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Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Clopidogrel Hypersensitivity — Mechanism and Treatment

By Andrew J. Boyle, MBBS, PhD
Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco

Dr. Boyle reports no financial relationships relevant to this field of study.

SOURCE: Cheema AN, et al. Characterization of clopidogrel hypersensitivity reactions and management with oral steroids without clopidogrel discontinuation. *J Am Coll Cardiol* 2011;58:1445-1454.

Clopidogrel therapy is indicated for many patients with cardiovascular disease, particularly those who have had percutaneous coronary intervention (PCI). An uncommon side effect of clopidogrel therapy is cutaneous hypersensitivity, and its optimal treatment strategy remains unknown. Should one discontinue the drug, change it to another thienopyridine, or continue it? Premature discontinuation of dual antiplatelet therapy in patients who have undergone PCI may result in stent thrombosis. Thus, Cheema and colleagues assessed patients with possible clopidogrel hypersensitivity reaction to determine the mechanism and test a treatment strategy that would allow uninterrupted continuation of clopidogrel therapy.

The authors screened 84 patients at a single center who were referred with suspected clopidogrel hypersensitivity and determined that 62 had definite or probable clopidogrel hypersensitivity, representing a prevalence of 1.6% of their patients undergoing PCI. There was no significant baseline clinical or demographic difference between those presenting with clopidogrel hypersensitivity and those who did not, with the one exception that drug-eluting stent use was higher in those presenting with clopidogrel hypersensitivity (71% vs 56%, $P = 0.02$). They described three patterns of clinical presentation.

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Clinical Cardiology [ALERT]

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Group 1 (79%) presented with generalized pruritic exanthemous rash predominantly affecting the trunk ± limbs. Group 2 (16%) presented with a localized rash, either focal or symmetrical, affecting the face, neck, back, hand, or axilla. Group 3 (5%) had angioedema with tongue/lip swelling or generalized urticaria. Time to onset of symptoms was 5 days for groups 1 and 2, and 1 day for group 3.

Patients with hypersensitivity had a mild increase in neutrophil count and a mild decrease in lymphocyte count from baseline, but no eosiniphilia. There was also a mild increase in platelet count, but impedance aggregometry showed therapeutic inhibition of aggregation in 90% of those tested. Skin testing for hypersensitivity was performed in 42 patients (68%). Skin prick testing did not elicit a reaction in any patient, and intradermal testing was only positive in those with angioedema. However, patch testing was positive in 81%. Cross-reactivity with ticlopidine was present in 24% and prasugrel in 17%.

All patients were treated with a 3-week tapering course of oral prednisone starting at 30 mg twice per day for 5 days followed by a decrease of 5 mg/day every 3 days for 15 days. Diphenhydramine 25 mg to 50 mg every 6 to 8 hours was prescribed for pruritus if present. Clopidogrel was continued uninterrupted in all patients. The hypersensitivity resolved completely in all but one patient in whom a mild localized rash continued and he was able to tolerate it with topical steroids until clopidogrel therapy was ceased and the rash resolved. Four patients actually had a second course of clopidogrel therapy, and again developed hypersensitivity that was successfully treated with this regimen. During a median follow-up of 576 days, there was one death, one myocardial infarction, and six target vessel revascularization procedures. The authors conclude that clopidogrel hypersensitivity is manifested as a generalized exanthema and is caused by a lymphocyte-mediated delayed hypersensitivity in most patients and that it can be managed with a short course of steroids without clopidogrel discontinuation. Allergenic cross-reactivity with ticlopidine or prasugrel is present in a significant number of patients.

■ COMMENTARY

This study by Cheema and colleagues has systematically described and defined the hypersensitivity reaction to clopidogrel. It is uncommon, occurring in 1.6% of patients, but with such a large number of patients taking clopidogrel, this represents a clinical problem that all of us will encounter. The vast majority (groups 1 and 2, 95%) had lymphocyte-mediated delayed type IV hypersensitivity, and only 5% had immediate type hypersensitivity. Interestingly, skin prick and intradermal testing had little response. Patch testing was more strongly associated with the clinical diagnosis; however, some patients with a clinical diagnosis also had negative patch testing. This underscores the difficulty of clinically diagnosing clopidogrel hypersensitivity, and makes the role of allergen testing unclear. These patients have often undergone PCI with administration of radiographic contrast dye, and thus separating contrast allergy from clopidogrel allergy is challenging. Furthermore, patients may have been exposed to other medications for the first time, such as statins, during the hospitalization for PCI, making the diagnosis even more unclear. The authors take a thorough clinical approach, including exposure to all new medications, timing in response to clopidogrel, and the type of reaction. Despite the inherent limitations of diagnosing this type of hypersensitivity, we can be reassured that their patients all tolerated continuation of clopidogrel with a short course of steroids. It may be that some of these patients did not have a true clopidogrel allergy, but in a similar clinical scenario, a trial of steroid taper with continuation of clopidogrel is a reasonable approach that seemed to yield excellent clinical results in this study. ■

ABSTRACT & COMMENTARY

Risk of Perioperative MI in Patients with Stents Undergoing Surgery

By Andrew J. Boyle, MBBS, PhD
Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco

SOURCE: Albaladejo P, et al. Non-cardiac surgery in patients with coronary stents: The RECO study. *Heart* 2011;97:1566-1572.

Patients who have had percutaneous coronary intervention (PCI) with either bare metal stents (BMS) or drug-eluting stents (DES) require dual antiplatelet therapy until the stent struts are endothelialized. However, patients who have had prior PCI often need to undergo surgery. There is thought to be less risk of perioperative myocardial infarction (MI) when surgery is performed late after PCI; however, the precise risk and the optimal management of dual antiplatelet therapy remains unknown. Albaladejo and colleagues performed a multicenter, prospective, observational study in 47 centers in France to address this question.

They enrolled 1134 patients undergoing non-cardiac surgery (including diagnostic endoscopy). DES were used in 55%, BMS in 32%, and unknown stent type in 13%. DES use was associated with younger age (67 ± 11 vs 70 ± 10 years, $P < 0.001$), higher prevalence of diabetes (33% vs 22%, $P < 0.001$), and higher number of stents per patient (2.3 ± 1.4 vs 1.6 ± 0.9, $P < 0.001$). There were no differences between DES and BMS patients in terms of preoperative antiplatelet therapy and the level of risk of the surgery. Continuation or discontinuation of antiplatelet therapy was not prespecified, but was at the discretion of the physician at the preoperative visit.

The primary endpoints were any major adverse cardiac and cerebrovascular events (MACCE) or hemorrhagic complication. MACCE was defined as MI, stent thrombosis, stroke, heart failure, significant arrhythmia, or cardiogenic shock. Bleeding was considered major if it resulted in death, fall in hemoglobin ≥ 2g/dL, transfusion, extra surgical or medical treatment, or if it was in a critical location (intracerebral, intraspinal, intraocular, pericardial retroperitoneal). All other bleeding was considered minor. All-cause mortality was a secondary endpoint.

MACCE occurred in 10.9%, typically around 3.3 ± 3.8 days after surgery, and was predominantly MI. Patients who experienced MACCE were older (71 ± 10 vs 68 ± 11 years, $P < 0.01$) and more likely to have heart failure (19.4% vs 8.4%, $P < 0.001$) and a high American Society of Anesthesiologists classification. There was no difference in gender or type of stent. Independent predictors of MACCE were: complete interruption of antiplatelet therapy for > 5 days preoperatively (odds ratio [OR] 2.11, $P < 0.01$), preoperative hemoglobin < 10 g/dL (OR 3.0, $P = 0.016$), creatinine clearance < 30 mL/min (OR 3.5, $P < 0.01$), urgent surgery (OR 3.1, $P < 0.001$), and high-risk surgery (OR 3.6, $P < 0.001$). Importantly, the time interval between stenting and surgery was not predictive of MACCE. Patients who experienced MACCE had a 14.5% mortality. Stent thrombosis (definite, probable, or possible) occurred in 2.5% when the delay from PCI to surgery was < 12 months, and 1.3% when the interval was > 12 months. The rate of stent thrombosis did not differ between DES and BMS. The mortality associated with stent thrombosis was 29%.

Bleeding complications occurred in 9.5%, typically occurred 5.3 ± 5.3 days after surgery, and were at the surgical site in 85%. Patients who experienced bleeding complications had lower body weight (75.7 ± 14.1 kg vs 78.4 ± 14.6 kg, $P = 0.04$) and a higher rate of congestive heart failure (16.7 vs 8.4%, $P = 0.001$). Independent predictors of bleeding complications were: preoperative hemoglobin < 10 g/dL (OR 2.6, $P < 0.05$), creatinine clearance 30-60 mL/min (OR 1.96, $P < 0.01$), high-risk surgery (OR 3.3, $P < 0.001$), and time from PCI to surgery < 3 months (OR 2.9, $P = 0.001$). Patients who experienced bleeding complications had a 12% mortality.

The authors conclude that patients with coronary stents undergoing an invasive procedure are at high risk of perioperative cardiovascular and bleeding complications, and that these are associated with a high mortality. Interruption of antiplatelet therapy > 5 days prior to an invasive procedure increased the rate of MACCE but did not change risk of bleeding.

■ COMMENTARY

Current guidelines recommend postponing

elective surgery for at least 6 weeks after BMS and 12 months after DES. This study is one of the largest series published to date and one of the few that reports both ischemic (MACCE) and bleeding complications together. Several factors are noteworthy in this dataset. Firstly, preoperative anemia and renal impairment predict both bleeding and ischemic complications. This may be because anemia and renal impairment are dangerous per se, or because they are indicators of severe underlying disease that predisposes to post-operative complications. In this series, high-risk surgery was a predictor of postoperative events as well, whereas in other series this has not been the case. One reason for this may be that this cohort included diagnostic endoscopy, which is not really a surgery and should have little bleeding and ischemic risk. This may introduce bias by lowering the rate of complications in the "low risk" category here because some of the low-risk surgeries were not actually surgeries. Many other series do not include endoscopy.

The type of stent (DES vs BMS) had no effect on MACCE. This contradicts the hype and dogma that stent thrombosis is a great danger with DES. In fact, this has been borne out in other series as well. Importantly, this cohort was recruited starting in 2007, when media attention on DES stent thrombosis was at fever pitch. Consequently, many DES patients in this cohort underwent surgery on dual antiplatelet therapy, which may have reduced their perioperative MACCE rate. It is also possible that the high bleeding rate in this study also may have been due to continuation of dual antiplatelet therapy throughout the operative period in many patients. This study does not inform us how to manage dual antiplatelet therapy in every patient with coronary stents prior to every surgery. We must continue to individualize treatment based on the surgical bleeding risk vs the risk of peri-operative MI. But it would seem prudent in light of these data, and other series showing similar findings, that antiplatelet therapy not be ceased for more than 5 days preoperatively. ■

ABSTRACT & COMMENTARY

Clinical Impact of EP Device Infections

By John P. DiMarco, MD, PhD
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Dr. DiMarco does research for Medtronic, is a consultant for Medtronic, Novartis, and St. Jude, and is a speaker for Boston Scientific.

SOURCE: Sohail MR, et al. Mortality and cost associated with cardiovascular implantable electronic device infections. *Arch Intern Med* 2011; Sept 12. [Epub ahead of print]

This paper describes the mortality and economic costs of infections associated with pacemakers and implantable defibrillators (ICDs) in Medicare recipients. The authors analyzed Medicare administrative data for inpatient admissions that involved implantation, replacement, removal, or revision of a pacemaker, an ICD, and cardiac resynchronization therapy pacemakers (CRT-P) and ICDs (CRT-D). Patients who also underwent other major cardiac procedures on the same admission were excluded. Procedures performed solely on an outpatient basis were also excluded. Four primary endpoints were assessed: admission mortality, intermediate term (current plus subsequent four quarters) mortality, admission length of stay (LOS), and admission cost. Endpoints were adjusted for age, gender, race, and 28 additional comorbidity measures. Costs were normalized using Medicare Inpatient Prospective Payment System rates.

Out of a total of 200,219 device-related Medicare admissions, there were 5817 (2.9%) that involved a device infection. Adjusted admission mortality ratios (mortality with vs without infection) for specific device types were 5.9 for pacemakers, 6.4 for ICDs, 4.8 for CRT-D devices, and 7.7 for CRT-P devices. Intermediate-term adjusted mortality ratios were also higher: 2.1 for pacemakers, 1.6 for ICDs, and 1.6 for CRT-D devices. The adjusted increments in intermediate-term total mortality ranged from 8.7% to 15.2%. The standardized adjusted total and incremental LOS were 15.5 and 9.4 days for pacemakers, 18.8 and 12.7 days for ICDs, 17.1 and 11.8 days for CRT-D devices, and 24.3 and 18.2 days for CRT-P devices.

Most admissions analyzed involved only one device implant, whether an infection occurred, and, therefore, there was usually only one device cost per patient. Despite this, infection raised the cost of the admission by 1.4-1.8 fold. Adjusted incremental costs with infection were $16,208 for pacemakers,

$14,360 for CRT-P devices, $15,893 for ICDs, and $16,498 for CRT-D systems. Intensive care and pharmacy costs accounted for most of the added expense with infection.

The authors concluded that pacemaker and ICD infections are associated with significant increases in admission, intermediate-term mortality, and hospital costs. They recommended that physicians managing these patients consider different management strategies (e.g., earlier device removal) that might shorten intensive care and overall LOS and reduce costs. The increased admission mortality is understandable due to the complications related to the infection, but the incremental increases in mortality after discharge require further study.

■ COMMENTARY

Standard and resynchronization pacemakers and ICDs, commonly grouped together as cardiac implantable electrical devices (CIEDs), are now used in millions of patients in the United States and throughout the world. The functionality and component reliability of CIEDs has improved dramatically in the last 20 years. CIED infection, however, remains a dreaded complication of device therapy and the absolute incidence of and the individual risk for a CIED infection appears to be increasing.

With the exception of minor wound infection in which the pocket is not directly involved, the recommended approach to most CIED infections is total removal of all involved hardware. With newly implanted (< 6 months post implant) systems, this is a relatively straightforward procedure that most implanting physicians can carry out. However, if any part of the system has been in place for a longer time, extraction can become more difficult and specialized training, facilities, and techniques are required. As CIED recipients live longer and undergo multiple repeat procedures for replacements and upgrades, the number of infections is sure to continue to rise. This paper, which reviews recent Medicare administrative data, highlights the clinical and economic importance of improving our approach to CIED infection. The authors clearly show that CIED infection substantially increases short- and intermediate-term mortality and results in a substantial total economic burden. The primary emphasis should be to prevent infection, but new strategies to identify infections early, stabilize patients quickly, and reestablish needed long-term treatment after the infection is cleared will also be important.

Although not specifically discussed by the authors in this paper, the reader should also note that intermediate-term mortality after any CIED procedure was quite high even in the absence of infection. Adjusted mortality rates during the index and four subsequent quarters ranged from 17.8% to 20.1%. These data suggest that CIEDs are often used in near end-of-life situations. Reducing inappropriate device prescriptions for patients with little prospect for an improved, meaningful survival would also be economically beneficial. ■

ABSTRACT & COMMENTARY

Incidence of Constrictive Pericarditis

By Michael H. Crawford, MD, Editor

SOURCE: Imazio M, et al. Risk of constrictive pericarditis after acute pericarditis. *Circulation* 2011;124:1270-1275.

Since there is a lack of prospective data on the frequency of which constrictive pericarditis (CP) develops after acute pericarditis (AP), this group of investigators from Torino, Italy, conducted such a study. From 2000 until 2008 all cases of first AP were followed and evaluated for the development of CP at 1 month, 3 months, and every 6 months thereafter for a median follow-up of 72 months (range, 24-120). Follow-up evaluation included ECG, blood tests, and echocardiograms. The study included 500 consecutive patients with AP; 416 (83%) had viral or idiopathic AP; 36 (7%) had pericardial injury (e.g., surgery) or connective tissue disease; 25 (5%) had neoplastic; 20 (4%) had tuberculosis; and three (0.6%) had purulent. Recurrent AP was the most frequent subsequent adverse event (30%), followed by tamponade (4%). Transient CP was detected by echocardiography in 15% with resolution in 3 months. Effusive CP was seen in 1%. CP developed in nine (1.8%): two had viral or idiopathic AP and seven had other etiologies of AP. Purulent and tuberculosis patients had the highest incidence of CP. All the patients with permanent CP were confirmed by surgery. Pathology showed normal pericardial thickness in 11% of the permanent CP patients. Those who

developed CP were more likely than those who did not to have fever (67% vs 15%), incessant course (56% vs 7%), non-idiopathic/viral etiology (78% vs 16%), large pericardial effusion (67% vs 9%), tamponade (44% vs 4%), and nonsteroidal anti-inflammatory drug failure (67% vs 19%), all $P < 0.002$. There was a trend toward more steroid use and a lower use of colchicine in those who developed CP, but these differences were not statistically significant. The authors concluded that CP is a rare complication of viral or idiopathic AP, but is more common with other etiologies such as bacterial pericarditis.

■ COMMENTARY

The important message of this prospective study is that we can reassure patients with viral or idiopathic pericarditis that the likelihood of them developing CP is very low. Thus, intense follow-up after the first 6 months is unwarranted in these patients. Also, recurrent AP in viral/idiopathic patients has a good prognosis.

Other etiologies are another matter. Tuberculosis has a higher rate of CP ranging from 5%-60% depending on the study and the stage of the disease. The relatively low rate of CP in tuberculosis in this study may be because it was infrequent or the follow-up was not long enough. Other etiologies, such as uremic and neoplastic, may have low rates because the patients do not survive long enough to develop CP. The described risk factors for CP may be a guide for whom to follow more closely. Most useful would be an incessant course, a large effusion, tamponade, or failure of anti-inflammatory therapy. Also of interest clinically was the observation that about 10% of those who developed CP had normal pericardial thickness on pathology and imaging. Thus, normal pericardial thickness does not exclude CP. Another interesting finding was that effusive CP was unusual, occurring in about 1% of the AP patients. Finally, transient CP was observed in 15% and it resolved in 3 months. Thus, surgery should not be considered until 3 months have passed with CP.

The study did not address drug therapy, although there was a trend for more CP in those treated with steroids. Also, the study confirms the use of colchicine as first-line therapy since lower colchicine use correlated with development of CP. ■

ABSTRACT & COMMENTARY

Left Atrial Pressure Estimation by Echo Doppler in Heart Failure Patients

By Michael H. Crawford, MD, Editor

SOURCES: Ritzema JL, et al. Serial doppler echocardiography and tissue doppler imaging in the detection of elevated directly measured left atrial pressure in ambulant subjects with chronic heart failure. *JACC Cardiovasc Imaging* 2011;4:927-934. Nagueh SF. Noninvasive estimation of LV filling pressures in heart failure and reduced ejection fraction: Revisited and verified. *JACC Cardiovasc Imaging* 2011;4:935-937.

The management of chronic heart failure patients would benefit from an accurate noninvasive way to estimate left atrial pressure (LAP). This study from New Zealand sought to determine the accuracy of Doppler echocardiography for this purpose. They studied 15 chronic outpatient heart failure patients who had a permanently implanted direct LAP measuring device (Heart POD, St. Jude Medical) by serial Doppler echo studies and compared several measures of diastolic function to the LAP. The 15 patients had 60 simultaneous echo and LAP measurements with a median of four per patient over 1 year. Patients with atrial fibrillation, stenotic valve disease, hypertrophic cardiomyopathy, moderate or more semilunar valve regurgitation, valve prostheses, or significant pericardial effusion were excluded. Baseline mean LAP was 17 mmHg and mean ejection fraction by echo was 32%. There was a large range of LAP measurements (5 to 39 mmHg). An LAP > 15 mmHg was seen in 52% and in 35% it was > 20 mmHg. Reliable tissue Doppler studies were obtained in > 80% and pulmonary venous flow was acquired in > 70%. The ratio of mitral E velocity to tissue Doppler mitral annular velocity (E/e'), averaging the medial and lateral early annular velocities (e'), was the best predictor of LAP > 15 mmHg: sensitivity 84, specificity 96, positive-predictive valve 95, negative predictive value 85, and accuracy 90. The average and the medial value were better than the lateral value for (e'). An average E/e' value of > 14, medial

> 15, or a lateral of > 12 had the best receiver operating curves. All three measures were superior to all the other echo Doppler parameters evaluated, with an area under the receiver operating curve of > 0.90. The authors concluded that the E/e' ratio can reliably predict LAP in chronic heart failure patients over time.

■ COMMENTARY

There has been considerable controversy regarding the use of left ventricular (LV) filling parameters to estimate LAP. Early studies based in the cardiac catheterization laboratory established a close relation between E/e' and mean LAP (pulmonary capillary wedge pressure) but less so with LV end diastolic pressure. Whether it would be accurate over time in ambulatory patients with various medication changes, progressive disease, and devices such as resynchronization was addressed by this study. They found the best accuracy with an average of the medial and lateral annular tissue Doppler velocities for determining e', but the medial velocity performed almost as well. A medial E/e' > 15 was associated with LAP > 15 mmHg (88% accuracy vs 90% by the average). With medial E/e' >18, LAP > 15 mmHg was almost certain and an E/e' < 12 essentially ruled out a LAP > 15 mmHg. The detection of a LAP > 20 mmHg was less robust with an accuracy of 79% for the medial E/e' > 15. The higher the LAP the less linear was the association with E/e'; perhaps because most patients with LAP > 25 mmHg had moderate mitral regurgitation which tends to elevate E out of proportion to any reduction in e'. The measurement of E/e' was also highly reproducible; intraobserver variability for E was 4% and e' 7%. Thus, E/e' should be an accurate method for detecting when patients have LAPs in the decompensated range.

Of course there are some pitfalls to this measurement. Not all patients will have technically adequate studies to make these measurements. For example, patients with rapid heart rates will have fusion of the mitral E and A velocities and significant mitral regurgitation will influence the E velocity as discussed above. Also, tissue Doppler velocity is not as reliable for assessing LAP in normals, patients with mitral valve disease, LBBB, paced rhythms, and constrictive pericarditis. In addition, there are few data in patients with hypertrophic cardiomyopathy and pericardial effusion. With these caveats in mind, Doppler echo measurements of E/e' should be a useful estimate of LAP in acute and chronic heart failure patients, no matter how they are treated. ■

CME Questions

1. Cutaneous hypersensitivity to clopidogrel can be treated effectively with:
a. clopidogrel withdrawal alone.
b. continuation plus Benadryl.
c. continuation plus prednisone.
d. continuation plus topical corticosteroids.

2. The optimal time for cessation of dual antiplatelet therapy before non-cardiac surgery is:
a. 48 hours.
b. 5 days.
c. 1 week.
d. 2 weeks.

3. Implanted EP device infections increase:
a. hospital mortality.
b. post-hospital discharge mortality.
c. hospital costs.
d. All of the above

4. Constrictive pericarditis most frequently follows:
a. viral pericarditis.
b. tuberculosis pericarditis.
c. uremic pericarditis.
d. Dressler's syndrome.

5. The best echo Doppler measurement for estimating left atrial pressure in heart failure is:
a. pulmonary vein flow reversal with atrial systole.
b. mitral E/A velocity ratio.
c. mitral inflow E velocity, tissue Doppler e' velocity ratio.
d. mitral E velocity.

CME Objectives

Upon completion of this educational activity, participants should be able to:

- discuss the most current information related to cardiac illness and the treatment of cardiac disease;
- explain the advantages and disadvantages, as well as possible complications of interventions to treat cardiac illness;
- discuss the advantages, disadvantages, and cost-effectiveness of new and traditional diagnostic tests in the treatment of cardiac illness; and
- discuss current data regarding outpatient care of cardiac patients.

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Medication Poisonings Are Increasing in Children

In this issue: Medication poisonings in children; rosuvastatin vs atorvastatin for atherosclerosis; saw palmetto for prostate symptoms; using atypical antipsychotics for off-label indications in adults; and FDA actions.

More medications, more poisonings

Medication poisonings among young children have increased in frequency in recent years despite safety measures to prevent them, according to a new study from *Pediatrics*. Researchers used patient records of more than 450,000 children 5 years old or younger from 2001-2008. The rate of poisoning increased by about a third during this time span compared to the prior decade. Child self-exposure was responsible 95% of the time with ingestion of prescription drugs causing more than half of the poisonings and more than 70% of significant injuries. The most dangerous drugs were opioids, sedative-hypnotics, and cardiovascular agents. The authors conclude that the number of children visiting emergency departments after medication exposure is increasing, with the majority of ingestions caused by children finding and ingesting medications by themselves. They suggest that efforts at poison-proofing homes with young children "may be a good, but insufficient, strategy." They further suggest that the increase in poisonings is in part due to the rise in number of medications in the environments of young children, with the number of adults taking medications, especially opioid medications, rising dramatically in the last 10 years. Other possible explanations include more siblings on medications, especially ADHD meds, as well as exposure to grandparents' homes where child-proofing may not be as rigorous. They further conclude that current preventive efforts are inadequate and new measures, such as efforts targeting home medication safety (including storage of medications and child-resistant closures) and repackaging (such as blister packs and flow restrictors on liquid medications), should be considered. (*Pediatrics* published online September 16, 2011.) ■

Rosuvastatin no better than atorvastatin

Rosuvastatin is no better than atorvastatin in slowing progression of coronary atheroma, according to AstraZeneca, the manufacturer of rosuvastatin and sponsor of the study. Researchers compared rosuvastatin 40 mg to atorvastatin 80 mg in the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin vs Atorvastatin (SATURN) trial. The primary efficacy endpoint was change from baseline in percent atheroma volume in a targeted coronary artery as assessed by intravascular ultrasound. After 104 weeks of treatment in some 1300 patients, there was a numerical greater reduction in favor of rosuvastatin, but the reduction did not reach statistical significance (astrazeneca.com/Media/Press-releases). The full results will be presented at the American Heart Association meeting in

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

November. The results come as a blow to the manufacturer of rosuvastatin (Crestor) who had hoped to gain a marketing advantage before the introduction of low-cost generic atorvastatin into the market, slated for December. ■

Saw palmetto for prostate symptoms

Saw palmetto is ineffective for treating lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH), even at higher doses, according to a new study. Previous studies have shown no benefit from saw palmetto, but researchers in this current study set out to test the efficacy of 2-3 times the normal daily dose on men over the age of 45 with significant LUTS. The main outcome was the difference in American Urologic Association Symptom Index score between baseline and week 72. Both saw palmetto and placebo led to an improvement in symptoms with a favorability toward placebo regardless of the dose of saw palmetto. Doses tested were a single 320 mg tablet per day with dose escalation to 2, then 3, tablets per day. The authors conclude that increasing doses of saw palmetto root extract did not lower LUTS more than placebo in men with BPH (*JAMA* 2011;306:1344-1351). This is the second rigorously controlled trial after the Saw Palmetto Treatment for Enlarged Prostates study (*N Engl J Med* 2006;354:557-566) to show no benefit from the supplement on LUTS in men with BPH. ■

Off-label use of atypical antipsychotics

Controversy surrounds the use of atypical antipsychotics for off-label indications in adults, especially the elderly with dementia. A new meta-analysis reviews the evidence of efficacy of these drugs for various off-label uses. Of more than 12,000 studies considered, 162 were included in the analysis. Drugs reviewed included risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), aripiprazole (Abilify), ziprasidone (Geodon), asenapine (Saphris), iloperidone (Fanapt), and paliperidone (Invega). For elderly patients with dementia, a small but statistically significant improvement in symptoms such as psychosis, mood alterations, and aggression were seen with aripiprazole, olanzapine, and risperidone. For generalized anxiety disorder, quetiapine was the most effective, while for obsessive-compulsive disorder, risperidone was associated with a 3.9 greater likelihood of favorable response, compared with placebo when used with antidepressants. There was no benefit seen with any of the drugs used in treating eating disorders, substance abuse, or insomnia, and only marginal benefit in personality disorders or posttraumatic stress disorder. All of these drugs have a boxed warning regarding increased mortality in elderly patients with dementia and increased risk of suicidality. Increased risk of death was seen in elderly patients with a number needed to harm (NNH) of 87. Also noted was increased risk of stroke, especially with risperidone (NNH = 53), extraparametal symptoms (NNH = 10 for olanzepine, NNH = 20 for risperidone), and urinary tract symptoms (NNH range = 16-36). Weight gain was also a problem in non-elderly adults, particularly with olanzapine (incidence of more than 40%), while akathisia was more common with aripiprazole. Other common side effects included fatigue, sedation, and extrapyramidal symptoms. (*JAMA* 2011;306:1359-1369). ■

FDA actions

The FDA has issued a warning regarding the potential for arrhythmia associated with the antinausea drug ondansetron (Zofran). The drug should be avoided in patients with QT prolongation as they are at particular risk of developing torsade de pointes. Ondansetron should be used with caution in patients with congestive heart failure, bradyarrhythmias, those predisposed to low potassium or magnesium, and in those taking drugs that cause QT prolongation. These patients should have electrocardiogram monitoring if ondansetron is indicated. The FDA is requiring new labeling changes to reflect these warnings.

The FDA is reminding physicians and patients that epinephrine inhaler (Primatene Mist), the only over-the-counter inhaler for asthma, will be removed from the market on December 31. The withdrawal is due to an international ban on chlorofluorocarbon propellant. The FDA is recommending that physicians ask their patients with asthma if they use Primatene Mist and talk to them about prescription alternatives.

The FDA has approved infliximab (Remicade) to treat moderate-to-severe ulcerative colitis (UC) in children 6 years and older who have had inadequate response to conventional therapy. The drug is already approved for adults with UC. The approval was based on a randomized, open-label trial of 60 children ages 6 to 17 with moderate-to-severe UC. The drug carries a boxed warning for serious infections and cancer. Infliximab is manufactured by Janssen Biotech. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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How Often Do You Really Have to See Patients on Warfarin?

Source: Rose AJ, et al. *Chest* 2011;140: 359-365.

IT HAS BEEN CUSTOMARY TO ASK PATIENTS on warfarin, once controlled and stable, to return on a monthly basis for recheck. This interval has been based on tradition, rather than any firm scientific basis. Frequent visits in otherwise stable patients present a significant burden of time, cost, inconvenience, and even the opportunity for overzealous "fine tuning," and may not enhance the amount of time spent in the therapeutic range. It would, therefore, be desirable to have better insight into whether stable patients might be safely allowed longer intervals without risking either toxicity of supratherapeutic warfarin dose, or thrombotic risk of subtherapeutic levels.

Rose et al report on data obtained from a large population of persons receiving anticoagulation from the U.S. Veterans hospital system (n = 104,451). By comparing the interval between an in-range international normalized ratio (INR) and the next INR measurement with the likelihood of being in the therapeutic range on follow-up visit, they were able to discern that the first two visits after a therapeutic INR measurement are time sensitive: that is, extending the time until next follow-up beyond 4 weeks was associated with progressively greater likelihood of finding an out-of-range INR at the next visit. This relationship, however, was not seen in persons with consistently in-range INR readings, i.e., if a patient had experienced three consecutive INR in-range visits, extending the length of time until next follow-up was not associated with greater likelihood of an out-of-range INR.

At the current time, another trial comparing monthly with quarterly INR monitoring is underway. Pending results from that trial, this evidence suggests that until patients have at least three consecutive stable INR measurements, the traditional 4-week return policy is best. After that, a longer interval until next INR measurement is acceptable, but has only been studied as far out as 38 days. ■

Replacing Carbohydrates with Nuts in the Diabetic Diet

Source: Jenkins DJ, et al. *Diabetes Care* 2011;34:1706-1711.

CONSUMPTION OF NUTS, ESPECIALLY WALnuts, has been associated with favorable health outcomes. For diabetics, maintenance of a healthy body weight, reduction of high-glycemic index foods, and lipid modulation through diet are each a potentially critical consideration. Because nuts have significant fat content, there has been concern that were diabetics to substitute nuts for other carbohydrates, a detrimental impact on either weight or lipids might be seen.

Jenkins et al randomized type 2 diabetics (n = 117) to substitute carbohydrates in their diets in one of three ways: mixed nut replacement, muffin replacement, or half-and-half nuts plus muffins. Based on energy requirements calculated with the Harris-Benedict equation, participants were asked to substitute their prescribed replacement supplement for whatever carbohydrate had previously comprised an equal caloric proportion of their diet. For instance, a person requiring 1600-2400 kcal/d was given 475 kcal of a replacement supplement. The trial lasted 3 months. The nut mix consisted of almonds, pistachios, walnuts, pecans, hazelnuts, peanuts, cashews, and macadamias. The muffin was whole wheat, with no sugar added. The absolute kcal content of the supplement was the same whether administered as nuts, muffin, or mixed.

The group supplemented with nuts enjoyed a statistically significant A1c reduction of 0.21%, but no significant A1c change was seen in the other two groups. Similarly, cholesterol, LDL, and cholesterol:HDL ratios were most favorably affected by the nut supplement. Nut replacement for carbohydrates has favorable effects in type 2 diabetes. ■

Hypertensive Emergency: The Prognostic Value of Elevated Troponins

Source: Afonso L, et al. *J Clin Hypertens* 2011;13:551-556.

HYPERTENSIVE EMERGENCY, CHARACTERized by marked elevation of blood pressure (typically > 180/120) associated with signs of target organ damage, is a common presenting issue in emergency departments. Since cardiac toxicity may be one of the signs of target organ damage, troponins are often measured, even though there may be no symptoms of myocardial ischemia or signs on EKG. Especially when troponins are measured in acute coronary syndromes, they have strong prognostic value. Whether they provide any discriminative value in per-

sons with hypertensive emergency has not been previously well-studied.

A retrospective analysis was done on all patients with hypertensive emergency seen at two inner-city population hospitals in Detroit (n = 567) in whom troponins had been measured. Among this group, one-third demonstrated troponin elevation (mean peak = 4.06 ng/mL). However, follow-up of these patients did not find that the presence or degree of elevation of troponins predicted subsequent mortality over the next 3 years.

Elevation of troponins is commonly seen in patients with hypertensive emergency, but in the absence of an acute coronary syndrome, is not prognostically valuable. ■

Is Mercury Really a Bad Guy in CV Disease?

Source: Houston MC. *J Clin Hypertens* 2011;13:621-627.

Mercury has a bad rap sheet: it decreases cellular oxidative defenses, increases oxidative stress, reduces the effectiveness of metalloenzymes, induces mitochondrial dysfunction, increases vascular inflammation, and worsens endothelial function. In addition, mercury toxicity is associated with increased carotid intima-media thickness. Omega-3 fatty acids, as contained in fish, can antagonize some of the detrimental effects of mercury. However, fish in the diet are also currently the major source of human exposure to mercury.

There is no known biologic or physiologic role of mercury in the body, hence it must be regarded as a toxin.

Observational data generally, but inconsistently, find an association between tissue levels of mercury and cardiovascular disease. For hypertension particularly, numerous different populations have found a relationship between tissue mercury levels and blood pressure (systolic, diastolic, and pulse pressure). Chronic mercury toxicity may be inexpensively measured by a 24-hour urine mercury level. The author does not include mention of any trials indicating favorable effects achieved by modulation of mercury, although selenium, by complexing with mercury, may mollify some of its toxic effects. ■

Long-Term Azithromycin for Prophylaxis of COPD Exacerbations

Source: Albert RK, et al. *N Engl J Med* 2011;365:689-698.

For many patients with moderate-severe chronic obstructive pulmonary disease, acute exacerbations (AECOPD) are highly problematic. For hospitalized AECOPD, the mortality rate is approximately 10%; loss of pulmonary function that typically accompanies an AECOPD is usually not regained; mortality during the year following an AECOPD is increased. Hence, reduction and/or delay of AECOPD is an important goal.

Macrolides are often the antimicrobial agents chosen to treat AECOPD. This trial in patients with COPD randomized subjects to azithromycin 250 mg qd (n = 570) or placebo (n = 572) for 1 year. The patient's background COPD treatments were unchanged. The primary outcome of the trial was time to first AECOPD. Secondary outcomes included QOL, and scores on the St. Georges Respiratory Questionnaire. More than three-fourths of study participants were receiving background inhaled steroids, long-acting beta agonists, and/or long-acting anticholinergics during the trial.

Azithromycin prophylaxis was associated with a statistically significant prolongation of time to first AECOPD, as well as a 27% relative-risk reduction in the frequency of AECOPD. The St. George's Respiratory Questionnaire scores were improved significantly more in the azithromycin group. One adverse effect analyzed was affect on hearing function: Azithromycin was associated with a slightly higher incidence of hearing decrement than placebo. However, improvements in hearing noted on follow-up occurred whether the drug was discontinued, suggesting that perhaps the incidence of hearing decrements were initially overestimated.

Azithromycin prophylaxis may provide important benefits in COPD, especially for persons with frequent AECOPD. ■

Unintended Medication Consequences of Hospital Admission

Source: Bell CM, et al. *JAMA* 2011;306: 840-847.

Most hospitalizations have a focused agenda: heart failure, pneumonia, acute trauma, etc. It is not at all difficult to conceive that as a consequence of intensified focus on one or more often acute problems, attention can be drawn away from the issues of lesser acuity, such as maintenance medications for dyslipidemia, dysglycemia, or thyroid disease. Sometimes because of discontinuity between persons involved in the patient's hospitalization and outpatient providers, inadvertent discontinuation of necessary chronic medications can be overlooked.

Using the database of patients in Ontario, Canada (n = 396,380; age 66 and older), Bell et al examined prescription data to see whether chronic medications from five different classes experienced discontinuation subsequent to hospitalization. The five classes were: statins, antiplatelet/anticoagulants, levothyroxine, respiratory inhalers, and gastric acid inhibitors.

Hospitalization was associated with an increased incidence of discontinuation of all five classes of agents. Hospitalization, which included ICU admission, was disproportionately likely to be associated with chronic medication discontinuation. Equally distressing, the data demonstrated an increased risk for death or subsequent hospitalization in persons who discontinued their chronic medications. Gaps in continuity of care are of significant consequence to hospitalized patients. ■

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