric absorption of warfarin. Therefore, patients treated with PPIs and VKAs in combination should be carefully monitored, with frequent measurements of INR, when treatment with a PPI is initiated or stopped.

The CRUSADE bleeding score[53] can be used to determine the likelihood of adverse bleeding events in patients who have had non-ST elevation ACS. This validated score can be used as an objective means of stratifying risk of GI bleeding and thus judging the need for GI-protective medications such as PPIs.

Currently available clinical outcomes data are mainly derived from retrospective studies, including registries, and, therefore, confounding cannot be excluded; PPIs may represent a marker of cardiovascular risk rather than the cause of reduced efficacy of antithrombotic drugs. Given the large number of patients treated with PPIs and antithrombotic drugs, even a minor reduction in the cardiovascular benefits of antithrombotic drugs may have substantial clinical impact. Accordingly, more studies are needed to elucidate the clinical importance of the drug interactions described in this position paper.

Concise Summary

No conclusive evidence to discourage PPIs with clopidogrel, but evidence of benefit in terms of bleeding reduction. Therefore, PPIs should be carefully prescribed if indicated.

A PPI with less CYP2C19 inhibitory capacity (e.g. pantoprazole) may represent a more optimal treatment option than a PPI with high CYP2C19 inhibitory capacity (e.g. omeprazole).

No evidence to discourage PPIs with prasugrel or ticagrelor.

Caution with PPI and VKA because of interaction, but PPIs should be given if indicated.

No evidence to discourage PPIs and oral factor Xa inhibitors or dabigatran.

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