Antibiotic-Coated CVCs Reduce Infection

The Clinical Effectiveness of Central Venous Catheters Treated With Anti-Infective Agents in Preventing Catheter-Related Bloodstream Infections: A Systematic Review.

Hockenhull JC, Dwan KM, et al;
Crit Care Med; 37 (February): 702-712

Anti-infective coated central venous catheters appear to reduce the risk of catheter-related bloodstream infection. Further research is needed to determine if this benefit persists in settings with intensive infection prevention.

Background: There is a pathophysiologic rationale that anti-infective coated central venous catheters (CVCs) could reduce the rate of infection. Previous meta-analyses confirmed that they can reduce the rate of catheter-related bloodstream infection (CRBSI), but substantial new data are now available.

Objective: To determine if anti-infective CVCs prevent CRBSI in hospitalized adults.

Design: Meta-analysis.

Methods: A systematic review of the literature was conducted using recognized methodology. Articles were chosen if they were randomized, controlled trials comparing anti-infective coated CVCs versus standard CVCs or other anti-infective treated catheters.

Results: A total of 38 trials met the specified criteria, and the overall methodological quality was poor. Twenty-seven articles reported CRBSI rates and revealed that anti-infective CVCs significantly reduced the rates of CRBSI compared to standard catheters (OR, 0.49). In subgroup analyses, the benefit persisted regardless of the anti-infective agent used.

Conclusions: This is the fourth but most recent meta-analysis showing that anti-infective CVCs substantially decrease the rates of CRBSI in hospitalized adults. Based on the published research, this also seems to be a potentially cost-saving intervention. The authors provide multiple caveats including concerns over poor methodological quality and the fact that the majority of studies were performed prior to the widespread implementation of intensive infection-control practices (catheter-insertion checklists, sterile technique, etc).

Reviewer's Comments: The data from this meta-analysis seem quite clear: anti-infective CVCs reduce rates of CRBSI. However, 2 important issues remain. First, as the authors point out, most of this research was done prior to better infection control practices, and it is not clear if the benefit will persist; as we say, "more research is needed." Second, the meta-analysis does not comment on increasing bacterial resistance, and it would be good to see over time if this is a potential downside of this intervention. For now, if you are using anti-infective catheters, keep it up. If you're not using them yet, your organization could consider their use, especially if you have high rates of CRBSI despite other preventive measures.

Additional Keywords: Bloodstream Infections

print tag: () Refer to original journal article.
Bound to Help—Lowering Phosphate May Reduce Mortality in Hemodialysis


Phosphorous Binders and Survival on Hemodialysis.

Phosphate binders in patients with kidney disease may confer survival benefits in those with even low-grade hyperphosphatemia.

**Background:** Even low-grade hyperphosphatemia is associated with increased mortality in patients with mild kidney disease, but high phosphate levels are inversely related to survival in patients on hemodialysis. While binders are often prescribed to patients with chronic kidney disease, their impact on reversing hyperphosphatemia’s contribution to mortality is not known.

**Design/Objective:** Prospective propensity score-matched cohort study looking at patients who did and did not receive phosphate binder therapy during the first 90 days of established hemodialysis.

**Participants:** Propensity-matched cohort of 3186 patients who either did or did not receive phosphate binders during the first 90 days of hemodialysis; groups were similar except that the treated group was statistically younger than the untreated group (61 vs 62 years; \( P =0.01 \)).

**Results:** Hazard ratios for mortality showed statistically significant reductions in mortality in patients with all levels of serum phosphate (except for those whose phosphate levels were low at incident dialysis).

**Conclusions:** Phosphate binders appear to confer a mortality benefit for patients initiating hemodialysis, even in those with normal serum phosphate levels. Further confirmatory randomized studies are needed.

**Reviewer’s Comments:** Observational data have shown a strong correlation with serum phosphate levels and risk of mortality in dialysis patients; lower levels of phosphate confer a lower likelihood of death from cardiovascular illness in this group. Whether causality is present (ie, phosphate levels cause the increase in risk, or phosphate levels are seen as a result of some other mechanism, which itself is putative for the increase in risk) is still unclear. This study (which looked at patients who did and did not receive phosphate binder therapy) suggests a 1-year mortality benefit for all patients who are starting on hemodialysis except those with already low phosphate levels. Interestingly, those with normal phosphate levels still had improved mortality when they received binders, suggesting that anyone with a normal or elevated phosphate level should probably be started on phosphate binding therapy if hemodialysis is imminent. The possible explanation on the protective effects of binding therapy is that binders decrease fibroblast growth factor-23 (FGF-23), a hormone thought to help normalize phosphate levels in patients with worsening renal function. Increased FGF-23 levels appear to be independently predictive of mortality (regardless of measured serum phosphate level), and binders appear to reduce FGF-23 through an unknown mechanism. For hospitalists, this means that phosphate binder therapy for patients who are starting or will start dialysis in the near term increasingly appears critical to decrease mortality in this cohort of high-risk patients.

**Additional Keywords:** Hemodialysis
Chlorhexidine Sponges May Reduce CRBSI

Chlorhexidine-Impregnated Sponges and Less Frequent Dressing Changes for Prevention of Catheter-Related Infections in Critically Ill Adults: A Randomized Controlled Trial.
Timsit J-F, Schwebel C, et al:
JAMA; 301 (March 25): 1231-1241

In critically ill patients with central venous catheters, the use of chlorhexidine sponges may reduce rates of CRBSI even when background infection rates are low.

**Background:** There are many proven interventions to prevent catheter-related bloodstream infections (CRBSIs), including the use of insertion checklists, maximal barrier precautions during insertion, preferential use of the subclavian site, and prompt removal of unnecessary catheters. Researchers wanted to determine if other care processes could further decrease CRBSI rates in the intensive care unit (ICU).

**Objective:** To determine if chlorhexidine-impregnated sponges reduce CRBSIs and if there is any hazard to increasing scheduled catheter dressing changes from 3 to 7 days.

**Design:** A 2 x 2 randomized, controlled trial (non-blinded).

**Methods/Participants:** From 2006 to 2008, patients admitted to 7 ICUs in France who required an arterial catheter, central-vein catheter, or both were enrolled. The patients were randomized to chlorhexidine sponges or control dressings and then randomized again (2 x 2 fashion) to either 3- or 7 day scheduled catheter dressing changes. Patients were followed up for the development of major catheter-related infections (either bloodstream infection or presumed sepsis from the catheter without positive blood cultures). In addition, catheter colonization rates were determined for all patients.

**Results:** A total of 1636 patients (mixed medical and surgical) were enrolled, involving 3778 catheters. The use of chlorhexidine-impregnated sponges decreased the rate of major catheter-related infections by 60% (from 1.1% to 0.5% of catheter-days). The number needed to treat to prevent 1 major catheter infection was 117. The use of chlorhexidine dressings was not associated with increased resistance in skin cultures done with removal of the catheter. Only a small number (n=8) of patients developed severe contact dermatitis from the chlorhexidine. Catheter colonization and catheter-related infection rates were similar in the 3- and 7-day scheduled change groups (7-day changes were non-inferior compared to 3-day changes).

**Conclusions:** Overall, this was a well-done multi-center study with generalizable results: in critically ill patients, chlorhexidine sponges can reduce catheter-related infections, and there is very little downside to their use. In a simple calculation, the authors suggest that the cost for chlorhexidine sponges to prevent 1 major catheter infection is $2106 compared to the $8000 to $28,000 it may cost to manage 1 catheter-related infection. In addition, the authors state that the interval between dressing changes for catheters can safely be extended from 3 to 7 days.

**Reviewer's Comments:** There is an increasing emphasis on reducing the rates of catheter-related infections in ICUs, and this well-done study provides another potential intervention. It would be nice to see this trial replicated in ICUs that employ other proven interventions to prevent CRBSIs to see if the effect persists. Still, for those who work on quality improvement in the ICU, this should stimulate an active discussion about purchasing the chlorhexidine sponges and potentially extending the days between scheduled dressing changes.

**Additional Keywords:** Chlorhexidine
Extra--Extra--Do Not Give Extra Aspirin!

Aspirin to Prevent Cardiovascular Disease: The Association of Aspirin Dose and Clopidogrel With Thrombosis and Bleeding.

Steinhubl SR, Bhatt DL, et al:
Ann Intern Med; 150 (March 17): 379-386

Aspirin 81 mg per day probably confers the safest balance between hemorrhage and prevention of cardiovascular disease.

**Background:** The ideal dose of aspirin for primary and secondary prevention of cardiovascular illness is not known.

**Objective:** (1) To evaluate the data from the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial to see if complications of aspirin therapy (specifically major or minor hemorrhage) were associated with aspirin dose; and (2) to determine if prevention of the primary end points of first myocardial infarction, death from a cardiovascular cause, or stroke were likewise associated with aspirin dose.

**Design:** Post-hoc analysis from CHARISMA, a multicenter, double-blind, placebo-controlled, randomized trial looking at aspirin alone or in combination with clopidogrel for primary prevention of cardiovascular disease. Stratification of patients for this study was based on doses of aspirin that were <100 mg, 100 mg, or >100 mg daily. The aspirin dose was determined by the clinician and was not randomized.

**Results:** Patients receiving higher-dose aspirin (>100 mg daily) tended to have worse coronary disease or cardiac risk factors, less diabetes, and prior history of antiplatelet therapy exposure. Patients given clopidogrel who also had aspirin doses >100 mg had a statistically significant increased risk of the primary end points of cardiovascular death and stroke, but not myocardial infarction. Doses of >100 mg of aspirin a day revealed a trend toward a higher frequency of primary end points. Bleeding tended toward an increase linearly with dose. Higher-dose aspirin also appeared to result in higher risks for primary end points for all demographic characteristics, with significant harm, particularly in diabetic patients (unadjusted HR).

**Conclusions:** Aspirin doses of 81 mg may strike a perfect balance of benefit without increasing harm, especially when added to clopidogrel.

**Reviewer's Comments:** This is a strongly worded study. Unfortunately, not only was it a post-hoc analysis, but also, the key hypothesis was not specifically tested in the original CHARISMA study design. Randomization in the original study was based on whether patients received clopidogrel, but all patients in CHARISMA were on aspirin on enrollment. What varied was the dose of aspirin, which was entirely up to the clinician seeing the patient. Selection bias (ie, sicker patients receiving higher-dose aspirin) is a real possibility, especially in light of the increased likelihood of primary end points (stroke, cardiovascular disease, or cardiovascular death) in patients who received dual antiplatelet therapy (aspirin doses >100 mg plus clopidogrel 75 mg). Major bleeds were more common with higher-dose aspirin or dual therapy as would be expected. The most important lesson that this study offers, however, is that it calls into question the "more is better" philosophy that seems to be increasing in patients treated for secondary prevention of cardiovascular disease. A prospective study that answers this question definitively is needed and would also need to address the risks of platelet resistance with higher-dose aspirin (not covered here).

**Additional Keywords:** Hemorrhage Risk

**print tag:** () Refer to original journal article.
Drug-Eluting Stents--May Be OK to Stop Thienopyridine But Continue Aspirin

Safety of Short-Term Discontinuation of Antiplatelet Therapy in Patients With Drug-Eluting Stents.


In patients with drug-eluting stents, short-term discontinuation of thienopyridine may be safe as long as aspirin is continued.

**Background:** Current guidelines recommend dual anti-platelet therapy (aspirin plus thienopyridine) for at least 12 months after placement of a drug-eluting stent. If patients have acute bleeding or require urgent surgery, the safety of short-term discontinuation of anti-platelet therapy is unclear.

**Objective:** To examine the safety of short-term anti-platelet discontinuation in patients with drug-eluting stents.

**Design:** Systematic literature review.

**Methods:** The authors identified all reported cases of late stent thrombosis (>30 days) in patients with drug-eluting stents for which detailed clinical information was available. Cases were categorized based on anti-platelet therapy at the time of stent thrombosis: (1) patients who stopped both treatments; (2) patients who stopped aspirin after already stopping thienopyridine; (3) patients who stopped thienopyridine treatment but continued aspirin; and (4) patients who did not stop dual anti-platelet therapy. The authors examined the median time to the event in the 4 groups.

**Results:** The literature from 2001 to 2008 was reviewed, and 161 cases of late stent thrombosis were identified from 84 articles. If patients stopped both agents, the median time to the event was 7 days. Similarly, if patients had previously stopped thienopyridine and subsequently stopped aspirin, the median time to thrombosis was 7 days. If aspirin was continued while thienopyridine was stopped, the median time to the event was 122 days.

**Conclusions:** Although limited by the observational methodology (looking only at cases reported in the literature), the data seem clear—patients with drug-eluting stents who stop their thienopyridine but continue their aspirin have a substantially longer time to stent thrombosis than patients who stop both. The authors state that, for patients who need to undergo procedures and are at risk for bleeding, the aspirin should be continued if at all possible.

**Reviewer's Comments:** A small number of events and not the randomized-controlled trial we might want, but yet this study could change or at least affect current practice. When faced with an individual patient with a drug-eluting stent on dual anti-platelet therapy who needs an urgent procedure or has active bleeding, these data help guide us. Preferably, we should continue aspirin if at all possible. The authors outline a strategy for patients with drug-eluting stents who need to undergo a procedure but have substantial bleeding risks. Ideally, the procedure should be delayed a year, but if that is not possible, thienopyridine could be stopped 5 days before the procedure and restarted 1 day postoperatively. If a patient is such high risk that both agents should be stopped, they should be stopped no sooner than 5 days before surgery and restarted as soon as possible after surgery.

**Additional Keywords:** Anti-Platelet Therapy

**print tag:** () Refer to original journal article.
HIT, Boom, Crash--Heparin and Thrombocytopenia Are Bad Combination

Evaluation and Management of Thrombocytopenia and Suspected Heparin-Induced Thrombocytopenia in Hospitalized Patients: The Complications After Thrombocytopenia Caused by Heparin (CATCH) Registry.
Crespo EM, Oliveira GBF, et al:
Am Heart J; 157 (April): 651-657

Immediate recognition of heparin-induced thrombocytopenia could mean a reduction in mortality. Delays in recognition, however, mean complications and death.

Background: Hospital-acquired thrombocytopenia and heparin-induced thrombocytopenia (HIT) carry elevated risks of morbidity and mortality.

Objective: To identify (1) the frequency of thrombocytopenia in hospitalized patients, (2) patients with suspected or confirmed HIT, and (3) complications directly related to these conditions.

Design/Methods: The Complications After Thrombocytopenia Caused by Heparin (CATCH) registry is a prospective observational study that involved 48 U.S. hospitals. A total of 3536 patients were identified over a 14-month period who had thrombocytopenia. Patients were stratified into 3 different categories: prolonged heparin stratum (PHS) (any heparin use 96 hours), cardiac catheterization unit (CCU) stratum, and HIT stratum (any patient on whom HIT serological studies were performed). Patients could belong to 1, 2, or all 3 strata. Thrombocytopenia was defined as a quantitative platelet count (PC) of <150,000 or a 50% drop in PC. HIT was suspected for any patient who underwent testing for HIT; HIT was confirmed by a positive HIT test plus hematologic consultation. A thromboembolic complication (TEC) was identified as any thrombosis occurring after hospitalization.

Results: Patients in the PHS developed thrombocytopenia 36.4% of the time and had an odds ratio (OR) of 1.5 (CI, 1.2 to 1.9) for TEC or death. Even when patients were at high risk for HIT as a diagnosis, clinicians’ awareness of the diagnosis was uncommon, delayed (taking 1 day to recognize after the patient became thrombocytopenic), and frequently did not prompt clinicians to change from heparin to a direct thrombin inhibitor (DTI). When patients underwent evaluation for HIT, the diagnosis was confirmed in 46.7% of the PHS and 31.4% of the CCU.

Conclusions: Thrombocytopenia was independently associated with worse outcomes. Often, when patients were at risk for the diagnosis of HIT, they were not actively treated for that possibility with a DTI. The delayed diagnosis resulted in morbidity and mortality. Once the diagnosis was clinically suspected, HIT was confirmed in almost one-third to one-half of cases.

Reviewer’s Comments: This sobering study underscores the very high toll of thrombocytopenia in hospitalized patients. Worse, the study demonstrated that HIT diagnosis and appropriate workup were surmised and performed rarely with devastating outcomes. Unfortunately, currently available testing is either exceptionally sensitive but not specific (heparin-PF4 ELISA), or labor intensive and not immediately available (serotonin release assay), so the pretest suspicion of HIT is relegated to the 4 Ts (degree of Thrombocytopenia, Timing of the development of thrombocytopenia, TEC, and oTher etiologies seeming more or less likely than HIT: a scoring system proposed by Warkentin et al. (Chest 2004; 126 [suppl 3] that offers a ballpark high, medium, or low probability of a patient having HIT). DTI therapy can be life-saving but also dangerous if used indiscriminately. Better tests are needed to un-muddy this morass of iatrogenic disease.

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Sorry, There Are No Great Screening Tests for OSA

A Meta-Analysis of Clinical Screening Tests for Obstructive Sleep Apnea.

Ramachandran SK, Josephs LA:
Anesthesiology; 110 (April): 928-939

Currently there are no easy, simple, accurate screening tests for OSA which can consistently identify patients with OSA.

**Background:** The prevalence of obstructive sleep apnea (OSA) is on the rise. OSA increases the risk for multiple diseases, including hypertension, stroke, pulmonary hypertension, and venous thromboembolism. Overnight polysomnography is the gold standard diagnostic test but is not practical in most clinical settings.

**Objective:** To determine the most accurate clinical screening test to identify patients with OSA.

**Design:** Meta-analysis.

**Methods:** A systematic review of the literature was conducted using recognized methodology. Articles were chosen that measured the accuracy of clinical screening tests (including questionnaires, clinical scoring systems, and/or prediction equations) compared to overnight polysomnography. Statistical analysis was used to determine sensitivity, specificity, and likelihood ratios for the different screening tools.

**Results:** A total of 26 articles (6794 total patients) met criteria for the final analysis, of which 8 examined questionnaires and 18 described clinical prediction tests. Overall, methodological quality varied substantially. In general, no single questionnaire or clinical prediction tool had adequate sensitivity to be used as a screening tool, as all of these methods had unacceptable false-negative rates. The 2 most accurate questionnaires were the Berlin questionnaire and the Sleep Disorders Questionnaire. Morphometry (the Kushida index, which involves measuring aspects of the head and mouth) and clinical cephalometry (involving clinical features and skull x-ray) were the most accurate prediction rules.

**Conclusions:** A robust and complex meta-analysis reveals that the current screening tools for OSA do not have adequate test characteristics to be used with confidence, especially in the perioperative setting. Clinicians should consider using the most accurate questionnaires or prediction rules if needed. More research is necessary to establish a quick, easy, and accurate screening tool for OSA.

**Reviewer's Comments:** Unfortunately, this thorough and well-done meta-analysis reveals that there is no single simple screening test for OSA. For hospitalists who would like to have a tool at their disposal, I would recommend the Berlin questionnaire—a simple, 1-page list of questions about snoring and daytime sleepiness. Although not a perfect test, it is excellent at identifying patients with severe OSA and is probably the quickest and easiest to use while we await further research.

**Additional Keywords:** Clinical Prediction Rules

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CABG Trumps PCI for Multi-Vessel and Left Main CAD

Percutaneous Coronary Intervention Versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease.

Serruys PW, Morice M-C, et al:

*N Engl J Med*; 360 (March 5): 961-972

In spite of the increasing superiority of drug-eluting stents for CAD, CABG still offers superior revascularization strategy.

**Background:** Drug-eluting stents (DES) have been shown to be superior to bare metal stents in single-vessel coronary artery disease (CAD). However, randomized trials of DES versus coronary artery bypass grafting (CABG) for multi-vessel and left main CAD have not been performed to date.

**Design/Methods:** The Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial is a prospective, clinical study that enrolled all comers (4337 patients) over a 25-month period ending in April 2007 who had triple-vessel CAD, isolated left main CAD, or both. After exclusion, 1800 patients from the United States and Europe were randomized to CABG (897 patients) or DES (paclitaxel stents, 903 patients). The 2 groups were very similar demographically; patients who received CABG had more complex lesions on catheterization, however.

**Results:** At 12 months, the primary end point of adverse cardiac or cerebrovascular events occurred in 12.4% of the CABG group and 17.8% of the DES group. The number needed to treat (NNT) in the CABG group to prevent the primary outcome was 19 versus 60 in the percutaneous coronary intervention (PCI) group. The NNT was 14 to prevent the need for revascularization, 71 for myocardial infarction, and 119 for death. Statistically significant higher rates of amiodarone use occurred in the CABG group (12.8% vs 1.5%). Statins, beta-blockers, ACE inhibitors, calcium channel blockers, and angiotensin receptor blockers were used more frequently in the DES group, while warfarin, non-thienopyridine antiplatelet drugs, and H2 blockers were used more commonly in the CABG group. Stroke occurred more often in the CABG group (2.2% vs 0.6%).

**Conclusions:** CABG remains the standard of care for triple-vessel and left main CAD.

**Reviewer’s Comments:** CABG may be an older treatment for coronary disease, but thus far nothing has been shown to be superior to this 40-year-old surgical technique for triple-vessel or left main CAD. There is obviously a lot of interest in creating minimally invasive techniques that pack the same punch as a technique that results in sternotomy and an extended hospital stay. However, even with drug-eluting stents in the picture, CABG has proven to be superior in preventing the need for revascularization, occurrence of MI, and incidence of death. Unfortunately, CABG still carries a higher risk of stroke (occurring in >1 in 50 CABGs), but has an NNT of only 19 to prevent the primary outcome of adverse cardiac or cerebrovascular events at 1 year (compared with an NNT of 60 for those randomized to PCI with DES).

**Additional Keywords:** Intervention

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Low Sugar May Not Be So Nice in ICU

*Intensive Versus Conventional Glucose Control in Critically Ill Patients.*

NICE-SUGAR Study Investigators:

*N Engl J Med;* 360 (March 26): 1283-1297

In a mixed medical-surgical ICU, intensive insulin therapy increased mortality compared with conventional control.

**Background:** Multiple large, randomized, controlled trials and meta-analyses have yielded conflicting results on optimal blood sugar management in the intensive care unit (ICU) setting.

**Objective:** To compare intensive glucose control to conventional glucose control in a mixed medical/surgical ICU.

**Design:** Randomized, controlled trial.

**Methods/Participants:** Adult patients admitted to 42 ICUs in multiple countries who were expected to require ICU care for >3 days were randomized. Those in the intensive glucose control group were managed with an insulin infusion with a goal blood sugar of 81 to 108 mg/dL. Those in the conventional control group had a target blood sugar of 180 mg/dL. The primary end point was death at 90 days.

**Results:** In total, 6104 patients were randomized, with two-thirds being medical and one-third being surgical patients. The overall average blood sugar was 118 mg/dL in the intensive control group and 145 mg/dL in the conventional group. Patients in the intensive control group had a higher mortality at 90 days than those in the conventional control group (27.5% vs 24.9%; *P* =0.02). The number needed to harm was 38. In subgroup analyses, there was no significant difference in the outcome in medical versus surgical patients or in those with or without diabetes. Severe hypoglycemia (glucose <40 mg/dL) was much more common in the intensive control group.

**Conclusions:** In a large, international, randomized, controlled trial, intensive glucose control in a mixed medical/surgical ICU increased overall mortality. The authors postulate that the increased mortality may be from hypoglycemia, insulin exposure, or other unknown factors.

**Reviewer's Comments:** Since the famous Van den Berghe trial published in the *New England Journal of Medicine* in 2001, intensive glucose control in the ICU has been widely investigated and hotly debated. Recent meta-analyses found no benefit to intensive glucose control in the ICU, but this is the first well-done randomized, controlled trial to show harm from the intervention. In reflection, there is probably enough evidence to recommend against intensive glucose control in any critically ill patient. Future research may help identify specific groups of patients who may benefit from this intervention but, at this time, there is no clear benefit and there may even be harm. What is the optimal blood sugar in ICU patients? We don't know the exact number, but it seems that a goal of 150 mg/dL may be the best balance between the risks seen here and the known risks of hyperglycemia.

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Platelet Inhibition or PPI--One or the Other, But Not Both

Risk of Adverse Outcomes Associated With Concomitant Use of Clopidogrel and Proton Pump Inhibitors Following Acute Coronary Syndrome.

Ho PM, Maddox TM, et al: JAMA; 301 (March 4): 937-944

PPIs interfere with the effectiveness of clopidogrel and increase the risk of adverse outcomes in patients after acute coronary syndrome.

**Background:** Proton pump inhibitors (PPIs) have the potential to interfere with the effect of clopidogrel and could thus increase the risk of recurrence of symptomatic coronary artery disease, especially in patients who are prescribed both drugs after an episode of acute coronary syndrome (ACS).

**Design:** Retrospective cohort study of all patients with ACS discharged from a Veterans Administration (VA) hospital during a 27-month period ending in January 2006.

**Methods:** Primary outcomes were all-cause mortality or rehospitalization for ACS following discharge from an index hospitalization for ACS. Patients were classified as receiving a prescription for clopidogrel alone or in combination with a PPI from the VA pharmacy.

**Results:** A total of 8205 patients with ACS were discharged on clopidogrel. Almost two-thirds of the patients (63.9%) received a simultaneous prescription of a PPI (omeprazole, 60%; another PPI, 40%) at discharge. The primary end point of death or recurrent ACS was reached in 29.8% of patients who received both clopidogrel and a PPI compared to 20.8% in the clopidogrel-alone cohort (adjusted OR, 1.25; 95% CI, 1.11 to 1.41). Mortality was similar in both groups. Patients with ACS who were not discharged on clopidogrel but were taking a PPI did not have a risk of the primary end point. Time appeared to increase the risk of an end point in those taking both clopidogrel and PPI.

**Conclusions:** A combination of PPI and clopidogrel use in patients discharged with ACS resulted in a higher rate of recurrent ACS. The combination of both medications should be prescribed with caution.

**Reviewer's Comments:** A lot of caveats compromise the impact of these conclusions, not the least of which is that the patients in the 2 cohorts were very dissimilar. Note that patients prescribed both clopidogrel and a PPI were statistically significantly older; had higher rates of diabetes, prior myocardial infarction, coronary artery bypass grafting, congestive heart failure, renal disease, prior clopidogrel use, cancer, chronic obstructive pulmonary disease, liver disease, and dementia; had higher TIMI risk scores; and had lower ejection fractions. That the patients prescribed a PPI and clopidogrel generally looked sicker based on all of the above demographics and also ended up getting sicker is no surprise. This study drew big headlines, however, because there is ample evidence that an interference of clopidogrel's antiplatelet effect does exist from the concomitant use of PPIs (everything from in vitro data showing decreased platelet inhibition of clopidogrel in the presence of a PPI to theoretical risks due to the inhibition of enzymatic activation of active clopidogrel metabolites through CYP2C19). Given the precarious possibilities of an increased risk of in-stent thrombosis from premature clopidogrel discontinuation, particularly in drug-eluting stents, and the relative commonality of PPI availability and use, it is probably important that patients be counseled to avoid taking a PPI without a clearcut indication.

**Additional Keywords:** Clopidogrel

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