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INSIDE

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Timing of Catheterization in ACS

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

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

Source: Sorajja P, et al. Impact of delay to angioplasty in patients with acute coronary syndromes undergoing invasive management: Analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. *J Am Coll Cardiol.* 2010;55:1416-1424.

Non-ST elevation (NSTE) acute coronary syndromes (ACS) can be managed by either an early invasive or early conservative strategy, with most data favoring an early invasive strategy in moderate- and high-risk patients. The most appropriate timing for intervention in patients being managed with an early invasive approach is the subject of some debate. Although there is a clear advantage to early revascularization in ST-elevation myocardial infarction, in NSTE-ACS it is not clear whether to delay and let the lesion "cool down" with anticoagulants/anti-platelet agents or proceed straight to the cath lab. Clinical studies have yielded conflicting results on this issue. Thus, Sorajja et al examined the ACUITY trial data to determine the effect of delay to angiography and intervention on outcomes in their patient population.

The ACUITY trial was a prospective, open-label, randomized, multicenter trial in which patients with NSTE-ACS undergoing an early invasive management strategy were randomized to receive one of three antithrombotic regimens: 1) unfractionated or low molecular weight heparin plus a glycoprotein IIb/IIIa inhibitor; 2) bivalirudin plus a glycoprotein IIb/IIIa inhibitor; or 3) bivalirudin alone. Patients were eligible for study participation if they were ≥ 18 years of age with symptoms of NSTE-ACS within the preceding 24 hours and if one or more of the following high-risk criteria were met: new ST-segment depression or transient elevation of ≥ 1 mm; elevations in the troponin I, troponin T, or creatine kinase-MB levels; known coronary artery disease; or all four other variables for predicting Thrombolysis In Myocardial Infarction (TIMI) risk scores for unstable angina. Exclusion criteria were ST-seg-

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ment elevation MI or cardiogenic shock; bleeding diathesis or major bleeding episode within two weeks; thrombocytopenia; a calculated creatinine clearance rate of < 30 mL/min; recent administration of abciximab, warfarin, fondaparinux, fibrinolytic agents, bivalirudin, or two or more doses of low molecular weight heparin; and allergy to any of the study drugs or to iodinated contrast medium that could not be controlled in advance with medication. Follow-up was performed at one month and 12 months. Three primary endpoints at 30 days were prespecified: composite ischemia (death from any cause, MI, or unplanned revascularization for ischemia), major bleeding (not related to coronary artery bypass grafting [CABG]), and net adverse clinical events (composite ischemia or major bleeding).

Results: Of the 13,819 patients enrolled in the ACUITY study, 7,749 patients underwent percutaneous coronary intervention (PCI) at the discretion of the operator. There were significant differences in the baseline demographics and angiographic features in the groups who had PCI < 8 hours, 8-24 hours, and > 24 hours after hospitalization. Patients who had delayed PCI more frequently had elevation of cardiac troponins, high TIMI risk score (5 to 7), left main culprit lesion, baseline TIMI flow grade 3, prior history of diabetes mellitus, MI, left main disease, CABG, and prior use of antithrombins and thienopyridines. There was no difference in procedural success after PCI for the three patient groups.

Delay in angiography > 24 hours was a significant predictor of death at 30 days and one year. After multivariable risk adjustment, patients whose PCI was delayed > 24 hours after admission had higher rates of death (hazard Ratio [HR] 2.1; $p < 0.001$) and death or MI (HR 1.5; $p < 0.001$) at 30 days. This was also seen at 12 months (death HR 1.6, death or MI HR 1.4; both $p < 0.001$). This relationship between delay and adverse outcomes was apparent across all levels of risk by TIMI risk score, and across all three anticoagulant regimen randomization groups. The authors conclude that delaying revascularization with PCI > 24 hours in patients with NSTE-ACS was an independent predictor of early and late mortality and adverse ischemic outcomes.

■ COMMENTARY

Several studies have examined the optimal timing of catheterization and PCI in patients presenting with ACS. The TIMACS study (*N Engl J Med.* 2009;360**:**2165-2175) suggested that earlier intervention (median 14 hours after admission) was superior to delayed intervention (median 50 hours) but only in high-risk patients. Analysis from the GRACE registry (*Am J Cardiol.* 2005;12:1397-1403) suggested the opposite: that delaying angiography was associated with better outcomes. The ABOARD study (*JAMA.* 2009;302:947-954) compared immediate angiography (average one hour) vs. delay until the next working day (average 21 hours). They showed no benefit to immediate cardiac catheterization. The current study by Sorajja et al suggests that PCI should be performed expeditiously, but not necessarily immediately upon admission. Their findings are consistent with both the TIMACS study and the ABOARD study, suggesting that catheterization should be performed within approximately 24 hours. However, studies that challenge that premise remain. It is important to note that this was not a randomized, controlled trial; it was a retrospective analysis, and we should not change management decisions based on post-hoc analyses such as this alone. However, the study is strengthened by the fact that it was performed on a large dataset with contemporary anticoagulant, anti-platelet, and PCI strategies. Clinicians should consider higher-risk ACS patients for early angiography and possible PCI, and in the absence of hemodynamic instability or ongoing ischemia, the optimal window for PCI seems to be within the first 24 hours. ■

Lenient vs. Strict Rate Control in Patients with AF

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD
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Dr. DiMarco is a consultant for Novartis and does research for Medtronic and Guidant.

Source: Van Gelder IC, et al. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med*. 2010 (e-published on March 15, 2010).

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The Rate Control Efficacy in Permanent Atrial Fibrillation (RACE II) study compared two different strategies for rate control in patients with permanent atrial fibrillation. Patients were eligible for the study if they had relatively recent onset atrial fibrillation (duration less than or equal to 12 months), an age of 80 years or younger, a mean resting heart rate above 80 bpm, and able to take appropriate anticoagulation therapy. Patients were randomly assigned to either a lenient rate control strategy or a strict rate control strategy. Resting heart rates were measured using a standard 12-lead electrocardiogram after two to three minutes of rest in the supine position. In the lenient rate control strategy, subjects had only a target resting heart rate below 110 bpm. Additional monitoring was not performed. In the strict control group, the target resting heart rate was 80 bpm. In addition, heart rate was measured during moderate bicycle exercise, with a target of less than or below 110 bpm during mild exercise. In addition, the strict control group also underwent routine 24-hour Holter monitoring to check for bradycardia. Rate control medications were titrated in both groups during follow-up outpatient visits every two weeks until the target was achieved and then on an annual basis.

The primary outcome was a composite of cardiovascular death, heart failure hospitalization, stroke or systemic embolism, major bleeding, serious arrhythmia, life-threatening adverse effects from the rate control therapy, and the need for implantation of a pacemaker or implantable defibrillator due to bradycardia or arrhythmia. Secondary outcomes were death from any cause, symptoms, and functional status. Outcome events were adjudicated by an events committee that was unaware of the randomized treatment assessments. The trial was designed as a noninferiority trial comparing the two strategies.

The study enrolled 311 patients in the lenient rate control group and 303 patients in the strict rate control group. The clinical characteristics of the two groups were well matched. The average age was 68 $\pm$ 6 years, and 66% were male. The median duration of atrial fibrillation was three months. Seventy-two percent had undergone a previous electrocardioversion. Hypertension, present in 61%, was the primary cardiac diagnosis. Most patients were in New York Heart Association (NYHA) functional class I (65%), with 30% in functional class II and only 5% in functional class III. The resting heart rate at study entry was 96 $\pm$ 13 bpm. After dosage adjustment, 98% of the lenient rate control group, compared to 67% in the strict rate control group, met their rate control target. Only 75% of the patients in the strict rate control group met their resting heart rate target, and only 72% met their exercise resting target. In the strict rate control group, Holter monitoring showed a mean heart rate of 78 $\pm$ 11 bpm. The maximum RR interval observed was 2.3 $\pm$ 0.6 seconds. In the lenient rate control group, only 75 non-routine visits were required to achieve target; whereas in the strict rate control group, 684 total visits were required. Among the 100 patients who failed to achieve their rate control target in the strict control group, 25 had drug-related serious adverse events, and in 22 the target was impossible to achieve with drug therapy.

Almost 65% of the patients in the lenient rate control group were controlled with one or fewer rate control agents. Beta adrenergic blocking agents were the drugs most commonly effective. In comparison, 67% of the patients in the strict rate control group required more than one agent.

The primary composite endpoint was reached by 38 patients (12.9%) in the lenient control group compared to 43 in the strict rate control group. Mortality was similar in both groups with 17 deaths (5.6%) in the lenient control group at three years compared to 18 deaths (6.6%) at three years in the strict rate control group. There was no significant difference in the prevalence of symptoms. Forty-five percent of patients in the lenient control group had persistent symptoms, compared to 46% in the strict control group. New York Heart Association functional class distribution, the frequency of hospitalizations, and other adverse events were similar between the two groups.

The authors conclude that lenient rate control was not inferior to strict rate control in patients with atrial fibrillation in terms of major clinical events. Lenient rate control strategy is more convenient and requires fewer outpatient visits and follow-up visits.

■ COMMENTARY

The AFFIRM trial (*N Engl J Med*. 2002;347:1825-1833) and the original RACE trial (*N Engl J Med*. 2002;347:1834-1840) were the two pivotal trials that established that rate control and rhythm control strategies were both valid in patients with atrial fibrillation. Those two studies, however, used different criteria for rate control. The AFFIRM trial used values similar to those in the strict control group, and the RACE trial used values similar to those in the lenient control group in RACE II. The current study shows that, at least within the heart rate limits here, a lenient rate control strategy may be easier to implement with no loss of efficacy.

This conclusion seems justified based only on the major endpoints included in this paper. Substudies from RACE II will deal with symptoms and quality of life, but these data have not yet been reported. Certainly, any approach that makes management of patients with atrial fibrillation easier without doing harm would be useful for clinicians. ■

Frail Elderly and Cardiac Surgery

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Lee DH, et al. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. *Circulation*. 2010;121:973-978.

Although age is a risk factor for morbidity and mortality with cardiac surgery, chronologic age does not always

reflect biological age. Although frailty has been shown to predict falls, hospitalization, institutionalization, and mortality in geriatric populations in the community, it has not been systematically studied in patients undergoing surgery. Thus, these investigators from Canada identified 157 frail patients undergoing cardiac surgery. Frailty was defined as having one of the following three characteristics: lack of independence in activities of daily living (64 patients), impaired ambulation (124), and dementia (22). The frail patients represented 4% of those undergoing cardiac surgery. On average, frail patients were older than non-frail patients, although the age ranges were similar (71 years, 61-78 vs. 66 years, 57-74 years). Frail patients were more likely to be female and have more comorbidities, which increases the risk of surgery. Logistic regression analysis showed that frailty was an independent predictor of in-hospital and two-year mortality (OR = 1.8 and 1.5) and discharge to an institution (OR = 6.3). The authors concluded that an assessment of frailty improves preoperative risk assessment in cardiac surgery and should be considered in decisions regarding processes of care.

■ **COMMENTARY**

As the U.S. population becomes increasingly older, frailty has emerged as a condition that impacts prognosis in general surgery and other procedures, but this is the first report of its impact on cardiac-surgery outcomes. There is no accepted definition of frailty, but most clinicians would liken it to art—"I know it when I see it." These investigators described it as a biologically reduced resistance to stress that is characterized by decreased activity, poor endurance, and the need for help in activities of daily living (dependence). They included dementia as a criterion because of other data showing that it impacts outcomes and leads to reduced activity and dependence.

They set a low bar for frailty, requiring only one of three factors: impaired ambulation, dependence, and dementia. Yet, they showed that frailty, by this definition, independently predicted mortality and discharge to an institution rather than home. Interestingly, the majority of patients classified as frail met the criterion of impaired ambulation, which is not infrequent. Although frail patients were older on average, the influence of frailty was independent of age. Several factors are independent predictors of mortality post-cardiac surgery, but only three had higher odds ratios than frailty (OR = 1.8): urgent surgery (OR = 5.1), renal failure (OR = 2.3), and congestive heart failure (OR = 2.2). In the prediction of need for institutionalization, frailty had the highest OR (6.3), followed by urgent surgery (4.5). Other factors had ORs of 2.0 or less.

These findings have implications for the management of patients being considered for cardiac surgery. The consent process should include this additional risk, since it is not accounted for in the STS or Euroscore risk models that are often used. Also, frail patients should be strongly considered for other management strategies rather than traditional cardiac surgery. ■

Extraction of Infected Pacemaker/ICD Leads

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Grammes JA, et al. Percutaneous pacemaker and implantable cardioverter-defibrillator lead extraction in 100 patients with intracardiac vegetations defined by transesophageal echocardiogram. *J Am Coll Cardiol*. 2010;55:886-894.

The number of patients with implantable pacemakers and implantable defibrillators has increased markedly in recent years. Unfortunately, cardiac rhythm device (CRM)-related infections have also increased, and management of these infections is often problematic.

In this paper, Grammes et al from Hahnemann University Hospital in Philadelphia describe their experience with device-related infections that were associated with intracardiac vegetations. The authors maintained a longitudinal database of all patients undergoing pacemaker or ICD lead extraction at their institution. They identified patients in the database who had device-related endocarditis, as defined by the modified Duke criteria. In most patients, preoperative transesophageal echocardiography (TEE) was used to risk stratify patients. Intracardiac vegetations were defined as discrete echogenic masses found by transthoracic or transesophageal echocardiography on a valve, lead, or endocardial surface. Lead extractions were performed either with manual traction or with powered electrosurgical or Excimer laser extraction sheaths. Occasional patients required a femoral snare or basket extraction technique for complete lead removal. When necessary, patients were maintained with a temporary pacing system with subsequent device reimplantation based on sterility of blood cultures and resolution of vegetations.

Over a 16-year period, 984 patients underwent CRM device extraction; 1,838 leads were removed. In 480 patients (49%), the reason for extraction was systemic or localized infection. Of these 480 patients, 100 patients (21%) had echocardiographic evidence of intracardiac vegetations. The size of the vegetations ranged from 0.2 to 0.4 cm, with a mean diameter of 1.6 cm. In these 100 patients with vegetations, 215 leads were removed using standard percutaneous techniques. The most common infectious organisms were methicillin-resistant *Staphylococcal aureus* and methicillin-sensitive *Staphylococcal aureus*. Other organisms identified included coagulase-negative *Staphylococcal* species, *Enterococcus faecalis*, *Streptococcus*, vancomycin-resistant *Enterococcus*, *Citrobacter,* and *Candida* species. In 16 patients, blood cultures were negative despite clinical evidence of infection and echocardiographic evidence of vegetations. In some, this may have been due to prior antiarrhythmic therapy.

The median implant duration was 32.5 months, with a range of 1 to 300 months. The median time for extraction of the first lead was three minutes, but the range was broad, from 1 to 187 minutes. Extraction times were similar to those in a reference population without endocarditis. In 54 patients, new CRM devices were reimplanted during the hospitalization, with a median time to reimplantation of seven days. Forty-six patients did not receive implants during the hospitalization. In 18 of these 46 patients, the devices were not reimplanted because of persistent systemic infection, despite complete device removal. Among the 54 patients who underwent device reimplantation during the original hospitalization, 51 were discharged in stable condition. None of these 51 patients had relapsing infections that required a second extraction.

Long-term follow-up was available in only 71 patients, since many patients were followed at other institutions. During follow-up, 19 of these patients died (27%). Ten patients died during the initial hospitalization and seven after discharge. Persistent septicemia was the cause of death in 11 patients. Seven patients died of unknown causes, without evidence for recurrent infection, and one patient had sudden death. Five patients had complications during lead extraction. These complications included embolization of the vegetation to the lungs in two patients, embolization of a lead fragment, severe tricuspid regurgitation with a posterior flail tricuspid leaflet, and prolonged hypotension in single patients. All of these five patients recovered and did well during follow-up.

The authors argue that percutaneous lead extraction is possible in patients with endocarditis and vegetations. Mortality is primarily related to persistent sepsis and multi-organ failure rather than complications of the lead extraction itself. The data from this series compare favorably with other results in the medical and surgical literature that included patients with and without vegetations.

■ COMMENTARY

Device-related infections are increasing in frequency as the number of implants increase and patients are able to live longer with these devices. The early infection risk after a CRM device implant is about 1%-1.5%. Over time, chronic leads may become infected in the setting of sepsis from another primary source, and devices may erode through the skin if the pocket was not created properly. The pocket infection rate with generator changes or device upgrades is higher than that seen with initial implants.

Successful treatment of a CRM device-related infection usually requires complete removal of all infected hardware. Up until about six months after implant, virtually all new leads can be removed with just manual traction, and special tools and skills are not usually required. After six months, the development of fibrosis may fix the lead to other leads, the blood vessel wall, or the endocardium, and manual traction may not be effective. If excess force is applied, the lead itself may break down, making eventual removal even more difficult. Removal of these leads often requires either special transvenous sheaths to break up the fibrotic adhesions or direct, open-chest surgical removal. Some authors have argued in the presence of visible vegetations on the lead, direct surgical extraction should be preferred to minimize the risk of embolization of the infected material.

In this paper, Grammes et al, from an experienced extraction referral center, show that most infected leads with vegetations may be safely removed with transvenous approaches. Complications directly related to the vegetations were uncommon. Although some patients died with persistent sepsis and multi-organ failure, these conditions were present before the extraction. Are there vegetations that are too big to remove transvenously? In this series, vegetations up to 4 cm in diameter were seen. Larger vegetations are rare but may be seen in some cases, especially with fungal endocarditis. Surgical management of such very large vegetations may still be required.

My current approach is similar to the one described by the authors. If there is a hemodynamic reason for a direct operation to replace an infected valve, the leads may be removed surgically at the same time. In most other cases, a transvenous extraction approach in a center with experienced operators is likely to be a better option. ■

Reproducibility of Mitral Regurgitation Quantitation

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Sources: Biner S, et al. Reproducibility of proximal isovelocity surface area, vena contracta, and regurgitant jet area for assessment of mitral regurgitation severity. *JACC*. 2010;3:235-243. Grayburn PA and Bhella P. Grading severity of mitral regurgitation by echocardiography: science or art? *JACC*. 2010;3:244-246.

The American Society of Echocardiography (ASE) has recommended that quantitative techniques be used to assess the severity of mitral regurgitation (MR) by echocardiography. Such measurements have been shown to accurately estimate the severity of MR with good reproducibility in research labs. These investigators, from Cedars Sinai Medical Center in Los Angeles, sought to assess interobserver agreement in the quantitation of MR in a typical clinical setting. The study focused on three measures of MR severity: color flow jet area, vena contracta (VC) width, and proximal isovelocity surface area (PISA) radius, which is the key measurement for the estimation of effective regurgitant orifice area (EROA). Web-based images from 16 consecutive patients were measured by 18 experienced cardiologists in 11 centers worldwide. Institutional variability was assessed by comparing the interobserver variability be-

tween those at the same institution to those at other institutions. The studies were all done at one center by the same technologist. Each echocardiogram was categorized as showing severe or non-severe MR for each measurement. Severe MR was defined as VC ≥ 7mm, EROA ≥ 40mm^2, or jet area grade of 3 or 4. Interobserver agreement was classified as substantial if ≥ 80%; fair if between 60% and 79%; and poor if below 60%.

Results: Interobserver agreement between the semiquantitative jet area grade and the two echo Doppler measurements were about the same and only fair: Kappa = 0.32 for MR grade; 0.28 for VC; and 0.37 for PISA. Multivariate predictors of substantial agreement (≥ 80%) included the ability to identify a regurgitant orifice to measure VC and a central regurgitant jet for PISA (p = 0.02). The authors concluded that the quantitative measurements of MR severity recommended by the ASE are only modestly reliable, but the identification of a distinct regurgitant orifice area and a central MR jet predict substantial interobserver agreement.

■ COMMENTARY

The accurate assessment of MR severity is critical today since asymptomatic patients with severe MR who have a repairable valve are candidates for surgery, according to the latest guidelines. In the Acorn Clinical Trial of corrective mitral valve surgery for heart-failure patients with MR, echo studies that showed significant MR were submitted to a core lab. The core lab found that more than 40% did not have significant MR: 7% had none; 11% were mild; and 23% were moderate. If sites selected for a research study cannot get it right, is there hope for the rest of us? This study explores the reproducibility of the critical quantitative MR parameters in clinical practice at multiple sites, and found similar results. Interestingly, the variability in measurements was the same between individuals at the same institution and in comparison to readers at other institutions. This suggests that even institutional attempts to standardize readings are not always successful.

The ASE recommends an integrated approach where all qualitative and quantitative measures are considered to assess MR severity. This approach has never been fully tested because of the lack of a suitable gold standard, but studies evaluating multiple measures have shown considerable overlap between those ultimately graded as moderate or severe MR. Other measures considered included jet intensity, pulmonary artery pressure, pulmonary venous flow pattern, left atrial size, and left ventricular volume. Other factors to consider are the etiology of MR, valve morphology, jet characteristics (i.e., eccentric), dynamic changes during systole, and the image degradation of stop frame images. This complexity has prompted some to suggest that the grading of MR is more art than science. Although not critically evaluated, others have suggested that if the left atrium and left ventricle are not dilated, then the diagnosis of severe MR should be questioned.

There are some limitations to this study. There were more cardiologists than subjects in the study. A larger study would have been more convincing. Also, only patients graded as moderately severe to severe were considered. Inclusion of patients with mild MR would probably have improved reproducibility. Finally, there was no gold standard, so the accuracy of the severity estimation was not tested. The accompanying editorial concludes that the solution to this problem is improvement in "training, continuing education, and credentialing for sonographers and physicians involved in the increasingly complex patients with MR." Oh come on, can't we invent a new technological solution? MRI, CT, anyone? ■

Non-Dilated Cardiomyopathy

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Doumas A, et al. Prevalence and clinical characteristics of non-dilated cardiomyopathy and the effect of atrial fibrillation. *Am J Cardiol*. 2010;105:884-887.

Little is known about the least common of left ventricular (LV) remodeling abnormalities, low ejection fraction (EF) with no cavity dilation or non-dilated cardiomyopathy. Thus, these investigators from the Lahey Clinic in Burlington, MA, retrospectively analyzed 98 such patients. To obtain the study population, they reviewed six months of echocardiograms (3,350) and selected those with an EF < 0.45 and a LV diastolic diameter < 5.6 cm. They excluded those with congenital, valvular, coronary disease with wall-motion abnormalities and cardiac amyloid. The prevalence of non-dilated cardiomyopathy in this echocardiographic laboratory population was 14% (98/3,350). One half had a history of hypertension and 43% had atrial fibrillation (AF). Symptoms were more common in those with EF < 30% (37%) vs. > 30% (12%, p < 0.01). Concentric remodeling was present in 41% and LV hypertrophy (mass > 105 g/m^2) in 12%. Therefore, increased wall thickness or mass was present in over half. About half the patients had a follow-up echocardiogram (average 422 days later), and the mean EF increased between studies (p < 0.01), mainly in the patients with AF (33% to 39%). The authors concluded that non-dilated cardiomyopathy is often associated with hypertension or AF, and an improvement in EF is seen in the majority during follow-up.

■ COMMENTARY

Among those referred to an echocardiographic laboratory with low EF, 14% had no LV dilation, which is similar to another reported experience (20%). In these patients, over half had either increased LV wall thickness or increased LV mass. This could be explained by the 50% incidence of hypertension in these patients, which is similar to other heart-failure trials. However, the incidence of AF in these patients was twice what

has been seen in large heart-failure trials (42% vs. 12%-25%). In a retrospective study, it is difficult to tell whether AF is causative or a marker for low EF. We know that unchecked rapid AF can cause reduced LV function (tachycardia-induced cardiomyopathy). This may explain many of these cases, since EF rose over time in the AF subgroup. Perhaps the heart rate was brought under control or AF was eliminated between the two echocardiograms. Regardless, it would appear that there is significant potential for improvement in patients with non-dilated cardiomyopathy and AF.

Those without AF may represent a transition stage between hypertrophy with diastolic dysfunction and early systolic dysfunction before dilation occurs. Against this hypothesis is that in the subgroups with two echoes, no increase in cavity volume was observed. Consequently, this could represent a separate disease state, the etiology of which is unclear, but is probably multifactorial. Interestingly, less than one-quarter were significantly symptomatic, but symptoms were more common in those with EF < 30%. Since the average EF was 34% (range 15%-45%), the number with significant symptoms (NYHA class III-IV) seems low at 22%. Perhaps the lack of LV dilation is associated with lower filling pressures. Unfortunately there is no diastolic function data in the report, and left atrial pressure cannot be estimated from the data given. Until more data on non-dilated cardiomyopathy are forthcoming, the clinical message is that this entity seems to have potential for improvement in LV function. Thus, aggressive therapy should be instituted. ■

Transcatheter Aortic Valve Implantation (TAVI) for AS Patients at High Surgical Risk

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

Source: Rodes-Cabau J, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk. *J Am Coll Cardiol.* 2010;55:1080-1090.

Surgical aortic valve replacement (SAVR) remains the gold standard treatment for calcific aortic stenosis (AS). However, AS is predominantly a disease of the elderly and, thus, many patients have significant comorbidities that make SAVR very high risk. Risk scores, such as the Society of Thoracic Surgeons (STS) risk score, can predict the likelihood of mortality after SAVR. Transcatheter Aortic Valve Implantation (TAVI) is an emerging therapy that has advanced significantly over recent years and may offer a reasonable alternative therapy for patients that are deemed to be at high surgical risk. An additional consideration in assessing the role for TAVI in clinical practice is the presence of a porcelain aorta or frailty. These conditions are often reasons that patients are considered inoperable or too high risk for SAVR, yet they are not included in risk scores. Thus, their role in evaluation for TAVI remains ill-defined. Therefore, Rodes-Cabau et al examined data from their multi-center registry in Canada to determine the outcomes of all patients who underwent TAVI by both the trans-apical and trans-femoral routes. In addition, they describe the outcomes in patients who were deemed inoperable due to frailty and porcelain aorta.

Since January 2005, TAVI has been approved in Canada for "compassionate use" in patients with severe symptomatic AS who were deemed too high risk for SAVR. Data have been prospectively collected in a multi-center registry at six Canadian centers. All patients were evaluated by a team that included an interventional cardiologist and a cardiac surgeon and were deemed too high risk or inoperable for SAVR, but suitable for TAVI. All patients underwent evaluation with echocardiography, coronary angiography, aorto-ilio-femoral angiography, and computed tomography. From January 2005 to June 2009, 339 patients underwent "compassionate use" TAVI, using exclusively the Edwards Sapien valve (three different generations of valve as the technology evolved), 167 via the trans-femoral route and 172 via the trans-apical route. Six patients had unsuccessful trans-femoral procedure and required a second procedure (five trans-apical, one trans-femoral). The patients were high risk: average age was 81 ± 8 years, 45% were male, mean aortic valve gradient was 46 ± 17 mmHg, valve area was 0.63 ± 0.17cm^2, renal impairment in 56%, COPD in 30%, porcelain aorta in 18%, frailty in 25%, and 91% were NYHA class III-IV heart failure.

Results: The procedure was successful in 93.3% of cases. Mean aortic valve gradient decreased from 46 ± 17 mmHg to 10 ± 4 mmHg ($p < 0.0001$) and mean valve area increased from 0.63 ± 0.17 cm^2 to 1.55 ± 0.41 cm^2. Aortic regurgitation was present after the procedure in 84% of cases (trivial or mild 78%, moderate 5%, severe 1%).

TAVI procedural mortality was 1.7% (n = 5), compared to the expected surgical AVR mortality of 9.8% ± 6.4% by STS score. Reasons for procedural death were major vascular complications (n = 2, 0.6%), severe left ventricular dysfunction after valve implantation (n = 2, 0.6%), and cardiac perforation (n = 1, 0.3%). In the 30 days following TAVI, there were an additional 30 deaths, for a cumulative 30-day mortality of 10.4%. The post-procedural deaths were due to multiorgan failure (n = 6), major bleeding (n = 5), pneumonia/septicemia (n = 4), stroke (n = 2), ventricular arrhythmia (n = 2), heart failure (n = 2), sudden unexplained death (n = 2), cardiogenic shock, myocardial infarction, late valve embolization, pulmonary embolism, peripheral embolism, aortic rupture, and severe mitral regurgitation due to leaflet perforation (n = 1 each). Importantly, patients with porcelain aorta and frailty had similar mortality acutely and at 30 days to the entire cohort, but frail patients were more likely to develop renal failure requiring dialysis after the procedure.

Multivariate analysis identified three predictors of 30-day mortality: pulmonary hypertension (Odds Ratio [OR] 2.1), severe MR (OR 3.0), and the need for peri-procedural hemodynamic support (OR 6.8). Frailty, porcelain aorta, and route of valve implantation were not significantly associated with mortality.

Survival at one year was 76% and at two years was 64%. Predictors of late mortality were post-procedural sepsis (Hazard Ratio [HR] 3.5), need for peri-procedural hemodynamic support (HR 2.6), pulmonary hypertension (HR 1.9), renal impairment (HR 2.3), and COPD (HR 1.8). The authors conclude that TAVI via both transapical and transfemoral routes was associated with comparable mortality, as predicted with STS score for the treatment of patients at very high or prohibitive surgical risk, including porcelain aorta and frail patients. Baseline and procedural factors, but not route of approach, predicted worse outcomes.

■ **COMMENTARY**

This is the largest series using the Edwards Sapien valve, and the data are made more robust by the fact that it is a multi-center study, not just performed in a single center with particular expertise. The procedural mortality compares favorably with the predicted surgical mortality by STS score, but there is significant mortality in the month and years following the procedure. Thus, TAVI does not appear to be a panacea for this patient group, which has significant co-existing medical problems. Importantly, the patients with porcelain aorta, who are often refused SAVR, had comparable outcomes with the entire cohort, even with ~ 50% being performed via the transfemoral route.

STS risk score was not predictive of poor outcomes in this series of patients undergoing TAVI. New risk predictors need to be established for this emerging technology in order to guide clinicians in appropriate patient selection. As data continue to accumulate in TAVI, it appears that this is a promising technology with the potential to benefit patients who have traditionally been untreatable or very high risk with SAVR. ■

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. ■

CME Questions

24. The best treatment for infected pacemaker leads is usually:

a. prolonged antibiotic therapy alone.
b. transvenous lead extraction.
c. surgical lead extraction.
d. radiation therapy to the lead.

25. To prevent major cardiovascular events, heart rate control in atrial fibrillation should be:

a. ≤ 80 bpm resting.
b. ≤ 110 bpm resting.
c. ≤ 80 resting and ≤ 110 with exercise.
d. 110-120 bpm resting.

26. Frailty in pre-cardiac surgery patients is defined as:

a. needing help with activities of daily living.
b. impaired ambulation.
c. dementia.
d. One or more of the above.

27. Non-dilated cardiomyopathy (low EF) is associated with:

a. hypertension.
b. atrial fibrillation.
c. excess alcohol.
d. A & B.

28. The reproducibility of mitral regurgitation severity quantitation is better if there is:

a. a distinct vena contracta in the color flow signal.
b. an eccentric jet.
c. a central jet origin.
d. A and C.

29. Percutaneous aortic valve replacement mortality is:

a. equal to the predicted surgical mortality.
b. higher than the predicted surgical mortality.
c. lower than the predicted surgical mortality.
d. lower with the retrograde aortic approach.

Answers: 24. (b); 25. (b); 26. (d); 27. (d); 28. (d); 29. (c)

Health Care Reform Update

What Health Care Reform Means to You A supplement to *Clinical Cardiology Alert*

Increased provider access tops list of what clinicians will like about HC bill

Changes will take a few years

HEALTH CARE CLINICIANS AND ORGANIZATIONS LIKELY will find that the new health care reform bill's positive features outweigh its drawbacks, experts say.

The Patient Protection and Affordable Health Care Act, signed into law on March 23, 2010, by President Barack Obama, provides a series of changes to take place to health care insurance coverage, Medicare, Medicaid, prescription drugs, quality improvement initiatives, medical malpractice, and other items. These are to be implemented from 2010 to 2014.

"The thing that is so big is the coverage for tens of millions of people who don't have health insurance now," says **Cecil Wilson**, MD, an internist in Winter Park, FL, and the president-elect of the American Medical Association in Chicago, IL.

People no longer will have to worry about losing health care coverage for existing diseases if they lose their jobs, and increasing numbers of people will have access to preventive care, primary care, and disease management, Wilson adds.

"Those are the big things that make this such a sea change in my opinion," he says. "For physicians, this is good because they won't have to worry about their patients' insurance being cut off, and thus putting their patients at risk."

Hospitals will find that significantly more patients will have health care coverage, resulting in a decline in uncompensated care, says **Caroline Steinberg**, vice president for trends analysis for the American Hospital Association in Washington, DC.

"We also would expect that demand for care from formerly uninsured patients will increase," Steinberg says. "Hopefully, we'll see some increases in primary care so by the time they hit the hospital they won't have some of the same kinds of problems they've had before."

The new bill provides billions of dollars in funding for clinics that provide primary care to uninsured, indigent, and immigrant patients. In 2014, it also expands Medicaid to all non-Medicare eligible individuals who have incomes up to 133% of the federal poverty level. These initiatives could help send more people to primary care services and keep them from using the emergency room for non-emergency care, Steinberg adds.

"We may [identify] more people with conditions that require specialty care because once people have access to coverage they tend to use more health care across all levels of the system," Steinberg says. "So that could go either way."

Plus, hospitals should expect the next few years to continue to be rough fiscally since most of the more significant provisions in the bill will not be fully implemented until 2014.

"Our hospitals are telling us that uncompensated care is going up because of job losses and loss of insurance, and these people show up in hospitals," Steinberg says.

There won't be much improvement in the immediate future until the economy recovers and the government provides more funding for Medicaid, she notes.

More oncology patients will have access to care, as a result of the bill's prohibition of lifetime limits on the dollar value of coverage, which begins Jan. 1, 2014. There is a temporary national high-risk pool to provide health care coverage to people with pre-existing medical conditions, which will be in place between June 2010 and 2014.

"Many cancer patients who need repeated courses of treatment can easily exceed their caps and find themselves unable to afford needed treatment and medication," says **Allen S. Lichter**, MD, chief executive officer of the American Society of Clinical Oncology (ASCO), in a statement issued after the bill was signed.

By this fall, insurers will not be able to exclude children with pre-existing conditions from being covered by their family policy, and this also is a positive move, Lichter says.

The bill's focus on prevention and wellness will benefit infectious disease and public health initiatives.

"There are a few things in the bill that we're pleased to see stay in the final version," says **Michael Ochs**, government relations associate with the Infectious Diseases Society of America (IDSA) in Arlington, VA.

The bill's emphasis on wellness and disease prevention with billions of additional federal dollars for these is one example, Ochs says.

The bill's impact on physician and other provider payments is a more mixed bag, however. *(See story on*

physician payments, below.)

"There's a 10% incentive pay for primary care and general surgery," says **Jason A. Scull**, program officer for clinical affairs at IDSA.

"They're focusing on primary care in a lot of these new innovative payment models, but I think primary care does need to be incentivized," Scull says.

But the drawback is that cognitive specialists, like infectious disease specialists, cardiologists, and neurologists, could be shortchanged as the pie is cut differently, but not expanded.

"There will be unintended consequences," Scull notes. "Already last year the Centers for Medicare & Medicaid Services eliminated payments for consultation codes that cognitive specialties use to give them money to distribute elsewhere in the fee schedule and to send more to primary care physicians."

This redistribution of payments might result in fewer medical students choosing to spend extra years of training beyond their general internal medicine residency, he adds.

While the sweeping health care reform provides some specifics on how changes will occur in the industry, no one knows precisely how things will change until the regulatory details emerge, the experts say.

"There are a lot of moving pieces to this," Scull says. "I think it's anybody's guess to where all of this ends up." ■

Doctors will be more closely scrutinized with bill's provisions

Experts talk about bill's negatives

PAY ATTENTION TO THE NEW HEALTH CARE BILL'S REGulatory details, experts warn providers.

There are some items in the sweeping legislation that could result in more documentation, work, and risk for physicians and other providers.

For instance, the new bill makes it clear that the government wants doctors to be doctors and not own hospitals, says **LaDale K. George**, JD, a partner with Neal, Gerber, Eisenberg in Chicago, IL.

The bill puts a moratorium on any physician-owned hospitals in non-rural settings that were not Medicare providers as of December 2010.

"The new law says that the practice of physicians owning hospitals no longer is allowed," he explains. "If a physician owns or has a financial interest in a hospital and refers patients to that hospital, then every service the patient receives at the hospital is a Stark violation of $25,000 per incident."

Also, the anti-kickback law has been changed by the new bill.

"The way the new act changes it is that it appears to eliminate the need to have actual knowledge or specific intent to violate the statute," George says. "It moves in the direction of where the Stark law is where if you do not meet the safe harbors in which providers can refer to one another and engage in commercial practices together then you will be viewed as being guilty."

From physicians' perspectives, some of the other requirements will be more onerous, particularly as far as documentation and accounting are concerned.

For instance, the bill's Physician Payment Sunshine Provision requires physicians to disclose every payment they receive from pharmaceutical and biotech companies in excess of $100, and this includes drug samples. This could prove to be an accounting problem for physician investigators and others.

This likely will be a headache to physicians, who will have to keep track of every sample they receive and every payment that flows through to them for research, George says.

The new health care bill also appears to give physicians incentives and/or penalties depending on their compliance with reporting data as part of the physician quality reporting initiative (PQRI), which was established with the 2006 Tax Relief and Health Care Act.

"What's clear is that Congress is moving into the direction of mandating physicians to participate in PQRI and also moving in the direction of mandating physician resource use reporting," says **Jason A. Scull**, program officer for clinical affairs at the Infectious Diseases Society of America.

"These are somehow merged into a value modifier that also will adjust payment based on the quality of care they provide," Scull says.

About one of six eligible physicians now makes the reports, and about half of these receive incentive payments, he adds. ■

Clinical Cardiology Alert

Reader Survey 2010

In an effort to ensure *Clinical Cardiology Alert* is addressing the issues most important to you, we ask that you take a few minutes to complete and return this survey. The result will be used to ensure you are getting the information most important to you.

Instructions: Mark your answers by filling in the appropriate bubbles. Please write in your answers to the open-ended questions in the space provided. Return the questionnaire in the enclosed postage-paid envelope. The deadline is **July 1, 2010.**

In future issues of *Clinical Cardiology Alert*, would you like to see more or less coverage of the following topics?

	A. more coverage	B. less coverage	C. about the same amount
1. interventional techniques	O A	O B	O C
2. clinical trials	O A	O B	O C
3. prevention	O A	O B	O C
4. pacing	O A	O B	O C
5. ECG	O A	O B	O C
6. ischemic heart disease	O A	O B	O C
7. cardiomyopathy	O A	O B	O C
8. heart failure	O A	O B	O C
9. congenital heart disease	O A	O B	O C
10. cardiac surgery	O A	O B	O C

11. What other topics would you like to see discussed in *Clinical Cardiology Alert*? _____

_____

12. Are the articles in *Clinical Cardiology Alert* written about issues of importance and concern to you?

O A. always O B. most of the time O C. some of the time O D. rarely O E. never

13. What type of information not currently provided in *Clinical Cardiology Alert* would you like to see added?

_____

_____

Please rate your level of satisfaction with the items listed.

	A. excellent	B. good	C. fair	D. poor
14. quality	O A	O B	O C	O D
15. article selections	O A	O B	O C	O D
16. timeliness	O A	O B	O C	O D
17. quality of commentary	O A	O B	O C	O D
18. clearness of abstracts	O A	O B	O C	O D
19. overall value	O A	O B	O C	O D
20. customer service	O A	O B	O C	O D

21. Are the articles in *Clinical Cardiology Alert*:

O A. too short O B. too long O C. about right

22. Please describe your work place.

O A. private practice O B. hospital O C. government institution O D. research

O E. Other (please specify) _____

23. To which other publications or information sources about cardiology do you subscribe?

_____

_____

24. Which publication or information source do you find most useful, and why? _____

_____

25. Please list the top three challenges you face in your job today.

_____

_____

_____

26. What do you like most about *Clinical Cardiology Alert*?

_____

_____

27. What do you like least about *Clinical Cardiology Alert* newsletter?

_____

_____

28. What issues would you like to see addressed in *Clinical Cardiology Alert*?

_____

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29. Has reading *Clinical Cardiology Alert* changed your clinical practice? If yes, how? _____

_____

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_____

Clinical Briefs in Primary Care™

The essential monthly primary care update

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.*

VOLUME 15, NUMBER 5 PAGES 9-10 MAY 2010

Statins and risk of developing diabetes

Source: Sattar N, et al. Statins and risk of incident diabetes. *Lancet* 2010;375: 735-742.

THERE IS LITTLE DISPUTE REGARDING THE beneficial reduction in CV events seen with statin treatment of dyslipidemic patients. At the same time, however, conflicting evidence has suggested that statin treatment might be associated with an increased risk of new-onset diabetes.

Sattar et al performed a meta-analysis of data from large statin clinical trials (n = 13), totalling almost 100,000 patients. During a mean follow-up of 4 years, 9% more individuals developed new diabetes on a statin than patients not treated with a statin. Since CV risk reduction was still favorably influenced by statin treatment, this small increase incidence of diabetes was either not sufficient to offset other beneficial vascular effects, or, once diabetes developed, statin protection was already on board, or perhaps both factors were influential.

You may recall that in hypertension treatment trials, a similar problem has been identified. Chlorthalidone (ALLHAT) had a significantly greater risk for incidence of new diabetes than comparators, yet this adverse effect did not seem to adversely affect CV event rates.

The mechanism by which statins increase risk for diabetes is obscure. This data analysis calculated that 255 subjects would have to be treated with a statin for 4 years to incur 1 additional new case of diabetes. Fortunately, if the small increase is real, it is strongly counterbalanced by well-documented reductions in CV events.

Maximize benefits of metform in DM2

Source: Brown JB, et al. Secondary failure of metformin monotherapy in clinical practice. *Diabetes Care* 2010;33:501-506.

TO DATE, CONTROLLED TRIALS INDICATE THAT no matter what pharmacotherapy is used to control glucose in type 2 diabetes (DM2), one can anticpate a progressive loss of control over time. Loss of efficacy is termed secondary failure: An initially effective medication later becomes insufficient to maintain control. It seems to me that this is too harsh an indictment of pharmacotherapy, since even if the medication continues with similar action over long time periods, confounders such as weight gain, inherent disease progression, and addition of confounding comorbidities might make it appear as if the medication is failing, when in reality, counterbalancing forces are increasing.

In any case, Brown et al performed an observational cohort study of DM2 subjects (n = 1799) initially treated with metformin monotherapy successfully (i.e., able to maintain an A1c < 7.0 without adding a second agent). Secondary failure was defined as either the addition of a second agent, or an increase of A1c above 7.0 while still on monotherapy. Subjects who required additional therapy within the first 6 months of metformin treatment were regarded as primary failure, and were excluded from this analysis.

In subjects able to maintain good control with initial metformin monotherapy, secondary failure occurred at a rate of 17% per year. Predictors of higher failure rates included longer duration of diabetes before treatment and higher baseline A1c at initiation of treatment. These data suggest that early initiation of treatment, especially when A1c is not yet markedly elevated, results in greater durability of metformin efficacy.

Prediabetes therapy and beta-cell function

Source: Hanley AJ, et al. Effect of rosiglitazone and ramipril on {beta}-cell function in people with impaired glucose tolerance or impaired fasting glucose. *Diabetes Care* 2010;33:608-613.

PREDIABETES (PDM) IS DEFINED AS EITHER impaired fasting glucose (FBG = 100-125 mg/dL), impaired glucose tolerance (IGT; 2-hour post-load glucose = 140-199 mg/dL), or supranormal but not diabetic A1c (A1c = 5.7-6.4). Untreated pDM predictably progresses to frank DM at a rate of about 7%-10% per year. Numerous interventions have been shown to alter the progression from pDM to diabetes, including diet, exercise, metformin, acarbose, orlistat, and thiazolidinediones; this year, nateglinide, an insulin secretagogue, was not confirmed to delay progression from pDM to diabetes.

Hopefully, treatments to prevent diabetes will also impact beta-cell function favorably, rather than simply compensate for progressive metabolic decline. The DREAM trial (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) randomized 5269 pDM subjects to ramipril and/or rosigliatoze. A substudy of DREAM (n = 982) had measurements of beta-cell function at baseline and periodically during the 3-year (median) follow-up, as well as measurements of progression from pDM to DM.

Subjects randomized to ramipril did not experience any meaningful change

in beta-cell function. In contrast, rosiglitazone-treated subjects enjoyed substantial improvements in beta-cell function. Benefits were less in pDM subjects who only manifest IFG compared with IGT or both.

In addition to reducing beta cells induced by glucotoxicity, thiazolidinediones lower free fatty acid levels, which may favorably affect beta-cell apoptosis.

Onychomycosis: Long-term follow-up

Source: Piraccini BM, et al. Long-term follow-up of toenail onychomycosis caused by dermatophytes after successful treatment with systemic antifungal agents. *J Am Acad Dermatol* 2010;62:411-414.

Although onychomycosis (ONCM) is often considered a cosmetic problem, some patients suffer significant disability due to foot pain, and difficulty wearing shoes. The treatment course for toenail ONCM is lengthy and costly. There are few data on long-term follow-up to ascertain recurrence rates, although prevailing opinion suggests recurrence is common.

Praccini et al performed a prospective study of ONCM patients (n = 73) who had been treated with pulse therapy (treatment 1 week/month for 6 months) with terbinafine or itraconazole. After clinical cure, subjects were prospectively followed for 7 years. Cure was defined as normalized clinical appearance and negative fungus culture.

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Patients were seen every 6 months during follow-up. Overall, recurrence developed in 16.4% of subjects. Each case of recurrence involved the same organism identified in the original infection. However, the recurrence rate for itraconazole was 3-fold greater than terbinafine. Terbinafine is widely regarded as the treatment of choice for toenail ONCM; this trial suggests superior durability of cure for terbinafine when compared with itraconazole.

Diagnostic yield of elective coronary angiography

Source: Patel MR, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med* 2010;362:886-895.

Current recommendations suggest that in stable persons under consideration for CAD evaluation, low-risk individuals be observed, high-risk patients be triaged to coronary angiography, and intermediate-risk persons be further stratified by means of non-invasive testing. Such guidance is structured to minimize unnecessary invasive investigations in low-risk individuals, and to identify — in the group of intermediate risk — those who merit follow-up with angiography.

The American College of Cardiology National Cardiovascular Data Registry provided information on patients without known CAD (n = 398,978) who received coronary angiography (electively) at hospitals in the United States during a 4-year interval commencing January, 2004.

Obstructive CAD was defined as at least 50% stenosis of the left main coronary artery (or greater degrees of stenosis of epicardial vessels). Catheterization determined that slightly more than one-third of patients had obstructive CAD. In addition to the disappointingly low percentage of individuals identified with CAD on angiography, this study also provided insights about the concordance of risk and use of non-invasive testing (i.e., stress testing). When non-invasive testing had preceded angiography, subjects' baseline risk category was at odds with the current recommendations focusing upon refinement of risk in persons at intermediate Framingham scores, in that those with high Framingham risk scores were disproportionately represented. The authors suggest that the diagnostic yield based upon current practice needs improvement.

Thyroid hormone analogue for dyslipidemia

Source: Ladenson PW, et al. Use of the thyroid hormone analogue eprotirome in statin-treated dyslipidemia. *N Engl J Med* 2010;362:906-916.

The role of statins in treatment of dyslipidemia is well established. There are, however, limitations of statins: Residual risk is substantial, not all persons can tolerate statins, and, even with full-dose statin treatment, some patients do not achieve lipid goals.

The role of the thyroid in lipid metabolism has long been a matter of scientific interest. It is recommended that patients with dyslipidemia undergo thyroid function testing since hypothyroidism, although only present in a small percentage of dyslipidemic patients, is readily correctible and offers meaningful lipid improvements. Enhancement of thyroid activity has favorable lipid effects. As far back as the 1960s, investigators were curious enough about thyroid hormone and vascular disease to enroll men in the Coronary Drug Project (1965) and randomize them to d-thyroxine, which was felt at the time (mistakenly) to have essentially no effect on sympathetic nervous system sensitivity, but favorable effects on lipids.

Eprotirome (EPR) is an analogue of thyroid homone which has preferential affinity for thyroid receptors that modulate lipid lowering, as compared to cardiac receptors. A randomized placebo-controlled, double-blind study was done among patients on an NCEP step 1 diet and a statin (simvastatin or atorvastatin). Patients (n = 329) received statin plus either EPR or placebo for 12 weeks.

At the end of the trial, very favorable lipid effects were reported with the addition of EPR to a statin: a 22%-32% reduction in LDL, a 6- to 9-fold increase in patients achieving an LDL < 100 mg/dL, as well as favorable effects on triglycerides and apoB (all dose-dependent). A small reduction in HDL was seen. There was no change in heart rate or BP. Selective activation of thyroid receptors may one day provide an additional path for successful lipid modulation.

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.*

Finding ACCORD in the Management of Type 2 Diabetes?

In this issue: Examining the three arms of the ACCORD trial; and FDA Actions: clopidogrel, dexlansoprazole, and tamsulosin.

ACCORD and type 2 diabetes

Every once in a while a medical study comes along that turns medical dogma on its ear. The Multiple Risk Factor Intervention Trial (MRFIT), published in 1982, was such a study, so was the Women's Health Initiative (WHI), published in 2002. Both studies challenged conventional wisdom and changed practice. MRFIT caused us to take a hard look at risk factor intervention especially hypertensive treatment, while WHI established that combination hormone therapy in postmenopausal women should no longer be routinely recommended because of the risk of breast cancer and heart disease.

The Action to Control Cardiovascular Risk in Diabetics (ACCORD) trial, published in March in the *New England Journal of Medicine*, is also such a study, and is destined to change medical practice in the treatment of type 2 diabetes. ACCORD looked at three aspects of care in type 2 diabetes, the first was the effects of intensive glucose lowering, the second was the effect of intensive blood pressure control, and the third was the effect of combination lipid therapy.

The intensive glucose lowering study was published early in 2008 when it was found that the intensive therapy group (targeting hemoglobin A1c < 6.0%) reported a higher mortality than the standard therapy group (targeting A1c 7.0%-7.9%). At the same time, intensive therapy did not significantly reduce major cardiovascular events (*N Engl J Med* 2008;358:2545-2559).

The second and third wings of the ACCORD trial were published on-line March 14, and the results were similarly discouraging for aggressive care. A total of 4733 participants with type 2 diabetes were enrolled in the intensive blood pressure control wing and were randomized to intensive therapy, targeting a systolic pressure < 120 mmHg, or standard therapy targeting a systolic blood pressure < 140 mmHg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After a mean follow-up of 4.7 years, mean target blood pressures were met in both groups. The annual rate of the primary outcome was 1.87% in the intensive therapy group and 2.09% in the standard therapy group (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.73-1.06; P = 0.20). The annual rates of death from any cause were 1.28% in the intensive therapy group and 1.19% in the standard therapy group (HR, 1.07; 95% CI, 0.85-1.35; P = 0.55). There was a slightly reduced risk of stroke in the intensive therapy group (0.32% vs 0.53%; P = 0.01); however, serious adverse events were more than double in the intensive therapy group. The authors conclude

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) 262-5468. E-mail: paula.cousins@ahcmedia.com.

that in patients with type 2 diabetes targeting systolic blood pressure < 120 mm Hg as compared to < 140 mm Hg did not reduce the rate of the composite outcome of fatal and nonfatal major cardiovascular events (*N Engl J Med* published on-line March 14, 2010). While these results are somewhat surprising, they may not change the general recommendation for more aggressive blood pressure management in type 2 diabetes to systolic blood pressure ≤ 130/80 mm Hg, which is consistent with most current guidelines (including JNC VII).

In the third wing of ACCORD, 5518 patients with type 2 diabetes who were being treated with the statin simvastatin were randomized also to receive fenofibrate or placebo. The primary outcome was first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. After a mean follow-up of 4.7 years, the annual rate of primary outcome was 2.2% in the fenofibrate group and 2.4% in the placebo group (HR 0.92; 95% CI, 0.79-1.08; P = 0.32). There were also no significant differences between the two study groups with respect to any secondary outcomes or death rate. Subgroup analysis suggested slightly higher benefit for men vs women and perhaps a benefit for those with high baseline triglycerides (> 204 mg/dL) and low HDL (≤ 34 mg/dL). The authors conclude that the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke compared with simvastatin alone (*N Engl J Med* published on-line March 14, 2010). This study does not in any way diminish the known benefit from aggressive statin therapy in type 2 diabetics, but does suggest that targeted treatment of triglycerides with fenofibrate is of no value. The FDA is reviewing the ACCORD data, but as of this time they have "made no new conclusions or recommendations regarding the use of simvastatin or other statin drugs and fenofibrate."

Do statins increase the risk of type 2 diabetes? It has been suggested that lipophilic statins may cause unfavorable metabolic side effects such as reduction of insulin secretion and worsening of insulin resistance. In a small single-blind, placebo-controlled parallel study, 40 to 44 patients were randomized to receive placebo, or atorvastatin 10, 20, 40, and 80 mg during a 2-month period. While atorvastatin significantly reduced LDL and apolipoprotein B levels, the drug was also associated with significantly increased fasting plasma insulin levels, as well as hemoglobin A1c levels (mean changes in fasting insulin levels, 25%, 42%, 31%, and 45%, respectively, for increasing dose; A1c increases of 2%, 5%, 5%, and 5%, respectively; P < 0.05 by paired t-test). Atorvastatin also decreased insulin sensitivity in a dose-responsive fashion. The authors conclude that atorvastatin resulted in significant increases in fasting insulin, hemoglobin A1c consistent with increased insulin resistance (*J Am Coll Cardiol* 2010;55:1209-1216). Previous studies have shown similar results with lipophilic statins including atorvastatin, rosuvastatin, and simvastatin, while pravastatin seems to reduce the risk of diabetes.

FDA Actions

The FDA has issued a warning to health care providers regarding the antiplatelet drug clopidogrel (Plavix®). It is recently been found that up to 14% of the population did not metabolize the drug effectively and may not fully convert the drug to its active form. Clopidogrel is dependent on CYP2C19 and those that genetically lack the enzyme may not convert the drug to its active form. Recent studies have suggested that reduced CYP2C19 activity was associated with higher risk for cardiovascular outcomes. A test is available to identify genetic differences in CYP2C19 function and the FDA is recommending that health care professionals consider use of other antiplatelet medications or use alternative dosing if patients are poor metabolizers. The manufacturer of Plavix is being asked to add a black box warning to the drug labeling to this effect. Previously, it was discovered that some proton pump inhibitors including omeprazole may also inhibit metabolism to the active drug. Meanwhile Eli Lilly's prasugrel (Effient®), a direct competitor to clopidogrel, is not affected by CYP genetic variants.

The FDA has approved Takeda Pharmaceutical's request to change the name of its proton pump inhibitor dexlansoprazole from Kapidex® to Dexilant™. The change is being made due to several dispensing errors that occurred between Kapidex and the prostate cancer drug Casodex® (bicalutamide) and the analgesic Kadian® (morphine).

The FDA has approved a generic version of Boeringer Ingelheim's tamsulosin (Flomax®) for the treatment of benign prostatic hyperplasia in men. Generic tamsulosin should be available later in 2010.