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Effects of Proton Pump Inhibitors in Patients Receiving Clopidogrel

Meta-Analysis versus Clinical Practice

With great interest we read the results of a meta-analysis by Kwok et al.[1] about the effects of proton pump inhibitors (PPIs) on adverse gastrointestinal events in patients receiving clopidogrel. The authors analysed the published literature in a field that has received much attention recently, mainly because of a suggested interaction between clopidogrel and PPIs. Of interest, the authors also published some months ago a meta-analysis on the cardiovascular outcomes of the combined use of clopidogrel and PPIs.[2] Based on both their publications, we would like to make two comments on (i) the heterogeneity of included studies; and (ii) the practical advice to physicians regarding the issue of potential interaction in clinical practice.

Kwok et al.[1] identified ten relevant studies that can be characterized by much heterogeneity in the results and also in study design, population, and outcomes. For example, only one study was a randomized clinical trial, two were retrospective cross-sectional studies, two were case-control studies and five were retrospective cohort studies. In their study, the authors acknowledged that heterogeneity in outcome definitions was present and they therefore performed subgroup analyses on separate outcomes. However, we question whether these studies can be pooled at all because of the variations as mentioned above.

Second, the results of both meta-analyses were used to convince both physicians and patients that the combined use of clopidogrel and PPIs is indeed not harmful. They stated that there are no clear differences in cardiovascular outcomes between clopidogrel users with or without a PPI,[2] and that PPIs are associated with a reduction in gastrointestinal bleeding.[1] However, these are all relative risks and mostly based on studies that performed many statistical adjustments. It is important to stress that physicians and patients face absolute risks in clinical practice instead of relative risks. In a recent publication by our group, which was not included by Kwok et al.,[1] we concluded that although there seems to be no clinical interaction, patients using the combination of clopidogrel and a PPI have a 2-fold increased unadjusted risk for cardiovascular outcomes, and even a 5-fold increased unadjusted risk for gastrointestinal outcomes.[3]

In conclusion, physicians should interpret the results of these meta-analyses with caution because it can be disputed whether these studies can be pooled. Based on our results, we conclude that patients using the combination of clopidogrel and a PPI are at an increased (absolute) risk of cardiovascular and gastrointestinal adverse outcomes. This is probably not due to the combined use of these medications but to the fact these patients have an inferior cardiovascular and gastrointestinal risk profile and the occurrence of channelling bias in the published studies.[3]

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The Authors' Reply

In our systematic reviews, we aim to present a comprehensive summary of the available evidence.[1,2] We believe this will help clinicians make up their own minds when confronted with this complex, confusing dilemma. We agree with Ioannidis et al.[3] who state that the aim of meta-analysis should not be limited solely to generating a single pooled estimate, but should extend to examining 'consistency of effects' as well as promoting 'understanding of moderator variables, boundary conditions and generalizability'.

Confronting and exploring heterogeneity in the studies is part and parcel of the meta-analytic process. The forest plots and subgroup analyses in our review serve to promote a deeper grasp of differences in outcomes and participants amongst the studies. Despite the obvious variations in study design and populations, the forest plots do indeed show a consistency of treatment effect in preventing gastrointestinal adverse events with proton pump inhibitors (PPIs) in patients receiving dual antiplatelet therapy.[2] This contrasts sharply with the substantial heterogeneity seen in the forest plots of our meta-analysis of cardiovascular events with clopidogrel and PPIs, and allows us to judge the reliability of the evidence overall.[3]

It is not our intention to evaluate the epidemiology of patients who are exposed to these drugs, and our primary aim is to determine whether the risks of cardiovascular and gastrointestinal events change when patients receiving clopidogrel are given a PPI. Indeed, we agree with the comment by van Oijen and Siersema that the underlying cause of increased adverse cardiovascular events may relate to channelling bias because patients receiving both medications may have unfavourable co-morbidities.

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