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Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Quality of Life in Atrial Fibrillation

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

SOURCE: Suman-Horduna I, et al. Quality of life and functional capacity in patients with atrial fibrillation and congestive heart failure. *J Am Coll Cardiol* 2013;61:455-460.

The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial randomized 1376 patients with AF and CHF to rhythm- or rate-control treatment strategies. The primary outcome in AF-CHF was cardiovascular mortality, and no difference in that endpoint was seen between the groups. Secondary outcomes including all-cause mortality, worsening heart failure, and stroke also showed no difference. This study examined the effects of rhythm-control and rate-control strategies on quality of life and functional capacity in AF-CHF.

Patients in AF-CHF had advanced heart failure and had not been in persistent AF for longer than 12 months. The rhythm-control strategy largely consisted of amiodarone with electrical cardioversions as needed. The rate-control strategy used target heart rates < 80 beats per minute at rest and < 110 beats per minute during 6-minute walk tests. A quality-of-life questionnaire, the Medical Outcome Short Form 36 (SF-36), was administered at baseline and at 4 months. The SF-36 was then subdivided into a physical component summary (PCS) and a mental component summary (MCS) score. Functional status (New York Heart Association [NYHA] Class) was determined at baseline, 3 weeks, 4 months, and then at four monthly intervals. Six-minute walk tests were also performed at these specified time points.

There were 833 patients who completed the baseline quality-of-life assessment before randomization and 749 patients who completed

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the 4-month follow-up questionnaire. Quality-of-life scores and functional capacity at baseline were depressed. The composite scores for physical and mental health improved from baseline to 4 months in both rhythm- and rate-control groups. When the prevalence of sinus rhythm was included as a variable, patients with a low prevalence of sinus rhythm had a nonsignificant trend toward greater improvement in both the physical and mental component scores than those with a lower prevalence of sinus rhythm. Similarly, the 6-minute walk test assessment of exercise capacity improved in both the rhythm- and rate-control groups. There was no significant difference in the improvement in 6-minute walk test distance in those in the high prevalence sinus rhythm vs the low prevalence sinus rhythm group. NYHA functional class changes showed a similar pattern. There was no difference between the rhythm-control and the rate-control groups, but those patients with a high prevalence of sinus rhythm were more likely to manifest an improvement in their NYHA functional class.

The authors conclude that quality of life and functional capacity in patients with AF and CHF are markedly depressed in many patients and can improve with both rhythm and rate control strategies. Patients in whom sinus rhythm can be maintained may have greater improvement in NYHA functional class and quality of life.

■ COMMENTARY

AF-CHF and the AFFIRM trial are the two studies that provide the most convincing evidence that mortality in AF is not improved with a pharmacologic rhythm-control as opposed to a rate-control strategy. AFFIRM previously reported that quality of life and functional status changes were similar with both strategies. Now, that observation has also been confirmed in AF-CHF. Finally, both trials have now reported that in patients in whom sinus rhythm could be maintained, a trend toward better quality of life was observed. However, this type of "responder analysis" should not be misinterpreted as proving that rhythm control is superior to rate control for all patients since responders are likely to be healthier than nonresponders in ways not accounted for in the reported analyses. I, therefore, still make at least an initial attempt to restore and maintain sinus rhythm in patients with any symptoms I think are due to AF. What I most importantly try to avoid is overzealous treatment with multiple cardioversions and high drug doses unless the patient's symptoms justify such attempts.

The observations from AF-CHF and AFFIRM apply strictly only to pharmacologic strategies for rhythm and rate control. Several reports have shown that responders to AF ablation procedures will have improved quality of life, and this is particularly true in patients with paroxysmal AF. We're still awaiting data from trials like CABANA to see if the same benefits can be achieved in older patients with persistent AF. ■

ABSTRACT & COMMENTARY

Renal Disease and Stroke Risk in Atrial Fibrillation

By John P. DiMarco, MD, PhD
Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

SOURCE: Piccini JP, et al. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation validation of the R2 CHADS2 index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for the prevention of stroke and Embolism Trail in Atrial Fibrillation) and ATRIA (AnTicogulation and Risk factors In Atrial fibrillation) study cohorts. *Circulation* 2013;127:224-232.

This study examines the influence of renal dysfunction on stroke risks in two atrial fibrillation (AF) study groups. The ROCKET AF trial was a trial comparing fixed-dose rivaroxaban, a direct factor Xa inhibitor, with adjusted-dose warfarin for prevention of thromboembolic events. Clinical variables were collected at study enrollment. A total of 14,264 patients were randomized. The median patient age at entry was 74 years with a median $CHADS_2$ score of 3.0. During median follow-up of almost 2 years, 4% of the population (575 patients) experienced a thromboembolic endpoint. Data on creatinine clearance were then combined with the $CHADS_2$ and $CHADS_2$ VASC scores and found to be a significant predictor of stroke or systemic embolism. The strength of association of creatinine clearance with stroke was secondary only to that of prior stroke or TIA. When creatinine clearance was examined as a continuous variable, the hazard ratio for a thromboembolic event increased 12% per 10 mL per minute decrease in creatinine clearance. A R_2 $CHADS_2$ risk score was then calculated with an additional 2 points ascribed for a creatinine clearance < 60 mL per minute. In the ROCKET AF cohort, the R_2 $CHADS_2$ model was associated with a C statistic of 0.587 compared with 0.575 for the $CHADS_2$ score alone and 0.578 for the CHA_2DS_2 VASC score. A model that included only creatinine clearance < 60 mL per minute and prior stroke or TIA had a C statistic of 0.590. These models were then applied to data from the ATRIA study cohort. The ATRIA cohort is an epidemiologic study of 13,559 adult patients with nonvalvular AF who were followed from 1996-2003 at Kaiser Permanente of northern California. In the ATRIA study cohort, the R_2 $CHADS_2$ risk score had a similar C statistic (discriminant power) to the $CHADS_2$ score but net stroke risk reclassification improved 17.4%. The authors conclude that impaired renal function is a potent predictor of stroke and should be included in risk stratification schemes for patients with AF.

■ COMMENTARY

Other studies have shown that moderate-to-severe renal dysfunction increases stroke risk in patients with AF. Patients with severe renal disease were excluded from ROCKET AF, so the observations here apply mainly to those with mild-to-moderate disease. As always, physicians prescribing anticoagulants must also consider the risk of bleeding and renal disease as a risk factor for bleeding. Therefore, the net gain by adding and "R" to $CHADS_2$ may not be very great. We must also remember that the new oral anticoagulants are cleared by the kidney and that leaves warfarin as the only option for patients with advanced renal disease. ■

ABSTRACT & COMMENTARY

Best Single Drug for Rate Control of Atrial Fibrillation

By Michael H. Crawford, MD, Editor

SOURCE: Ulimoen SR, et al. Comparison of four single-drug regimens on ventricular rate and arrhythmia-related symptoms in patients with permanent atrial fibrillation. *Am J Cardiol* 2013;111:225-230.

Beta-blockers are widely considered first-line therapy for heart rate control in patients with permanent atrial fibrillation (AF), but few comparative effectiveness data with other drugs are available. Thus, this group of investigators from Norway conducted a randomized prospective, crossover, single-blinded (investigator) study of four different drugs in 80 AF patients. Exclusion criteria included the presence of ischemic heart disease, systolic heart failure, and AF other than permanent. After 80 patients were randomized, 20 patients were excluded for medical contraindications (4), adverse effects (12), or other events (4), including a cerebral bleed and a stroke. The frequency of adverse events was similar in the four drug groups: diltiazem (3), verapamil (1), metoprolol (5), and carvedilol (3). Treatment with each drug was for 3 weeks to allow for washout of the previous drug. On the last day of each drug treatment, resting and 24-hour average heart rate were obtained. The results were 24-hour heart rate was lowest on diltiazem ($P < 0.001$); baseline 96 beats per minute (bpm), diltiazem 75 bpm, verapamil 81 bpm, metoprolol 82 bpm, and carvedilol 84 bpm. However, all drugs reduced heart rate compared to baseline ($P < 0.001$ for all). Symptom frequency and severity were significantly reduced by diltiazem, but verapamil only reduced symptom frequency and

the two beta-blockers reduced neither. The authors concluded that in patients with permanent AF who needed heart rate control, diltiazem was more effective than verapamil, metoprolol, and carvedilol for reducing heart rate symptoms.

■ COMMENTARY

This study is interesting because very few comparative efficacy studies of marketed drugs are done and rate control in permanent AF is a common clinical problem. The biggest issue with such studies is selecting comparable doses of the drugs tested. Diltiazem was given at the maximum recommended U.S. dose (360 mg/day). The verapamil dose was half of the maximal recommended dose (240 mg/day), which may have explained its poorer performance relative to diltiazem. Also, a relatively short-acting form of verapamil was used. The metoprolol dose (100 mg/day) and the carvedilol dose (25 mg/day) were mid-range. Thus, dosing considerations alone would seem to favor diltiazem.

It is noteworthy that all four drugs given once daily were effective in significantly reducing 24-hour mean heart rate compared to the baseline. At the doses used, calcium antagonists did better at controlling heart rate and symptoms. The strengths of the study included the relatively large size, random crossover design, and the inclusion of women (one-third of the final study population). Also, the study was not funded by the pharmaceutical industry. Although the study had flaws, I believe it highlights the efficacy of the non-dihydropyridine calcium antagonists for controlling heart rate in patients with permanent AF. ■

ABSTRACT & COMMENTARY

GRACE Score for Diagnosis of Acute Coronary Syndrome

By Michael H. Crawford, MD, Editor

SOURCE: Bajaj RR, et al. Treatment and outcomes of patients with suspected acute coronary syndromes in relation to initial diagnostic impressions (insights from the Canadian Global Registry of Acute Coronary Events [GRACE] and Canadian Registry of Acute Coronary Events [CANRACE]). *Am J Cardiol* 2013;111:202-207.

The accurate and timely recognition of acute coronary syndromes (ACS) may facilitate the deployment of evidence-based therapies that could impact outcomes. The TIMI risk score is widely used for this purpose, but wasn't designed for triaging and has significant limitations due to equal weighting of markedly disparate clinical features, e.g., aspirin use and elevated troponin. The Global Registry of Acute Coronary Events (GRACE) risk score is believed to be more robust, but is more complicated and difficult to use without an online calculator. Thus, assessing the real-world accuracy of the GRACE score for triaging potential ACS is of interest. These investigators from Canada studied more than 16,000 patients with suspected ACS who were categorized as possible or definite ACS on admission by the treating physician. Patients with possible ACS had higher GRACE scores vs those with definite ACS (130 vs 125) and were less likely to receive evidence-based therapy in the first 24 hours. The possible ACS patients had more myocardial infarctions (9 vs 2%, $P < 0.05$) and heart failure (12 vs 9%, $P < 0.05$). The GRACE score exhibited excellent discrimination on in-hospital mortality in all the patients and both subgroups (predictive accuracy was 0.85 for all patients, 0.83 for possible ACS, and 0.86 for definite ACS). The authors concluded that the GRACE score accurately assessed risk regardless of the initial clinical impression.

■ COMMENTARY

About one-third of the patients were categorized initially as possible ACS, yet 76% had a final diagnosis of ACS. Predictors of ACS included the GRACE score and two components of this score, positive biomarkers and ischemic ECG changes. The GRACE score was very accurate, more so than the initial clinical impression. This study has limitations. It is a multicentered registry study and the clinical criteria for the initial categorization of the patients may differ between institutions. In addition, there was no uniform definition of what constituted ACS. Despite these limitations, I believe the study supports the use of the GRACE score for the initial triage of possible ACS patients and suggests that those with high scores get evidence-based medical and invasive therapy regardless of the initial clinical impression. ■

ABSTRACT & COMMENTARY

Completeness of Revascularization Matters

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: Farooq V, et al. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: The SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. *J Am Coll Cardiol* 2013;61:282-294.

During coronary artery bypass graft (CABG) surgery, the aim is to achieve complete revascularization of all the coronary arteries. However, with percutaneous coronary intervention (PCI), there is debate regarding whether we should revascularize only the "culprit" vessel or whether we should aim for complete revascularization. Farooq and colleagues addressed this issue by examining the SYNTAX trial database and studying the effects of incomplete revascularization (ICR) vs complete revascularization (CR) on the long-term clinical outcomes. In addition, they explored the effects of chronic total occlusions (CTOs) of coronary arteries on these outcomes.

The SYNTAX program consisted of a randomized, controlled trial of CABG vs PCI in patients with multivessel coronary artery disease (CAD) or left main disease, and nested registries of PCI and CABG that enrolled patients who were not randomized. The authors performed a post-hoc study, consisting of patients in the randomized SYNTAX trial (n = 1800) and the nested PCI (n = 198) and CABG (n = 649) SYNTAX registries. They analyzed 4-year clinical outcomes in patients with and without angiographic CR, in the PCI and CABG arms, and also for patients with and without CTOs in both study arms.

Angiographic CR was achieved in 53% of the PCI arm and 67% of the CABG arm. Within the PCI and CABG arms, ICR (compared with CR) was associated with higher rates of clinical comorbidities and more anatomically complex CAD. ICR was also associated with significantly higher frequencies of 4-year mortality, all-cause revascularization, and major adverse cardiac and cerebrovascular events (MACCE) in both the CABG and PCI arms, as well as less stent thrombosis in the PCI arm.

The presence of a CTO was the strongest independent predictor of ICR after PCI (hazard ratio 2.70, $P < 0.001$). Eight hundred and forty patients (PCI 26.3%, CABG 36.4%; $P < 0.001$) were identified to have 1007 CTOs. The findings associating ICR (compared with CR) with higher frequencies of 4-year mortality and major adverse cardiac and cerebrovascular events remained consistent in the CTO groups in the PCI and CABG arms. The authors conclude that within the PCI and CABG arms of the all-comers SYNTAX trial, angiographically determined ICR has a detrimental impact on long-term clinical outcomes, including mortality, and this effect remained consistent in patients with and without CTOs.

■ COMMENTARY

There is mounting evidence that CR is associated with better clinical outcomes. While it has long been the standard in CABG that we should aim for the most complete revascularization possible, in treating patients with PCI there is debate between aiming for CR and the "less is more" approach of treating only the culprit lesion. The results of this paper are consistent with other recent post-hoc analyses of randomized trials. In the BARI 2D trial, patients with type 2 diabetes mellitus and less CR had more long-term cardiovascular events.[1] In the ACUITY trial of patients undergoing PCI for acute coronary syndromes, depending on the threshold used, incomplete revascularization was present in 17-75% of patients with ACS after PCI. Regardless of the threshold, incomplete revascularization was strongly associated with 1-year MI, ischemia-driven unplanned revascularization, and MACE.[2] Other studies have discussed "reasonable" ICR for vessels that are small or subtend small areas of ischemic potential. It is important to note that these studies are all post-hoc analyses, and are therefore subject to bias. Whether an upfront strategy of attempting CR in all patients at all times is warranted remains unknown, and should be tested in prospective randomized trials. However, I think that will be difficult to achieve. For now, these data will not change clinical practice guidelines. Each case should be assessed and treated on its merits. If a more complete revascularization strategy can be

achieved without significant increase in patient risk, then it may be reasonable to aim for CR. ■

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2. Rosner GF, et al. Impact of the presence and extent of incomplete angiographic revascularization after percutaneous coronary intervention in acute coronary syndromes: The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. *Circulation* 2012;125:2613-2620.

ABSTRACT & COMMENTARY

Diagnostic Use of Rapid Volume Infusion

By Michael H. Crawford, MD, Editor

SOURCE: Fujimoto N, et al. Hemodynamic responses to rapid saline loading: The impact of age, sex, and heart failure. *Circulation* 2013;127:55-62.

Volume infusion during right heart catheterization has been recommended to distinguish patients with pulmonary hypertension (PH) from those with heart failure with preserved ejection fraction (HFpEF). However, few data exist on the normal response to volume loading, especially in older individuals who are expected to have stiffer ventricles. This is especially so for older women. Thus, these investigators studied 60 healthy subjects and 11 HFpEF patients before and during warm saline infusion at 100-200 mL/min. The normal patients were about evenly divided into four groups by sex and age ≥ 50 years or < 50 years. The normal patients were given about 1 liter and the HFpEF patients got about 0.5 liter for safety reasons, but both groups got the same volume indexed to total blood volume (0.20-0.22). In the normal subjects, a second infusion was performed 6-8 minutes after the first one. In the normals, pulmonary capillary wedge pressure (PCWP) increased from an average of 10 mmHg to 16 mmHg after the first liter of saline and to 20 after the second liter. PCWP values > 15 were observed in 62% of the normals after one liter and 93% after the second liter. Older women showed a 25% steeper increase in PCWP with volume loading than younger women or men ($P < 0.05$). Mean pulmonary artery pressure (MPAP) increased by about 80% in all four groups and there was a modest increase in systemic blood pressure. MPAP indexed to cardiac output increased more in women compared to men. HFpEF patients showed a steeper rise in PCWP from a higher baseline and all pressure measurements were higher than the controls after the first infusion. The authors concluded that LV filling pressures rise significantly with volume loading in healthy controls and HFpEF patients. The largest increases in PCWP were observed in HFpEF patients and older women.

■ COMMENTARY

This study makes two important points. First, most healthy controls exceeded the upper limit of PCWP of 15 mmHg with rapid volume expansion. Since well-compensated patients with HFpEF often have a resting PCWP < 15, the rise to > 15 with volume loading was thought to define HFpEF. Clearly this criterion is flawed. This study did show that HFpEF patients had larger rises in PCWP than healthy controls. Thus, there may be an opportunity to redefine the hemodynamics of HFpEF patients, but I doubt that there will be one reliable hemodynamic measure to diagnose HFpEF.

Second, women > 50 years of age exhibited a more rapid rise in PCWP than men or younger women. This finding may explain why HFpEF is more common in elderly women. However, many HFpEF patients also have systemic hypertension and diabetes, so it may not be as simple as a sex-related trait.

There are limitations to this study. The number of HFpEF patients was small. The saline infusion rates varied between subjects and women in general got less volume expansion. Also, blood volume was estimated, not measured, in the HFpEF patients. More studies need to be done in larger numbers of HFpEF patients and multiple clinical parameters should be considered. There may be a combination of factors or an algorithm that can be developed to aide in the diagnosis of HFpEF. ■

ABSTRACT & COMMENTARY

Outcomes with Isolated Right Bundle Branch Block

By Michael H. Crawford, MD, Editor

SOURCE: Bussink BE, et al. Right bundle branch block: Prevalence, risk factors, and outcome in the general population: Results from the Copenhagen City Heart Study. *Eur Heart J* 2013;34:138-146.

The appearance of right bundle branch block (RBBB) and incomplete RBBB (IRBBB) in otherwise healthy individuals is believed to be benign, but several cardiac and pulmonary diseases are known to be associated with RBBB and IRBBB. Thus, the prognosis of subjects with incidentally discovered RBBB is unclear. Investigators from Denmark have explored this issue in the Copenhagen City Heart Study prospective database of almost 19,000 subjects entered from 1976-2003. Patients with prior myocardial infarction (MI), heart failure, or left BBB were excluded, leaving 18,441 individuals followed until 2009. The primary endpoints were all-cause mortality, major cardiovascular (CV) events, and admission for chronic obstructive pulmonary disease (COPD). Complete RBBB and IRBBB were defined as QRS complexes on the ECG with terminal slowing with a cut point of 120 msec QRS duration defining the two types. History, physical examination, and pulmonary spirometry data were collected on each subject. Follow-up was complete in 99.5% of the subjects over a median time of 20 years. Men had a higher incidence of IRBBB (4.7% vs 2.3%, $P < 0.001$) and RBBB (1.4% vs 0.5%, $P < 0.001$). IRBBB was more common in men and women < 40 years old and in men > 80 years old. RBBB increased in frequency with age in both sexes. RBBB was associated with higher blood pressure in men and higher cholesterol in women. IRBBB was associated with lower BMI in both sexes. Among the 10,327 subjects free of BBB at the first examination who returned for the second evaluation 5 years later, 133 men and 116 women developed IRBBB. Multivariate analysis in them showed an association with male sex, increasing age, and low BMI. Similarly, in the 33 men and 18 women who developed RBBB, multivariate predictors were male sex, increasing age, high blood pressure, and initial IRBBB. The risk of CV events and death were similar for both sexes with the exception of MI (more common in men). RBBB was associated with a higher risk of all-cause and CV mortality (hazard ratio [HR] 1.31; 95% confidence interval [CI], 1.11-1.54) and (HR 1.87; 95% CI, 1.48-2.36), respectively. RBBB was also associated with a higher risk of myocardial infarction (HR 1.67; 95% CI, 1.16-2.42) and pacemaker insertion (HR 2.17; 95% CI, 1.22-3.86), but not heart failure, atrial fibrillation, or COPD. IRBBB was not associated with adverse outcomes. The authors concluded that RBBB on ECG is twice as common in men and is associated with increased all-cause mortality and major CV events in both sexes, whereas IRBBB was not.

■ COMMENTARY

Occasionally, I am asked to see someone because of a new RBBB on a routine ECG. Usually if the person has no symptoms or signs of heart disease, I assume this is a benign finding based on the results of the U.S. Air Force (USAF) study. However, the USAF study almost exclusively involved young men who were arguably very healthy. We know that RBBB can be a sign of cardiac disease, especially conduction system disease, and more recent studies in older hospital-based populations have suggested that RBBB is associated with CV disease and adverse outcomes. Thus, this population-based study from Denmark is of interest.

The strengths of this study are that it includes all adults of both sexes who are free of overt CV disease, it is large, and long-term follow-up for 20 years was almost 100%. They had two groups of RBBB subjects: those with RBBB on intake and those who developed it during the study. RBBB on intake was uncommon, ranging from 0.6% in women < 40 years old to 14% in men > age 80, and it was more common (2-3 fold) in men. Initial RBBB was associated with systemic hypertension and older age, but not other CV risk factors in men, suggesting a degenerative process. Those who developed RBBB had a higher risk of death and major CV events, including pacemaker insertion, but not heart failure or atrial fibrillation. Since most of the events occurred in older men, it is difficult to tease out the pathophysiologic relationship between RBBB and the CV events, as CV events are more common in older men. Although RBBB has been associated

with the development of right ventricular hypertrophy, in this study it was not predictive of hospitalization for COPD.

IRBBB did tend to progress to RBBB, but was not predictive of CV events. This is consistent with the USAF study where recruits with IRBBB who underwent right and left heart catheterization had no increase in cardiac disease compared to a control group. I was somewhat surprised by this since IRBBB can be a sign of right ventricular volume overload, e.g., atrial septal defect. However, the majority of ASD patients with IRBBB also have right axis deviation. Details about the ECG frontal plane axis are not given in the paper. A lack of detailed clinical information is the main limitation of this study. Given that in apparently healthy subjects there was a 30% increase in CV disease events if RBBB developed, some sort of evaluation of these patients seems to be in order. What would be reasonable beyond the history, physical examination, and the ECG? A chest X-ray seems reasonable and perhaps an echocardiogram to assess cardiac structure and function. The association with coronary disease was weak in this study, so stress testing would seem optional, only if there was high suspicion of this disease and coronary angiography would probably be overkill in most subjects. A more detailed evaluation of a random sample of this study might provide better guidance for how to manage a new RBBB on ECG. ■

CME Questions

1. Which of the following drugs reduces mean heart rate in permanent atrial fibrillation?
   a. Diltiazem
   b. Verapamil
   c. Metoprolol
   d. All of the above

2. In patients with suspected acute coronary syndrome, which of the following accurately predicts mortality?
   a. Initial clinical assessment
   b. History of myocardial infarction
   c. GRACE risk score
   d. Diabetes

3. Rapid volume infusion will only increase PCWP to > 15 mmHg in which patients?
   a. Men of any age
   b. Older women
   c. Heart failure with normal EF patients
   d. All of the above

4. Which is most correct concerning new RBBB on ECG?
   a. It is a benign finding
   b. It predicts increased mortality
   c. LV dysfunction has developed
   d. COPD has developed

5. Renal dysfunction can improve stroke prediction in atrial fibrillation by:
   a. 8%.
   b. 17%.
   c. 26%.
   d. 37%.

6. Quality of life in atrial fibrillation patients can be improved by:
   a. rate control strategy.
   b. a maintain sinus rhythm with drugs strategy.
   c. ablation strategy.
   d. All of the above

7. In CABG and PCI patients, incomplete revascularization is associated with:
   a. increased mortality.
   b. reduced subsequent revascularization.
   c. good outcomes in patients with complete total occlusions.
   d. fewer strokes.

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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When One Antihypertensive Med is Not Enough: Which Combination?

Source: Kato J, et al. *J Am Soc Hypertens* 2012;6:393-398.

THE ALLHAT TRIAL IS THE LARGEST HYPERtension clinical trial ever done, originally enrolling more than 42,000 individuals. That trial concluded that a thiazide diuretic (chlorthalidone) was at least as good as — and in some situations superior to — a calcium channel blocker ([CCB] amlodipine) or an angiotensin converting enzyme inhibitor ([ACE] lisinopril), and that an alpha blocker (doxazosin) was inferior to any of the three others.

But ALLHAT also demonstrated that only about 25% of hypertensives are able to maintain control on one medication. So, when one antihypertensive med is not enough, which combination should we choose?

The ACCOMPLISH trial was the first to address this question on a large-scale basis (n = 11,506) by directly comparing ACE/CCB (benazepril/amlodipine) with ACE/diuretic (benazepril/hydrochlorothiazide). In this trial, outcomes were superior for ACE/CCB.

Not everyone can tolerate an ACE, most commonly due to cough. Kato et al performed a clinical trial to compare in 58 hypertensive elderly patients (mean age, 72 years) the efficacy of an angiotensin receptor blocker (ARB)/CCB (mostly olmesartan/amlodipine) with ARB/diuretic (mostly olmesartan/indapamide).

At the conclusion of the trial, the ARB/CCB combination provided superior blood pressure reduction to ARB/diuretic. The diuretic used in ALLHAT was chlorthalidone, which is definitely more potent than hydrochlorothiazide; whether substitution of chlorthalidone for indapamide in this trial might have tipped the scales in another direction remains unknown. ■

Vitamin D for Osteoarthritis: NOT

Source: McAlindon T, et al. *JAMA* 2013; 309:155-162.

FOR A BURGEONING POPULATION OF BABYboomers who wish to continue being physically active despite advanced years, tools to provide symptomatic relief from osteoarthritis (OA) are valuable (e.g., topical and systemic NSAIDs, opioids, physical therapy), but disease-modification is really the "holy grail." At the current time, we do not possess any disease-modifying pharmacotherapy for OA.

Since vitamin D (VID) is an important player in bone health, might it influence symptoms or disease progression of OA? McAlindon et al performed a 2-year randomized, placebo-controlled trial of VID in subjects with symptomatic OA of the knee. VID dose was titrated from 2000 IU/d up to as much as 8000 IU/d, depending on attainment of a goal plasma VID level between 36-100 ng/mL. In this population of mostly Caucasian adults (mean age, 62 years) living in the Boston area, it is perhaps not surprising that baseline levels of VID averaged 22 ng/mL.

At the end of the trial, no effect (positive or negative) was seen from supplementation with VID on either OA symptoms or evidence of disease progression as measured by degree of cartilage loss. ■

Early Identification of COPD Exacerbations

Source: Yanez AM, et al. *Chest* 2012; 142:1524-1529.

ACUTE EXACERBATIONS OF CHRONIC OBstructive pulmonary disease (AECOPD) are consequential: 10% of patients admitted to the hospital die, 25% of those admitted to the ICU die, and the mortality rate in the year following an AE-COPD hospitalization for those who are discharged home is as high as 43%. Even after successful recovery from an AE-COPD, decrements in pulmonary function from pre-event status are noted that are not regained. Early identification of AE-COPD, with an intent-to-treat with minimum delay, might possibly alter the ominous natural history of AE-COPD.

Historically, it has been shown that the increasing dyspnea characteristic of AECOPD typically begins about 5 days before patients seek consultation from their clinician. For asthma, wider swings in variation between morning and evening peak flow rate herald an acute deterioration, even before patients are overtly symptomatic. In a similar vein of thought, the authors postulated that changes in respiratory rate would signal an impending AE-COPD.

Oxygen-dependent COPD patients (n = 89) were asked to monitor respiratory rate daily for 3 months. Monitoring of daily respiratory rate (DRR) was performed automatically by installing a monitoring device to the patients' oxygen delivery systems. Although respiratory rate was monitored at three different times each day, only the mean DRR rate was used for evaluation.

During 3 months of follow-up, 30 of

the 89 patients required hospitalization for AE-COPD. Baseline average DRR for the group as a whole was 16 breaths/minute; among the subgroup ultimately admitted for AE-COPD, baseline DRR was 15.2. In the 5 days prior to an AE-COPD admission, their DRR increased to 19.1, but no meaningful change in DRR was seen in patients not requiring hospital admission. DRR may provide a new window into early identification of AE-COPD. ■

CKD: Consistency of GFR and Albuminuria as Risk Predictors

Source: Hallan SI, et al. *JAMA* 2012;308: 2349-2360.

CLINICIANS HAVE BECOME INCREASINGLY aware of the disease burden associated with chronic kidney disease (CKD), especially since the routine inclusion of a calculated estimated glomerular filtration rate (eGFR) within metabolic profile testing. Promulgation of CKD stages by national organizations and encouragement of clinicians to consider referral of patients with CKD at an earlier stage (usually by CKD stage 3-B) has prompted the clinical community to address eGFR as well as the presence, absence, and severity of urinary albumin excretion on a more consistent basis. Because of inherent renal functional decline associated with increased age, accompanied by decrease in muscle mass that contributes to the generation of creatinine, some have questioned whether current stratification of CKD by eGFR, albuminuria, or both holds true throughout the lifespan.

Hallan et al performed a meta-analysis on data from more than 2 million individuals in Asia, Australasia, Europe, and North/South America to investigate whether eGFR and the presence of albuminuria remain consistently predictive of adverse outcomes.

Although at older ages the *absolute* risk imparted by CKD was greater than in younger folks (simply because a larger absolute number of older individuals die than younger individuals, whether or not they have CKD), overall, the hazard ratio (HR) for mortality decreased with increasing age. For example, at an eGFR of 45 mL/min, the HR for death (when compared to a normal eGFR) was 3.5 for persons ages 18-54, 2.2 for ages 55-64, and 1.35 for ages > 75 years. A similar relationship was noted for albuminuria.

Albuminuria and reduction in eGFR are associated with adverse outcomes throughout the lifespan, although the HR for risk appears to lessen as we age. ■

Changing Outcomes for Patients with Chronic Hepatitis C

Source: van der Meer AJ, et al. *JAMA* 2012;308:2584-2593.

CHRONIC HEPATITIS C (HEPC) HAS AN INcreased risk for liver cancer, end-stage liver disease, and all-cause mortality. Fortunately, current antiviral treatments for HEPc (e.g., ribavirin and interferon) are effective in the majority of subjects. As many as 80% of HEPc patients who complete a therapeutic course will obtain what is called a sustained virological response (SVR); that is, no detectible HEPc virus 6 months *after* completion of therapy. SVR might reasonably be titled "cure," since indications are that absence of virus at 6 months is indicative of permanent eradication.

Nonetheless, some patients enjoying SVR already have experienced inflammatory hepatic changes resulting in fibrosis. It has not been sufficiently elucidated whether achievement of SVR ultimately reduces risk for mortality, liver cancer, or hepatic failure, especially in a group with already established hepatic fibrosis.

Using an international multicenter database (n = 540), the outcomes of HEPc patients with long-term follow-up (mean 8.4 years), as well as biopsy-proven fibrosis, were investigated to compare those who attained SVR vs those who did not. The mortality rate was essentially three times greater in those who did not attain SVR (26% vs 8.9%); the comparative cumulative incidence rate of liver-related mortality or transplantation was even more dramatic: 1.9% (SVR) vs 27.4% (SVR not attained). The attainment of SVR is associated with substantial long-term reductions in mortality as well as less need for liver transplantation. ■

Is Fructose a Primary Culprit in Obesity?

Source: Page KA, et al. *JAMA* 2013;309: 63-70.

SORTING OUT THE CAUSES OF THE CURRENT pandemic of obesity has not been easy and appears to have contributions from various life quadrants: activity, genetics, absolute calorie ingestion, and — most recently — characteristics of the calories we ingest. For instance, whereas in the recent past one might simplistically think that a gram of ice cream and a gram of broccoli should result in similar metabolic impact, recognition of the glycemic index (variation in glucose rate of absorption from different food sources) has taught us that a calorie is not necessarily always a calorie in the grander scope of things.

Fructose, an increasingly commonplace component of fast foods, snacks, etc., has recently come under fire as a potential culprit exacerbating the obesity pandemic. Mechanistically, fructose could be metabolically detrimental because (compared to glucose, that is) it blunts satiety-inducing GLP-1, and fails to shut off appetite-stimulating ghrelin.

Page et al measured regional cerebral blood flow in response to glucose and fructose ingestion. They found that fructose did not produce the same reduction in hypothalamic cerebral blood flow (associated with satiety and fullness) as did glucose. Disproportionate consumption of fructose may be a significant contributor to weight management problems. ■

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Aspirin Use and Age-Related Macular Degeneration

In this issue: Aspirin use and AMD risk; using NSAIDs and antihypertensive agents; and FDA actions.

Does aspirin cause AMD?

Does regular aspirin use put patients at risk for age-related macular degeneration (AMD)? That is the finding in a highly publicized study from Australia published in *JAMA Internal Medicine* (formerly *Archives of Internal Medicine*). A prospective analysis was conducted from an Australian population-based cohort that included four examinations in 15 years as well as questionnaires regarding aspirin use. Of the 2389 participants with follow-up available, 257 (10.8%) were regular aspirin users and 63 of these (24.5%) developed neovascular (wet) AMD. Regular aspirin users were more likely to develop neovascular AMD: The 15-year cumulative incidence was 9.3% in aspirin users and 3.7% in non-users. After adjustment for age and multiple cardiovascular risk factors, regular users of aspirin had an odds ratio of neovascular AMD of 2.46 (95% confidence interval [CI], 1.25-4.83). The association showed a dose response effect, with daily users at higher risk. Aspirin was not associated with geographic atrophy (dry AMD). The authors conclude that "regular aspirin use is associated with increased risk of incident neovascular AMD independent of a history of cardiovascular disease and smoking." (*JAMA Intern Med* published online Jan. 21, 2013. doi:10.1001/jamainternmed.2013.1583). A related editorial points out that age-related AMD is the leading cause of blindness in Western countries, and this study suggests that regular aspirin is associated with an approximate 2.5-fold greater risk in incident AMD. The study is not a randomized trial, and although there is some biological plausibility in the association between aspirin use and development of AMD, this study is "not sufficiently robust to be clinically directive." (*JAMA Intern Med* published online Jan. 21, 2013. doi:10.1001/jamainternmed.2013.2530.) The take-home message for now is that for patients who are likely to benefit from aspirin (secondary prevention of cardiovascular disease), practice should not change. However, for those patients who take aspirin for indications that are less compelling, we may want to rethink the recommendation until good trials on the relationship between aspirin use and AMD can be assessed. ■

NSAIDs and antihypertensive agents

Mixing certain antihypertensive agents with nonsteroidal anti-inflammatory drugs (NSAIDs) increases the risk of renal failure, according to a new study. In a retrospective cohort study of nearly 500,000 users of antihypertensive drugs in the United Kingdom, rate ratios of acute kidney injury associated with current use of certain antihypertensive agents with NSAIDs were assessed. After a mean follow-up of 5.9 years, 2215 cases of acute kidney injury were identified. Overall, current use of a single antihypertensive (either diuretics, angiotensin-converting enzyme inhibi-

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tors [ACEIs], or angiotensin receptor blockers [ARBs]), along with an NSAID was not associated with increased rate of acute injury. However, combining a diuretic with either an ACEI or ARB along with an NSAID increased the rate of acute kidney injury significantly (rate ratio 1.31, 95% CI, 1.12-1.53). This 31% increased risk of acute kidney injury was driven by a nearly two-fold increased risk in the first 30 days of use. The authors conclude that triple therapy consisting of diuretics with an ACEI or ARB along with an NSAID was associated with an increased risk of acute kidney injury, especially at the start of treatment (*BMJ* published online January 8, 2013. doi.org/10.1136/bmj.e8713). ■

FDA actions

An advisory committee to the FDA has recommended moving hydrocodone/acetaminophen (Vicodin, Norco) from schedule III to schedule II later this year. The move would put the drug in the same category as morphine and oxycontin, and would require a handwritten, tamper-proof prescription for every prescription and refill. Vicodin — the most widely prescribed drug in this country — is at the center of the controversy regarding prescription drug abuse, which has become "epidemic" in this country, according to the CDC. The United States consumes 99% of all the hydrocodone produced worldwide, and deaths attributable to prescription opioid abuse skyrocketed in the last 2 years, outpacing deaths from illegal opioid drugs, including heroin. The move is supported by some advocacy groups, including an endorsement by the American Academy of Pain Medicine, but not by others. Some physicians are concerned that the schedule change will be a major inconvenience for legitimate pain patients and their physicians, who will be required to write a tamper-proof prescription for each refill of the drug.

The FDA has approved an over-the-counter version of topical oxybutynin for the treatment of overactive bladder in women ages 18 and older. The approval is for women only, with oxybutynin available to men by prescription only. The anticholinergic drug has been used for years by prescription for this indication. In studies of more than 5000 subjects, it was determined that consumers can understand the labeling and "properly select whether the product is right for them." Merck will market the product as a patch that is replaced every 4 days under the trade name Oxytrol for Women.

The FDA has lowered the recommended doses for zolpidem (Ambien) for women. The agency based its recommendation on findings that the popular insomnia drug might impair alertness the next morning if taken at recommended doses. The recommendation is also based on findings that zolpidem stays in the body longer than previously thought, especially in women who process the drug somewhat slower. The new recommended maximal dose for women has been lowered from 10 mg to 5 mg for the immediate-release product, and from 12.5 mg to 6.25 mg for the extended-release (Ambien CR). The FDA further recommends that zolpidem and all insomnia drugs should be used at the lowest dose needed to treat symptoms in both men and woman.

The FDA has approved alogliptin for the treatment of type 2 diabetes. The drug is the fourth dipeptidyl peptidase-4 inhibitor after sitagliptin (Januvia), saxagliptin (Onglyza), and linagliptin (Tradjenta). Takeda Pharmaceuticals has been seeking approval for more than 5 years, dealing with the FDA's tighter standards for new diabetes drugs. The approval was based on 14 trials involving about 8500 patients as well as five ongoing postmarketing trials. The agency also approved two additional combinations of alogliptin with metformin and pioglitazone. Alogliptin alone will be marketed as Nesina, alogliptin/metformin will be marketed as Kazano, and alogliptin/pioglitazone will be marketed as Oseni. Both combination products carry boxed warnings (for lactic acidosis associated with metformin and heart failure associated with pioglitazone). All three are distributed by Takeda Pharmaceuticals.

Johnson & Johnson is one step closer to approval of canagliflozin, the first of a new type of diabetes drug. The Endocrionologic and Metabolic Drugs Advisory Committee voted 10 to 5 in favor of approving the drug while still expressing some concern about the cardiovascular safety of the agent. Canagliflozin is an oral inhibitor of the sodium glucose cotransporter 2 (SGLT2) that reduces reabsorption of glucose in the kidney, resulting in increased urinary glucose excretion with a consequent lowering of plasma glucose levels as well as weight loss. If eventually approved by the FDA, it would be the first SGLT2 inhibitor on the U.S. market. The FDA denied a similar drug 1 year ago (dapagliflozin) because of increased risk of bladder and breast cancer. The favorable vote was based on clinical trials of more than 10,000 patients worldwide which showed that the drug improves blood sugar levels and led to modest weight loss as well as reduction in blood pressure. ■