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Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Beta-Blockers and CAD?

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: Bangalore S, et al. Beta-blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *JAMA* 2012;308:1340-1349.

Beta-blockers have long been a cornerstone of therapy for patients who have suffered myocardial infarction (MI). However, most studies of beta blockade following MI were performed before the current era of reperfusion therapy, statins, and antiplatelet agents. Whether beta-blockers have a clinical benefit over more modern therapies is not known. Accordingly, Bangalore and colleagues studied patients from a large international registry to determine whether beta-blocker use is associated with lower rates of cardiovascular events in the modern era. They grouped the patients into three cohorts: those with prior MI, those with known coronary artery disease (CAD) but without prior MI, and those with CAD risk factors only. Within each of these cohorts, they compared the rate of cardiovascular events in patients who were taking beta-blockers to those who were not. Because of significant baseline differences between those who were and those who were not taking beta-blockers, the authors performed propensity matching to account for 27 baseline clinical variables. The primary endpoint of the study was a composite of cardiovascular death, nonfatal MI, or nonfatal stroke. The secondary outcome was the primary outcome plus hospitalization for atherothrombotic events or a revascularization procedure (coronary, cerebral, or peripheral). Tertiary outcomes were all-cause mortality, cardiovascular mortality, nonfatal MI, nonfatal stroke, and hospitalization, which were considered as separate outcomes. The median duration of follow-up was 44 months.

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Clinical Cardiology [ALERT]

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In each cohort, there were more than 3000 matched pairs of patients. In the prior MI cohort comparing patients taking beta-blockers to those who were not, there was no difference in the rate of the primary endpoint (16.9% vs 18.6%; $P = 0.14$), the secondary endpoint (31.0% vs 33.1%; P = NS), or any tertiary endpoints. In the CAD without MI cohort, comparing patients taking beta-blockers to those who were not, there was no difference in the rate of the primary endpoint (12.9% vs 13.6%; $P = 0.31$). The rate of the secondary endpoint was higher in those taking beta-blockers (30.6% vs 27.8%; $P = 0.01$). There was no difference in the tertiary endpoints. In the risk factors alone cohort, the event rates were higher in those taking beta-blockers compared to those who weren't for the primary endpoint (14.2% vs 12.1%; $P = 0.02$) and the secondary endpoint (22.0% vs 20.2%; $P = 0.04$), but there was no difference in the tertiary endpoints. To confirm these findings, the authors performed secondary statistical analyses and found that these agreed with their initial results. The authors conclude that in this observational study of patients with either CAD risk factors only, known prior MI, or known CAD without MI, the use of beta-blockers was not associated with a lower risk of composite cardiovascular events.

■ COMMENTARY

This is a very important and interesting study. The current ACC/AHA guidelines give a class 1 recommendation for beta-blocker use after MI for up to 3 years, but a class 2a recommendation for longer use. Beta-blockers receive a class 2b recommendation in other patients with coronary or peripheral arterial disease. The salubrious effects of beta-blockers in patients following MI are often extrapolated to patients in other clinical situations, such as those with multiple risk factors. This study casts doubt on this practice, and suggests that the effects of beta-blockers in the modern era are not as profound as they were in times past. There are potentially patient subgroups that benefit from beta-blockade. This study suggests that the higher the patient's risk, the more potential there is to receive benefit from beta-blockers. Beta-blockade was associated with a trend toward improvement in the prior MI cohort, no improvement in the CAD without MI cohort, and worse outcomes in the risk-factor only cohort, suggesting that there may be more benefit from beta-blockers in patients at the higher end of the spectrum of risk. However, many questions remain. First, this study did not separate the different agents within the beta-blocker family, and there may be distinct differences between them. Along the same lines, we are not told what doses were used, nor how they were titrated. Second, the region of MI (i.e., anterior, inferior, or lateral) and the left ventricular function are not mentioned, and these factors may change the patient's risk profile and likelihood of deriving benefit from beta-blockers. Third, the time from MI to study inclusion is not stated. Fourth, this was a registry study, not a randomized study, and thus there may be unmeasured confounders. What should we do with these data? Should we abandon beta-blockers altogether? The answer is no. We should continue to treat post-MI patients with beta-blockers if they can tolerate them. Despite the limitations of this study, it raises important questions about the need for beta-blockers in these patient populations in the current era. Future randomized controlled trials are needed to address these questions. ■

ABSTRACT & COMMENTARY

High-Risk PCI with Hemodynamic Support — Impella or IABP?

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

SOURCE: O'Neill WW, et al. A prospective, randomized clinical trial of hemodynamic support with impella 2.5 versus intra-aortic balloon pump in patients undergoing high-risk percutaneous coronary intervention: The PROTECT II study. *Circulation* 2012;126:1717-1727.

In patients with severe coronary artery disease (CAD) and depressed left ventricular (LV) function, coronary artery bypass graft (CABG) surgery remains the recommended treatment. However, for some patients, CABG is not an option and high-risk percutaneous coronary intervention (PCI) is the only potential mode of revascularization. In these patients, the transient cessation of coronary artery flow during balloon inflation may result in hemodynamic compromise or even collapse. In extreme cases, this can lead to cardiac arrest. The use of hemodynamic support may improve outcomes in high-risk PCI, but there have been no direct comparisons of devices. Thus, O'Neill and colleagues performed a randomized, controlled, international multicenter trial of intra-aortic balloon pump (IABP) vs the Impella 2.5 percutaneous left ventricular support device. The Impella is an axial flow pump that is placed across the aortic valve and can pump up to 2.5 L/min from the left ventricle to the aorta. The study included a very high-risk population of patients requiring PCI and either left main disease or last remaining vessel with LV ejection fraction (EF) ≤ 35%, or triple vessel disease with LVEF ≤ 30%. Exclusion criteria were recent myocardial infarction (MI) with persistent elevation of cardiac enzymes, platelet count of < 75,000/mm^3, creatinine ≥ 4 mg/dL (those on dialysis already were eligible), and severe peripheral arterial disease precluding the passage of the support devices. At 112 sites, the investigators were instructed to aim for the most complete revascularization possible in a single procedure, but details such as anticoagulation strategy, use of IIb/IIIa inhibitors, types of stents used, and use of closure devices was left to the operator's discretion.

The primary endpoint was the composite rate of major adverse events at discharge or 30-day follow-up (whichever was longer). Major adverse events included death, MI, stroke or transient ischemic attack (TIA), repeat revascularization, acute renal insufficiency, need for cardiac or vascular operation, severe intraprocedural hypotension requiring therapy or cardiopulmonary resuscitation, ventricular tachycardia, aortic regurgitation, and angiographic procedural failure. A prespecified secondary endpoint was 90-day follow rate of the primary endpoint.

The study was terminated early because of futility. Ultimately, 448 patients were randomized to support with IABP (n = 223) vs Impella 2.5 (n = 225). Baseline characteristics were similar between groups except that the Impella group had higher rates of prior CABG (38% vs 29%; $P = 0.033$) and heart failure (91% vs 83%; $P = 0.014$). This was a very high-risk cohort, with 51% diabetic, average LVEF 24 ± 6%, and an average SYNTAX score of 30 ± 15. In both groups, an average of 2.9 lesions were treated per patient. Impella provided better intra-procedural hemodynamic support than IABP. The patients in the Impella group had higher rates of rotational atherectomy, lower use of IIb/IIIa inhibitors and non-heparin anticoagulants, and required shorter durations of hemodynamic support.

The LVEF rose from 27 ± 9% to 33 ± 11% and the proportion of patients in New York Heart Association functional class III/IV improved from 62% to 26%, with no difference between groups. Intention-to-treat analysis showed no statistically significant difference in the primary composite endpoint at 30 days (35.1% Impella vs 40.1% IABP; $P = 0.277$). There was no difference in the components of the primary composite endpoint with the exception of a lower rate of stroke/TIA in the Impella group (0.0 vs 1.8; $P = 0.043$). At 90 days, the primary composite endpoint trended in favor of Impella (40.6% vs 49.3%; $P = 0.066$). In a per-protocol analysis (excluding those who were randomized but did not receive the treatment), the primary composite endpoint was more in favor of the Impella group, with a trend at 30 days (34.3% vs 42.2%; $P = 0.092$) and a significant benefit at 90 days (40.0% vs 51.0%; $P = 0.023$). The authors present several exploratory endpoints of interest. The Impella group appeared to have better outcomes at 90 days in those patients who did not have atherectomy, those with triple vessel disease (compared to left main disease), those with predicted mortality < 10% by Society of Thoracic Surgeons (STS) score, after excluding the first patient at each site, and after the first year of the trial. The authors conclude that the 30-day incidence of major adverse events was not different for patients with IABP or Impella 2.5 hemodynamic support. However, trends for improved outcomes were observed for Impella 2.5-supported patients at 90 days.

■ COMMENTARY

This study recruited the highest risk cohort of any PCI study to date. Based on the initial feasibility study, PROTECT 1, the power calculation required 654 patients for this study to show benefit of Impella over IABP. However, at 50% enrollment, the data safety monitoring board terminated the study because the projected outcomes would not reach the primary endpoint. This effectively underpowered the study, which ultimately recruited just 69% of the projected enrollment. The authors point out that there

was a learning curve with this new device, as shown by the improved results in the later years of the study and by excluding the first patient at each institution. This may have contributed to less than expected benefit with Impella early on in the study. How should we interpret these results now that we have an underpowered study with improving results over the course of the trial? First, the learning curve needs to be acknowledged and physicians and staff need to be adequately trained in the use of Impella. Second, despite a slightly higher clinical risk profile and a higher procedural risk profile, the Impella patients tended to do better than the IABP patients. This is very reassuring from a safety perspective. However, from an efficacy standpoint, because the study was underpowered and the results were trends toward better outcomes with Impella, we cannot definitely conclude for or against the use of Impella over IABP in high-risk PCI patients on the basis of these data. The exploratory endpoints are interesting and suggest that there may be subgroups who benefit from the Impella over IABP. But these must be considered hypothesis-generating and need further study. It is important to note that this study was performed in the non-emergent setting, and these results should not be extrapolated to patients with acute coronary syndromes or those in cardiogenic shock. Overall, there may be a role for Impella in the setting of high-risk elective PCI, but the results of this study are not conclusive and should form the basis of future studies of this technology. ■

ABSTRACT & COMMENTARY

Non-Cardiac Surgery After Coronary Stenting

By Michael H. Crawford, MD, Editor

SOURCES: Wijeysundera DN, et al. Risk of elective major noncardiac surgery after coronary stent insertion — A population-based study. *Circulation* 2012;126:1355-1362. Matteau A, Mauri L. Optimal timing of noncardiac surgery after stents. *Circulation* 2012;126:1322-1324.

The risks of noncardiac surgery after stent implantation are unclear, but have important implications for patient management. Thus, these investigators from Toronto, Canada, used province-wide revascularization registry data in Ontario and various administrative databases to study more than 8000 patients who had non-cardiac surgery from 2003-2009 and had coronary stent implantation within 10 years before their surgery. About 34% had stent implantation within 2 years of surgery and one-third of these received drug eluting stents. These patients were compared to 300,000 surgical patients who had not had revascularization within 10 years of their surgery. The primary endpoint was a combination of mortality, readmission for acute coronary syndrome, or repeat revascularization for 30 days after surgery. The secondary endpoint was these events 1 year after surgery. The combined endpoint was observed in 2.1% at 30 days and in 9.8% at 1 year. Mortality was 1.2% and 5.2%. Multivariate analysis showed that stent type and the PCI to surgery time interval were associated with both endpoints. The 30-day endpoint was highest for drug-eluting stents and surgery within 45 days (20%). The 30-day events with bare-metal stents were also highest in the first 45 days (6.7%). In the 45- to 180-day interval, the event rate in bare-metal stents was 2.6%, similar to patients without revascularization. For drug-eluting stents, the rate fell to 1.2% after 180 days, which approximated that of the control group. The authors concluded that the optimal delay of non-cardiac surgery after stenting is > 45 days for bare-metal stents and > 180 days for drug-eluting stents.

■ COMMENTARY

The major strength of this observational study is the large number of patients included. This allows for substantial sub-populations. For example, 36% were diabetic and 23% had vascular surgery. The study is very relevant to physician decision making in that emergency or urgent surgery patients were excluded because these decisions are often driven by the high risks of the condition requiring surgery. In more elective surgery, considering possible cardiac complications takes the stage. This study suggests the current recommendations that if surgery can be delayed 6 weeks after bare-metal stent placement, it can be accomplished with a low risk of stent thrombosis. The study does not

support the current ACC/AHA guidelines to wait 1 year after drug-eluting stent placement, but rather suggests that 6 months may be adequate. This is supported by other smaller studies and is common practice in Europe. On the other hand, for both types of stents after 1 year, the rate of acute cardiac events is equivalent to the rate observed in the control group without stents.

The major limitation to the study is that it is based on registry and administrative data that do not detail drug therapy. We can only assume that standard practices were followed. Also, we don't have details on the coronary anatomy and stenting procedure. In addition, this was a relatively low-risk group with 75% having a revised cardiac risk index of 1-2 and thus, there were very few events. Finally, we don't know the cause of the events. They could be from stent thrombosis, new plaque ruptures, or in-stent restenosis, which is more frequent during the first year after implantation. The accompanying editorial suggests that these weaknesses are profound enough that we should not yet change guidelines. ■

ABSTRACT & COMMENTARY

Safety of High- vs Moderate-Intensity Exercise for Cardiac Rehabilitation

By Michael H. Crawford, MD, Editor

SOURCE: Rognmo O, et al. Cardiovascular risk of high- versus moderate-intensity aerobic exercise in coronary heart disease patients. *Circulation* 2012; 126:1436-1440.

Current guidelines recommend cardiac rehabilitation using moderate exercise programs for most ischemic heart disease (IHD) patients. Also, studies have shown that the intensity of exercise is directly related to the cardioprotective effects. However, there is concern that high-intensity exercise may be dangerous in IHD patients. Thus, these investigators from Norway studied almost 5000 IHD patients in cardiac rehabilitation units that employed both high-intensity interval exercise and moderate-intensity continuous exercise training sessions. High-intensity exercise was defined as achieving > 85% of maximum predicted heart rate (mpHR) at intervals and moderate as 60-70% of mpHR continuously. The sessions lasted 1 hour and the patients underwent an average of 37 sessions. The primary outcome measure was cardiac arrest or acute myocardial infarction (MI) during or within 1 hour after a session. There were > 129,000 moderate-intensity sessions and > 46,000 high-intensity sessions. There were two non-fatal cardiac arrests during high-intensity exercise and one fatal cardiac arrest in the moderate group. There were no MIs. The authors concluded that both types of exercise training are associated with a low incidence of events and that the presumed benefits of high-intensity exercise training outweigh these risks.

■ COMMENTARY

This study is in agreement with other studies of cardiac rehabilitation that showed very low event rates. What distinguishes this study is the use of high-intensity exercise in some of the patients. In their protocol, after a warm-up period, high-intensity exercise was done for 4 minutes and then the patients did low-level exercise until they were symptomatically recovered and were at 50-70% mpHR. This cycle was repeated for almost an hour

[Thus, the issue of vigorous vs moderate exercise for cardiac rehabilitation remains somewhat controversial, especially in post-MI patients. My take is that in carefully selected patients, in a supervised program, vigorous interval exercise is safe. However, if patients are doing their own rehabilitation at home or in their gym, then I recommend they stick to moderate exertion.]

ending with a cool-down, low-exercise period. The patients were carefully selected clinically and by formal exercise testing. Those with symptoms or signs of ischemia were excluded. Also, these were not all post-MI patients; only 7% were post-MI. Most were post revascularization patients. Thus, this was a low-risk group.

The major limitation of this study was that it was not randomized. However, given the low event rate observed, they estimated that for a randomized trial to show any difference in the two levels of exercise, more than 10,000 patients would be required in each group. Previous randomized trials were all underpowered, and observational studies have inherent biases. Thus, the issue of vigorous vs moderate exercise for cardiac rehabilitation remains somewhat controversial, especially in post-MI patients. My take is that in carefully selected patients, in a supervised program, vigorous interval exercise is safe. However, if patients are doing their own rehabilitation at home or in their gym, then I recommend they stick to moderate exertion. ■

ABSTRACT & COMMENTARY

Defibrillation Testing: Is it Necessary with ICD Implantation?

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: Brignole, M, et al. Clinical evaluation of defibrillation testing in an unselected population of 2,120 consecutive patients undergoing first implantable cardioverter-defibrillator implant. *J Am Coll Cardiol* 2012;60:981-987.

This paper reports the results of the Safety of Two Strategies of ICD Management at Implantation (SAFE-ICD) study. This study was a registry conducted in 41 Italian centers that followed outcomes after initial implantable cardioverter-defibrillator (ICD) implant to determine if performing defibrillation testing at the time of implant had clinical value. During a 13-month period, 2120 patients who received a new ICD at the participating centers were enrolled in the registry. Defibrillation testing was at the time of the initial implant according to the centers' current practice. Intraoperative complications and events during follow-up were then used as endpoints.

The 2120 patients enrolled constituted 97% of all new ICD recipients in the 41 participating centers. The frequency of defibrillation testing was quite variable ranging from 0-100% of ICD implants at individual centers. Of the patients enrolled, 836 (39%) had defibrillation testing and 1284 (61%) did not. Patients who did not have defibrillation testing were likely sicker since they had, on average, a higher New York Heart Association functional class, lower left ventricular ejection fractions, and more frequently received cardiac resynchronization therapy devices. The method of defibrillation testing varied from center to center. Among the patients who underwent defibrillation testing, one single VF induction-defibrillation was performed in 720 patients, two inductions in 100 (12%), and more than three in 16 (2%). At least one external shock was needed at the time of testing in 30 patients (3.6%) because of an ineffective ICD shock at maximum energy. Of these 30 patients, four had a cardiopulmonary arrest requiring three or more external shocks for termination. In eight patients, the defibrillator was unable to convert VF with any internal shock at the time of implant.

The primary combined endpoint was a composite of implant-related complications and events during follow-up. These occurred in 18 patients who underwent defibrillation testing and 16 patients who did not. The slightly higher event rate in the defibrillation testing patients was due to the higher intraoperative complication rate. When the event rates were weighted for baseline clinical variables by propensity scoring, the difference between the groups remained very small. Mortality between the two groups was slightly lower among patients who had defibrillation testing than among patients who did not, but adjustment for baseline variables by propensity scoring showed that the hazard ratio (HR) was not significant (HR -0.97; 95% confidence interval: 0.76 to 1.23). During clinical follow-up, appropriate effective shocks occurred in 223 patients, with a similar proportion

receiving shocks in the two groups. Appropriate ineffective shocks were seen in 13 patients and again these were evenly distributed between the two groups. There were nine sudden cardiac deaths, two instantaneous deaths, and two deaths within 5 minutes in the defibrillation testing group compared to 11 sudden cardiac deaths and three instantaneous deaths in the group that did not have testing. The authors conclude that defibrillation testing is safe but it does not appear to be necessary to ensure safety.

■ COMMENTARY

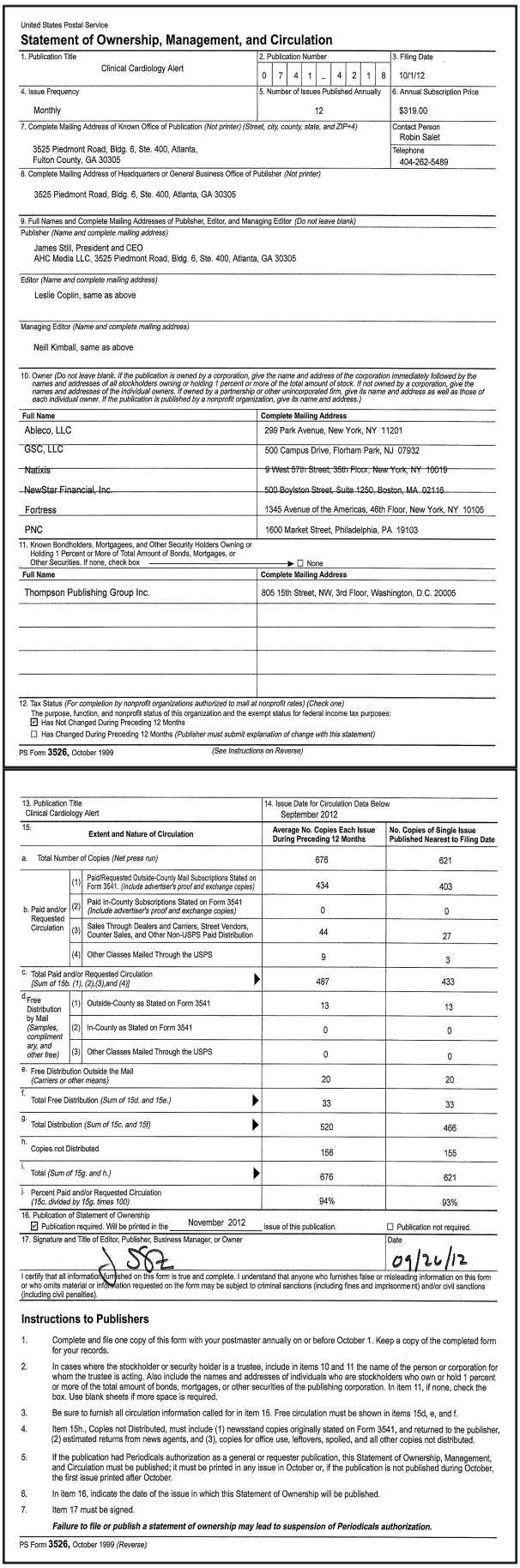
There has been considerable controversy recently about the need for defibrillation testing. Some authors have proposed that defibrillation shocks by themselves may damage the heart, increase the risk for implant complications, and result in long-term adverse affects.

Defibrillation testing was an intrinsic part of the implant procedure from the early days of ICD therapy. The initial systems that used epicardial patches and the early transvenous systems often had high defibrillation thresholds and failure to defibrillate at maximum energy was not uncommon. New generation ICD systems have more effective defibrillation waveforms and pathways and much shorter charge times. The latter makes it unnecessary to program shock energy levels to the lowest effective setting. As a result, it is now rare for there to be a failure at the time of defibrillation testing and it has not been possible to correlate a testing failure at implant with failure during clinical use.

Should defibrillation testing still be routine? This study strongly suggests the answer is no. In our laboratory, we now perform testing on a limited basis, mostly in patients with unusual anatomy or lead placement and at generator changes in patients with ICD leads under recall.

In this study, the authors show that there is a low complication rate with defibrillation testing, but that defibrillation testing does not appear to offer any significant benefits. In our laboratory, we now usually do not do defibrillation testing if we can achieve a stable standard lead position.

One of the early reasons for defibrillation testing was to program the energy as low as possible. However, as the charge times have decreased, programming to a lower energy output has become less important and, therefore, I don't think this should be a reason for continuing to do defibrillation testing. ■



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   a. decreases long-term mortality.
   b. reduces inappropriate shocks.
   c. reduces procedural complications.
   d. None of the above

2. Contemporary outcome data on beta-blocker use in CAD shows:
   a. death, MI, and stroke were reduced in post-MI patients.
   b. death, MI, and stroke were reduced in CAD patients without MI.
   c. death, MI, and stroke were increased in patients with risk factors for CAD.
   d. adding cardiac hospitalizations negated any significant results.

3. Impella 2.5 vs IABP for high-risk PCI resulted in:
   a. better outcomes at 30 days.
   b. less stroke/TIA.
   c. no difference in outcomes at 90 days.
   d. All of the above

4. Interval high-intensity (IHI) as compared to continuous moderate-intensity (CMI) exercise during cardiac rehabilitation showed what with regards to acute cardiac events?
   a. More acute coronary events in the IHI group
   b. More cardiac arrests in the CMI group
   c. Very low cardiac event rates in both groups
   d. All of the above

5. Noncardiac surgery after coronary stent placement is most safe for drug-eluting stents after:
   a. 1 month.
   b. 3 months.
   c. 6 months.
   d. 1 year.

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.

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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Secondary Prevention of Lacunar Stroke

Source: SPS3 Investigators. *N Engl J Med* 2012;367:817-825.

LACUNAR STROKES (L-CVA) ARE SMALL subcortical brain infarctions that may comprise as many as 25% of ischemic strokes. Aspirin (ASA) monotherapy is already established as appropriate treatment for secondary prevention of ischemic stroke, as is clopidogrel (CLOP) monotherapy. In the CAPRIE trial, CLOP provided a *marginal* advantage over ASA for major adverse cardiovascular events (absolute risk reduction = 0.5%) in the overall study population, leading some to advocate clopidogrel routinely over ASA. It is often underrecognized that in the CAPRIE trial, study subjects who enrolled specifically because of previous stroke did *not* experience any statistically significant stroke reduction with CLOP compared to ASA; the outcomes were the same.

The Secondary Prevention of Small Subcortical Strokes (SPS3) trial is the first published trial to compare the efficacy of ASA monotherapy vs ASA + CLOP in reference to L-CVA. The study population included more than 30% Hispanics, concordant with the observation that L-CVA is more common in Hispanics.

At the conclusion of the trial (3.4 years mean), ASA + CLOP was *not* more effective than ASA alone in preventing L-CVA. Among the study population (n = 3020 adults with prior L-CVA), most new strokes were L-CVA (71%).

Unfortunately, as has been seen in other studies of combined ASA + CLOP, bleeding risk was significantly increased compared to ASA alone, as was all-cause mortality. Two prior trials in vasculopathic populations (MATCH, CHARISMA) have arrived at similar conclusions: For persons with stable non-acute vascular disease, ASA + CLOP is not more beneficial than ASA alone, but incurs greater bleeding risk. ■

Quality-of-life Effects of PSA Screening

Source: Heijnsdijk EA, et al. *N Engl J Med* 2012;367:595-605.

THE EUROPEAN RANDOMIZED STUDY OF Screening for Prostate Cancer (ERSPC) is a clinical trial in which adult men (n = 162,243) were randomized to prostate-specific antigen (PSA) screening or no screening. While this trial did find a statistically significant reduction in prostate cancer deaths, overall mortality was not affected, supporting the current recommendations by the United States Preventive Services Task Force (USPSTF) that PSA screening be abandoned. Although the USPSTF decision was based on the "hard" data about mortality, there is likely also substantial quality-of-life (QOL) burden engendered from PSA screening, since many — indeed, the vast majority of — men diagnosed with prostate cancer through PSA screening will die with, not from, their prostate cancer. Additionally, adverse effects of intervention for (the mostly) early prostate cancer detected through screening are not uncommon, and include erectile dysfunction and incontinence. Finally, even in men who elect not to have a surgical intervention in response to prostate cancer detected as a result of PSA screening, it would take little imagination to envision substantial ongoing concerns/anxieties referable to that diagnosis.

Heijnsdijk et al report that per 1000 men screened by PSA, nine fewer prostate-cancer related deaths would occur and 73 life-years would be gained. After adjustment for overdiagnosis and overtreatment of prostate cancer subsequent to PSA screening, these benefits were reduced by almost one-fourth. In an era when PSA screening is no longer supported because of an insufficiently favorable risk:benefit ratio, recognition of the negative QOL impact of PSA screening may help clinicians (and their patients) better come to terms with the now well-recognized limitations of PSA screening. ■

PSA Elevations After Prostate Cancer Radiotherapy

Source: Crook JM, et al. *N Engl J Med* 2012;367:895-903.

SINCE PROSTATE CANCER (PCA) IS OFTEN ANdrogen-dependent, PCA recurrences after radiotherapy are often treated with androgen deprivation by means of regimens consisting of continuous luteinizing hormone-releasing hormone agonists (LHRHa) combined with antiandrogens. Unfortunately, such treatment is associated with hot flashes, decreased libido, urinary symptoms, and fatigue. Might intermittent androgen deprivation be equally effective, but less problematic as far as adverse effects?

Crook et al randomized patients who had undergone radiation treatment for PCA but had a post-treatment PSA > 3.0 ng/dL to continuous or intermittent androgen deprivation.

For overall mortality, intermittent androgen deprivation was non-inferior to continuous treatment. The time to development of castration-resistant disease (the stage at which androgen deprivation no longer represses disease progression) was significantly longer for intermittent treatment. Similarly, the adverse effects of hot flashes, libido, and urinary symptoms were all significantly fewer in the intermittent treatment group. In addition to necessitating a substantially reduced amount of medication (and of course, expense), intermittent androgen deprivation regimens are non-inferior for overall mortality, and are associated with superior quality of life. ■

Attenuated CV Benefits of Clopidogrel in Diabetes

Source: Andersson C, et al. *JAMA* 2012; 308:882-889.

There is no controversy over whether antiplatelet therapy (e.g., aspirin, clopidogrel, prasugrel) reduces cardiovascular (CV) events when used for secondary prevention (i.e., post-acute coronary syndrome, post-myocardial infarction [MI], post-stroke). It is equally apparent that risk reduction through antiplatelet therapy is not equal among all risk groups. For instance, although aspirin (ASA) consistently shows CV risk reduction in mixed populations post-MI, two clinical trials of ASA comprised solely of diabetics failed to show benefit. Diabetics are known to have greater platelet reactivity, and their platelets are relatively resistant to antiplatelet effects as measured by medication-induced platelet aggregation inhibition testing.

Comparative benefits of clopidogrel in diabetics vs non-diabetics have not been described well enough. To assess whether diabetics fare as well with clopidogrel post-MI as non-diabetics, Andersson et al reviewed data from the Danish nationwide administrative registries of patients discharged from the hospital post-MI (n = 58,851), of which 12% had diabetes.

One-year follow-up compared outcomes among all persons treated with clopidogrel. Although all groups did have CV risk reduction from clopidogrel treatment, there was a significant difference between diabetics and non-diabetics, favoring non-diabetics. For instance, the hazard ratio (HR) for all-cause mortality was more than twice as favorable for non-diabetics (HR = 0.75, a 25% reduction) than diabetics (HR = 0.89, an 11% reduction).

The obstacle of clopidogrel-resistant platelets can be overcome by dose intensification (i.e., more clopidogrel), combination therapy (i.e., clopidogrel + ASA), or consideration of another P2y12 agent (i.e., prasugrel). Unfortunately, however, each of these methods has been associated with an increased risk for bleeding. Optimization of antiplatelet therapy in diabetics remains somewhat elusive. ■

Is A1c Always the Best Game in Town to Monitor Type 2 Diabetes?

Source: Wright LAC, Hirsch IB. *Diabetes Spectrum* 2012;25:141-148.

Even as time-honored a metric as A1c has limitations. There are, for instance, situations in which A1c can markedly mis-estimate actual sustained glucose concentrations. Since A1c measurement requires hemoglobin to be exposed to excess glucose for the entire life of a red cell (90-120 days), anything that shortens red cell life (e.g., thalassemia, Hgb C, HbS, hemolysis) will *underestimate* actual sustained glucose levels (since red cells don't live long enough to become fully glycosylated). Hemoglobin F, which is persistent in a small percentage of adults, glycosylates so rapidly that even very modest elevations of glucose can induce marked elevations of A1c (A1c 12%-17% or greater), grossly *overestimating* sustained glucose levels.

Fructosamine is a composite measure of relatively short-lived serum proteins that have become converted into irreversible ketoamines, of which glycated albumin is the primary component (approximately 90%). Since this process occurs over a few weeks, red cell life span — shortened or not — has no impact. Similarly, however, the measurement of fructosamine only provides an observation window of the sustained glucose levels in the preceding 2-3 weeks. Any condition that alters serum protein turnover (eg, thyroid dysfunction, hypopoproteinemia, nephrotic syndrome) can invalidate fructosamine measurement.

Glycated albumin, the primary protein constituent of fructosamine, has been compared with A1c and fructosamine in patients with advanced chronic kidney disease, and found to be the most accurate marker in this population, although it is subject to the same perturbations as fructosamine mentioned above.

One other serum marker not used commonly in the United States, but widely used in Japan, is 1,5 anhydroglucitol (1,5-AG), which reflects sustained glucose over a 2-14 day period. Normally, 1,5-AG is reabsorbed by renal tubules; when plasma and urine glucose are high, they compete with 1,5-AG for reabsorption, resulting in loss of 1,5-AG in the urine, with a corresponding diminution in plasma 1,5-AG. This metric has been found to be particularly useful in measurement of postprandial glucose excesses.

For the time being, A1c will remain the metric of choice for most patients. When A1c and individual glucose measurements are discordant, consideration of another metric is appropriate. ■

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Do Benzodiazepines Cause Dementia in the Elderly?

In this issue: Dementia and benzodiazepines; effectiveness of omega-3 fatty acid and *Ginkgo biloba* supplements; and FDA actions.

Benzodiazepines and dementia

Can benzodiazepines increase the risk for dementia? Researchers in France studied 1063 men and women with an average age of 78 who were free of dementia and did not start taking benzodiazepines until they had been followed for at least 3 years. During a 15-year follow-up, 253 cases of dementia were confirmed. New use of benzodiazepines occurred in 9% of the study population and was associated with an increased risk of dementia (32% benzodiazepine group vs 23%, adjusted hazard ratio 1.60, 95% confidence interval [CI] 1.08-2.38). After correcting for the existence of depressive symptoms as well as age and diabetes, the hazard ratio was unchanged. A secondary analysis looking at participants who started benzodiazepines at different times during follow-up also showed an elevated risk of dementia. Results of the complementary, nested, case-control study showed that ever use of benzodiazepines was associated with an approximate 50% increased risk of dementia compared with never users. The authors conclude that in this prospective, population-based study new use of benzodiazepines was associated with a significantly increased risk of dementia. They further conclude that "indiscriminate widespread use should be cautioned against" (*BMJ* 2012;345:e6231). The obvious criticism of the study was the presence of confounders — whether use of benzodiazepines was a marker for early onset dementia rather than a cause. While the authors feel the study was carefully controlled, selection bias cannot be completely ruled out. They further state that the research should be done on younger patients to see if starting benzodiazepines at ages younger than 65 may have deleterious effects. They also recommend that "physicians and regulatory agencies should consider the increasing evidence of potential adverse effects of this drug class for the general population." ■

Popular supplements' use questioned

Two popular supplements — omega-3 fatty acids and *Ginkgo biloba* — may be of limited value, according to two recent studies. Omega-3 fatty acids are thought to have a number of benefits, including lowering triglyceride levels, preventing arrhythmias, decreasing platelet aggregation, and lowering blood pressure. But the fish oil supplement's ability to prevent major cardiovascular events has been debated in the literature. Twenty studies of nearly 67,000 patients were included in a meta-analysis looking at the effect of omega-3 on all-cause mortality, cardiac death, sudden death, myocardial infarction, and stroke. After correcting for dose and comorbidities, there was no difference in the absolute or relative risk of any of the outcomes associated with omega-3 supplementation. The authors concluded that marine-derived omega-3 polyunsaturated fatty

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acid supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke (*JAMA* 2012;308:1024-1033).

Ginkgo biloba for the prevention of Alzheimer's disease (AD) was studied in a randomized, parallel group, double-blind, placebo-controlled trial of adults age 70 years or older who spontaneously reported memory complaints to their primary care physician in France. Patients were randomized to a twice per day 120 mg standardized *Ginkgo biloba* extract or matching placebo and followed for 5 years. The primary outcome was conversion to probable AD. More than 2800 patients were enrolled with about 1400 patients in each group. By 5 years, 61 participants in the ginkgo group were diagnosed with AD vs 73 in the placebo group (hazard ratio 0.84, 95% CI 0.60-1.18; $P = 0.306$). Adverse events were the same between both groups and mortality was roughly the same as well. Sixty-five participants in the ginkgo group had a stroke compared to 60 in the placebo group ($P = 0.57$). The authors conclude that long-term use of standardized *Ginkgo biloba* extract did not reduce the risk of progression to AD compared to placebo (*Lancet Neurology* 2012;11:851-859). ■

FDA actions

The FDA has approved teriflunomide for the treatment of relapsing forms of multiple sclerosis (MS). The approval was based on a 2-year study in which the drug reduced relapses by nearly a third compared to placebo — results that are about the same as other MS drugs and no better than Merck's popular injectable interferon beta 1a (Rebif). Side effects include diarrhea, abnormal liver function tests, nausea, and hair loss. It should not be used during pregnancy. Teriflunomide has the advantage of being a once-daily oral medication, the second oral MS medication after Novartis' fingolimod (Gilenya). Teriflunomide will be marketed by Sanofi Aventis as Aubagio. A third oral MS medication, Biogen Idec's BG-12, was recently found to reduce MS relapses by about 50% (*N Engl J Med* 2012;367:1087-1097; 1098-1107). BG-12 is not yet approved by the FDA, but a decision is expected before the end of the year.

The FDA has delayed the approval of apixaban (Eliquis) once again. Pfizer and Bristol-Myers Squibb's novel oral anticoagulant (NOAC) was expected to be approved last spring after publication of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, which showed that the drug was effective in preventing strokes in patients with non-valvular atrial fibrillation — data that suggested that the drug was perhaps even more effective than the two other NOACs, dabigatran (Pradaxa) and rivaroxaban (Xarelto). In June, the FDA told the manufacturers they needed "additional information on data management and verification from the ARISTOTLE trial." Now, the agency says that the review date will be March 17, 2013. No reason was given by the FDA for the delay.

About 25% of Internet consumers have purchased prescription medications online, while at the same time, the prevalence of fraudulent Internet pharmacies has grown. The FDA has now launched a national campaign to raise public awareness called BeSafeRx – Know Your Online Pharmacy, a resource that provides patients and caregivers with a better understanding of who they are buying from, and makes sure the medication they buy matches what their doctor prescribed. The FDA recommends that patients only buy medications from online pharmacies that require a prescription, are located in the United States, have a licensed pharmacist available for consultation, and are licensed by the patient's state board of pharmacy. More information can be found at www.FDA.gov/BeSafeRx.

The FDA has approved enzalutamide to treat men with late-stage, castration-resistant prostate cancer under the agency's priority review program. The drug was approved based on a study of nearly 2000 men with metastatic prostate cancer who had been previously treated with docetaxel. Men treated with enzalutamide lived an average of 18.4 months vs 13.6 months for men treated with placebo. Enzalutamide is co-marketed by Astellas and Medivation as Xtandi.

The FDA has also approved a new agent for the treatment of advanced colorectal cancer. Regorafenib is a multi-kinase inhibitor that was also approved under the FDA's priority review program. In a study of 760 patients with previously treated metastatic colorectal cancer, regorafenib extended survival about 45 days to 6.4 months from 5 months for placebo as well as progression-free survival of 2 months vs 1.7 months for placebo. Regorafenib is marketed by Bayer as Stivarga. ■