AHC Media

Vol. 31, Issue 8, August 2012
www.ahcmedia.com

Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Invasive or Conservative Strategy in Diabetics with ACS?

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: O'Donoghue ML, et al. An invasive or conservative strategy in patients with diabetes mellitus and non–ST-segment elevation acute coronary syndromes. A collaborative meta-analysis of randomized trials. *J Am Coll Cardiol* 2012;60:106-111.

Patients with diabetes mellitus (DM) are at increased risk of developing acute coronary syndromes (ACS). Furthermore, after hospitalization with ACS, patients with DM are at increased risk of suffering repeat hospitalization for ACS. In recent years, a number of trials have tested the strategy of routine early invasive approach (i.e., diagnostic angiography with a view to revascularization) vs an early conservative strategy (i.e., medical management with coronary angiography only performed in cases of refractory ischemia). The invasive strategy is generally preferable in patients at high risk of clinical events, and this is reflected in the ACC/AHA guidelines. Diabetes is known to confer an increased risk of clinical events. Whether patients with DM and ACS should routinely undergo an invasive strategy is not known. O'Donoghue and colleagues performed a collaborative meta-analysis of nine clinical trials that tested invasive vs conservative strategies in patients with ACS, comparing outcomes between diabetic and non-diabetic patients. The primary endpoint was a composite of death, myocardial infarction (MI), and repeat hospitalization for ACS.

The authors studied 9904 patients in nine trials, of whom 18.2% were diabetic. Patients with DM tended to be older and were more likely to be female, have hypertension, hyperlipidemia, and a history of MI. In addition, patients with DM had

Financial Disclosure: *Clinical Cardiology Alert's* Editor, Michael H. Crawford, MD, reports no financial relationships relevant to this field of study, and peer reviewer, Ethan Weiss, MD, is a scientific advisory board member for Bionovo. Managing Editor, Neill Kimball, and Executive Editor, Leslie Coplin, report no financial relationships relevant to this field of study.

Clinical Cardiology [ALERT]

Clinical Cardiology Alert, ISSN 0741-4218, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road, NE Building 6, Suite 400 Atlanta, GA 30305.

POSTMASTER: Send address changes to *Clinical Cardiology Alert*, P.O. Box 105109, Atlanta, GA 30348.

SUBSCRIBER INFORMATION
1-800-688-2421
customerservice@ahcmedia.com

Editorial E-Mail:
neill.kimball@ahcmedia.com

Subscription Prices
United States
1 year with free AMA Category 1 credits: $319
Add $17.95 for shipping & handling. (Student/Resident rate: $125). Multiple Copies: Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.
Canada Add GST and $30 shipping.
Elsewhere Add $30 shipping.

Back Issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

GST Registration Number: R128870672. Periodicals Postage Paid at Atlanta, GA, 30304 and at additional mailing offices.

ACCREDITATION
AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 2*5 AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity. This CME activity is intended for the cardiologist. It is in effect for 36 months from the date of the publication.

AHC Media

more extensive coronary artery disease and were more likely to undergo coronary artery bypass graft (CABG) surgery than non-diabetics. Diabetics had higher rates of death (9.3% vs 3.2%; $P < 0.001$), nonfatal MI (11.3% vs 7.1%; $P < 0.001$), and rehospitalization with ACS (18.1% vs 13.0%; $P < 0.001$) compared with non-diabetic patients. The primary endpoint was reduced by an invasive strategy to a similar extent in patients with DM (relative risk [RR] 0.87; 95% confidence interval [CI] 0.73-1.03) and those without (RR 0.86; 95% CI, 0.70-1.06). Randomization to an invasive strategy reduced non-fatal MI in diabetic patients (RR 0.71; 95% CI, 0.55-0.92) but not in non-diabetics (RR 0.98; 95% CI, 0.74-1.29). The absolute risk reduction in MI with an invasive strategy was greater in diabetic than non-diabetic patients (absolute risk reduction: 3.7% vs 0.1%). There were no differences in death or stroke between diabetics and non-diabetics. Interestingly, patients with DM received a benefit from an invasive strategy regardless of whether they had positive biomarkers or not. In contrast, non-diabetics only received benefit from an invasive strategy if they were biomarker positive.

The authors conclude that an early invasive strategy yielded similar RR reductions in overall cardiovascular events in diabetic and non-diabetic patients. However, an invasive strategy appeared to reduce recurrent non-fatal MI to a greater extent in diabetic patients. These data support the updated guidelines that recommend an invasive strategy for patients with DM and non-ST-segment elevation ACS.

■ COMMENTARY

This meta-analysis confirms that diabetics have a higher risk of cardiac events than non-diabetics. It also demonstrates that diabetics and non-diabetics who present with ACS receive a similar benefit from an early invasive strategy. This confirms the current ACC/AHA guidelines that suggest markers of increased risk in patients with ACS should include the presence of diabetes.

Several limitations of this study should be mentioned. First, meta-analyses are subject to biases including which studies were included, selection bias, and individual study protocol differences that are not mentioned. Second, diabetics were more often treated with CABG than non-diabetics (31% vs 25%) and we are not told whether the outcomes were influenced by the use of CABG instead of PCI. It is possible that the higher rates of CABG in diabetics resulted in superior clinical outcomes. Third, this meta-analysis was a study-level rather than a patient-level meta-analysis. Thus, individual covariates were not examined.

Importantly, many of the studies included in this meta-analysis were in the era of bare-metal stents (BMS). Drug-eluting stents (DES), particularly the newest generation of DES, lead to better outcomes in diabetics compared to BMS. Use of DES may result in an even greater magnitude of improvement in outcomes in diabetic patients who undergo invasive treatment. Patients with ACS should be risk-stratified and higher-risk patients considered for an invasive strategy. Diabetic patients should be considered in this high-risk group. ■

ABSTRACT & COMMENTARY

TEE Before Cardioversion of AF

By Michael H. Crawford, MD, Editor

SOURCE: Grewal GK, et al. Indications for TEE before cardioversion for atrial fibrillation: Implications for appropriateness criteria. *J Am Coll Cardiol Img* 2012;5:641-648.

In an effort to reduce unnecessary testing, these investigators performed a retrospective observational study of 671 TEE-guided direct current cardioversions (DCC) for atrial fibrillation (AF) to evaluate the indications used for TEE and the outcomes with regard to thromboembolism post DCC. Using the ACCF/ASE appropriateness criteria, the indications for TEE were classified as appropriate or inappropriate. Those

studies unable to be classified were excluded (< 2%). If the TEE had more than one indication, the most serious was considered the main indication. In the 659 remaining patients, the most common indications for TEE prior to DCC of AF were marked symptoms (174) and heart failure or hemodynamic compromise (174): so that DCC could be expedited. Inappropriate indications (n = 18) comprised 2.7% of studies: stable INR for > 3 weeks (11), AF for < 48 hours (3), permanent AF (2), and hospitalized but asymptomatic (2). Left atrial thrombus or sludge was observed in 54 (8%). The TEE indications most likely to exhibit thrombus/sludge were high stroke risk (18%), hospitalized and symptomatic (14%), heart failure/hemodynamic compromise (10%), and subtherapeutic anticoagulation (7%). The lowest incidences of thrombus/sludge occurred in those with new onset AF for > 48 hours (5%) and inappropriate (0%). During a mean follow-up of 18 months, thromboembolism occurred in 15 patients (2.5%) and occurred in all indications except inappropriate. One thromboembolism occurred 3 days after DCC, the remainder occurred 2-18 months later. The authors concluded that TEE usage for DCC is largely used appropriately to expedite DCC in patients with significant symptoms or signs of decompensation due to AF.

■ COMMENTARY

This study was designed to evaluate the appropriateness of TEE usage in DCC using the new ACCF/ASE appropriate use criteria. Not surprisingly, more than 97% of TEEs were judged appropriate. In some ways, TEE use is a straw man, since no one seriously believes it is being overutilized. After all, patients don't like it, it takes more physician time and resources than can ever be profitable, and it has risks. I thought the study was interesting to see the outcomes of the modern approach to DCC for AF with selective use of TEE per guidelines.

TEE was mainly used to expedite DCC for patients who were very symptomatic with AF or had hemodynamic compromise; avoiding the 3-4 week wait for oral anticoagulants to work on eliminating atrial thrombi. This approach largely worked as there was only one stroke in the peri-DCC period at 3 days post-DCC. The total thromboembolic event rate was low (2.5%) and all but one occurred from 2 to 18 months after DCC. It is hard to blame these events on DCC in these patients with high risk of recurrent AF and other comorbidities. Thus, I believe the modern approach to DCC is highly safe.

The highest incidences of left atrial thrombus or sludge (18%) were observed in the group deemed at high risk for stroke because of a prior history of stroke/TIA, prior left atrial thrombus, and hypertrophic obstructive cardiomyopathy. Also, this group had the highest incidence of subsequent thromboembolism (6%). Thus, this group should have TEE-guided DCC, rather than relying on a month of anticoagulants alone to ensure safety.

One indication for TEE deemed appropriate is new onset AF for the first time, which has lasted > 48 hours. The theory here is that rapid cardioversion will prevent remodeling (enlargement) that will make it less likely to hold sinus rhythm when cardioverted after a month of anticoagulation. Left atrial thrombus/sludge was seen in 5%, and 2.5% of these patients had an embolic event over 18 months. This indication accepts the clinical adage that you can safely cardiovert first-time AF if it has lasted < 48 hours. Some of the TEE-guided cardioversions were in this latter category, and none had left atrial thrombus, sludge, or an embolic event over 18 months. Thus, the old clinical saw was upheld by this study. ■

ABSTRACT & COMMENTARY

A Randomized Trial of Early Surgery for Infective Endocarditis

By Michael H. Crawford, MD, Editor

SOURCES: Kang DH, et al. Early surgery versus conventional treatment for infective endocarditis. *N Engl J Med* 2012;366:2466-2473.
Gordon SM, Pettersson GB. Native-valve infective endocarditis — When does it require surgery? *N Engl J Med* 2012;366:2519-2521.

Early surgery for infective endocarditis (IE) has been supported by several observational studies, but the lack of randomized, controlled data has led to conflicting recommendations by major societies. Thus, this group of investigators from Korea conduced a randomized, controlled trial in 76 patients with native left heart valve IE, as defined by the modified Duke criteria, who had severe valve disease and large (> 10 mm) vegetations, and were potential candidates for early

surgery. Patients with definite indications for urgent surgery were excluded: heart failure, heart block, annular abscess, fistulas, or fungal infection. Also excluded were patients with major contraindications to surgery (e.g., stroke). All patients were evaluated by transesophageal echocardiography and CT angiography of the brain and abdomen. Patients assigned to surgery were required to have it within 48 hours of randomization. Those in the medical therapy group could have surgery if complications requiring surgery developed. The primary endpoint was hospital deaths or clinical embolic events within 6 weeks of randomization. Results: All of the early surgery group underwent surgery within 48 hours, and 30 of the 39 (77%) medical group eventually underwent surgery, most during the initial hospitalization (90%). The primary endpoint occurred in one patient (3%) in the early surgery group, compared to nine (23%) in the conventional treatment group (hazard ratio, 0.10, 95% confidence interval, 0.01-0.82, $P = 0.03$). One early surgery patient died and almost all of the conventional group patients who had an endpoint had clinical emboli (eight of nine). All the endpoints in the conventional group occurred before any crossover to surgery. The authors concluded that early surgery in patients with large vegetations decreases the risk of systemic embolism.

■ COMMENTARY

This is an important study because it is the first randomized trial of surgery in IE. Its focus is on the patients with moderate-to-severe regurgitation and large vegetations (> 10 mm) who are not in heart failure and don't have any of the other class I indications for surgery such as an abscess, fistula, or heart block. Accordingly, it took almost 5 years for them to enroll 76 patients. However, this is one of the more controversial areas in IE management where observational studies are conflicting. Some, but not all, studies support early surgery for vegetations > 10 mm and if severe valve regurgitation is present. The center of the controversy is the risk of a catastrophic complication that would preclude surgery, such as an embolic stroke vs several days of antibiotics to stabilize the patient and reduce the likelihood of surgical complications or reinfection of the prosthetic valve. The risk of emboli is highest the first week after diagnosis, but drops rapidly after 10-14 days of effective antibiotic therapy. Hence, the focus of this study on early surgery to reduce the early embolic risk vs waiting until surgery was necessary due to complications of IE, with the hope that some could avoid surgery.

The study clearly shows that early surgery prevents clinical thromboembolic events without increasing mortality. Both early and 6-month mortality were not significantly different between the two groups. However, there were so few deaths that the trial was not powered to definitively answer this question. Also, the incidence of recurrent IE was very low and not different between the two groups. As expected, more than three quarters of the conservative treatment group eventually required surgery; almost all of which occurred during the initial hospitalization. So, in some ways, this was a study of surgical timing and it doesn't appear that waiting gains much. Even the quarter of the conservative group who had not had surgery by 6 months had severe valve regurgitation and it could be argued would eventually need surgery. Among the eight patients with emboli in the conservative group, five had strokes with residual defects.

Since the two most common causes of death in IE are heart failure and thromboemboli, it makes sense to operate early to prevent these complications. Current opinion and guideline recommendations are to operate early for heart failure with IE, despite a paucity of data. It appears that based on this randomized trial, moderate-to-severe valve regurgitation with large vegetations can be confidently added to this list. ■

ABSTRACT & COMMENTARY

Survival After Out-of-Hospital Cardiac Arrest

By John P. DiMarco, MD, PhD

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

Dr. DiMarco does research for Medtronic, is a consultant for Medtronic, Novartis, and St. Jude, and is a speaker for Boston Scientific.

SOURCE: Dumas, F, et al. Long-term prognosis following resuscitation from out of hospital cardiac arrest: Role of percutaneous coronary intervention and therapeutic hypothermia. *J Am Coll Cardiol* 2012;60:21-27.

In this paper, the authors reviewed long-term survival data from a large population of out-of-hospital cardiac arrest patients who were discharged alive after their arrest. All patients who have a cardiac arrest in Seattle and King County, Washington, are entered into a registry organized

to follow the Utstein guidelines for reporting cardiac arrest. During the 8-year period from 2001 to 2009, the survival rate to hospital discharge was 16.8% (1101 of 5958 adult patients) after EMS treated nontraumatic out-of-hospital cardiac arrest. Factors associated with long-term survival after hospital discharge were then examined. The factors analyzed included the use of therapeutic hypothermia, percutaneous coronary interventions (PCI), implantable cardioverter defibrillators (ICDs), neurologic status upon hospital arrival, and ST-segment elevation on the initial hospital ECG. In this cohort of survivors to hospital discharge, 38% received a PCI during the hospitalization after arrest. Six percent were conscious at hospital admission and were not candidates for therapeutic hypothermia. Among the 941 patients who were unconscious at hospital admission, 245 (26%) received therapeutic hypothermia. Both PCI and therapeutic hypothermia were employed in 9.9% of the cohort, with 80% of the PCIs occurring within 6 hours of hospital arrival. Of those who received PCI within 6 hours, 71% had evidence of ST-segment elevation on the initial hospital ECG.

The median age in the group was 61 and two-thirds of the patients were male. Eighty percent had a cardiac etiology for their arrest and almost 70% had an initial shockable rhythm detected. Patients who received PCI were younger and were more likely to have the following characteristics: male gender, an arrest due to a cardiac etiology, a witnessed arrest in a public location, and bystander CPR. After hospital discharge, 348 of the 1101 patients died. Life table analysis gave survival estimates of 87% at 6 months, 82% at 1 year, and 64% at 5 years. Both PCI and therapeutic hypothermia were associated with favorable effects on mortality. Patients who received both PCI and therapeutic hypothermia had the highest survival estimates at both 1 and 5 years. Cox regression analysis showed that PCI, therapeutic hypothermia, and ICD implantation were each independently associated with improved survival after discharge. The hazard ratios for risk of death were 0.46 for PCI and 0.70 for therapeutic hypothermia. The hazard ratio for death was lowest for those who received PCI during an ST segment elevation MI (0.41). A further analysis using a nested cohort pairing for each intervention showed similar favorable hazard ratios associated with both therapeutic hypothermia and PCI.

The authors conclude that in this observational analysis, both PCI and therapeutic hypothermia produced survival benefits among patients who survived to hospital discharge. Since only patients who were discharged from the hospital were analyzed in this study, improved in-hospital survival could not be assessed but has been demonstrated in other reports.

■ COMMENTARY

This report from a large, well-organized registry of out-of-hospital cardiac arrest victims provides further data to support the routine use of coronary angiography followed, when indicated, by PCI and therapeutic hypothermia in resuscitated cardiac arrest victims admitted to the hospital. The largest benefit shown was for ST elevation patients and this report confirms that both PCI and therapeutic hypothermia can and should be used in these patients. In patients without STEMI, the best timing for coronary angiography remains controversial, but certainly detecting and treating high-grade coronary lesions where present should be considered at some time during the hospital stay.

Recently, some hospitals have been cited by state boards or other groups for increased adjusted mortality rates among PCI patients. In several cases, most of the PCI-related deaths occurred in patients who presented in shock or after a resuscitated cardiac arrest. The risk-adjustment schemes did not fully account for the much higher than expected mortality in such patients. Therefore, the American Heart Association has recommended that patients in shock or after arrest be separately classified from other PCI patients when data are reported. The data in this paper support this idea since we should not punish hospitals that accept the burden of treating these very high-risk patients. ■

ABSTRACT & COMMENTARY

Rapid Rule Out for Patients with Chest Pain

By Andrew J. Boyle, MBBS, PhD

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

SOURCE: Than M, et al. 2-hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: The ADAPT trial. *J Am Coll Cardiol* 2012;59:2091-2098.

Chest pain presentations to the emergency department (ED) are common and very costly to the health care system. Although the event rates are low in patients with a low clinical risk profile, the price of a missed diagnosis is high. Some low-risk patients who are discharged from the ED may suffer a myocardial infarction (MI) and potentially even die. Our ability to predict who will go on to suffer an acute coronary syndrome (ACS) is imperfect. Thus, many patients are unnecessarily admitted to the hospital for observation. A more rapid means to assess low-risk chest pain (i.e., rule out MI) in the ED may facilitate earlier discharge and lead to substantial savings for the health care system.

Than and colleagues developed an accelerated diagnostic protocol (ADP) to rapidly rule out MI in low-risk patients presenting to the emergency room with chest pain. Their aim is to facilitate early discharge from the ED in these patients, and the ADAPT (2-Hour Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker) trial is a prospective, observational study performed at two urban EDs. Their protocol identified low-risk chest pain patients as those with a Trials In Myocardial Infarction (TIMI) risk score of 0, no ischemic ECG changes, and negative cardiac troponin I (cTnI) upon arrival and at 2 hours. The TIMI risk score applies 1 point for each of the following parameters: age > 65 years, ≥ three cardiac risk factors, aspirin use in the preceding 7 days, known coronary stenosis ≥ 50%, ≥ two episodes of chest pain in the preceding 24 hours or ongoing pain, ST segment changes on the ECG, and elevation of biomarkers. All patients had cTnI drawn at 0 and 2 hours after arrival. Importantly, the 2-hour cTnI was not communicated to the physicians, so usual care was performed (which usually entailed a 6-12 hour cTnI measurement). The primary endpoint of the study was major adverse cardiac events (MACE) occurring within 30 days of presentation (including during the initial hospitalization). MACE included: death (unless clearly non-cardiac), MI, cardiac arrest, emergency revascularization procedure, cardiogenic shock, ventricular arrhythmia needing intervention, and high-degree atrioventricular block needing intervention. Follow-up was by review of hospital records, national death index, and telephone contact.

Of the total 1975 patients enrolled, 302 (15.3%) had a MACE within 30 days. The ADP classified 392 patients (20%) as low risk. No patients were lost to follow-up. One (0.25%) of these patients had a MACE, giving the ADP a sensitivity of 99.7% (95% confidence interval [CI]: 98.1% to 99.9%), negative-predictive value of 99.7% (95% CI: 98.6% to 100.0%), specificity of 23.4% (95% CI: 21.4% to 25.4%), and positive-predictive value of 19.0% (95% CI: 17.2% to 21.0%). Because the results of the cTnI were not communicated to the treating physician, most ADP-negative patients had further investigations (74.1%), and therapeutic (18.3%) or procedural (2.0%) interventions during the initial hospital attendance and/or 30-day follow-up. The authors performed a post-hoc analysis to determine the sensitivity and specificity of each parameter of the ADP using combinations of two parameters. They found that using all three parameters of the ADP (TIMI risk score of 0, non-ischemic ECG, and negative cTnI) performed best.

The authors conclude that when using the ADP, a large group of patients was successfully identified as having low short-term risk of a MACE and therefore suitable for rapid discharge from the ED with early follow-up. This approach could decrease the observation period required for some patients with chest pain.

■ COMMENTARY

Any strategy that can safely facilitate the more rapid discharge of patients from the ED would be most welcome. This study from Than and colleagues represents a step in that direction. The identification of low-risk patients who may be suitable for early discharge by simple clinical risk features, ECG, and a 2-hour cTnI measurement may help alleviate ED crowding. The rate of MACE in their low-risk cohort (one patient with a missed MI; 0.25%) was low, and is in the range that many ED physicians would call "acceptable." However, exactly what one considers an acceptable rate of missed MI remains the subject of considerable debate.

This study has several strengths that should be noted. First, they used a current fourth-generation troponin assay that is similar to those widely used in the United States today. Second, this was a prospective, two-center study performed in two countries (but not in the United States). These features add weight to the conclusions that can be drawn. However, several limitations should also be noted. First, by not allowing the physicians access to the 2-hour troponin result, these patients were not actually discharged early. They all underwent 6- to 12-hour follow-up troponin and the majority underwent stress testing or invasive treatments. The MACE endpoint included emergency revascularization, but not elective treatment/revascularization. It is possible that some of the treatments received may have reduced the MACE

rate. I would like to have seen data on what treatments these patients received. Second, the patients were predominantly caucasian males, so the results may not be generalizable to women and non-caucasian populations. This study is exciting in that it may lead to earlier discharge of these low-risk patients from the ED. However, until the strategy of discharge is actually tested prospectively, this study should be considered hypothesis generating rather than practice changing.

Where this approach will fit in the evolving world of chest pain assessment is not clear. Computed tomography coronary angiography is increasingly being used to rule out MI in low-intermediate risk groups. In addition, highly sensitive troponin assays are emerging and show potential to diagnose or rule out MI earlier, albeit with a trade-off of more "false" positives. Dedicated chest pain centers with after hours stress testing facilities are appearing. Future studies will define the best use of all of these new approaches, and will hopefully reduce ED crowding and the economic burden of chest pain presentations on the health care system. ■

ABSTRACT & COMMENTARY

Cardiac Resynchronization Therapy: Who Responds?

By John P. DiMarco, MD, PhD

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

SOURCE: Hsu JC, et al. Predictors of super-response to cardiac resynchronization therapy and associated improvement in clinical cutcome: The MADIT-CRT study. *J Am Coll Cardiol* 2012;59:2366-2373.

This study examines the patterns of response to cardiac resynchronization therapy (CRT) among patients enrolled in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) trial. MADIT-CRT was a study that looked at the effects of CRT among defibrillator candidates who had QRS durations over 130 msec and less severe heart failure symptoms (NYHA class I or II) as part of the protocol. 2-D echocardiograms were obtained prior to study enrollment and at 1 year. This study reports an analysis of the 752 patients randomized to the CRT-D therapy group who had complete clinical and electrocardiographic data collected both at baseline and at the 12-month follow-up. Patients with baseline and 12-month echocardiograms were divided into quartiles of left ventricular ejection fraction (LVEF) response. Patients in the highest quartile were termed "super responders," patients in the second and third quartiles were termed "responders," and patients in the lowest quartile were "hypo-responders." Echocardiographic response was then associated with the primary endpoints in the study, which were nonfatal heart failure events or all-cause death, whichever came first, and the secondary endpoints of all-cause death or appropriate ICD therapy.

Super responders experienced a mean absolute LVEF increase of 17.5 ± 2.7%. The cutoff for entry into the super responder cutoff quartile was an LVEF improvement ≥ 14.5%. The mean LVEF increase in the responder group was 11.1 ± 1.8% with a range of 7.9 to 14.4%. The mean absolute LVEF increase among hypo-responders was 4.4 ± 3.2%. More than 70% of the super responders had an increase in LVEF to ≥ 45% at 12 months. Super responders were more often female and had a nonischemic heart failure etiology, baseline left bundle branch block, and longer QRS durations. Super responders were less likely to have histories of revascularization, myocardial infarction, smoking, or ventricular arrhythmias. Cox regression analysis showed that female gender, absence of prior myocardial infarction, QRS duration > 150 msec, left bundle branch block conduction pattern, body mass index less than 30 kg/m^2, and smaller baseline left atrial volume index were independent predictors of super responder status. The primary endpoint of heart failure admission or death also correlated with responder status. The primary endpoint occurred in 2.6% in the super responder group, 7.8% in the responder group, and 19% of the hypo-responder group. A similar pattern was seen for the secondary endpoint of all-cause death: 1.6% among super responders, 2.7% among responders, and 6.3% among hypo-responders.

The authors conclude that dramatic responses to CRT can be predicted by clinical variables easily ascertained at baseline.

■ COMMENTARY

Cardiac resynchronization therapy can improve outcomes in many patients, but we must remember that it has several potential disadvantages. The implant procedure is longer and has an increased complication risk compared to simple single- or dual-chamber ICD implantations. CRT-D devices are more expensive and the battery longevity is shorter. Therefore, it would be of considerable clinical value to be able to estimate accurately the potential benefit to individual patients with mild heart failure symptoms before committing them to the more complex device. In this paper, the authors identify six easily identified clinical or echocardiographic characteristics (female gender, QRS duration ≥ 150 ms, LBBB, body mass index ≤ 30, no history of myocardial infarction, and left atrial volume index) that can be used to predict potential long-term benefit from CRT. In patients with these characteristics, the risk-benefit ratio appears to favor CRT strongly. In patients with milder grades of heart failure without these characteristics and with predictors of a poor response (ischemic heart disease with revascularization or prior MI, a smoking history or established ventricular arrhythmia), the risk-benefit ratio may not be as favorable. In the latter group of patients, it may be wise to use a simpler ICD wait until heart failure worsens or QRS duration increases before attempting CRT. ■

CME Questions

1. Proven predictors of a good response to cardiac resynchronization therapy can be derived from which of the following?
a. Electrophysiology testing
b. Radionuclide synchrony analysis
c. Tissue Doppler analysis
d. Clinical parameters

2. Which of the following are independent predictions of long-term survival after out-of-hospital cardiac arrest?
a. Therapeutic hypothermia
b. Percutaneous coronary intervention
c. ICD placement
d. All of the above

3. The most compelling reason for TEE prior to atrial fibrillation cardioversion is:
a. new atrial fibrillation for < 48 hours.
b. to expedite cardioversion in symptomatic patients.
c. patient convenience.
d. to avoid oral anticoagulant therapy.

4. The only indication for early surgery in infective endocarditis proven by a randomized trial is:
a. a large vegetation.
b. a stroke on presentation.
c. heart failure.
d. annular abscess.

5. Rapid triage of ED patients with chest pain relies on:
a. absence of LBBB on ECG.
b. normal blood pressure.
c. baseline and 2-hour troponin level.
d. TIMI risk score ≤ 3.

6. In non-ST elevation coronary syndromes, which patient characteristic strongly argues for an early invasive approach?
a. T-wave inversions on the ECG
b. Troponin I > 2.0
c. Chest pain at presentation
d. Diabetes

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.*

FDA Approves First New Anti-Obesity Drug in Years

In this issue: Lorcaserin for weight loss; statins and fatigue; treatment-resistant gonorrhea; hydrocodone classification changes; USPSTF recommendations; and FDA actions.

Magic bullet for weight management?

The FDA has approved lorcaserin, the first new weight loss medication in more than a decade. The drug is approved for chronic weight management in adults with a body mass index of 30 or greater, or 27 or greater in those with weight-related conditions such as high blood pressure, type 2 diabetes, or hypercholesterolemia. Lorcaserin works by activating the serotonin 2C receptor in the brain, which promotes satiety. Approval was based on the results of three randomized, placebo-controlled trials of nearly 8000 obese and overweight patients with and without type 2 diabetes. All participants received lifestyle modification and reduced-calorie diets as well as exercise counseling. Lorcaserin was associated with an average weight loss of 3-3.7% compared to placebo over 1 year. Those with type 2 diabetes experienced favorable changes in glycemic control. There is no evidence of valvulopathy associated with the drug; although serotonin syndrome is a concern, especially when the locaserin is taken with an SSRI or some migraine drugs. The most common side effects include headache, dizziness, fatigue, nausea, dry mouth, and constipation as well as hypoglycemia in diabetic patients. Lorcaserin will be marketed by Arena Pharmaceuticals as Belviq. ■

Do statins cause fatigue?

Statins may be associated with fatigue and exertional intolerance, according to a small study from UC San Diego. Researchers randomized just over 1000 patients (692 men and 324 women) to simvastatin 20 mg (lipophilic statin), pravastatin 40 mg (hydrophilic statin), or placebo for 6 months. The outcomes were self-ratings of change in baseline in "energy" and "fatigue with exertion." Statin users were more likely to report worsening energy and fatigue compared to placebo ($P = 0.002$) Fatigue and exertional intolerance was worse with simvastatin compared to pravastatin (simvastatin, $P = 0.03$; pravastatin, $P = 0.01$). Women were more severely affected than men. The authors acknowledge that these findings are based on small numbers and findings are provisional. However, they also state that "this is the first randomized evidence of affirming unfavorable statin effects on energy and exertional fatigue." They further suggest that these effects "germane to quality of life, merit consideration when prescribing or contemplating use of statins, particularly in groups without expected morbidity/mortality benefit." (*Arch Intern Med* published online June 11, 2012. doi: 10.1001/archinternmed.2012.2171). The study also raises the potential issue of increased adverse effects of lipophilic statins such as simvastatin. The various risks and benefits of lipophilicity have been debated for years. It is clear that highly lipophilic statins, such as the now removed cerivastatin (Baycol), may have more muscle toxicity, and may have more CNS adverse effects as well. Of currently marketed statins, simvastatin is the most lipophilic, while pravastatin and rosuvastatin are the least. ■

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.

Call to action for resistant gonorrhea

The World Health Organization (WHO) is calling for urgent action to prevent the spread of "untreatable gonorrhea" around the world. The concern is based on reports from several countries, including Japan, United Kingdom, Australia, France, Sweden, and Norway, of gonorrhea that is resistant to cephalosporin antibiotics — the last remaining treatment option. According to WHO, more than 100 million people are infected with gonorrhea annually, and the world is faced with "dwindling treatment options." WHO is calling for greater vigilance on the correct use of antibiotics and more research into alternative treatment regimens for gonococcal infections. The agency also calls for increased monitoring and reporting of resistant strains as well as better prevention, diagnosis, and control of gonococcal infections. Single-dose treatment to assure adherence is also important as is the treatment of partners. WHO also stresses education and prevention, with special attention to high-risk groups such as sex workers and men who have sex with men. Cephalosporin-resistant gonorrhea has not been reported in the United States yet, but surveillance systems are in place. According to a recent CDC editorial in the *New England Journal of Medicine,* "It is time to sound the alarm. During the past 3 years, the wily gonococcus has become less susceptible to our last line of antimicrobial defense..." (*N Engl J Med* 2012; 366:485-487). ■

Changes on horizon for hydrocodone drugs

Could Vicodin soon be a Schedule II drug? The answer may be yes depending on congressional action this summer. The U.S. Senate recently passed The FDA Safety and Innovation Act (S 3187) with an amendment to classify all hydrocodone-containing products from Schedule III to Schedule II. The House of Representative's version of the bill did not contain similar language, and the proposal is under consideration for the final bill to be sent to the President for signature later this summer. Meanwhile, lawmakers in New York are moving forward with legislation that would make all hydrocodone-containing drugs Schedule II. If enacted, these laws would categorize hydrocodone containing drugs, such as Vicodin and Norco, in the same group with morphine, oxycodone, and methadone. Schedule II drugs cannot be phoned in, and patients are required to receive a new prescription for each refill. The proposed tightened regulations are in response to the explosion of prescription opioid abuse nationwide. Meanwhile, pharmacy groups, such as the American Pharmacists Association, are opposed to the legislation and are actively lobbying against it, arguing that it is unnecessarily restrictive to patients who legitimately need access to these drugs. ■

Vitamin D and calcium supplements

The U.S. Preventive Services Task Force (USPSTF) has now recommended that vitamin D and calcium supplements above the usual recommended daily allowances are of no benefit to help prevent bone fractures in healthy older women, and may actually cause harm. In a draft recommendation statement issued in early June, the USPSTF concluded that there is insufficient evidence to recommend vitamin D for prevention of cancer or combined vitamin D and calcium for the prevention of fractures in postmenopausal women or men. They further recommend against daily supplementation of more than 400 IU of vitamin D and 1000 mg of calcium carbonate. Older adults who are at risk for falls may continue to take vitamin D (www.uspreventiveserviestaskforce.org/draftrec3.htm). The draft recommendation was issued just after a study was published showing calcium plus vitamin D supplements appear to be associated with lower mortality in older individuals. In a large meta-analysis, patients receiving both calcium and vitamin D had a 9% reduction in mortality (hazard ratio, 0.91; 95% confidence interval, 0.84-0.98), although vitamin D alone did not affect mortality (*J Clin Endocrinol Metab* published online May 17, 2012, doi: 10.1210/jc.2011-3328). ■

FDA actions

The FDA has issued opinions on two oral novel anticoagulants. The agency turned down Janssen's application for approval of rivaroxaban (Xarelto) for the treatment of acute coronary syndrome, at least for now. The FDA did not release the reasons for the decision, but speculation is they want more information from the ATLAS-ACS trial. Rivaroxaban was approved last year for prevention of venous thromboembolism after hip or knee replacement surgery, and also for stroke prevention in patients with non-valvular atrial fibrillation (AF). The FDA also delayed the approval of apixaban (which would represent the third novel oral anticoagulant along with dabigatran and rivaroxaban) for the prevention of stroke and systemic embolism in patients with non-valvular AF. It had been widely speculated that the drug would be approved this spring, especially given that the FDA had granted a priority review for apixaban last November. The delay is similarly due to the need for additional information from the ARISTOTLE trial. Once approved apixaban will be marketed by Bristol-Myers Squibb as Eliquis. ■

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 17, NUMBER 8 PAGES 15-16 AUGUST 2012

Another Look at Bleeding Risk from Aspirin

Source: De Berardis G, et al. *JAMA* 2012; 307:2286-2294.

THE ROLE OF ASPIRIN (ASA) FOR PRIMARY prevention of cardiovascular (CV) events has been a beleaguered topic for more than a decade. Although the risk reduction from ASA for secondary prevention of CV events clearly outweighs the bleeding risk, the balance for primary prevention of CV events is much less weighted toward the benefits side of the equation. Indeed, recent consensus groups have relied on the additional ASA benefits for prevention of colon cancer to make a case that when added to marginal CV event reduction, total risk reduction is sufficiently powerful to give primary prevention the green light.

De Berardis performed an analysis of bleeding risk among adults in Puglia, Italy, during the 2003-2008 interval. To qualify as a bleeding event, the study subject had to be hospitalized for either a gastrointestinal or intracerebral bleeding episode. A direct comparison between adults who received new prescriptions for low-dose (≤ 300 mg/d) ASA (n = 186,425) and matched controls who had not been prescribed ASA (n = 186,425) was done. A second question was whether the effects of ASA were different in diabetics than in others.

In the population as a whole (on ASA and control), diabetics had a higher risk of bleeding than non-diabetics, independent of ASA. Given that two recent randomized, controlled trials of ASA in diabetics have failed to show a CV benefit, the apparently inherently increased risk for bleeding in diabetics is concerning. ■

Can Aspirin Prevent Recurrence of Thromboembolism?

Source: Becattini C, et al. *N Engl J Med* 2012;366:1959-1967.

CURRENT RECOMMENDATIONS FOR MANagement of proximal deep venous thrombosis or pulmonary embolus suggest a minimum of 6 months treatment with a vitamin K antagonist (warfarin). Although more prolonged use of warfarin does continue to reduce the risk of recurrent DVT, the cost, inconvenience, and bleeding risk of long-term warfarin is substantial. Since as many as 20% of persons with an unprovoked thromboembolic event will suffer a recurrence within 2 years of warfarin discontinuation, well-tolerated agents to reduce this risk would be very welcome.

Becattini et al randomized patients (n = 402) who had sustained unprovoked thromboembolism and completed a standard therapeutic course of warfarin (6-18 months) to either 100 mg/d ASA or placebo. Study participants were followed for 2 years, looking at the incidence of new thromboembolism (primary efficacy outcome) and major bleeding events (primary safety outcome).

Risk of thromboembolism was reduced by 42% in the ASA group compared to placebo (6.6% vs 11.2% new events/yr). Major bleeding was uncommon and not different between the groups (one event each group).

At the conclusion of an approved course of warfarin post-pulmonary embolus, clinicians and patients are presented with the difficult choice of whether to continue warfarin long-term. These results are encouraging that low-dose ASA has a meaningful potential role in long-term secondary prevention of thromboembolism, especially when warfarin continuation is not a desirable option. ■

A New Approach to Tinnitus

Source: Cima RFF, et al. *Lancet* 2012; 379:1951-1959.

I WAS SURPRISED TO LEARN THAT AS MANY AS 21% of adults will develop tinnitus (TIN) during their lifetime, as stated by Cima et al in the introduction to this clinical trial. Persons who develop TIN can experience a major decrement in quality of life. Despite thorough investigation, it is uncommon to find a correctible cause for TIN, which often persists indefinitely. Sufferers are left with sound-based therapies (e.g., a "masking" sound or neutral sound that distracts from the annoyance of the TIN sound) or cognitive behavioral treatment. Clinical trials to support either of these modalities are thus far somewhat insufficient.

Cima et al randomized TIN patients in the Netherlands to usual care vs specialized care (intervention). Components of specialized care included 8 weeks of intensive audiological diagnostics, audiological rehabilitation sessions, and individual cognitive behavioral therapy, followed by 12 weeks of group cognitive behavior therapy.

At 12 months, the intervention group enjoyed a significant improvement in quality of life compared to usual care. TIN can create TIN-related catastrophic thinking; this aspect of the disorder was also im-

proved to a greater degree with the specialized care. The authors note that efficacy was not altered by TIN severity; hence, all TIN sufferers might benefit from consideration of this methodology. ■

Coffee Might be One Less Thing We Have to Worry About

Source: Freedman ND, et al. *N Engl J Med* 2012;366:1891-1904.

In the United States and Europe, coffee is a staple of diet and social activities for most adults. Increased sympathetic tone — as generated by the autonomic nervous system, hyperthyroidism, cocaine, sympathetic amines, etc. — can be quite toxic. Caffeine also is a stimulant, albeit of short-lived duration. An association of coffee with higher LDL levels has also been noted. Could the commonplace life-long ingestion of coffee be toxic also?

The NIH-AARP Diet and Health Study solicited questionnaires from AARP members 50-71 years of age (n = 617,119) in 1995-96. Usable information for analysis was obtained from 402,263 of these. Many dietary aspects were addressed, but this communication was focused on coffee. Respondents grouped themselves into categories ranging from zero to more than six cups of coffee daily, subgrouped into caffeinated and decaffeinated.

By multivariate analysis (correcting for such confounders as smoking), there was an *inverse* relationship between coffee consumption and mortality for both men and women. For example, men who drank at least six cups of coffee daily had a 10% lower risk of death and women had a 15% lower risk. CV events, diabetes, and infectious disease causes of death were inversely associated with coffee drinking, and it did not appear to make a difference whether coffee was caffeinated or decaffeinated.

Given the observational nature of this trial, it is not possible to establish causation. Hence, while coffee consumption is associated with reduced mortality, we cannot yet say coffee consumption *causes* reduced mortality. Nonetheless, it is reassuring that a dietary habit so widespread among adults appears to be benign, and possibly even beneficial. ■

ED, Lower Urinary Tract Symptoms, and Ejaculatory Dysfunction

Source: Kwa JS, et al. *Int J Impot Res* 2012;24:101-105.

That erectile dysfunction (ED) increases with age is not the least bit surprising. Nor, with but a moment's consideration, is the correlation of age with lower urinary tract symptoms (LUTS) counterintuitive. After all, as men age, the prostate continues to enlarge, and nocturia, frequency, dribbling, difficulty starting/stopping stream commonly ensue. A curious observation within the last decade, however, is that there is an association between the presence of LUTS and ED that is independent of age. That is, at any age, men with LUTS have a higher frequency of ED, and the ED is correlated with the severity of LUTS. A mechanism interconnecting these two otherwise seemingly separate phenomenons has been elusive. However, a hypersensitivity to sympathetic tone has been noted both in ED and LUTS, and may be a central link. The common bond between ED and LUTS is further reflected by the recent approval of PDE5 inhibitors — which had heretofore been considered ED drugs — for management of benign prostatic hyperplasia (BPH).

In the data provided by Kwa et al on 250 mid-life men, it was again found that ED and LUTS increase with age. What they also note is that ejaculatory dysfunction (EjD) — which includes premature ejaculation, anejaculation, dry ejaculation, and decreased ejaculatory volume — also increases with age, although premature ejaculation alone was not associated with age.

EjD, ED, and LUTS have interrelatedness that is closely linked with age, but there may be other pathophysiologic correlates between them. ■

The Allure of Shared Medical Appointments in Diabetes Care

Sources: Ridge T. *Diabetes Spectrum* 2012;25:72-75. Miselli V, et al. *Diabetes Spectrum* 2012;25:79-84.

Two articles in the spring edition of the journal *Diabetes Spectrum* touch on the concept of shared medical appointments (e.g., group visits) to enhance management of type 2 diabetes. The appeal of group visits stems from several sources. First, in a busy clinical environment, the ability to share fundamental management concepts with multiple patients at the same time seems much more efficient. Second, group bonding and sharing experiences may foster team efforts that enhance knowledge, confidence, self-efficacy, and possibly even outcomes. The literature on this topic is generally favorable. The review article by Ridge describes various reports suggesting improved quality of life, knowledge, and (sometimes) diabetes control in persons who participate in group visits when compared with "usual care."

Miselli et al provide the details of their structured Group Care Model and the results of a 4-year study of their model. Patients with type 2 diabetes were randomized into group care or usual care. At the end of 4 years, BMI, fasting glycemia, A1c, total cholesterol, and blood pressure had improved in the group care cohort, whereas they had either stayed the same or worsened in the control group. Similarly, quality of life, diabetes knowledge, and healthy behaviors improved comparatively in the group care subjects.

The idea of group visits is not new, but it has been slow to take hold in clinical settings in the United States. The group visit model may make sense both from an economic and health outcomes perspective. ■

Clinical Briefs in Primary Care™ is published monthly by AHC Media.

Executive Editor: Leslie Coplin.
Editor: Stephen Brunton, MD.
Managing Editor: Neill L. Kimball.
This is an educational publication designed to present scientific information and opinion to health professionals, stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for the layman.

Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: neill.kimball@ahcmedia.com
World Wide Web: www.ahcmedia.com
Address Correspondence to: AHC Media, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305.

AHC Media