CLINICAL CARDIOLOGY

New studies cast doubt on clopidogrel-PPI interaction

MARCH 22, 2010 | Sue Hughes

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ACC Atlanta, GA - Treatment with proton-pump inhibitors (PPIs) did not affect clinical outcomes in patients receiving clopidogrel after PCI in a study presented at last week's American College of Cardiology 2010 Scientific Sessions.

For the study, researchers led by Dr Kishore Harjai (Guthrie Health System, Sayre, PA) reviewed all patients in the Guthrie PCI database who had undergone PCI between 2001 and 2007 and were discharged without having experienced postprocedural MI, target vessel revascularization, or stroke—2646 patients in total. Of these, 28% were prescribed a PPI at discharge. Patients were tracked for cardiac events for the following five years.

The patients had a mean age of 65 years, 69% were male, and 28% diabetic. The PPI group was older and had greater prevalence of female gender, hypertension, diabetes, dyslipidemia, peripheral artery disease, and prior CABG, MI, and PCI than the non-PPI group. But patients given a PPI at discharge were less likely to have presented with an MI and were on a slightly lower aspirin dose than the non-PPI group. The median duration of dual antiplatelet therapy was 13 months.

Results showed no difference in event rates between those prescribed a PPI and those not given a PPI.

Clinical events in PCI patients as to whether they were discharged on a PPI or not

End point	PPI (%)	No PPI (%)
MACE	6.4	6.4
Death	2.8	2.5
MI	3.3	3.0
Death/MI	5.6	5.1
TVR	2.2	3.0
Stent thrombosis	1.8	1.5

MACE=Major adverse cardiovascular events (death, MI, TVR, or stent thrombosis)

TVR=Target vessel revascularization

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A propensity-adjusted multivariable analysis used to adjust for baseline variables showed no significant impact on any of the outcomes of PPI prescription.

Because interactions are reported to be highest for two specific PPIs—omeprazole and esomeprazole—a separate subset analysis including patients prescribed these two agents (12% of the population) was conducted.

Harjai reported that he was "surprised" to find that patients who were on one of these two PPIs at the time of discharge had a lower incidence of major adverse cardiovascular events (MACE) than patients not taking a PPI (3.9% vs 6.1%). Also, target vessel revascularization appeared to be lower in patients taking omeprazole or esomeprazole than those not on a PPI (1% vs 3%), a significant difference. In multivariate analysis, the use of omeprazole or esomeprazole vs no PPIs was actually independently associated with significantly lower MACE rates, with a hazard ratio of 0.51 (95% CI 0.28-0.92).

Harjai concluded: "In patients who have undergone successful PCI and are discharged on aspirin and clopidogrel, the concomitant use of proton-pump inhibitors did not worsen cardiovascular outcomes."

Suggesting possible reasons for a lack of interaction seen with PPIs in this study, Harjai noted that clopidogrel use at six months was greater in the omeprazole/esomeprazole group than in the no-PPI group (78% vs 70%). Someone from the audience commenting on this finding after Harjai's presentation said, "Perhaps this shows that staying on your clopidogrel trumps the PPI interaction."

Harjai also pointed out that this study was conducted in a predominantly white population, which is less likely to carry the CYP2C19 loss-of-function alleles, and he said the relevance of the clopidogrel-PPI interaction may vary across races.

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Also in the news, a retrospective cohort study published in the March 16, 2010 issue of the *Annals of Internal Medicine* suggests that concurrent use of PPIs in patients with serious coronary heart disease treated with clopidogrel is associated with fewer hospitalizations for gastroduodenal bleeding [1].

Using automated data from the Tennessee Medicaid program, Dr Wayne A Ray (Vanderbilt University School of Medicine, Nashville, TN) and colleagues identified 20 596 patients (including 7593 concurrent users of clopidogrel and PPIs) who received clopidogrel between 1999 through 2005 after hospitalization for MI, coronary artery revascularization, or unstable angina.

Concurrent PPI use included pantoprazole in 62% and omeprazole in 9% of patients. Compared with nonusers of PPIs, concurrent PPI users had a 50% lower adjusted incidence of hospitalization for gastroduodenal bleeding (hazard ratio [HR] 0.50; 95% CI 0.39-0.65). PPI use was associated with an absolute reduction of 28.5 (95% CI 11.7-36.9) hospitalizations for gastroduodenal bleeding per 1000 person-years, for those patients at highest risk for bleeding.

For the entire cohort, the HR associated with concurrent PPI use for risk of serious cardiovascular disease was 0.99 (95% CI 0.82-1.19). For the subgroup of patients who had PCI with stenting during the qualifying hospitalization, HR was 1.01 (95% CI 0.76-1.34).

In an accompanying editorial [2], Dr Michael E Griswold (University of Mississippi Medical Center, Jackson) and colleagues observe: "Consistency in the overall results for Ray and colleagues' analyses is comforting and offers a counterpoint to previous studies. Given multiple other studies with conflicting or uncertain results, we believe that the safety of coprescription of PPIs and clopidogrel remains an unanswered question."

- Laurie Barclay

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Sources

1. Ray WA, Murray KT, Griffin MR, et al. Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study. *Ann Intern Med* 2010; 152:337-345. PUBMED
2. Griswold ME, Localio R, and Mulrow C. Propensity score adjustment with multilevel data: Setting your sites on decreasing selection bias. *Ann Intern Med* 2010; 152:393-395. PUBMED

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- Clopidogrel receives boxed warning for reduced benefit in poor metabolizers
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- Cardiologists shocked by new FDA alert on clopidogrel-PPI interaction
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Amit Bhargava

A Desperate Attempt ...
Clinical research seems to have become more of a promotional tool that actual research.
Are we seriously expected to believe that the researchers actually undertook this study with science and medicine and patient-well-being in mind? Who has that kind of funds? Is this how allocation of funds prioritized? Strange indeed.

Are we expected to overlook all the evidence from past prospective and randomized clinical trials in favor of a mild "retrospective" analysis?!?!?!?
And even if one agrees that Pantoprazole may not cause increase of cardiac risk, is use of Clopidogrel so important that we have to restrict our choice of PPI to Pantoprazole? And especially when we have better options in the form of Prasugrel and other reversible inhibitors scheduled for approval?
I think it is high time that practice of medicine takes precedence over retrospective statistical games.

2 of 2 March 24, 2010 02:36 (EDT)

George Muhindo

PPI class effect
This could could give some relief on the use of both PPI and Clopidogrel. I would expect the class effect to be more important than individual PPIs. I hope more studies put this issue at rest.

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