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Clinical Cardiology [ALERT]

Critical analysis of the latest clinical research in cardiovascular medicine

ABSTRACT & COMMENTARY

BNP-Guided Heart Failure Prevention

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

SOURCE: Ledwidge M, et al. Natriuretic peptide-based screening and collaborative care for heart failure. The STOP-HF randomized trial. *JAMA* 2013; 310:66-74.

Heart failure (HF) is associated with a high mortality rate, debilitating symptoms, impaired quality of life, and major financial costs. As our society ages, the prevalence of heart failure (HF) is increasing. Current treatments for HF are imperfect and prevention of HF is the best possible option. In this study, the authors target patients at risk for developing HF and study a strategy of using serum brain-type natriuretic peptide (BNP) measurement in the primary care setting to guide referral and therapy aids in preventing left ventricular (LV) dysfunction and HF. The study recruited patients from 39 primary care practices in Ireland.

Patients were referred from primary care to the study if they were older than 40 years and had one or more risk factors for developing HF, including hypertension, hyperlipidemia, obesity (body mass index > 30), vascular disease (coronary, peripheral, or cerebral), diabetes, arrhythmia requiring treatment, or moderate/severe valvular disease. Exclusion criteria were the presence of established LV dysfunction or prior HF, or any other cause of limited life expectancy. Patients were randomized 1:1 to intervention (BNP-driven collaborative care between the primary care physician [PCP] and specialist cardiovascular center; n = 697) or control (routine PCP management; n = 677) groups. All patients had BNP testing but the results were only available to the PCP in the intervention group. The control group received advice on lifestyle modification and risk factor intervention as determined by their PCP. In the

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intervention group, BNP results were made available to the PCP, with protocol-driven echocardiography, referral to a cardiologist, and further lifestyle counseling and management if the BNP was > 50 ng/L. Those with BNP < 50 ng/L received usual care. Patients and treating physicians could not be blinded, but at study completion all patients underwent echocardiography and clinical evaluation by a blinded cardiologist. The primary endpoint was development of LV systolic or diastolic dysfunction with or without HF. Secondary endpoints included emergency hospitalization for arrhythmia, transient ischemic attack, stroke, myocardial infarction, peripheral or pulmonary thrombosis/embolus, or HF.

Patients were followed for 4.2 ± 1.2 years. A total of 263 patients (41.6%) in the intervention group had at least one BNP reading of 50 pg/mL or higher. The primary endpoint of LV dysfunction with or without HF occurred in 59 of 677 (8.7%) in the control group and 37 of 697 (5.3%) in the intervention group (odds ratio [OR] 0.55; $P = 0.003$). Asymptomatic LV dysfunction was found in 6.6% of control patients and 4.3% of intervention-group patients (OR 0.57; $P = 0.01$). Heart failure occurred in 2.1% of controls and 1.0% of intervention-group patients (OR 0.48; $P = 0.12$). The incidence rates of emergency hospitalization for major cardiovascular events were 40.4 per 1000 patient-years in the control group vs 22.3 per 1000 patient-years in the intervention group (incidence rate ratio, 0.60; $P = 0.002$). The intervention group underwent more cardiovascular investigations (control group, 496 per 1000 patient-years vs intervention group, 850 per 1000 patient-years; incidence rate ratio, 1.71; $P < 0.001$) and received more renin-angiotensin-aldosterone system (RAAS) inhibitors (control group, 49.6%; intervention group, 56.5%; $P = 0.01$). Blood pressure reductions were similar in the control and intervention groups. In patients with BNP < 50 ng/L, there was no change in BNP level over the 4.2-year follow-up. However, in those with BNP > 50 ng/L, the BNP level increased over the study period, but the increase was significantly attenuated in the intervention group. The authors conclude that among patients at risk of HF, BNP-based screening and collaborative care reduced the combined rates of LV systolic dysfunction, diastolic dysfunction, and HF.

■ COMMENTARY

This study is an interesting and important one. First, it confirms that BNP measurement in patients at risk of HF can predict the development of future LV dysfunction. Second, this strategy also reduces emergency admissions to the hospital from a variety of cardiovascular causes. Unfortunately, though, there was no prespecified intervention in this study, so we are left to ponder what it was that resulted in the better outcomes in the intervention group. Was it the increased use of RAAS inhibition? Was it the extra patient counseling that improved compliance? Was it engagement of the patients with the specialist care and the extra diagnostic testing that facilitated a more tailored pharmacological management of these patients? These should all be tested in prospective studies.

Several limitations of this study should be noted. First, it was performed in a small area of Ireland and the results may not be generalizable to other populations. Second, because the participants could not be blinded, there is a possibility of some confounding, which would likely but not definitely create bias toward a negative result. Third, new onset HF was defined as requiring hospitalization for HF. This definition would have missed HF that was treated as an outpatient. Despite these limitations, BNP-guided therapy for patients at risk for HF seems to be a reasonable strategy. I hope we will see a formal cost-effectiveness analysis from this dataset, as the intervention group had higher rates of diagnostic testing but lower rates of hospitalization, and the overall effect on health care budgets remains unknown. ■

ABSTRACT & COMMENTARY

Who Should Get an ICD?

By Michael H. Crawford, MD, Editor

SOURCE: Dewland TA, et al. Consideration of patient age and life expectancy in implantable cardioverter-defibrillator referral. *Am Heart J* 2013;166: 164-170.

The relationship between patients' prognosis and age in decisions regarding implantable cardioverter-defibrillator (ICD) therapy in the primary prevention of sudden death in heart failure patients is poorly understood and not addressed in randomized device trials. Thus, Dewland and colleagues created a survey that was sent to 3000 randomly selected primary care physicians and general cardiologists nationwide. The survey contained questions directed at primary prevention ICD guidelines and this report focused on patient age and life expectancy. The survey was completed by 65% of those selected. An upper age cutoff was reported by 27%, most of whom were cardiologists, and it averaged 84 ± 6 years. Life expectancy was a determinant for 77% of the respondents and they were least likely to be family practitioners. The median life expectancy selected was 2 years (range 1-5 years), but in 13% it was < 1 year. The authors concluded that about 25% of referring physicians use an upper age cutoff for ICD referral and some refer patients with an estimated life expectancy of < 1 year.

■ COMMENTARY

ICD implantation guidelines clearly state that only patients with an estimated life expectancy of > 1 year should be considered and age per se is not an exclusion. The results of this survey of referring physicians demonstrates that a significant proportion do not consider life expectancy and use an upper age cutoff. These results could equate to both over and underuse of ICDs for primary prevention of sudden death.

Because clinical trials usually include a paucity of the very old, it is understandable why physicians may have a sense of an upper age cutoff for these devices. However, meta-analyses of the trials have not demonstrated an age above which an ICD is no longer beneficial. In fact, since sudden death is more common the older one is, the benefits are actually greater in older patients. Thus, the guidelines do not specify an age cutoff.

This report also underscores a lack of understanding among referring physicians of the importance of life expectancy in the ICD referral decision. About 25% did not consider this variable and only about half used the > 1 year cutoff. This is very important to avoid the appearance of overuse of ICDs and one cannot expect the electrophysiology (EP) physician to be the best judge of this. The general physician taking care of the patients should have a much better handle on the patients' overall prognosis due not only to their heart failure, but also to other comorbidities and their frailty. The use of a higher life expectancy cutoff (e.g., 2-5 years) is not supported by the trial data since sudden death rates decreased significantly in < 2 years. Thus, it is important that primary care and general cardiology physicians understand the indications for ICD placement for the primary prevention of sudden death. Finally, this study emphasized the need for more communication between referring and EP physicians so that the most appropriate patients are selected for this expensive, yet highly effective therapy.

The Table below lists the major class I indications for an ICD, with the caveats that the patient has an estimated survival of > 1 year with good functional status on optimal medical therapy, which may include revascularization where appropriate. ■

Table. Major Class I Indications for an ICD

1. Prior MI, resuscitated VF, significant LV dysfunction.
2. ≥ 40 days post-acute MI, NYHA class II-III heart failure, EF < 30-40%.
3. LV dysfunction from a prior MI, unstable sustained VT.
4. Non-ischemic cardiomyopathy, sustained VT/VF, significant LV dysfunction.
5. NYHA class II-III heart failure, EF < 30-35%.

Source: ACC/AHA/ESC Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *J Am Coll Cardiol* 2006;48:e247-e346.

ABSTRACT & COMMENTARY

Is Bileaflet Mitral Valve Prolapse Associated with Sudden Death?

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Dr. Gerstenfeld does research for Biosense Webster, Medtronic, and Rhythmia Medical.

SOURCE: Sriram CS, et al. Malignant bileaflet mitral valve prolapse syndrome in patients with otherwise idiopathic out of hospital cardiac arrest. *J Am Coll Cardiol* 2013;62:222-230.

Mitral valve prolapse (MVP), characterized by displacement of the mitral valve into the left atrium during systole, was first described by Barlow in 1966. MVP "syndrome" refers to the association of MVP with palpitations and atypical chest pain in young patients. There has been some association of MVP with sudden cardiac arrest (SCA), primarily from autopsy studies finding pathologic signs of MVP in up to 10% of SCA survivors. However, given the high prevalence of MVP in the general population, a true association with SCA risk has been controversial.

The laboratory at the Mayo clinic analyzed records from 1200 consecutive patients seen in their genetic Heart Rhythm clinic between July 2000 and December 2009. In this database, all patients had received transthoracic echocardiography and standard electrocardiograms, and the majority received 24-hour Holter monitors. All patients underwent extensive genetic testing and those found to have inherited channelopathies were excluded. All other patients who experienced unexplained cardiac arrest, resuscitated ventricular tachycardia, or ventricular fibrillation were included. A blinded reviewer reviewed all echocardiograms and strictly defined the presence of single or bileaflet MVP as systolic displacement of the mitral valve > 2 mm into the left atrium in the parasternal long axis view, along with thickened or myxomatous mitral valve leaflets.

The authors identified 24 patients with unexplained cardiac arrest, normal QT intervals, and negative genetic testing (median age 33.5 years, 67% women). Bileaflet MVP was identified in 10 of 24 patients (42%, 9 females) with mitral regurgitation graded as mild in five, moderate in four, and severe in one patient. Biphasic or inverted T waves in the inferior leads were more commonly found in bileaflet MVP patients. Holter monitors were available in 9 of 10 SCA patients, and had significantly higher burden of premature ventricular contractions ([PVCs] 67 vs 23 PVCs/hr, $P = 0.002$), nonsustained ventricular tachycardia (7/9 patients), and ventricular bigemeny (9/9 patients) compared to those without MVP. A pattern of PVCs with alternating axis originating from the left ventricular outflow tract and papillary muscle/fascicular system was noted in seven of nine MVP patients who experienced SCA. Three patients underwent invasive electrophysiologic study and were found to have multiple PVC foci, typically originating near the left ventricular papillary muscles. After a mean of 1.8 years additional follow-up after the incident SCA, the only predictor of recurrent ventricular arrhythmias requiring defibrillator therapy was the presence of bileaflet MVP (odds ratio, 7.2; 95% confidence interval 1.1 to 48; $P = 0.028$). The authors concluded that there is a small subset of MVP patients characterized by bileaflet prolapse, female sex, and frequent complex ventricular ectopy who can have life-threatening ventricular tachyarrhythmias.

■ COMMENTARY

The prevalence of MVP in the general population using strict echocardiographic criteria is 2-3%; however, some reports have more loosely described MVP in up to 30% of asymptomatic patients. The association of MVP with sudden death in autopsy studies often creates concern among patients informed they have MVP. However, a true association with MVP and sudden death has remained controversial. The current small series is interesting because all the patients who experienced SCA had echocardiograms and electrocardiograms available for review. The presence of bileaflet MVP in 42% of the cohort with unexplained SCA is certainly notable. However, several important qualifiers apply. The authors studied the incidence of SCA in a highly selected and specific population of SCA survivors. Thus, analogous to the early repolarization syndrome, which was recently described in a disproportionate number of survivors of cardiac arrest,[1] the overall risk in the general

population with MVP remains small. However, cardiologists are often asked to evaluate patients with recurrent syncope or cardiac arrest, or family members of SCA patients. This study highlights some important characteristics of a high-risk cohort that are worth noting. First, all of the described patients had "bileaflet" prolapse, which may be more specific than the single leaflet prolapse often described. These patients also had repolarization abnormalities (biphasic or inverted T waves) in the inferior leads, and Holter monitors showing complex ventricular ectopy, typically ventricular bigemeny in an alternating pattern of inferior and superior axis. Although the mechanism of these PVCs is unclear, it is certainly plausible to speculate that these originate from structural abnormalities in the mitral valve apparatus. Also noteworthy is the finding that the majority of patients experiencing SCA were young women and many of the patients had only mild or moderate mitral regurgitation.

Therefore, before giving a patient the diagnosis of MVP, strict echocardiographic criteria should be applied. The majority of patients with asymptomatic single leaflet MVP have a benign prognosis. However, this report brings to light a potential higher risk cohort of patients with bileaflet MVP, repolarization abnormalities in the inferior ECG leads, and complex ventricular ectopy. While implantation of an implantable defibrillator in such patients is certainly premature, close follow-up or referral of high-risk patients for further evaluation is certainly warranted. Prospective studies of such patients will be difficult given the small population with these characteristics, but would certainly be useful for determining the optimal management strategy for these patients. ■

REFERENCE

1. Haïssaguerre M, et al. Sudden cardiac arrest associated with early repolarization. *N Engl J Med* 2008;358:2016-2023.

ABSTRACT & COMMENTARY

Same-Day Discharge After PCI

By Andrew J. Boyle, MBBS, PhD

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SOURCE: Brayton KM, et al. Same-day discharge after percutaneous coronary intervention. A meta-analysis. *J Am Coll Cardiol* 2013;62:275-285.

Complication rates following percutaneous coronary intervention (PCI) have fallen in recent years. Overnight observation in the hospital after PCI remains the standard of care in the United States. However, because of the low complication rates, there has been a move toward same-day discharge in some countries. In the current environment of cost containment, this approach may represent a way for the health care system to realize substantial cost savings. The Society for Cardiac Angiography and Intervention (SCAI) and the American College of Cardiology (ACC) released a consensus statement in 2009 identifying patients suitable for same-day discharge following PCI, but this has not become part of the ACC/AHA guidelines for PCI. Thus, the use of same-day discharge after PCI remains low in the United States. In this study, Brayton and colleagues update our evidence base by performing a study-level meta-analysis of 37 clinical studies of same-day discharge after PCI.

Their meta-analysis includes 30 studies (enrolling 10,065 patients) that were observational and seven studies (enrolling 2738 patients) that were randomized controlled trials (RCTs). Two-thirds of patients underwent PCI for stable coronary artery disease (CAD). There were some differences between the RCTs and observational study cohorts, in particular the use of transradial PCI was 61% in the randomized trials and 30% in the observational studies. The authors focused mainly on the RCTs to limit selection bias. Their primary efficacy endpoint was the rate of death/myocardial infarction (MI)/target lesion revascularization (TLR) and their primary safety endpoint was the rate of major bleeding/vascular complications. In the RCTs, there was no difference in the incidence of the primary efficacy endpoint of death/MI/TLR (odds ratio [OR] 0.90; $P = 0.78$), or in the rates of major bleeding/vascular complications (OR 1.69; $P = 0.15$) between patients randomized to same-day discharge vs overnight observation. In the observational studies, the incidence of death/MI/TLR was 1.0% and bleeding/vascular complications was 0.7% in those discharged on the same day as PCI, confirming low actual event rates in real-world practice. Importantly, the results were largely consistent in studies conducted within the United States vs elsewhere, in studies

that included acute coronary syndrome patients and those that did not, and whether radial or femoral arterial access was used.

In patients randomized to same-day discharge, 13% were not actually discharged the same day. When the authors drilled down on the reasons, they found that around half of these were from a trial that randomized patients before PCI instead of after. Deferral of same-day discharge in the other trials was due to access site complications (33%), physician preference (30%), patient preference (17%), recurrent chest pain (11%), noncardiac reasons (4.9%), orthostasis (2.4%), and arrhythmias (1.2%). The authors conclude that in selected patients undergoing largely elective PCI, same-day discharge was associated with a low rate of major complications and appeared to be as safe as routine overnight observation.

■ COMMENTARY

Technical advances in PCI technique have resulted in lower rates of cardiac complications following PCI. In addition, the use of bleeding avoidance strategies, such as radial access, use of smaller guide catheters, and the more widespread use of bivalirudin, have resulted in lower bleeding rates. The rationale for overnight observation of patients after PCI appears to be less compelling in the modern era. However, clinical trial data supporting same-day discharge have been lacking. In particular, there has been concern about the rates of uncommon but serious complications, and most trials to date are underpowered to detect differences in uncommon outcomes. The strength of meta-analyses such as this one is that they have large numbers of patients, allowing detection of less common outcomes. However, there are some important limitations to this paper. First, this is a study level meta-analysis and individual patient-level data were not available to the authors, which may confound the data. Second, the studies that they reported had varied outcomes over different periods of observation, making standardization difficult. Third, the event rates were not always specified as occurring in the 24 hours after PCI and may have occurred later, but the timing was not reported in some of the original studies. Fourth, each study had its own inclusion and exclusion criteria, making extrapolation to different patient groups difficult. Despite these limitations, this paper shows us that in carefully selected patients, largely elective PCI for stable CAD, same-day discharge after PCI is a reasonable alternative. The observational data presented in concert with the RCT data confirm that the actual event rates are low in real-world settings. The authors go on to offer a protocol for choosing patients for same-day discharge after PCI. Our practice has been that patients having elective PCI for stable, single-vessel CAD are considered for same-day discharge if the procedure is uncomplicated, the patients are at low risk for complications, and there are adequate home supports. However, the patient and lesion characteristics that are optimal for same-day discharge still need to be defined by large prospective, randomized trials. ■

ABSTRACT & COMMENTARY

Long-Term Results of Dabigatran vs Warfarin for Stroke Prevention in AF Patients

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Dr. Gerstenfeld does research for Biosense Webster, Medtronic, and Rhythmia Medical.

SOURCE: Connolly SJ, et al. The long-term multicenter observational study of dabigatran treatment in patients with atrial fibrillation (RELY-ABLE) study. *Circulation* 2013;128:237-243.

Dabigatran etexilate, a direct thrombin inhibitor, is one of a new class of oral anticoagulants that was recently demonstrated in a Phase 3 trial to be effective for the prevention of stroke or systemic embolism (SSE) in patients with atrial fibrillation (AF). The original Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial randomized 18,113 patients with AF and at least one stroke risk factor to either warfarin or one of two blinded doses of dabigatran, 150 mg twice daily or 110 mg twice daily.[1] The 150 mg dose was superior to warfarin for preventing SSE with a similar rate of major bleeding, while the 110 mg

was noninferior to warfarin for preventing SSE, but had a reduced risk of major bleeding after a mean follow-up of 2 years. The RELY-ABLE study continued to follow patients in the RE-LY study who were randomized to receive either dose of dabigatran for an additional 2.25 years.

Patients were eligible for RELY-ABLE if they were randomized to dabigatran and had not discontinued the medication at the last study visit. They continued on the original randomized, blinded dose of dabigatran. The outcomes of RELY-ABLE were identical to those of RE-LY.

There were 5851 patients (48% of those randomized to dabigatran in RE-LY) enrolled and followed for a mean of 2.3 additional years after the conclusion of RE-LY. The rates of SSE in RELY-ABLE were 1.46% and 1.60% per year for the dabigatran 150 mg and 110 mg doses, respectively (hazard ratio [HR], 0.91; 95% confidence interval [CI], 0.69-1.20). There were no differences in the rates of ischemic or hemorrhagic stroke between the two groups. Annual rates of major bleeding were significantly higher with the 150 mg dose compared to the 110 mg dabigatran dose (3.74% vs 2.99% per year; HR, 1.26; 95% CI, 1.04-1.53). There was no difference in mortality between the two groups. The authors concluded that long-term follow-up of dabigatran 150 mg vs 110 mg twice daily therapy showed similar rates of stroke and death, but a higher incidence of major bleeding on the 150 mg dose.

■ COMMENTARY

Dabigatran is one of a new class of anticoagulants that is rapidly replacing the old standard, warfarin, for prevention of thromboembolism in patients with AF and stroke risk factors. The major advantages of the newer anticoagulants over warfarin are: 1) fixed dosing without need for frequent blood tests, 2) lack of dietary interactions, and 3) lower rate of intracerebral hemorrhage. The negatives include cost, nuisance side effects such as dyspepsia, and lack of reversibility. Based on the results of the RE-LY trial, the Food and Drug Administration (FDA) approved the 150 mg twice-daily dose for the prevention of SSE in AF patients, but not the 110 mg dose. This was in part because the 150 mg dose met criteria for superiority to warfarin while the 110 mg dose met only the criteria for noninferiority, despite a reduction in major bleeding with the 110 mg compared to warfarin. Interestingly, the FDA also approved a twice-daily 75 mg dabigatran dose in patients with renal insufficiency based on pharmacokinetic studies, even though that dose was not included in the RE-LY randomized trial.

For those physicians who have yet to adopt the use of the newer anticoagulants over warfarin, the RELY-ABLE data should provide additional evidence supporting the long-term use of dabigatran for prevention of SSE in AF patients. The rates of stroke and major bleeding in RELY-ABLE remained similar to those reported in the original RE-LY trial, with a very low rate of intracerebral bleeding (0.13-014%/year) after a mean of 4.3 years of follow-up. The major question remaining is why the FDA did not approve the twice-daily 110 mg dabigatran dose. The dose was clearly shown to be equivalent to warfarin in preventing SSE with a lower risk of bleeding in a prospective randomized multicenter study — the "gold-standard" of evaluating new drug therapies. The RELY-ABLE data provide further support that the 110 mg dose provides stroke reduction in AF patients with a lower bleeding risk than the 150 mg dose. The lack of availability of the 110 mg dose in the United States has handicapped physicians and patients concerned about bleeding risk, particularly in elderly patients. Hopefully the RELY-ABLE data will persuade the FDA to reconsider this decision.

In summary, dabigatran 150 mg twice-daily has been shown to be superior to warfarin for the prevention of SSE in AF patients and should be considered preferred over warfarin in newly diagnosed AF patients with a CHADS2-Vasc score ≥ 1 who were eligible for the RE-LY study. For elderly AF patients or those with a higher bleeding risk, there are now several agents available for physicians and patients to consider. Cardiologists should also be aware that there remains a paucity of data regarding the safety of the newer anticoagulants in patients already on aspirin/clopidogrel therapy after stent implantation. ■

REFERENCE

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CME Instructions

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CME Questions

1. Which of the following is an important criteria for ICD placement?
   a. Age < 85 years
   b. > 1 year estimated survival
   c. A LVEF < 20%
   d. All of the above

2. Serum BNP measurements as a prevention strategy make sense in subjects with:
   a. hypertension.
   b. significant valvular disease.
   c. vascular disease.
   d. All of the above

3. Long-term follow-up of dabigatran 150 mg twice daily vs 110 mg twice daily showed:
   a. more strokes.
   b. higher mortality.
   c. more major bleeds.
   d. All of the above

4. Same-day discharge after PCI is most feasible in patients:
   a. undergoing elective PCI.
   b. whose PCI was uncomplicated.
   c. who had a radial artery approach.
   d. < 85 years old.

5. Mitral valve prolapse patients at risk for sudden cardiac death are characterized by:
   a. bileaflet prolaspe.
   b. female sex.
   c. frequent complex ventricular ectopy.
   d. All of the above

CME Objectives

Upon completion of this educational activity, participants should be able to:

- discuss the most current information related to cardiac illness and the treatment of cardiac disease;
- explain the advantages and disadvantages, as well as possible complications of interventions to treat cardiac illness;
- discuss the advantages, disadvantages, and cost-effectiveness of new and traditional diagnostic tests in the treatment of cardiac illness; and
- discuss current data regarding outpatient care of cardiac patients.

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Once-daily Tadalafil for ED: Efficacy and Safety

Source: Seftel AD, et al. *Int J Impot Res* 2013;25:91-98.

THE UTILIZATION OF PDE5 INHIBITION (PDE5-i) for restoration of sexual function in men suffering erectile dysfunction (ED) is well established, beginning with the introduction of sildenafil (Viagra) in 1998. In the earliest years of PDE5-i treatment, regimens were typically targeted to PRN use. Almost a decade later, consideration of lower-dose, daily use of tadalafil became popular.

In this retrospective analysis, Seftel et al report on the safety and efficacy of once-daily tadalafil (TAD-QD) in doses ranging from 2.5-10.0 mg/day. The rationale for their study was to specifically define whether age impacts the efficacy of TAD-QD, since older men (age > 50 years, by their definition) might be more refractory to PDE5-i than younger men (age < 50 years). Additionally, they wished to examine the tolerability profile of TAD-QD in men with mild-moderate ED, who comprise the largest segment of men taking PDE5-i. The dataset used in this analysis included 522 men, predominantly Caucasian (> 75%), most of whom had long-standing ED and about half of whom had comorbidities of hypertension and/or diabetes.

TAD-QD more than doubled the rates of successful intercourse (from 33.4% pretreatment to 76.8% on treatment), with no discernible difference in younger men vs older men. TAD-QD was also well tolerated, with the most common adverse events — headache, dyspepsia, and myalgias — consistent with what has been seen in prior literature.

The authors conclude that TAD-QD provides substantial improvements in ED, independent of age, in men with mild-moderate ED, and is well tolerated. ■

Psychological Disorders: How to Give Patients What They Want and What They Need

Source: McHugh RK, et al. *J Clin Psych* 2013;74:595-602.

COMMONPLACE PSYCHIATRIC DISORDERS such as anxiety, depression, post-traumatic stress disorder, and obsessive compulsive disorder respond to pharmacotherapy, psychotherapy, and their combination. The National Comorbidity Survey Replication data have indicated that persons with psychiatric disorders often do not use mental health services because of perceived barriers to access (e.g., cost, logistics). Identification of patient preferences for treatment is of value not only for patient satisfaction, but also because clinical outcomes are better among patients who receive their treatment of choice. Additionally, patients who are concordant with the therapeutic choice have been reported to be more adherent with therapy.

Data from 34 clinical trials (total patient n = 90,071) were assessed by meta-analysis. Overall, patients expressed a preference for psychological treatment over pharmacotherapy by 3:1. This preference was consistent irrespective of the underlying psychiatric disorder studied, including depression, anxiety, and hypochondriasis. The availability of additional alternatives (e.g., combination treatment, watchful waiting, no treatment) did not affect the balance of patient preferences.

At the current time, treatment of patients with mild-moderate psychiatric disorders with pharmacotherapy vs psychotherapy is at equipoise. Hence, identification of patient preference — in situations where outcomes are similar between choices — is a sensible direction to take. This large literature base suggests that as many as 75% of patients with commonplace psychiatric issues prefer psychological treatment to pharmacotherapy. Although pharmacotherapy is often a more expedient path for primary care clinicians, the importance of addressing patient preference is well highlighted by this study. ■

Reducing Stroke Risk After TIA or Minor Ischemic Stroke

Source: Wang Y, et al. *N Engl J Med* 2013;369:11-19.

THE VERY LARGE CLOPIDOGREL FOR HIGH Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) clinical trial concluded that dual antiplatelet therapy in stable ambulatory vasculopathic patients who are distant — at least 1 year post-MI, post-stroke — from their vascular event does not meaningfully reduce risk over monotherapy, and is associated with increased risk of bleeding. As convincing as this dataset is, it only addresses populations who are distant from their vascular event, rather

than subjects who are in the higher risk period immediately following an acute event.

The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial enrolled — within 24 hours of onset — Chinese subjects (n = 5170) who had sustained a minor ischemic stroke or transient ischemic attack (TIA). Subjects were randomized to treatment (double-blind) with low-dose aspirin (75 mg/d-300 mg/d) plus clopidogrel (300 mg on day 1, then 75 mg/d [CLO + ASA]) or low-dose aspirin plus placebo (ASA). The primary outcome was incidence of stroke (ischemic or hemorrhagic) over 90 days of follow-up.

CLO + ASA was associated with a 32% reduction in risk for stroke compared to aspirin alone. Risk for central nervous system hemorrhage was no different in the CLO + ASA group than ASA alone. In the immediate post-TIA/minor stroke period (up to 90 days), dual antiplatelet treatment meaningfully reduced risk without increasing bleeding. ■

Long-term Mortality Among Adults with Asthma

Source: Ali Z, et al. *Chest* 2013;143: 1649-1655.

In the United States, approximately 5000 persons die each year from asthma. Counterintuitively, deaths in asthma are equally distributed among patients identified as mild, moderate, and severe. Studies of patients with near-fatal asthma have found a decreased sensitivity to hypoxia, hypercapnea, and resistance loading, suggesting that persons destined to succumb to asthma may not fully appreciate the severity of their symptoms, placing them at risk for unrecognized deterioration.

The long-term picture of causes of death in asthmatic adults was the subject of this report by Ali et al. The authors drew on a population of asthmatics enrolled from 1974-1990 in Denmark at their first visit for asthma to the Copenhagen Frederiksbergy Hospital Allergy and Chest Clinic, having been referred there by their general practitioners in the community. More than 75% of the enrollees were younger than 50 years of age at the time of enrollment.

Compared with age- and sex-matched control subjects, all-cause mortality in asthmatic subjects was essentially doubled over 25 years of follow-up. The excess risk for death was primarily due to obstructive airways disease, but was unrelated to smoking status (hence deaths were predominantly *not* related to chronic obstructive pulmonary disease). Degree of peripheral blood eosinophilia correlated with mortality, intimating that unmitigated atopy in asthmatics may contribute to adverse outcomes. ■

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Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

Source: The Look AHEAD Research Group. *N Engl J Med* 2013;369:145-154.

Type 2 diabetes (DM2) is characterized by increased risk for cardiovascular (CV) events, which are not only more frequent but also more severe than similar events in non-diabetics. Most DM2 patients in America are overweight or obese. Weight loss and exercise have been shown to improve glucose control, lipids, blood pressure, and progression from pre-diabetes to diabetes, but no large clinical trials have confirmed risk reduction for CV events attributable to lifestyle intervention.

The Look AHEAD trial randomized overweight or obese DM2 patients (n = 5145) to intensive lifestyle or control (the control group still received education and support in reference to care of their DM2). The goal of intensive lifestyle was to reduce weight by at least 7% and participate in at least 175 minutes/week of moderate-intensity physical activity.

The trial was originally intended to go on for 13.5 years, but was stopped early (at 9.6 years) because futility analysis demonstrated no likely possible benefit of the intensive intervention for CV events compared to controls, despite greater weight loss and improved glycemic control attained in the intensive lifestyle group.

Intensive lifestyle intervention in DM2 improves glycemic indices and body mass index, but does not appear to improve CV risk. ■

New Hope for Hepatitis C Patients

Source: Jacobson IM, et al. *N Engl J Med* 2013;368:1867-1877.

The Centers for Disease Control and Prevention has recently advocated routine screening for hepatitis C (HEP-C) among all adults born from 1945-1965. These recommendations stem from the observation of the ever-growing burden of persons with HEP-C and its consequences who do not necessarily endorse traditionally recognized risk factors for HEP-C such as intravenous drug use, tattoos, etc. Early identification allows for potential cure of HEP-C, since as many as 80% of previously untreated individuals can achieve sustained virologic response with "standard" antiviral regimens (e.g., ribaviron plus interferon).

This does, however, leave a substantial minority of HEP-C patients (those who fail treatment, who are intolerant of treatment, or who have contraindications to it) at risk. Fortunately sofosbuvir, a new polymerase inhibitor, has demonstrated high efficacy in both untreated HEP-C and treatment failures.

Sofosbuvir was studied in two populations of HEP-C genotype 2 or 3: persons with contraindications to interferon and cases that had not responded to interferon therapy. Sustained virologic response was seen in 78% of subjects with interferon contraindications, and (at 16 weeks) 73% of interferon failures. Sofosbuvir was generally well tolerated, with a discontinuation rate of 1-2%. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Do Statins Prevent Parkinson's Disease?

In this issue: Statins and Parkinson's disease; safety and tolerability of statins; apixaban and venous thromboembolism; and FDA actions.

Statins and Parkinson's disease

In 2012, the FDA expanded warnings on statins to include cognitive impairment, such as memory loss, forgetfulness, and confusion, based on adverse event reports from some statin users. There have been few data to confirm cognitive changes or other neurologic side effects associated with these drugs other than case reports. But still, many media outlets have reported that this warning is evidence of increased risk for Alzheimer's disease and other brain disorders. To the contrary, in last year's warning, the FDA specifically stated that memory changes are reversible when the medication is stopped. Other studies have suggested that highly lipophilic statins such as simvastatin, which crosses the blood-brain barrier easily, may in fact protect against dementia — although other studies refute this finding. Parkinson's disease (PD) has also been studied with regard to statin therapy, and those data may be a bit more compelling in favor of statins. A recent study from Taiwan took a unique approach to this problem. Reasearchers looked at the incidence of PD in patients who discontinued statin therapy compared to those who continued. Among the nearly 44,000 statin initiators, the incident rate for PD was 1.68 per 1.000,000 among lipophilic statin users and 3.52 among hydrophilic statin users. Continuation of lipophilic statins was associated with a marked decrease in the risk of PD compared to discontinuation (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.27-0.64]). This finding was not affected by comorbidities or other medications. Hydrophilic statins did not reduce the occurrence of PD. Among the lipophilic statins, simvastatin had the greatest effect (HR, 0.23; 95% CI, 0.07-0.73), while atorvastatin was also beneficial (HR, 0.33; 95% CI, 0.17-0.65). The effect among women was even more dramatic with a nearly 90% reduction in the incidence of PD for simvastatin and a 76% reduction for atorvastatin. Most of the benefit was seen in the elderly subgroup. The authors suggest that continuation of a lipophilic statin was associated with a decrease in the incidence of PD as compared to discontinuation, especially in women and the elderly (*Neurology* published online July 24, 2013. DOI: 10.1212/WNL.0b013e31829d873c). An accompanying editorial suggests that the lipophilic statins may reduce oxidative stress, and may have other direct actions in the brain that reduce the risk of PD, although more research is needed. The authors add, "For those who have to be on statins, it is a comforting thought that there is potential added advantage of having a lower risk of PD, and possibly other neurologic disorders as well." (*Neurology* DOI: 10.1212/WNL.0b013e31829d87bb). ■

Safety and tolerability of statins

Overall statin safety and tolerability was the focus of a recent (non-company sponsored) meta-analyses of more than 135 trials involving nearly 250,000 individuals. Statin therapy was no differ-

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ent from control with regard to myalgia, creatine kinase elevation, cancer, or discontinuation due to adverse events. There was a higher incidence of diabetes associated with statin use (odds ratio [OR], 1.09; 95% CI, 1.02-1.16). Transaminases were also elevated more commonly (OR, 1.51; 95% CI, 1.24-1.84). The safest statins appeared to be simvastatin and pravastatin. When similar doses were compared, there were higher discontinuation rates with atorvastatin and rosuvastatin. The highest dose (80 mg) of simvastatin was associated with a significantly increased risk of creatine kinase elevation (OR, 4.14; 95% CI, 1.08-16.24). The authors conclude that statins, as a class, are well tolerated, except for a higher risk of diabetes. Simvastatin and pravastatin seem to be more tolerable than other statins (*Circ Cardiovasc Qual Outcomes* published online July 9, 2013. DOI: 10.1161/CIRCOUTCOMES.111.000071). ■

AMPLIFY trial results

Currently, there are three novel oral anticoagulants on the market — dabigatran, rivaroxaban, and apixaban. All are approved for stroke prevention in patients with nonvalvular atrial fibrillation, but only rivaroxaban is approved for deep vein thrombosis/pulmonary embolism (PE) prevention and treatment. That may change with the publication of the AMPLIFY trial, which compared apixaban with conventional anticoagulant therapy in patients with acute venous thromboembolism (VTE). In a randomized, double-blind study, apixaban was compared with enoxaparin/warfarin (conventional therapy) in nearly 5400 patients with acute VTE. The primary outcome was recurrent symptomatic VTE or death related to VTE. The principal safety outcomes were major bleeding alone and major bleeding plus clinically relevant nonmajor bleeding. The primary outcome (recurrent VTE) occurred in 59 of 2609 patients (2.3%) in the apixaban group compared with 71 of 2635 (2.7%) in the conventional therapy group (relative risk [RR] 0.84; 95% CI, 0.60-1.18). Major bleeding occurred in 0.6% of those in the apixaban group and 1.8% in the conventional therapy group (RR, 0.31; 95% CI, 0.17-0.55; $P < 0.001$ for superiority). The composite outcome of major bleeding and nonmajor bleeding occurred more than twice as often in the conventional therapy group. Rates of adverse events were similar. The authors conclude that a fixed-dose regimen of apixaban alone was noninferior to conventional therapy for the treatment of acute VTE and was associated with less bleeding. The findings were the same for patients with PE or extensive disease (*N Engl J Med* published online July 1, 2013. DOI: 10.1056/NEJMoa1302507). An accompanying editorial states that this is "an exciting time in thrombosis care," although more information is needed on reversal strategies and monitoring of these new agents (*N Engl J Med* July 1, 2013. DOI: 10.1056/NEJMe1307413). The option to safely treat VTE with fixed-dose oral options is very appealing. Both dabigatran and apixaban are expected to be reviewed for these indications in the near future. ■

FDA actions

The FDA has issued a Safety Communication regarding the oral antifungal ketoconazole that includes limiting the drug's use. The warning states that ketoconazole should never be used as a first-line agent due to the risk of liver toxicity, adrenal insufficiency, and drug interactions. The new guidance states that ketoconazole should only be used "when alternative antifungal therapies are not available or tolerated." In addition, the agency has revised the list of indications for the drug, removing dermatophyte and *Candida* infections.

The FDA has also issued a Safety Communication about the antimalarial drug mefloquine hydrochloride regarding neurologic and psychiatric side effects. The drug is used for treatment of malaria but more commonly for prevention of *Plasmodium falciparum* (including chloroquine-resistant *P. falciparum*) and *P. vivax*. Neurologic side effects — which may be permanent — include dizziness, loss of balance, and tinnitus. Psychiatric side effects include anxiety, paranoia, depression, or hallucinations. The brand form of mefloquine (known as Lariam) is no longer marketed, but several generic forms of the drug are available. The new warnings are contained in a boxed warning — the FDA's most serious warning. The drug was recently in the news regarding a number of violent military incidents among soldiers taking the drug, including the murder of 16 Afghan civilians last year.

A nasal steroid spray may soon be available over the counter (OTC). The FDA's Nonprescription Drugs Advisory Committee has recommended the switch to OTC for Sanofi's triamcinolone acetonide (Nasacort AQ), the popular steroid nasal spray for the treatment of seasonal and perennial allergic rhinitis. The drug was originally approved in 1996 for use in adults and children ages 2 years and older, and has been widely used since. If approved by the full FDA later this year, it would be the first nasal steroid to be sold OTC. The drug has been available as a generic since 2008. ■