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Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Pacemaker Lead Recall

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: Birnie DH, et al. Clinical predictors of fidelis lead fracture: A report from the Canadian Heart Rhythm Society device committee. *Circulation* 2012;125:1217-1225.

This report from a consortium of Canadian implantable cardioverter-defibrillator (ICD) implantation centers analyzed predictors of failure of the Medtronic Sprint Fidelis lead. The Canadian Heart Rhythm Society Device Committee collected data from 23 adult Canadian ICD implant centers. For this report, the failure rate for the Medtronic Sprint Fidelis lead was calculated for each center and data from the median center and five low and high failure rate centers were analyzed. These data included clinical and device interrogation data from the ICD databases at each site and from local clinical records. Items analyzed included demographics, lead model, failure mechanisms, and potential clinical predictors of failure including age, number of additional leads, prior device procedures, implant vein, ejection fraction, and type of underlying heart disease. Lead failure was defined as an abrupt rise in chronic pacing or defibrillation impedance or signal noise on the rate sensing circuit electrogram. Cases of failure not related to lead malfunction were not included. The clinical predictors of lead failure were assessed using a Cox Proportional Hazard model.

There were 3169 Fidelis leads included in this survey. The largest group was dual coil active fixation leads (model 6949) but smaller numbers of other Fidelity leads were also included. The median follow-up duration was 3.4 years. The patient group was 82% male with a mean age of 62.8 years. During follow-up, 16.5% of the patients died, 6.4% of the leads were electively

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Clinical Cardiology [ALERT]

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replaced, and 2.2% were removed from service for reasons other than failure (cardiac transplantation or systemic infection). A total of 251 Fidelis lead failures were observed. The failure rates at 1-, 2-, 3-, 4-, and 5-year time points were 0.2%, 2.1%, 5.3%, 10.6%, and 16.8%, respectively. Most failures (92%) were in the rate/sense circuit with 8% in the high voltage circuit. The highest failure rate was seen with single coil active fixation lead (model 6931) and the lowest failure rate was seen with model 6948 dual coil passive fixation leads. Analysis of the lead survival curves showed that the failure rate increased significantly with time. Patients with ICDs that had been uploaded with a lead integrity alert system were less likely to receive inappropriate shocks but among those with inappropriate shocks, the number of shocks was not changed. In addition to lead type, three other independent predictors of failure were identified: female gender, access vein, and center. The hazard ratio for females was 1.51. Access using a site other than the cephalic vein resulted in hazard ratios of 1.94 for the axillary vein and 1.63 for the cephalic vein. An additional risk factor for failure was if the Fidelis lead was inserted as a replacement lead as opposed to an initial implant. The hazard ratio for these leads was 3.12. If the failure rate continues as predicted by the survival curves, the authors estimate that 23% of leads with normal function 5 years post implant will fail over the next 5 years.

The authors conclude that lead replacement should be strongly considered at the time of their next elective generator change in patients with Fidelis leads in place.

■ COMMENTARY

It is now well recognized that there is a substantial risk for complications associated with repeat device procedures. When lead failure rates are low, most authorities recommend a conservative lead management approach with lead extraction and/or replacement only when electrical problems are confirmed. However, when the pocket must be reopened for a generator change, the risk:benefit equation for changing the lead may shift toward benefit if the risk for lead failure is high. The data presented here suggest that doctors should strongly consider replacing Fidelis leads at the time of elective generator changes if the change can be accomplished without markedly increasing the procedure risk.

The current recommendations on the Medtronic Fidelis site are listed below.

- In the event of a device change out or upgrade procedure, with no manifestation of lead fracture, consider the patient age and lead model data above, as well as patient life expectancy, comorbidities, ease of extraction related to implant time, patient preference, etc., for the following options:
  - — Leave a properly performing lead intact.
  - — Implant a new ICD lead without extraction of the existing lead.
  - — Carefully consider all factors before prophylactic placement of a pace-sense lead given the data in Table 1, which shows an increased risk of high voltage conductor fracture if a pace-sense conductor fracture has previously occurred.
- Individual patient circumstances may warrant extracting and implanting a new ICD lead. If warranted, Medtronic's Independent Physician Quality Panel recommends the lead extraction procedure be performed by a physician with extensive lead extraction experience.[1]

Thus, the weight of evidence may be tilting toward a more aggressive approach to lead replacement. ■

Reference

1. Medtronic Dear Doctor Letter. Sprint Fidelis® Lead Patient Management Recommendations Update Models 6949, 6948, 6931, 6930. April 2011. www.medtronic.com/product-advisories/physician/sprint-fidelis/PHYSLETTER-2011-04. Accessed March 12, 2012.

ABSTRACT & COMMENTARY

New Indications for CRT

By John P. DiMarco, MD, PhD

Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

SOURCE: Stevenson WG, et al, and the Heart Failure Society of America Guideline Committee. Indications for cardiac resynchronization therapy: 2011 update from the Heart Failure Society of America Guideline Committee. *J Card Fail* 2012;18:94-106.

This paper reviews the recent data on the effectiveness of cardiac resynchronization therapy (CRT) in patients with milder forms of heart failure (NYHA classes 1 and 2) and revises the Heart Failure Society of America's (HFSA) 2010 Guidelines. The important trials reviewed were the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction study (REVERSE), the Multicenter Automatic Implantable Defibrillator Trial with Cardiac Resynchronization Therapy (MADIT-CRT), and the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT).

The updated guidelines change recommendations in several areas. The new guidelines reflect the observation that the greatest benefit of CRT is seen in patients with left bundle branch block and a wide (≥ 150 ms) QRS duration. In such patients, CRT is now recommended in patients with a left ventricular ejection fraction below 36% and class II and class III heart failure symptoms. For ambulatory class IV patients, the QRS duration is increased from 120 msec to 150 msec. For patients with shorter QRS durations or a non-left bundle type IVCD, the evidence for benefit is less strong and the recommendation is that CRT *may* be considered. CRT is recognized as beneficial in Class II-III patients with a wide QRS and atrial fibrillation if ventricular pacing can be maintained. The evidence that CRT is of benefit in class I patients was not thought sufficient enough to warrant a positive recommendation.

The guidelines also comment on several other factors that are now recognized to affect the response to CRT. Most studies show more benefit in women than in men. The authors stress that the reasons for this are unknown and they do not support differences in practice or delivery of care based on gender. In MADIT-CRT, little improvement was seen with apical lead positions, and the guidelines now state that this should be avoided whenever possible. Finally, they state that the evidence for routine noninvasive assessment of dyssynchrony for patient selection and for post-procedure optimization of timing is uncertain and no single approach can be recommended.

■ COMMENTARY

CRT has now been an accepted disease-modifying therapy in patients with class III heart failure symptoms, a widened QRS, and a severely depressed left ventricular ejection fraction for more than 10 years. Almost 50% of the ICDs implanted in the United States are now CRT-D devices. However, a significant proportion of patients fail to respond to CRT. CRT therapy is more frequently associated with complications and is more expensive. Recent studies have tried to expand the indications for CRT. These updated guidelines provide a very helpful overview of the recent CRT data, and recognize that patients with a wide left bundle branch block are the ones most likely to benefit. In contrast, patients with right bundle branch block are unlikely to benefit. The guidelines also argue that extending CRT to patients with very mild heart failure, NYHA class I, is probably not worth the increase in complications and cost. ■

ABSTRACT & COMMENTARY

Myocardial Infarction Symptom Presentation

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: Canto JG, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA* 2012;307: 813-822.

Timely recognition and treatment of myocardial infarction (MI) are crucial if we are to achieve optimal outcomes for our patients. Silent ischemia, or the absence of classical symptoms of ischemia, may delay the diagnosis. In patients presenting with MI, delay in diagnosis and treatment may have disastrous outcomes. Accordingly, Canto and colleagues analyzed data from the National Registry of MI (NRMI) to assess the frequency with which men and women were admitted for MI without chest pain and the effect that presenting without chest pain has on mortality.

The investigators studied more than 1.1 million patients (42% women) presenting with MI, both ST elevation MI (STEMI) and non-ST elevation MI (non-STEMI) from 1994-2006. The in-hospital mortality rate was 14.6% for women and 10.3% for men ($P < 0.001$). The proportion of MI patients who presented without chest pain was an alarming 35%. Women presenting with MI were more likely than men to present without chest pain (42% vs 31%; $P < 0.001$). In addition, advancing age was associated with higher rates of MI without chest pain, but interestingly the gender differences actually became less pronounced with age. Patients presenting without chest pain were more likely to have diabetes, to have delayed presentation, to present with non-STEMI, and to present in Killip class III or IV, whereas those with chest pain were more likely to present with anterior MI and STEMI. Patients without chest pain were less likely to receive aspirin, beta-blockers, antithrombins, antiplatelet agents, or reperfusion therapy. Furthermore, when they did receive the appropriate treatments, those who presented without chest pain experienced significant delays.

After statistical adjustment for clinical characteristics, comorbidities, treatments received, and delays, younger men and women who suffer MI without chest pain were more than twice as likely to die from their MI than those who had chest pain. However, with advancing age this difference was attenuated, and at age ≥ 75 years men were 32% more likely to die and women were 8% more likely to die than their counterparts with chest pain. The authors conclude that in patients hospitalized with MI, women were more likely than men to present without chest pain and had higher mortality than men within the same age group, but sex differences in clinical presentation without chest pain and in mortality were attenuated with increasing age.

■ COMMENTARY

I am struck by the significant rate of MI without chest pain (35%) in this study. Although this was higher in women (42% vs 31%), the rate of MI without chest pain is still alarmingly high in both sexes and we should have a high index of suspicion for acute MI in patients with atypical presentations. One may intuitively think that non-STEMI were more likely to present without chest pain than STEMI. This is true in the current study, but interestingly more than one-third of all STEMI also presented without chest pain. Delays in treatment were seen in patients without chest pain, and this could lead to serious outcomes in MI patients. This was demonstrated by the higher mortality in those without chest pain in this study. Interestingly, the difference between genders became less apparent with age, but the total proportion of patients presenting with MI without chest pain increased. The reasons for this remain unknown.

The major limitation of this study is that it is a retrospective analysis of registry data. The participating hospitals may not have collected data equally, and the hospitals participating in the NRMI registry may not serve populations that are truly representative of all regions throughout the United States. However, this is an incredibly large study — involving more than a million patients — which strengthens the conclusions made. We should continue to be vigilant for atypical presentations of MI, particularly in women and older patients. Hopefully, increased awareness of painless MI presentation may hasten diagnosis and avoid treatment delays for our patients. ■

ABSTRACT & COMMENTARY

Newer is Better! New Generation DES outperform older DES and BMS

By Andrew J. Boyle, MBBS, PhD

Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco

SOURCE: Sarno G, et al. Lower risk of stent thrombosis and restenosis with unrestricted use of 'new-generation' drug-eluting stents: A report from the nationwide Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *Eur Heart J* 2012;33:606-613.

For those who perform percutaneous coronary intervention (PCI), the newer generation stents have obvious benefits during the procedure. Newer metal alloys with thinner struts and newer stent designs mean that the newest generation are lower profile and more flexible, and are thus more deliverable to where they need to go. In short, they make the procedure faster, easier, and less traumatic to the patients' coronary arteries. Newer antiproliferative drugs used on these stents have reduced the clinical event rate. The clinical trials that brought the newer drug-eluting stents (n-DES) to market showed equivalence or even superiority to the older generation of drug-eluting stents (o-DES) both in terms of in-stent restenosis (ISR) and stent thrombosis (ST). However, these pivotal clinical trials that brought the newer stents to market tend to enroll less complex coronary lesions than are seen in real-world practice. Furthermore, we are treating more and more complex patient populations as stent technology evolves. Thus, the clinical effectiveness of n-DES in the real world has not been fully defined. In this large registry study, the authors sought to determine the real-world safety and efficacy of bare metal stents (BMS), o-DES, and n-DES.

Using the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), the authors report on all cases of PCI performed in Sweden since the release of n-DES in 2006. This registry is compulsory for all patients undergoing PCI in Sweden and captures these patients wherever follow-up occurs throughout the country. The authors present data on more than 94,000 patients undergoing PCI during that time: 64,631 received BMS, 19,202 received o-DES, and 10,551 received n-DES. They defined o-DES as sirolimus-eluting Cypher, zotarolimus-eluting Endeavor, and paclitaxel-eluting Taxus stents, and n-DES as everolimus-eluting Xience, Xience Prime, Promus and Promus Element stents, and zotarolimus-eluting Endeavor Resolute stents. Patients were followed for 2 years after the index PCI in this study.

Overall, the clinical risk profile was higher in both DES groups than the BMS group, with no difference between the clinical risk profile of o-DES and n-DES. The one exception was that BMS were used more often in ST-elevation myocardial infarction. The baseline clinical and demographic data were similar between groups receiving BMS, o-DES, and n-DES. In addition, the procedural characteristics demonstrate that both DES groups were treating more complex lesions than the BMS group. After multi-variable adjustment for clinical and procedural variables, the use of n-DES was associated with lower rates of ISR, ST, and death compared not only with BMS, but also with o-DES.

The adjusted hazard ratio [HR] for ISR in the n-DES group compared to BMS was 0.29 and compared to o-DES was 0.62. The HR for definite ST (by the academic research consortium definition) in the n-DES group was 0.38 vs BMS and 0.57 vs o-DES. The HR for mortality in n-DES was 0.55 vs BS and 0.77 vs o-DES. All these HRs are statistically significant. The authors conclude that PCI with n-DES is associated with a 38% lower risk of clinically meaningful restenosis, a 43% lower risk of definite ST, and a 23% lower risk of death compared to o-DES in this observational study from a large real-world population.

■ COMMENTARY

This is a compelling study presenting data from a very large cohort. It comes as no surprise that the use of n-DES is associated with lower rates of ISR. Some prior smaller randomized studies have shown lower rates of ST with some of the newer stents, but not all. It is reassuring to see that the ST rates in the real world are lower. The study is strengthened by the large number of patients enrolled, by the rigorous nationwide follow-up, and by linking the PCI registry with the national death database to ascertain accurate mortality figures. The authors also performed statistical adjustment for a large number of clinical and procedural variables, which strengthens their data further. However, there are several limitations to this study. First, these are retrospective observational data and thus there may be additional confounders that were not accounted for statistically. Second, the duration of, and the compliance with, dual antiplatelet therapy was not stated. This may have a significant effect on the rates of ST and death. Third, whether data from a single European nation can be extrapolated to the heterogeneous U.S. population is not known. Fourth, there was not complete angiographic follow-up, as there often is in prospective studies. Patients were referred for repeat angiography and/or PCI for clinical indications, thus the authors' use of the term "clinically meaningful restenosis" in their conclusion. I don't see that as a significant limitation as that is what we all do in routine clinical practice.

The role of large registries like this one is controversial. We generally consider randomized, controlled trials to be the ultimate in clinical

evidence. However, randomized, controlled trials are rarely large enough to compare three treatments like this study does, they usually have many exclusion criteria and that limits their generalizability, and they are often (by necessity) funded by industry. This government-funded large registry, and others like the ACC National Cardiovascular Data Registry, provide important data that never can, nor will, be tested in randomized trials. Large registries, therefore, remain the best way to address certain questions in real-world populations. This study by Sarno and colleagues tells us that the evolution of our PCI technology is saving lives and reducing repeat procedures. A formal cost-effectiveness study based on these data would be most welcome and would likely make an even more compelling case for n-DES in this era of health care reform. ■

ABSTRACT & COMMENTARY

Value of C-reactive Protein in Managing Cardiovascular Risk

By Michael H. Crawford, MD, Editor

SOURCE: Sever PS, et al. Evaluation of C-reactive protein prior to and on-treatment as a predictor of benefit from atorvastatin: Observations from the Anglo-Scandinavian Cardiac Outcome Trial. *Eur Heart J* 2012;33:486-494.

The value of high sensitivity C-reactive protein (CRP) measurements in the management of patients at risk for cardiovascular (CV) events is controversial. Thus, these investigators performed a nested case-control study of participants in the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) blood pressure lowering study to determine the ability of CRP to predict CV events. They also evaluated the lipid-lowering arm of ASCOT to test whether CRP predicted CV events after 6 months of therapy with atorvastatin 10 mg a day. The participants in ASCOT hypertension had to have three or more risk factors for CV disease, but patients with a history of CV events were excluded. The original trial compared amlodipine to atenolol-based therapy. The lipid arm included those with total cholesterols < 250 mg/dL. Atorvastatin 10 mg/day vs placebo was tested. ASCOT lipid was stopped early due to significant benefits in the atorvastatin arm. The primary endpoint was a combination of CV death, myocardial infarction, coronary revascularization, and stroke. Two or three control patients were selected to be matched with each CV event case. The cases had a somewhat worse clinical profile than the controls.

Baseline LDL cholesterol and CRP predicted CV events (odds ratio [OR] 1.3, 95% confidence interval [CI] 1.1-1.6, $P = 0.002$ for LDL-C and OR 1.2, CI 1.1-1.3, $P = 0.006$ for CRP), but baseline CRP did not predict the magnitude of atorvastatin's effect. After 6 months of atorvastatin, LDL was decreased 40% and CRP 27%. The magnitude of LDL reduction on atorvastatin predicted the reduction in CV events (OR 0.41, CI 0.22-0.75, $P = 0.004$), but this was not the case for CRP (OR 0.86, CI 0.49-1.51, $P = 0.6$). The authors concluded that among high-risk hypertensive patients, CRP did not appreciably improve CV risk prediction and a reduction in CRP on statin therapy was not predictive of CV outcomes.

■ COMMENTARY

Since statins reduce LDL cholesterol and CRP, it is difficult to parse out the relative importance of each effect. This study suggests that on-statin CRP is not associated with CV outcomes, which differs from the results of JUPITER and PROVE IT-TIMI 22. There are significant differences in the patients in these trials. PROVE-IT included only patients with known coronary heart disease. JUPITER recruited healthy subjects with LDL cholesterol < 130 mg/dL, but with elevated CRP (mean, 4.3). ASCOT blood pressure subjects were hypertensive and had at least three more risk factors for CV disease. ASCOT lipid subjects had mainly elevated total cholesterol, but < 250 mg/dL. In addition, JUPITER included soft outcomes such as hospitalization, whereas ASCOT only included hard events. Not surprisingly ASCOT had higher CV event rates than JUPITER.

The authors argue that the ASCOT subjects are a more typical population considered at increased risk for CV events than the JUPITER population, and the higher event rates in ASCOT attest to this observation. The modest increment in risk prediction by CRP in the ASCOT patients is not likely to be clinically significant. This conclusion

is in line with other prospective studies and adds to our knowledge about the use of CRP measurements.

CRP may be useful in JUPITER-type patients for making a decision on whom to treat with a statin. Healthy individuals with LDL cholesterol between 100-130 mg/dL may not need statin therapy unless they have other risk factors for CV disease or their CRP is elevated. Those with other risk factors or known disease would be treated with LDL-C levels in this range and CRP would add little value. This statement is likely to be controversial. The more contentious finding of this study is that CRP was not predictive of CV outcome in patients on statin treatment. Thus, the use of CRP to establish the utility of statin therapy should also be discouraged. ■

ABSTRACT & COMMENTARY

Is a Family History of Cardiovascular Disease Valuable?

By Michael H. Crawford, MD, Editor

SOURCE: Qureshi N, et al. Effect of adding systematic family history inquiry to cardiovascular disease risk assessment in primary care: A matched-pair, cluster randomized trial. *Ann Intern Med* 2012;156:253-262.

Although a routine part of a complete medical history, the value of systematically collecting family history has not been shown in controlled trials. Thus, these investigators from the United Kingdom sought to determine the feasibility of collecting a detailed family history and whether this information would identify more high-risk individuals for cardiovascular (CV) disease. Matched Family Practice pairs were randomly assigned to the family history intervention or usual care. Both groups received standard CV risk assessment. The intervention group family history was collected by a self-administered questionnaire. The primary outcome measure was the number of subjects classified as high risk for CV disease based on the two approaches (10-year risk > 20%). Also, anxiety levels were assessed by a standard questionnaire.

A total of 748 subjects from 24 family practices with no history of CV disease participated. The family history questionnaire was completed by 98% of the subjects. The increase in high-risk patients was 41% in the questionnaire group vs 6% in the usual care group where family history was obtained from the medical records. Anxiety levels were not increased by this intervention. The authors concluded that systematically obtaining family history identifies more subjects with high CV risk who may benefit from more aggressive preventive interventions.

■ COMMENTARY

This study objectively confirms the value of family history in CV disease prevention. A preliminary survey by the investigators demonstrated that often family history was not recorded in the medical record. One reason for this is the limited time available during the health visit. This was overcome in the intervention group by having the subjects fill out a questionnaire before the visit, which was feasible 98% of the time in this study population. The risk profile of the control group was obtained from the Framingham score, which does not incorporate family history but is widely used in the United Kingdom and the United States.

One of the strengths of the study was the pairing of practices involved with the same patient population, which eliminates ethnic or cultural differences in the groups that were compared. However, a weakness of the study is that few ethnic minorities or low education level subjects were included. Also, there were not a lot of smokers in the subjects studied. However, among the usual care group no one quit smoking, but 6 (20%) smoked less at 6 months of follow-up. Among the intervention group, 10 quit and 8 reduced their smoking (62%). Aspirin use increased among the intervention group as compared to the control group (48 vs 31% increase), but increases in statin use were the same. The patients reclassified as high risk in the intervention group were in the moderate-risk group before (Framingham risk 10-20% over 10 years). In the United Kingdom, aspirin use is not recommended for such patients. Unfortunately,

there are no outcome data in this study. Clearly, employing a more robust analysis of family history is feasible in some primary care practices, but whether this influences therapy and prevents CV events remains to be proven. ■

CME Instructions

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice, or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the evaluation is received, a credit letter will be sent to you. ■

CME Questions

1. Medtronic Fidelis ICD leads should be replaced:
a. immediately.
b. when problems are detected.
c. when the generator needs replacing.
d. B and C
e. None of the above

2. Cardiac resynchronization device therapy is now recommended for patients with class II heart failure if they have:
a. left bundle branch block with a QRS > 150 ms.
b. an ejection fraction < 36%.
c. noninvasive imaging shows dyssynchrony.
d. A and B
e. All of the above

3. The occurrence of acute myocardial infarction without chest pain is about:
a. 5%.
b. 10%.
c. 25%.
d. 35%.
e. None of the above

4. Newer drug-eluting stents exhibit which of the following advantages over older stents?
a. Reduced mortality
b. Less in-stent restenosis
c. Less stent thrombosis
d. All of the above
e. None of the above

5. A systematically taken family history of cardiovascular disease can:
a. improve the identification of high-risk individuals.
b. increase patient anxiety.
c. not be successfully accomplished in busy practices.
d. not impact smoking behavior.
e. All of the above

6. Elevated hsCRP in patients with risk factors for cardiovascular disease:
a. predicts cardiovascular events.
b. predicts the response to statins.
c. predicts events in those on statins.
d. All of the above
e. None of the above

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.*

Statins and the Risk of Diabetes

In this issue: Statins and diabetes risk; new treatment guideline for diabetes; new pertussis vaccine recommendation; antibiotics and rhinosinusitis; fluoroquinolones and cystitis; and FDA actions.

Do statins increase the risk of diabetes?

Studies have suggested that statins may increase the risk of diabetes in the elderly, women, and Asians. A new study reviews data from the 162,000 postmenopausal women enrolled in the Women's Health Initiative to investigate whether the incidence of new onset diabetes mellitus (DM) is associated with statin use among these women. This study reviewed records from women who were enrolled between 1993 and 1998 through 2005. More than 7% of the women in the study reported taking statins. Statin use at baseline was associated with an increased risk of DM (hazard ratio, 1.71; 95% confidence interval, 1.61-1.81). This association remained after adjusting for other potential confounders, including obesity, and was observed for all types of statin medications. The authors conclude that statin medication use in postmenopausal woman is associated with an increased risk for DM and that this may be a medication class effect (*Arch Intern Med* 2012;172:144-152). As pointed out in a brief comment in the same issue, observational data are potentially susceptible to "bias (confounding) by indication." In other words, women who would be prescribed statins may be inherently at risk for DM. This study did a good job of evaluating women with and without a history of cardiovascular disease and found that there was still an increased risk of DM. This finding "may have important implications for the balance of risk and benefit of statins in the setting of primary prevention in which previous meta-analyses show no benefit on all-cause mortality." The FDA has issued a new warning about statins and the risk of diabetes (see FDA actions). ■

Oral medications for diabetes

The American College of Physicians has published a new guideline for the "Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus" in the February 21 issue of the *Annals of Internal Medicine*. The guideline suggests that if diet, exercise, and weight loss fail to improve hyperglycemia, oral drug therapy should be initiated. Most diabetes medicines lower HbA_{1c} levels to a similar degree, and none of the medications have compelling outcomes data to suggest one class is superior to another class with regard to cardiovascular or all-cause mortality. But metformin "was more effective than other medications as monotherapy as well as when used in combination therapy with another agent for reducing HbA_{1c} levels, body weight, and plasma lipid levels (in most cases)." Therefore, the guideline recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy for most patients with type 2 diabetes. Metformin is effective at reducing glycemic levels and is not associated with weight gain. Additionally, the drug helps reduce LDL cholesterol and triglyceride levels. Metformin is contraindicated in patients with impaired kidney function, decreased tissue perfusion or hemodynamic instability, liver disease, alcohol abuse, heart

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.

failure, and any conditions that might lead to lactic acidosis. For patients with persistent hyperglycemia despite metformin, a second drug should be added. No good evidence supports one combination over another. Sulfonylureas have a higher risk for hypoglycemia and thiazolidinediones are associated with an increased risk for heart failure. There are no specific recommendations for the use of the glinides (nateglinide or repaglinide) or the DPP-4 inhibitors (linagliptin, saxagliptin, or sitgliptin). The guideline does not make a recommendation for combinations of more than two oral agents. Injectables, such as the various insulins and GLP-1 analogs, were not addressed in the guideline. (*Ann Intern Med* 2012; 156:218-231). ■

New recommendation for Tdap vaccine

The Advisory Committee on Immunization Practices, a division of the Centers for Disease Control and Prevention, is recommending that all adults get immunized against pertussis (whooping cough). Previously the committee had recommended that only adults who spend time around infants or young children should be immunized. The goal of the expanded recommendation is to prevent teenagers and adults from spreading the disease to infants. In 2010, California experienced a pertussis outbreak that infected 9000 people and resulted in 10 infant fatalities. The adult vaccine combines tetanus, diphtheria, and acellular pertussis (Tdap). ■

Antibiotics not needed for rhinosinusitis

Physicians now have more ammunition for not treating patients with acute rhinosinusitis with antibiotics, based on the results of a new study that shows amoxicillin is of no benefit in these patients. Researchers at Washington University in St. Louis randomized 166 adults with uncomplicated, acute rhinosinusitis to a 10-day course of amoxicillin 500 mg three times a day or matching placebo. The main outcome (change in the Sinonasal Outcome Test) was not significantly different between the two groups at day 3 or day 10. There was a slight improvement in the antibiotic group at day 7. The authors conclude that "treatment with amoxicillin for 10 days offers little clinical benefit for patients clinically diagnosed with uncomplicated acute rhinosinusitis." Patients with symptoms indicative of serious complications were excluded from the trial (*JAMA* 2012;307:685-692). ■

Fluoroquinolones for cystitis

Cefpodoxime is inferior to ciprofloxacin for short-course treatment of acute uncomplicated cystitis in women, according to new study. In a randomized, double-blind trial, 300 women ages 18-55 with uncomplicated cystitis were randomized to ciprofloxacin 250 mg orally twice daily for 3 days or cefpodoxime 100 mg twice daily for 3 days. The overall clinical cure rate with the intent-to-treat approach in which patients lost to follow-up were considered as having a clinical cure was 93% for ciprofloxacin compared to 82% for cefpodoxime. For the intent-to-treat approach in which patients lost to follow-up were considered as not having responded to treatment, the clinical cure rate was 83% for ciprofloxacin compared to 71% for cefpodoxime. The microbiological cure rate was 96% for ciprofloxacin compared with 81% for cefpodoxime. At follow-up, 16% of women in the ciprofloxacin group had vaginal *Escherichia coli* colonization compared with 40% in the cefpodoxime group. The authors conclude that cefpodoxime did not meet criteria for non-inferiority to ciprofloxacin for treating uncomplicated cystitis in women (*JAMA* 2012;307:583-589). The study is somewhat disappointing given the increasing rates of fluoroquinolone resistance in the community and the need for effective alternatives. ■

FDA actions

The FDA has issued a new warning and is requiring label changes to all statins regarding the risk of elevated blood sugar and reversible cognitive changes. The agency is making these changes after a comprehensive review of multiple studies that show increases in blood sugar associated with the drugs. A separate labeling change warns that cognitive effects have been reported with statin use, including transient memory loss and confusion — symptoms that are reversible with stopping the medication. There is no evidence that statins are associated with long-term cognitive changes or dementia. Statins affected by these warnings include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. In a separate warning, lovastatin is now contraindicated with strong CYP3A4 inhibitors, such as itraconazole and erythromycin. This is a similar warning to that issued for simvastatin in 2011.

In one of the strangest stories of the year, the FDA is warning oncologists that a counterfeit version of bevacizumab (Avastin) may have been purchased and used by some medical practices in the United States. The counterfeit version does not contain any active drug and may have resulted in patients not receiving needed therapy. Counterfeit bevacizumab was purchased from a foreign supplier known as Quality Specialty Products or Montana Health Care Solutions. The FDA is recommending that physicians stop using bevacizumab purchased from the suppliers and call the FDA immediately. ■

Clinical Briefs in Primary Care™

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By Louis Kuritzky, MD

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Rationale for Zinc Supplementation in Older Adults with Wounds

Source: Sallit J. *Ann Long-Term Care: Clin Care Aging* 2012;20:39-41.

Zinc deficiency is defined as a serum zinc level < 60 mg/dL. Unfortunately, there is some question about the reliability of zinc levels to accurately reflect zinc status, since some persons with prototypic symptoms of zinc deficiency (loss of appetite, diarrhea, hair loss, delayed wound healing, and smell and taste disturbances) have normal zinc levels. Residents of long-term care facilities are at risk for zinc deficiency, both because they may be consuming diets that are lower in zinc and also because they may not absorb zinc from the diet as well as younger persons. For instance, one clinical trial of patients from nursing homes (n = 617) found that almost half had subnormal zinc levels. Some medications can compound the issue — diuretics can deplete zinc.

The roles of zinc in wound healing are diverse, including collagen and protein synthesis, cell proliferation, and immune function. The body's demands for zinc are thought to increase at the time of injury, and continue through the early inflammatory phase; hence, zinc deficiency at this time can delay wound healing.

When a long-term care facility resident sustains a wound, although it is reasonable to ascertain zinc status through serum levels and treat accordingly, it appears equally reasonable based upon a high level of suspicion of zinc deficiency to simply supplement zinc at moderate doses (15-30 mg/d), since such dosing is well tolerated. Indeed, a clinical trial at slightly higher supplementation doses (25-50 mg/d × 3 months) has been documented to have a beneficial effect on wound healing in zinc- deficient individuals. The authors suggest that 40 mg/d be the maximum dose administered to non-deficient persons, due to tolerability issues (diarrhea, nausea, vomiting, vertigo). ■

Occupational Stress and Hypertension

Source: Rosenthal T, Alter A. *J Am Soc Hypertens* 2012;6:2-22.

The consequences of job-related stress (JRS) have been the object of a great deal of research. Of course it is difficult to determine the best measurement tool for JRS, and it is equally difficult to explain how similar levels of JRS are interpreted and managed variably by different individuals. Some of the data on JRS and its relationship to blood pressure suggest that JRS need not necessarily be perceived to be associated with adverse effects. Nonetheless, several lines of evidence lead to the conclusion that identification of JRS is replicable and consequential in some settings.

For instance, a review of data from 34 studies on professional drivers (e.g., bus drivers) found a consistent increased risk of heart disease and hypertension, attributed to the wide range of psychological and physical stressors. To describe the inherent stressful conflict of bus drivers, the authors remind us that the drivers are constantly dealing with the competing agendas of staying on time and optimizing safety.

Despite the large amount of descriptive data that help us identify the negative impact of job stress on health, there is little substantive information that anyone has found highly effective methods to improve outcomes from JRS. It is likely that reducing JRS and its consequences will require interventions on a public health level. ■

Association of Psoriasis with CV Risk Factors

Source: Shapiro J, et al. *J Am Acad Dermatol* 2012;66:252-258.

In the last decade, the recognition that rheumatoid arthritis (RA) is associated with adverse cardiovascular (CV) outcomes has been increasingly highlighted, to the point that some voices suggest including the presence of RA as a formal CV risk factor of similar impact to having a low HDL. Psoriasis (PSR) and RA share some common features, especially including their responsiveness to similar disease-modifying therapies, suggesting common pathophysiology. The mechanism by which RA imparts increased CV risk is unclear, though it is commonly attributed simply to the deleterious effects of chronic inflammation. Might PSR also be associated with CV risk?

To examine this issue, Shapiro et al performed a case-control study that compared PSR inpatients (n = 1079) to age- and gender-matched inpatient controls who had other non-psoriatic dermatitis issues, such as atopic dermatitis and contact dermatitis (n = 1079).

Multivariate logistic regression found that PSR was associated with greater odds

ratio (OR) for diabetes (OR = 1.43) and hypertension (OR = 1.31). Although PSR was associated with CVD, the association was no longer present when correcting for obesity and hypertension. Although the pathogenesis of increased CV risk associated with PSR is uncertain, the fact that PSR produces systemic effects on tumor necrosis factor alpha and other inflammatory markers may be critically linked. ■

Our Patients May Not be Getting the Message About Colon Cancer Screening

Source: Barton MK. *CA Cancer J Clin* 2012;62:1-2.

In its most recent guidance regarding colon cancer screening (CCS), the American Cancer Society iterated a new position on choice of tests, basically stating that "the best test is the test you can get done." This new orientation reflects both the philosophical and logistical realities that of the preventable cancers, CCS is the area in which we see the most missed opportunity. Currently, only about 60% of individuals are receiving any of the age-appropriate CCS available.

Barton reports on an observational study performed in 26 clinics in Michigan in which physicians volunteered to have patient visits audio-recorded, understanding that investigators were evaluating communication in general, but the study physicians were not told about any particular disease-state focus. Prior to the office visit, patients (n = 415) wrote down what information they felt they needed to understand to decide whether to participate in CCS.

Of the patients who indicated that information about test accuracy was very important, such information was imparted by the physician only 7% of the time. Even though most patients (77%-89%) rated information about pros/cons of testing and alternative testing methods as very important, communication about these components was similarly lacking (4% and 29%, respectively).

About half of patients did have questions about CCS, but clinicians invited questions in only about 5% of interviews. These well-demonstrated communication gaps provide an important opportunity for meeting patient needs, which will hopefully translate into better adherence with CCS recommendations. ■

BMD Testing: What's the Appropriate Interval?

Source: Gourlay ML, et al. *N Engl J Med* 2012;366:225-233.

Several national and international guidelines provide advice about when to consider bone mineral density (BMD) screening to identify osteoporosis (OSPS) based upon age, ethnicity, gender, and other risk factors. However, conspicuously lacking from these guidelines is an evidence-based path for when to recheck BMD, once a baseline is established.

The Study of Osteoporotic Fractures enrolled mid-life American women without OSPS at baseline (n = 4957; age ≥ 67) in an observational study. After baseline DEXA, scans were performed again at year 2, year 6, year 8, year 10, and year 16. The primary outcome of the trial was the interval after a baseline DEXA at which point 10% of participants would progress from normal BMD or osteopenia to OSPS.

As might be completely intuitive, the interval for progression to lower BMD levels was proportional to the degree of bone loss at baseline. That is, the interval before progression to OSPS for women with normal BMD or mild osteopenia at baseline was about 17 years; for those with moderate osteopenia, the interval was 4.7 years, and 1.1 years for women with advanced osteopenia (T-score = -2 to -2.49).

Based on these data, the authors suggest that for women with baseline T scores > -1.5, there is little likelihood of progression to osteoporosis (< 10%) over 15 years, and — in the absence of additional new risk factors to dictate otherwise — re-testing BMD might be reasonably put off for that same interval. For women with lower levels of BMD at baseline, however, a shorter interval for re-testing would be appropriate: 5 years for those with moderate osteopenia, and only 1 year for those with advanced osteopenia. ■

How Common is Vitamin B12 Deficiency in Patients on Metformin?

Source: Reinstatler L, et al. *Diabetes Care* 2012;35:327-333.

It has been recognized since the first published metformin clinical trials that B_{12} levels were impacted. For instance, a recent clinical trial found a 19% reduction in B_{12} levels (compared with placebo) after 4 years. Perhaps because common clinical signs of B_{12} deficiency (e.g., anemia, neuropathy, cognitive impairment) related to metformin treatment are rarely seen, clinicians have had low levels of apprehension about the effects of metformin on vitamin B_{12} levels.

How common is B_{12} deficiency in patients on metformin? An answer can be found in the NHANES data. Comparing adults with (n = 1621) and without (n = 6867) type 2 diabetes, Reinstatler et al report that biochemical deficiency of B_{12} (defined as level B_{12} < 148 pmol/L) was seen in 5.8% of diabetics on metformin; this was more than twice as frequent as the prevalence among diabetics not on metformin (2.4%), and about more than 1.5 times as frequent as in non-diabetics (3.3%).

One curious finding from this study was that consumption of B_{12} supplements by diabetics did *not* reduce the frequency of deficiency. It might be that the amount typically found in over-the-counter multivitamin supplements (6 mcg) is insufficient, even though the amount recommended by the Institute of Medicine is only 2.4 mcg/day. ■

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