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Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Avoid NSAIDs after Myocardial Infarction

By Andrew J. Boyle, MBBS, PhD
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Dr. Boyle reports no financial relationship relevant to this field of study.

SOURCE: Schjerning-Olsen AM, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: A nationwide cohort study. *Circulation* 2011;123:2226-2235.

Current American College of Cardiology/American Heart Association (ACC/AHA) Guidelines recommend withholding nonsteroidal anti-inflammatory drugs (NSAIDs) from patients who have suffered a myocardial infarction (MI) and substitution of another analgesic such as acetaminophen. If NSAID therapy is unavoidable, the guidelines recommend the shortest duration possible. However, there are few data about the cardiovascular risk of each individual NSAID agent, and what constitutes a safe duration of therapy. Schjerning-Olsen and colleagues studied the effects of NSAID use, and the duration of use, in adults after their first MI. They made use of the nationwide registries of hospitalization and drug dispensing in Denmark to identify individuals with their first MI, and then identified those who had purchased NSAIDS. Linking the patient hospitalization registry and the death registry identified those who were readmitted with recurrent MI and those who died. They identified 102,138 patients with first-time MI over a 10-year period; 82% (83,675) were discharged alive and were included in the analysis. Of these, at least one prescription for NSAIDs was filled for 35,405 patients (42%).

The use of NSAIDs following MI was associated with an approximately 50% increased risk of death, as well as an increase in the combined endpoint of death or MI. This risk increased within the first week and persisted throughout the entire duration of NSAID use. The authors then analyzed the five most

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Clinical Cardiology [ALERT]

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popularly prescribed individual NSAIDS in Denmark: celecoxib, rofecoxib, diclofenac, ibuprofen, naproxen; the researchers combined all the other less commonly used agents into a single group. Similar increases in the rate of death were seen with all five individual NSAIDs and with the combined group, suggesting there is no "safe" NSAID in patients after MI. In addition, the COX-2 selective agents celecoxib and rofecoxib did not appear to have lower or higher risk of death or recurrent MI.

The only real difference between agents was that diclofenac appeared to have the highest rate of death and recurrent MI, and this risk was elevated early. Rofecoxib, celecoxib, ibuprofen, naproxen, and the combined group did not have an increased risk within the first 7 days of use, but the risk did rise after that to a similar order of magnitude. If anything, naproxen appeared to have the lowest rate of death or MI. Importantly, the risk returned to baseline shortly after ceasing NSAID use, except in the rofecoxib group.

The authors conclude that even short-term treatment with most NSAIDs was associated with increased risk of death and recurrent MI in patients with prior MI. Neither short- nor long-term treatment with NSAIDs is advised in this population, and any NSAID use should be limited from a cardiovascular safety point of view.

■ COMMENTARY

This is a very large study utilizing nationwide registries, and thus has a wide cross-section of patients. In addition, the data are strengthened by the fact that the use of medications and the adjudication of repeat hospitalization and death are very complete in these datasets. It is important to acknowledge, however, that the datasets lack complete information about comorbid conditions, such as smoking status, blood pressure, left ventricular function, and renal function, that could impact the risk of recurrent MI and death. Thus, it is possible that unmeasured confounders such as these that would alter the risk of death or MI could be present. Furthermore, the population in Denmark is more racially homogeneous than in the United States, so differences in the effects of NSAIDs in different ethnic groups are not addressed here. Thus, these data should not be considered definitive proof of toxicity of NSAIDs, but rather they should be considered hypothesis-generating.

Other clinical studies and registries have suggested that NSAIDs in patients with coronary artery disease may increase the risk of MI or death. The current study supports previous trials and extends the findings by suggesting that not even short duration of NSAID treatment is safe. It is unlikely that we will ever have a randomized controlled trial of NSAID use after MI, so as clinicians we will be left to use the available data from these types of observational studies. This study supports the current guidelines that recommend patients try to avoid NSAID use after MI. ■

ABSTRACT & COMMENTARY

Use of Optimal Medical Therapy in PCI Patients

By Michael H. Crawford, MD, Editor

SOURCE: Borden WB, et al. Patterns and intensity of medical therapy in patients undergoing percutaneous coronary intervention. *JAMA* 2011;305:1882-1889.

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) study showed that in patients with stable coronary artery disease (CAD) put on optimal medical therapy (OMT) that randomization to a percutaneous coronary intervention did not improve survival or prevent myocardial infarction. Thus, these authors interrogated the National Cardiovascular Data Registry (NCDR) Catheterization

Percutaneous Intervention (PCI) subregistry to assess the use of OMT before and after PCI and before and after publication of COURAGE. Data from 19 months before COURAGE publication and data 3-24 months after COURAGE were examined. OMT was defined as therapy with aspirin or a thienopyridine, beta-blocker, statin, or documental contraindication to these therapies. Renin angiotensin system blocker use was also assessed in appropriate subgroups (i.e., ejection fraction < 40%). The study population included 467,211 patients (28% of the Cath PCI subregistry) who had elective PCI for stable CAD. In general, OMT use increased after PCI (65% vs 44%; $P < 0.001$). Before PCI, OMT was deployed in 43.5% before COURAGE and in 44.7% after, which was statistically significant ($P < 0.001$) but of little clinical importance. After PCI before COURAGE, OMT was used in 64% vs 66% after COURAGE ($P < 0.001$). The authors concluded that in stable CAD patients undergoing PCI, fewer than half were on OMT before PCI and about two-thirds were on OMT after PCI. The results were not clinically different after the COURAGE trial was published.

■ COMMENTARY

This study suggests that we are missing a large opportunity to improve patient outcomes after PCI is performed, since only about two-thirds were on OMT 2 years after PCI. By comparison in the COURAGE trial, 79% were on OMT at 5 years. They point out that this deficiency is not just the purview of the interventional cardiologist, but also the responsibility of the primary care provider. Perhaps there needs to be better coordination between these providers.

Publication of the excellent results of OMT in the COURAGE trial did not appreciably change the number of patients on OMT. This observation shows the difficulty of translating clinical trial data into practice and it is not clear why. Perhaps practitioners do not believe the results or think they do not apply to their patients. However, when the individual medications are examined, antiplatelet therapy increased from 89% before PCI to 99% afterward. Of course the role of antiplatelet therapy after PCI has been extensively studied and reported upon. Beta-blockers went from 63% to 75% and statins from 63% to 84%. These are individually significant improvements, but you had to be on all three medications to qualify as OMT. This suggests that contraindications to one or more medications may not have been documented or were missed by those reviewing the records.

Other factors may have impacted the decision to prescribe certain drugs. There are fewer data on the benefits of beta-blockers beyond angina prevention in patients with chronic stable CAD. Also, some patients not on statins may have had the high triglyceride low HDL pattern and were put on niacin or fibrates. Renin angiotensin blockers may have been avoided in the hospital due to fear of augmenting renal damage caused by the contrast agents used in cardiac catheterization and were never started after discharge. Data have shown that patients are more likely to remain on drugs started in the hospital than those started later.

It is likely that there is an opportunity to improve our care of stable CAD patients, but the magnitude may not be as great as this study suggests. ■

ABSTRACT & COMMENTARY

Diagnosis of Thoracic Aorta Dissection

By Michael H. Crawford, MD, Editor

SOURCE: Rogers AM, et al. Sensitivity of the aortic dissection detection risk score, a novel guideline-based tool for identification of acute aortic dissection at initial presentation. *Circulation* 2011;123:2213-2218.

Thoracic aortic dissection is notoriously difficult to diagnose. Since the presenting symptoms are protean, it is not feasible to image everyone with symptoms that could be due to dissection. Thus, a risk assessment tool was devised by an expert committee, but it has never been validated clinically. These investigators applied the risk score to the International Registry of Acute Aortic Dissection database to test its utility for diagnosing aortic dissection. More than 2500 patients in the registry were categorized by 12 clinical markers: five predisposing conditions, three pain features, and four exam features. Those with no risk markers were scored 0; those with markers in at least one of the three categories were scored 1; and

markers in two or three categories were scored 2 or 3, respectively. Score 0 was considered low risk; score 1 was intermediate risk; and 2 or 3 was high risk. A score of 0 was found in 4%; 1 in 37%; and 2 or 3 in 59%. Among the 108 low-risk score 0 patients, 72 had chest x-rays and 49% had a widened mediastinum. Using an algorithm based upon score and chest x-ray when appropriate, the overall sensitivity for the detection of aortic dissection was 96%. The most common of the 12 individual risk markers were abrupt onset of pain (79%); severe pain (73%); ripping or tearing pain (22%); new murmur of aortic regurgitation with pain (24%); and a pulse deficit or upper extremity blood pressure differences (20%). The authors concluded that this clinical risk marker score was highly sensitive for detecting aortic dissection.

■ COMMENTARY

This is an interesting study because clinical factors believed to be helpful in the diagnosis of aortic dissection were collated into a proposed risk score by a group of experts without any clinical testing. Of course this happens all the time and we often never know exactly how useful these scores will be. In this case, a large database was used to test the scores utility in retrospect. Although it did well (sensitivity 96%), a prospective study would give us more confidence in its utility. However, it is difficult to study a low incidence event like aortic dissection prospectively.

Inspection of the 12 individual markers shows that some were much more useful than others: Abrupt onset of pain and severe pain occurred in more than 70%. A new murmur of aortic regurgitation in conjunction with pain, ripping or tearing pain, and a pulse deficit or systolic blood pressure difference between limbs occurred in 20%-24%. These three features of the pain history and two physical examination findings seem more specific for aortic dissection than other less common findings such as known thoracic aortic aneurysm, known aortic valve disease, focal neurologic deficit, and hypotension or shock, which occurred in 11%-16%. The other three markers (Marfan Syndrome, family history of aortic disease, and recent aortic manipulation) occurred less than 5% of the time.

Unfortunately, this study cannot assess specificity because all the patients had aortic dissection. It is likely that specificity — and hence positive-predictive valve — will be lower than the sensitivity. This puts the aortic dissection score in the category of other highly sensitive tests with high negative predictive values such as d-dimer, troponin, and BNP. How much use of such a score will cut down on excessive imaging in the emergency department remains to be seen. ■

ABSTRACT & COMMENTARY

Radial vs Femoral Arterial Access for Coronary Angiography and Intervention in Acute Coronary Syndromes

By Andrew J. Boyle, MBBS, PhD

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SOURCE: Jolly SS, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): A randomised, parallel group, multicentre trial. *Lancet* 2011;377:1409-1420.

Several studies have shown lower rates of arterial access site complications when performing cardiac catheterization via the radial artery compared to the femoral artery, but these have largely been retrospective studies or registries. Jolly and colleagues performed a prospective randomized trial of radial vs femoral access for patients undergoing cardiac catheterization during hospitalization for acute coronary syndromes (ACS). In this large study, more than 7000 patients were enrolled. Initially, this study began as an investigator-initiated substudy within the OASIS-7 trial, which compared high and low doses of aspirin and clopidogrel, but after that study ended they continued the RIVAL trial as a stand-alone clinical trial. The primary endpoint was a composite of death, myocardial infarction (MI), stroke, and non-coronary artery bypass graft (CABG) major bleeding.

Patients presenting with ACS, including unstable angina (UA), non-ST-elevation MI (NSTEMI), and ST-elevation MI (STEMI), who were scheduled to undergo invasive management, were randomized to radial (n = 3507) or femoral (n = 3514) arterial access. The study was performed at high volume radial centers and involved operators facile with either femoral or radial access (≥ 50 radial procedures in the preceding year). There were no differences in the baseline demographics between groups: approximately 74% were male, mean age was 62 ± 12 years, 21% were diabetic, 45% presented with UA, 27% had non-STEMI, and 28% had STEMI.

Of the 7021 who underwent coronary angiography, 66.4% had percutaneous coronary intervention (PCI), 8.5% had CABG, and the remainder received medical therapy alone. Smaller sheath sizes were used more often in the radial cases, but PCI success was 95% in each group. Access site crossover occurred more frequently in the radial group (7.6% vs 2.0%; $P < 0.0001$). Based on intention-to-treat analysis, the rate of occurrence of the primary endpoint did not differ between groups (3.7% vs 4.0%; $P = 0.50$); nor did the rate of the individual components of the primary endpoint (death 1.3% vs 1.5%; MI 1.7% vs 1.9%, stroke 0.6% vs 0.4%, non-CABG major bleeding 0.7% vs 0.9% in the radial and femoral groups, respectively). Radial access was associated with a lower rate of major vascular complications (1.4% vs 3.7%; $P < 0.0001$).

The authors performed subgroup analyses to determine whether patients presenting with STEMI had different outcomes. In those presenting with STEMI, the primary endpoint favored radial access (3.1% vs 5.2%; $P = 0.026$), as did the rate of death (2.7% vs 4.6%; $P < 0.01$). In patients at the highest volume radial centers, there also was a significantly better primary outcome (1.6% vs 3.2%; $P = 0.015$). In all subgroup analyses, the rate of vascular access complications favored radial and the rate of access site crossover favored femoral. The authors conclude that both radial and femoral approaches are safe and effective for PCI. However, the lower rate of local vascular complications may be a reason to use the radial approach.

■ COMMENTARY

The RIVAL trial showed no difference between radial and femoral access in the composite primary endpoint of death, MI, stroke, and major non-CABG bleeding, but radial access was associated with a lower rate of vascular access complications. It seems intuitive that the site of access would have little effect on death, stroke, and MI in patients experiencing ACS. But why was there no significant improvement in bleeding outcomes? The authors offer several explanations. First, the rate of major bleeding in the femoral group was unexpectedly low (0.9%), much lower than other contemporary PCI trials in this patient population, so that made it difficult to show a difference between groups. It is important to note that in the RIVAL trial two-thirds of bleeding events occurred remotely from the access site. So the site of access is not likely to make much difference to bleeding outcomes. Second, their definition of major bleeding was very strict and did not include vascular access complications and major hematomas. In fact, they performed an exploratory analysis using a definition of bleeding that included hematoma and vascular access site complications requiring intervention (the ACUITY major bleeding definition) and found that radial access was associated with a lower primary outcome event rate. The authors also note that the rate of vascular closure device use was only 26% in the femoral group, and that those receiving a vascular closure device had a lower rate of bleeding.

The subgroup analyses were interesting. In the highest volume radial centers, and in patients presenting with STEMI, there was a lower incidence of the primary endpoint in the radial group. This suggests that there may be benefit to radial access in the highest bleeding risk patients (STEMI) and in high-volume centers. There is certainly a significant learning curve with using radial access, and in this trial only high-volume radial operators were involved. Even so, there were better outcomes at the highest volume centers within the study, suggesting the learning curve involves the entire institution.

This study confirms that radial and femoral arterial access are acceptable alternatives in patients presenting with ACS who are undergoing invasive treatment. Both result in equivalent efficacy outcomes, although radial access may slightly reduce access site complications. Physician preference and experience should be taken into account when deciding on the access site. ■

ABSTRACT & COMMENTARY

Intermediate Dose Dabigatran for Atrial Fibrillation

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: Eikelboom JW, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: An analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011;123:2363-2372.

The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial compared two doses of dabigatran, a direct thrombin inhibitor, with warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. Patients were randomized to dabigatran 110 mg bid, dabigatran 150 mg bid, or adjusted dose warfarin. Based on the overall results of RE-LY, the Food and Drug Administration (FDA) approved the 150 mg bid dose and not the 110 mg bid dose. A 75 mg bid dose was approved for patients with moderately severe renal insufficiency. This report from the RE-LY investigators offers a rationale why the 110 mg bid dose might have advantages.

RE-LY randomized 18,113 patients to one of its three arms. In the entire study group, dabigatran 110 mg twice per day compared with warfarin was associated with lower risks of major bleeding (2.87% vs 3.57 %), intracranial bleeding (0.23% vs 0.76%), and life-threatening bleeding (1.24% vs 1.85%). Dabigatran 150 mg twice per day and warfarin had comparable risks for major bleeding (3.31% vs 3.57%) and extracranial bleeding (3.02% vs 2.84%). However, again compared to warfarin, dabigatran 150 mg twice per day was associated with more gastrointestinal bleeding (1.85% vs 1.25%) but less intracranial bleeding (0.32% vs 0.76%). In terms of stroke protection, dabigatran 110 mg bid was non-inferior and dabigatran 150 mg bid was superior to warfarin.

The authors then analyzed the data by patient age. They noted an increased risk of bleeding in older patients. By using an age cutoff of 75 years to define age subgroups, there was a strong interaction between age and treatment effect for major and extracranial bleeding with dabigatran 110 mg bid showing less bleeding risk in those older than age 75. There was no interaction with age when protection from stroke was the endpoint.

The authors conclude that for patients older than 75 years of age with an increased risk for bleeding, the lower dabigatran dose might be considered an effective means to reduce the risk of stroke and control risks for bleeding.

■ COMMENTARY

Dabigatran has many advantages over warfarin. When the RE-LY trial data were first analyzed by the FDA, they agency concluded that there was no substantial overall lowering of bleeding risk at the 110 mg bid dose compared to 150 mg bid and efficacy was superior at the higher dose. The data presented in this substudy, however, suggest that selective use of a lower dose of dabigatran may have some advantages in older patients or those at high risk for bleeding. The lower dose would preserve many of the efficacy benefits associated with dabigatran yet allow physicians to mitigate risks for bleeding. Dabigatran at both 110 and 150 mg doses is available in several other countries. We will have to see if the FDA reconsiders its position. ■

ABSTRACT & COMMENTARY

Risks of ICD Implantation

By John P. DiMarco, MD, PhD
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SOURCE: Haines DE, et al. Implantable cardioverter-defibrillator registry risk score models for acute procedural complications or death after implantable cardioverter-defibrillator implantation. *Circulation* 2011;123:2069-2076.

In this paper, Haines and his coauthors propose a scoring system to predict risks associated with implantable cardioverter-defibrillator (ICD) implant procedures. The authors analyzed data from the national ICD Registry which tracks in-hospital complications after most ICD procedures performed in the United States. They analyzed data reported between January 1, 2006, and June 30, 2008. They identified 29 variables captured by the registry and tested them for inclusion in a risk model. This was accomplished using multivariate logistic regression analysis on the 29 selected variables with the endpoints of in-hospital complications or in-hospital mortality. Once risk factors were identified, the risk score model was re-evaluated in a validation cohort.

The authors excluded 5012 implants that required thoracotomy for lead placement, leaving a final study cohort of 268,701 implants. In these patients, there were 8559 acute procedure-related complications (3.2%). The most common complications were: hematoma (0.93%), lead dislodgement (0.93%), pneumothorax (0.42%), and cardiac arrest (0.03%). Other complications noted at lower frequencies included: cardiac perforation, myocardial infarction, pericardial tamponade, and infection. The in-hospital mortality rate was 0.38%. Patients who were admitted for reasons other than elective ICD implants had a significantly higher risk for both any complication or death (4.58% vs 2.51%, $P < 0.0001$) and of in-hospital death alone (0.91% vs 0.12%, $P < 0.0001$). Patients were more likely to suffer complications or death if they were older, female, had a lower left ventricular ejection fraction, or had a prolonged QRS duration on ECG. Complications were more common in those with nonischemic dilated cardiomyopathy, congestive heart failure, atrial fibrillation or flutter, prior valve surgery, cerebral vascular disease, chronic kidney disease, and chronic lung disease. The complexity of the procedure was also associated with an increased complication rate with the lowest rates seen with simple device changes for generator replacement and single-chamber ICDs and higher rates with dual-chamber or biventricular devices. Ten variables were strongly associated with increased risk for complications and were assigned points in the scoring system. These included: age older than 70 years (1 point); female gender (2 points); New York Heart Association heart failure class III (1 point) or IV (3 points); atrial fibrillation or flutter (1 point); prior valve surgery (3 points); dual chamber (2 points) or biventricular (4 points) devices; chronic lung disease (2 points); BUN greater than 30 mg/dL (2 points); previous ICD reimplantation (6 points); and non-elective ICD implantation (3 points). The risk for any in-hospital complication increased from 0.6% with a total risk score < 5 (8.4% of the total population) to 8.4% among patients with a risk score of > 19. There was an almost linear increase in rate of complications as the risk score rose. A similar model using seven factors was constructed for in-hospital mortality.

The authors conclude that the risk for acute ICD complications can be predicted using a simple scoring system. For patients with the highest risk for complications, knowledge of this increased risk might change the risk-benefit equation leading to device implantation.

■ COMMENTARY

This is a useful paper for both implanting physicians and those who refer patients for ICD implants. For implanting physicians, this scoring system allows them to risk-adjust their own or their institution's performance against a national standard. For referring physicians, knowledge of the risk for complications will allow them to be more transparent in their discussions with patients about the risks and benefits of the procedure. We also must recognize that the data here refer to only in-hospital complications and are a lower estimate of the actual risks. Elective procedures are usually performed on an overnight stay basis. This, at least partly, explains why complications are lower with elective implants in patients admitted solely for the procedure. We also need to remember that some complications often typically occur outside the 1-2 day window often reported in the ICD registry. Pocket infections, lead dislodgements, and lead malfunctions, particularly with LV leads, fall into this early after discharge category.

ICDs are important tools for prevention of sudden death. However, we need to be frank with both ourselves and our patients that complications with these devices are common and the risk of complications should be part of any discussion with patients concerning an ICD procedure. ■

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CME Questions

1. NSAIDs should be avoided in patients with:
a. diabetes.
b. pericarditis.
c. prior myocardial infarction.
d. lupus valvulitis.

2. The sensitivity of a new clinical score for aortic dissection is:
a. 65%.
b. 75%.
c. 86%.
d. 96%.

3. Radial artery access vs femoral artery results in fewer:
a. major adverse cardiac events.
b. access site complications.
c. crossovers to the alternate access site.
d. hospital days.

4. The use of optimal medical therapy in CAD patients increased importantly after:
a. the publication of COURAGE.
b. simvastatin was generic.
c. the patients had PCI.
d. Obamacare was passed by Congress.

5. Which procedure has the highest risk of complications?
a. Biventricular pacemaker
b. Non-elective ICD implantation
c. Dual-chamber pacemaker
d. Single-lead pacemaker

6. Which of the following is most correct concerning dabigatran 110 mg bid vs warfarin?
a. Superior for stroke prevention
b. Higher risk of intracranial bleeding
c. Higher risk of major bleeding in those older than 75 years of age
d. Lower risk of major bleeding

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.

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By Louis Kuritzky, MD

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

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COPD in Never Smokers

Source: Lamprecht B, et al. *Chest* 2011; 139:752-763.

Unless there is another overt cause, such as occupational exposure to toxic inhalants, we generally expect chronic obstructive pulmonary disease (COPD) to be secondary to cigarette smoking. The pulmonology literature consistently suggests that a substantial minority — at least 20% — is NOT related to cigarette smoking. This multinational survey by Lamprecht et al provides a fresh appraisal of the burden of COPD unrelated to smoking.

The Global Initiative for Obstructive Lung Disease (GOLD) guidelines were used to define COPD through spirometry. Primary cigarette smoking, exposure to secondary smoke, occupational exposure, and biomass exposure (for instance, cooking or home heating using wood, coal, dung, or crop residue) were all queried among 10,000 subjects from 14 countries.

Of the 4291 never smokers, 12.2% fulfilled GOLD criteria for COPD. Of all persons ultimately defined as meeting COPD criteria, just over one-fourth were never smokers. Women were disproportionately represented in the group of persons with moderate-severe COPD. It has been suggested that women may have greater susceptibility both to tobacco smoke as well as other potentially toxic inhalants.

COPD is now the third most common cause of death in America. Pulmonologists have suggested that COPD remains underdiagnosed. Based on these results, the authors suggest that symptomatic persons, even if never smokers, should be screened for COPD. ■

Early Prostate Cancer: Prostatectomy vs Watchful Waiting

Source: Bill-Axelson A, et al. *N Engl J Med* 2011;364:1708-1717.

The management of early prostate cancer (PCA) remains controversial. Although surgical and radiation interventions offer the opportunity for cure, many more men with early PCA die with the disease than from it. Were definitive interventions without risk, there likely would be little discussion about whether to intervene; however, because the potential consequences of intervention are significant (e.g., incontinence, erectile dysfunction), clarification of the risk:benefit ratio is critical.

A randomized multinational study of subjects from Sweden, Finland, and Iceland (n = 695) randomized men < 75 years of age with localized, moderately well to well-differentiated prostate cancer to either radical prostatectomy or watchful waiting. Men were followed for 12.8 years.

At 12.8 years, all-cause mortality was statistically significantly less in the surgery group (166/347) than the watchful waiting group (201/348). Similarly, PCA-related death was superior in the surgically treated group (14.6% vs 20.7%). Benefits were clear from men < 65 years of age, but only a trend toward benefit (results not statistically significant) could be determined from the data in older men, possibly because of the smaller number of men in this age group.

Adverse effects of surgery were substantial. For instance, at 1 year, 32% of men had incontinence and 58% had impotence. Younger men with early PCA appear to enjoy mortality benefit from surgical intervention, though at a substantial adverse event cost. Competing causes of death in older men diminish the relative benefits of surgery. ■

Dietary Vitamin D and Incident Diabetes

Source: Gagnon C, et al. *Diabetes Care* 2011;34:1133-1138.

The beta cells of the pancreas possess a vitamin D receptor, so perhaps we should not be surprised that vitamin D might be associated with diabetes (DM). Preliminary evidence has suggested that dietary vitamin D (VTD) might be associated with risk for DM, but prior to this report, no large population study has provided sufficient information to be definitive.

Gagnon et al researched subjects involved in the AusDiab studies, which included 11,247 noninstitutionalized adults free of DM at baseline who underwent a 75 g oral glucose tolerance test (GTT) at baseline. Five years later about half (6537) of these had a repeat GTT, of which 80% were still not diabetic.

The investigators found a linear relationship between reported dietary VTD and incident DM over a 5-year interval: for every 25 nmol/L increase in VTD, there was a 24% reduced risk of DM. Also studied in this same data set was calcium intake, which did not correlate with incident DM. Subjects in the top quartile of VTD intake enjoyed a 44% risk reduction for incident DM.

Because these are observational data, causation cannot be established. Prospective, randomized, placebo-controlled trials of VTD supplementation will be necessary to confirm the preventive capacity of VTD. ■

Functional Cobalamin Deficiency in Diabetes

Source: Solomon LR. *Diabetes Care* 2011;34:1077-1080.

It has been suggested that as many as 30% of senior citizens have so-called functional cobalamin deficiency (FCD), defined as the presence of elevated metabolites such as methylmalonic acid in the face of ostensibly normal cobalamin levels. Since methylmalonic acid should accumulate primarily in the circumstance of vitamin B12 insufficiency, there appears to be some functional deficiency in cobalamin, manifested as increased levels of methylmalonic acid.

The intersection of diabetes with FCD occurs because previous trials have noted that diabetics comprise up to one-third of subjects experiencing improvements in neuropathic signs with vitamin B12 supplementation, and the vast majority of these subjects (88%) did not have decreased vitamin B12 levels.

To better define the epidemiologic profile of FCD, a retrospective review of patients evaluated for cobalamin deficiency from 1993-2005 characterized levels of cobalamin in relation to methylmalonic acid. Because renal insufficiency is associated with increases in methylmalonic acid, creatinine > 1.4 mg/dL was an exclusion criterion.

Among nondiabetics there was an inverse relationship between methylmalonic acid and cobalamin. Among diabetics, however, increasing cobalamin levels were not associated with decreasing methylmalonic acid, suggesting that there was a relative cobalamin resistance.

Equally noteworthy, neuropathy was much more frequent in persons with elevated methylmalonic acid than without (62% vs 18%) and more than 85% of persons treated with pharmacologic doses of cobalamin experienced improvement in neuropathy.

There is substantial controversy over the existence of functional cobalamin deficiency. Considering that cobalamin supplementation has no known important toxicity, clinicians may wish to re-examine the issue of cobalamin treatment for diabetic subjects with elevated levels of methylmalonic acid, even in the face of normal cobalamin levels. ■

Should Leukotriene Antagonists Have Higher Priority for Asthma Control?

Source: Price D, et al. *N Eng J Med* 2011;364:1695-1707.

Current asthma guidelines suggest that once an asthma patient has progressed to the stage of persistent asthma (even mild-persistent asthma), inhaled corticosteroids (ICS) should be the preferred initial "controller" (maintenance) medication. Nonetheless, comparator trials of leukotriene inhibitors (LKT) with ICS have produced inconsistent findings, sometimes indicating superiority of ICS, but other times suggesting equal efficacy of the two classes. Because concerns about adverse effects of ICS in obstructive airways diseases have persisted for several decades, the absence of similar concerns with LKT agents promotes consideration of how to maximize their positive potential.

Two trials comprise the data reported in this publication. In the first, persons initiating controller therapy for persistent asthma (n = 306) were randomized to either ICS or LKT. In the second trial, asthma subjects who had already received ICS for controller medication but who required advancement of pharmacotherapy (n = 352) were randomized to either LKT or long-acting beta agonist (LABA). The primary outcome was the score on the Mini Asthma Quality of Life Questionnaire at 2 months. Secondary outcomes included the same questionnaire results at 2 years and frequency of asthma exacerbations.

At 2 months, the LKT proved equivalent to ICS as initial therapy, and equivalent to LABA as add-on treatment. At 2 years, although not able to achieve the statistical threshold defining equivalence, the outcomes were very similar. There was no difference in the frequency of exacerbations between LKT and ICS or between LKT and LABA when added to ICS. There was no placebo control in this trial, and the trial was open label. Nevertheless, these data suggest that in a "real world" setting, the efficacy of LKT in asthma may have been underestimated. ■

Selenium Impacts Orbitopathy in Graves Disease

Source: Krassas GE, et al. *N Eng J Med* 2011;364:1920-1931.

Ocular abnormalities associated with Graves disease are sometimes called Graves' orbitopathy (GORB) and occur in as many as half of Graves' disease cases. Treatments for GORB include glucocorticoids and irradiation, but are generally reserved for moderately severe disease. Mild GORB has been shown to spontaneously regress (20%), remain stable/unchanging (65%), or advance (15%). Hence, a safe intervention to prevent advancement of GORB would be desirable. The antioxidant effects of selenium led to consideration of its potential favorable impact upon GORB.

This controlled trial randomized patients (n = 107) to selenium sulfide 100 mcg twice daily or placebo for 6 months. GORB evaluation was done at baseline, 3, 6, and 12 months. The primary outcome was the percentage of patients improving from baseline. The study hypothesis was that active treatment would improve the number of persons with GORB regression by 25%: from 20% (as seen in naturalistic follow-up of untreated GORB) to 45%.

By 6 months, there was a statistically significant improved quality of life and regression of GORB, which was reconfirmed at 12 months. There were no serious adverse effects seen with selenium.

Although it would have been nice to have seen selenium levels before and after treatment, and hopefully a correlation between selenium repletion and outcomes, these preliminary data are still quite supportive of a

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PHARMACOLOGY WATCH

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Two New Drugs Approved for Treatment of Hepatitis C

In this issue: Two new drugs for treatment of hepatitis C; NSAIDs and myocardial infarction risk; AIM-HIGH clinical trial stopped; and FDA actions.

Two new drugs for hepatitis C

The FDA has approved two new drugs for the treatment of hepatitis C — the first new drugs to be approved in years. The approvals came within days of each other, pitting the two drugs (and their companies' marketing departments) against each other in this multibillion dollar market. Both drugs are protease inhibitors and both have similar indications. First to be approved was Merck's boceprevir (Victrelis), which is indicated for adults with hepatitis C who still have some liver function and who either have not been treated previously with drug therapy or who have failed drug therapy. Boceprevir is approved for use in combination with peginterferon alpha and ribavirin. The approval was based on two phase 3 clinical trials of 1500 adults in which two-thirds of patients in the boceprevir, interferon, and ribavirin treatment group experienced a significantly increased sustained virologic response at 24 weeks compared to 38% with interferon and ribavirin alone. Boceprevir is taken orally three times a day with food. The second drug approved was Vertex Pharmaceutical's telaprevir (Incivek), which also was approved for patients with hepatitis C who either have not received interferon-based drug therapy or who have not responded adequately to prior therapies. Telaprevir is also approved for use with peginterferon alpha and ribavirin. Approval was based on three phase 3 clinical trials of over 2000 adults. In previously untreated patients, 79% of patients in the telaprevir group experienced a sustained viral response compared to 46% for standard treatment. Most patients experienced virologic response at 24 weeks suggesting that treatment times may be reduced from 48 weeks to 24 weeks. Telaprevir is also taken orally three times a day with food. Both drugs are approved to treat genotype-1, the most common form of hepatitis C and the most difficult to treat. The drugs have similar side effects, which include anemia and serious rashes. Several other drug manufacturers have similar drugs in the pipeline with approval expected within the next year or two. It is estimated that about 170 million people worldwide and 3.2 million Americans are infected with chronic hepatitis C, which is the most common cause of progressive liver disease leading to liver transplant. Telaprevir is expected to cost nearly $50,000 per treatment course, while bocepavir is expected to cost between $26,000 to $48,000 per treatment course depending on the duration. ■

NSAID use in patients with prior MI

A new study points out the risk of nonsteroidal anti-inflammatory drug (NSAID) use in patients who have had a myocardial infarction (MI) — suggesting that even brief use increases the risk for death and recurrent MI. Researchers from Denmark reviewed the records of nearly 84,000 patients who were admitted with first time MI and their subsequent NSAID use. The risk of death and recurrent MI was correlated to the duration of NSAID treatment. From 1997-2006, 42.3% of patients received NSAIDs. There

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were more than 35,000 deaths or recurrent MIs in the cohort of whom 43% had filled a prescription for an NSAID. Use of an NSAID was significantly associated with an increased risk of death or recurrent MI at the beginning of treatment (hazard ratio [HR] 1.45; 95% confidence interval [CI], 1.29 to 1.62) and persisted throughout the NSAID treatment course (HR 1.55; 95% CI, 1.46 to 1.64 after 90 days), returning to baseline soon after stopping the drug. The risk of death or recurrent MI varied with different drugs and was somewhat higher with increased COX-2 selectivity. Diclofenac was associated with the highest risk (HR 3.26; 95% CI, 2.57 to 3.86). Duration of therapy was also reviewed with diclofenac causing an increased risk from the beginning of treatment and persisting throughout the treatment course. Ibuprofen showed an increased risk when used for more than one week, whereas celecoxib showed an increased risk after 14-30 days of treatment. Naproxen was not associated with a statistically significant increased risk of death or MI for the entire treatment duration. The authors conclude that short-term treatment with most NSAIDs is associated with increased cardiovascular risk. This suggests that there is no apparent safe therapeutic window for NSAIDs in patients with prior MI and "challenge the current recommendations of low-dose and short-term use of NSAIDs as being safe" (*Circulation* 2011;123:2226-2235). One interesting aspect of this study was the use of rofecoxib (Vioxx) prior to its withdrawal in 2004. While rofecoxib was found to increase cardiovascular risk (the reason for its withdrawal from the market), it appeared to be no more dangerous than other commonly used NSAIDs and was apparently safer than diclofenac. ■

NHLBI stops AIM-HIGH trial

Niacin may not be effective in preventing cardiovascular disease. The National Heart Lung and Blood Institute (NHLBI) has prematurely stopped the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health (AIM-HIGH) clinical trial 18 months earlier than planned. Analysis of the data found that adding high-dose, extended-release niacin to statin treatment in people with heart and vascular disease did not reduce the risk of cardiovascular events. AIM-HIGH participants had well-controlled low-density lipoprotein levels on a statin, however they were at risk of cardiovascular disease due to previous history of cardiovascular disease and a combination of low high-density lipoprotein (HDL) cholesterol and high triglycerides. During the nearly 3 years of the study, patients who took high-dose, extended-release niacin with a statin had increased HDL cholesterol and lower triglyceride levels compared to those who took a statin alone; however, the combination was not effective at reducing fatal or nonfatal heart attacks, strokes, hospitalizations for acute coronary syndrome, or revascularization procedures. There also was a "small and unexplained increase in ischemic stroke rates in the high-dose, extended-release niacin group" that contributed to the decision to halt the trial. Termination of the AIM-HIGH trial was announced by press release from the NHLBI on May 26. ■

FDA actions

The FDA has approved linagliptin for the treatment of type 2 diabetes in adults. The drug is an inhibitor of DPP-4, an enzyme that degrades incretin hormones (GLP-1 and GIP). It is approved for use as a stand-alone therapy or in combination with other drugs for type 2 diabetes including metformin. The approval was based on eight double-blind, placebo-controlled trials of nearly 4000 patients that showed improved blood glucose control compared to placebo. Linagliptin is marketed by Boehringer Ingelheim Pharmaceuticals as Tradjenta.

The FDA has approved rilpivirine, a new non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of adults with HIV-1 infections who are treatment naïve. Rilpivirine is to be used as part of a highly active antiretroviral therapy (HAART). The approval was based on two phase 3 trials of nearly 1400 adults with HIV who were observed for 48 weeks, and an additional 96-week trial in which the drug was compared to efavirenz as part of multidrug combinations. Rilpivirine was found to be comparable to efavirenz with regard to percentage of patients with undetectable HIV viral load. Patients who failed rilpivirine are more likely to develop drug resistance than patients who failed efavirenz. Rilpivirine is marketed by Tibotec Therapeutics as Edurant.

Rosiglitazone (Avandia) remains on the U.S. market, but its days may be numbered. In a new step to restrict use of the drug, the FDA has updated the Risk Evaluation and Mitigation Strategy to include a restricted access in distribution plan. Physicians and patients must enroll in the distribution program in order to receive the drug. Rosiglitazone will no longer be available in commercial pharmacies after mid-November and will only be available by mail order through certified pharmacies. Use of the drug is limited to patients who are currently on rosiglitazone and whose diabetes is not controlled by other treatments and who are unwilling to change to pioglitazone (Actos). ■

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- 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.

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