CLINICAL PHARMACOLOGY UPDATES

Abstracts related to latest developments in Clinical Pharmacology & Therapeutics

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BMJ

High potency statin use found to be associated with acute kidney injury

Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases.

Dormuth CR, Hemmelgarn BR, Paterson JM, James MT, Teare GF, Raymond CB, Lafrance JP, Levy A, Garg AX, Ernst P; Canadian Network for Observational Drug Effect Studies (CNODES).

OBJECTIVE:

To quantify an association between acute kidney injury and use of high potency statins versus low potency statins.

DESIGN:

Retrospective observational analysis of administrative databases, using nine population based cohort studies and meta-analysis. We performed as treated analyses in each database with a nested case-control design. Rate ratios for different durations of current and past statin exposure to high potency or low potency statins were estimated using conditional logistic regression. Ratios were adjusted for confounding by highdimensional propensity scores. Meta-analytic methods estimated overall effects across participating sites.

SETTING:

Seven Canadian provinces and two databases in the United Kingdom and the United States.

PARTICIPANTS:

2 067 639 patients aged 40 years or older and newly treated with statins between 1 January 1997 and 30 April 2008. Each person hospitalized for acute kidney injury was matched with ten controls.

INTERVENTION:

A dispensing event was new if no cholesterol lowering drug or niacin prescription was dispensed in the previous year. High potencystatin treatment was defined as ≥10 mg rosuvastatin, ≥20 mg atorvastatin, and ≥40 mg simvastatin; all other statin treatments were defined as lowpotency. Statin potency groups were further divided into cohorts with or without chronic kidney disease.

MAIN OUTCOME MEASURE:

Relative hospitalization rates for acute kidney injury.

RESULTS:

Of more than two million statin users (2 008 003 with non-chronic kidney disease; 59 636 with chronic kidney disease), patients with similar propensity scores were comparable on measured characteristics. Within 120 days of current treatment, there were 4691 hospitalizations foracute kidney injury in patients with non-chronic kidney injury, and 1896 hospitalizations in those with chronic kidney injury. In patients with non-chronic kidney disease, current users of high potency statins were 34% more likely to be hospitalized with acute kidney injury within 120 days after starting treatment (fixed effect rate ratio 1.34, 95% confidence interval 1.25 to 1.43). Users of high potency statins with chronic kidney disease did not have as large an increase in admission rate (1.10, 0.99 to 1.23). χ(2) tests for heterogeneity confirmed that the observed association was robust across participating sites.

CONCLUSIONS:

Use of high potency statins is associated with an increased rate of diagnosis for acute kidney injury in hospital admissions compared with low potency statins. The effect seems to be strongest in the first 120 days after initiation of statin treatment.

(BMJ. 2013 Mar 18;346:f880.)

JAMA®
The Journal of the American Medical Association

Time to say good-bye to Hydroxyethyl starch in volume resuscitation.

Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patientsrequiring volume resuscitation: a systematic review and meta-analysis.

Zarychanski R, Abou-Setta AM, Turgeon AF, Houston BL, McIntyre L, Marshall JC, Fergusson DA.

IMPORTANCE:

Hydroxyethyl starch is commonly used for volume resuscitation yet has been associated with serious adverse events, including acutekidney injury and death. Clinical trials of hydroxyethyl starch are conflicting. Moreover, multiple trials from one investigator have been retracted because of scientific misconduct.

OBJECTIVES:

To evaluate the association of hydroxyethyl starch use with mortality and acute kidney injury.

DATA SOURCES:

Randomized controlled trials from MEDLINE, EMBASE, CENTRAL, Global Health, HealthStar, Scopus, Web of Science, the International Clinical Trials Registry Platform (inception to October 2012), reference lists of relevant articles, and gray literature.

STUDY SELECTION:

Two reviewers independently identified randomized controlled trials
comparing hydroxyethyl starch with other resuscitationfluids
in critically ill patients receiving acute volume resuscitation.

DATA EXTRACTION:

Two reviewers independently extracted trial-level data including population characteristics, interventions, outcomes, and funding sources. Risk of bias was assessed using the risk of bias tool; the strength of evidence was adjudicated using the GRADE methodology.

RESULTS:

We included 38 eligible trials comparing hydroxyethyl starch to crystalloids, albumin, or gelatin. The majority of trials were categorized as having an unclear risk or high risk of bias. For the
10,880 patients in studies contributing mortality data, the risk ratio (RR) for death
among patientsrandomized to receive hydroxyethyl starch was 1.07 (95% CI, 1.00 to 1.14; I2, 0%; absolute risk [AR], 1.20%; 95% CI, -0.26% to 2.66%). This summary effect measure included results from 7 trials performed by an investigator whose subsequent research had been retracted because of scientific misconduct. When we excluded these 7 trials that involved
590 patients, hydroxyethyl starch was found to be associated with increasedmortality among
10,290 patients (RR, 1.09; 95% CI, 1.02 to 1.17; I2, 0%; AR, 1.51%; 95% CI, 0.02% to 3.00%), increased renal failure among 8725patients (RR, 1.27; 95% CI, 1.09 to 1.47; I2, 26%; AR, 5.45%; 95% CI, 0.44% to 10.47%), and increased use of renal replacement therapy among 9258 patients (RR, 1.32; 95% CI, 1.15 to 1.50; I2, 0%; AR, 3.12%; 95% CI, 0.47% to 5.78%). CONCLUSION AND RELEVANCE:
In critically illpatients requiring acute volume resuscitation, use of hydroxyethyl starch compared with other resuscitation solutions was not associated with a decrease in mortality. Moreover, after exclusion of 7 trials performed by an investigator whose research has been retracted because of scientific

misconduct, hydroxyethyl starch was associated with a significant increased risk
of mortality and acute kidney injury. Clinical use of hydroxyethylstarch for acute volume resuscitation is not warranted due to serious safety concerns.

(JAMA. 2013 Feb 20;309(7):678-88.)

Clopidogrel safe during hip surgery?

Safety of clopidogrel in hip fracture surgery.

Feely MA, Mabry TM, Lohse CM, Sems SA, Mauck KF.

OBJECTIVE:

To compare postoperative outcomes of hip fracture surgery in patients who were and were not taking clopidogrel at the time of surgery.

PATIENTS AND METHODS:

Using the Rochester Epidemiology Project database, we performed a population-based, retrospective cohort study comparing patients who were and were not taking clopidogrel at the time of hip fracture surgery between January 1, 1996, and June 30, 2010. Primary outcomes were perioperative bleeding and mortality. Secondary outcomes were perioperative thrombotic events.

RESULTS:

During the study period, 40 residents of Olmsted County, Minnesota (median age, 83 years), who were taking clopidogrel underwent hip fracture repair. These 40 patients were matched 2:1 with 80 control patients (median age, 84 years). The groups were similar in age, sex, American Society of Anesthesiologists score, type of surgical procedure, and use of deep venous thrombosis prophylaxis. The mean time from admission to surgery was less than 36 hours for each cohort. Perioperative bleeding complications and mortality were not significantly different between patientswho were and were not taking clopidogrel at the time of hip fracture surgery. Combined bleeding outcome criteria was met in 48% of the clopidogrel cohort and 45% of the control cohort (relative risk, 1.06; 95% CI, 0.70-1.58; P=.80). One-year mortality was 28% in the clopidogrel cohort and 29% in the control cohort (hazard ratio, 1.33; 95% CI, 0.84-2.12; P=.23).

CONCLUSION:

Although the small sample size precludes making a definitive conclusion, we found no evidence that prompt surgical treatment of hip fracture in patients taking clopidogrel compromises perioperative outcomes.

(Mayo Clin Proc. 2013 Feb;88(2):149-56.)