Cardiology News /Recent Literature Review / First Quarter 2014

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Athens Cardiology Update 2014: Athens (Crown Plaza Hotel), 10-12/4/2014

HRS Meeting: San Francisco, 7-10/5/2014

EuroPCR: Paris, 20-23/5/2014

CardioStim: Nice, 18-21/6/2014

ESC Congress: Barcelona, 30/8-3/9/14

TCT: Washington, 12-17/9/14

HCS Annual Meeting: Athens, 23-25/10/2014

AHA: Chicago, 15-19/11/14

Cutting Inappropriate ICD Shocks: Long Arrhythmia-Detection Time Strategy Confirmed

Programming implantable cardioverter defibrillators (ICDs) to delay the time they take to treat ventricular arrhythmias cuts mortality by 23% and inappropriate shocks by more than one-half in a meta-analysis encompassing ~4900 patients. The included studies were prospective and multicenter and covered both primary and secondary prevention and patients with either ischemic or nonischemic cardiomyopathy. The risk of syncope did not rise significantly with longer detection times, despite traditional concerns that lots of patients would not tolerate prolonged arrhythmia exposure before their ICD is allowed to deliver therapy, either shocks or antitachycardia pacing (ATP). Instead, the extra time frequently gave devices a better chance to exclude non–life-threatening arrhythmias like atrial fibrillation and to let otherwise self-terminating ventricular arrhythmias play out on their own. Current nominal settings used by some ICD manufacturers are likely to be too aggressive, with arrhythmia detection times that in some cases may be as short as 1-3 s. These results highlight the importance of setting longer default ICD detection times. The analysis included 4896 patients from the MADIT-RIT, ADVANCE 3, and PROVIDE randomized trials and the RELEVANT nonrandomized study. Overall, 264 patients received appropriate shocks and 253 experienced inappropriate shocks at follow-up (12 - 17 months). The relative risk (RR) of death from any cause was 0.77 (p=0.02) in the prolonged-detection-time groups compared with controls; the risks of inappropriate shocks and appropriate and inappropriate ATP also fell significantly. Why there were fewer deaths with longer detection times is unclear but it may derive from less exposure to potential hazards of shocks and ATP; inappropriate shocks may up mortality, and ATP poses a small risk of inducing ventricular fibrillation; or it may be due to some other factor, e.g. avoidance of treatment for multiple ICD therapies (e.g., prescription of antiarrhythmic drugs) (Scott PA et al, ***Heart Rhythm*** 2014; DOI:10.1016/j.hrthm.2014.02.009. Epub 2014 Feb 12).

MRI Aids in Atrial Fibrillation Ablation Success

The Delayed Enhancement-MRI Determinant of Successful Catheter Ablation of Atrial Fibrillation (DECAAF) study, which shows that magnetic resonance imaging (MRI) can be used to detect the degree of atrial fibrosis and predict ablation success, is now published. Atrial tissue fibrosis in the left atrium contributes to the progression of atrial fibrillation (AF); the more fibrosis there is, the more likely the arrhythmia will persist following ablation. Briefly, atrial fibrosis estimated by delayed-enhancement MRI in 260 AF patients, including 65% with paroxysmal AF, was a significant predictor of recurrence. Each 1% increase in fibrosis was associated with a 6% increased risk of recurrence. The extent of atrial disease was the only predictor of outcomes. When you look at MRI, you can predict the chance of patient having a recurrence, independent of the operator, experienced centers, and type of lesions. This is another major finding, that encircling the pulmonary veins with lesions as seen on the MRI was not important in terms of treatment success. At one year, 88% of patients with stage 1 fibrosis were free of AF. For those with stage 2, 3, or 4 fibrosis, respectively, 69%, 55%, and 45% were free of recurrence at one year. At 475 days, 86%, 64%, 51%, and 35% of those with stage 1, 2, 3, and 4 fibrosis were free of AF, respectively (Marrouche et al, ***JAMA*** 2014;311:498-506).

Distinguishing Ventricular Arrhythmia Originating from the Right Coronary Cusp, Peripulmonic Valve Area, and the Right Ventricular Outflow Tract: Utility of Lead I

Outflow tract ventricular arrhythmias (OTVA) can be complicated to target for ablation when originating from either the periaortic or pulmonary valve (PV) region. Both sites may present with a small R wave in lead V1. However, the utility of lead I in distinguishing these arrhythmia locations is unknown. Thirty-six consecutive patients (mean age 41 ± 14 years) underwent catheter ablation for OTVA. OTVA origin was determined from intracardiac electrogram tracings and electro-anatomic maps. Observers blinded to results measured QRS waveform amplitude and duration from standard 12-lead ECG tracings. Measurements with highest diagnostic performance were modeled into an algorithm. Sites of successful ablation were anterior right ventricular outflow tract (RVOT; n = 6), posterior RVOT (n = 4), PV (n = 18),

and right coronary cusp (RCC; n = 8). Highest performing surface ECG discriminators were from lead I to V1 vectors: RCC, lead I R wave≥1.5 mV, and V1 R wave≥2.0 mV (sensitivity 87%, specificity 93%); PV, V1 R wave > 0 mV, and lead I R/(R+S) ≤ 0.75 (sensitivity 78%, specificity 72%); anterior RVOT, V1 R wave = 0 mV, and lead I R/(R+S) <0.4 (sensitivity 67%, specificity97%); posterior RVOT, V1 R wave > 0 mV, and lead I R/(R+S) > 0.75 (sensitivity 75%, specificity 84%). Sequential algorithmic application of these criteria resulted in an overall accuracy of 72% in predicting site of OTVA origin. A relatively large R wave in lead I is seen with RCC origin but not PV origin (Ebrille et al, ***J Cardiovasc Electrophysiol***, Epub Jan 8, 2014).

Bacteremia Appears to Increase 30-Day Risk of MI or Stroke

Patients who had bacteremia mainly urinary tract infections, pneumonia, or sepsis when admitted to hospital were much more likely to have an MI or stroke within 30 days, compared with healthy controls or patients hospitalized for other reasons. This study corroborates that acute infection may trigger cardiovascular events. It is the first study to demonstrate that many different bacterial infections may affect MI and stroke risk. The research suggests that bacteremia should be considered a risk factor for MI and stroke, but only for a short period of time after onset of infection, and it hints that infection with Staphylococcus aureus may confer a particularly high risk. Patients admitted with signs of acute infection and bacteremia/sepsis should be monitored closely for complications, and treated early with fluid therapy, oxygen, and antibiotics. Moreover, it seems prudent to increase vaccination efforts (e.g., influenza and pneumococcal vaccination), particularly in patients who already have established cardiovascular disease, since infection may trigger new cardiovascular events. Future studies are needed to clarify whether specific cardiovascular therapies (e.g., antithrombotic or anti-inflammatory drugs) may reduce the risk of cardiovascular complications in patients with bacteremia, An estimated one million Americans have an acute MI or stroke each year, and it would be useful to understand how acute infections might trigger these events, but most previous studies lacked laboratory confirmation of infection. Using population-based databases, they identified 4389 patients (mean age 73 years) in Northern Denmark who had positive blood cultures when admitted to hospital (1992-2010). The pathogens were E. coli, S. pneumoniae, S aureus, other bacteria, and fungi. Most patients had urinary tract infections or pneumonia, while others had central nervous system infections, endocarditis, and other infections. Based on age, gender, and date of admission, each patient was matched with ~5 patients hospitalized for other reasons and ~10 individuals in the general population. Researchers identified all incident MI and stroke events that occurred within 0-30 days, 31-180 days, and 181-365 days after the day of hospitalization. Patients with community-acquired bacteremia had a greatly increased risk of MI or stroke within 30 days. At 31-180 days, these patients had a modestly higher risk of MI or stroke compared with healthy controls, but not compared with other hospitalized patients. No differences in cardiovascular risk were seen after >6 months. Increased efforts should be made to improve suboptimal vaccination rates among patients with cardiovascular disease. Further studies would be required to assess whether antiplatelet, beta-blocker, or statin therapies might result in lower cardiovascular complications and possibly better outcomes after acute infection (Dalager-Pedersen et al, ***Circulation*** 2014; doi: 10.1161/CIRCULATIONAHA. 113.006699. Epub 2014 Feb 12).

In-hospital Switching of Oral P2Y12 Inhibitor

In the context of the GReek AntiPlatelet REgistry (GRAPE), Alexopoulos et al assessed the prevalence, predictive factors and short-term outcome of in-hospital P2Y12 inhibitor switching in 1794 ACS patients undergoing PCI. Switching occurred in 636 (35.5%) patients of which in the form of clopidogrel to a novel agent, novel agent to clopidogrel and between prasugrel and ticagrelor in 574 (90.4%), 34 (5.3%) and 27 (4.3%) patients, respectively. Presentation to non PCI-capable hospital, bivalirudin use, age ≥75 years (inverse predictor), and regional trends emerged as predictive factors of switching to a novel agent. In-hospital switching in initially clopidogrel treated patients was not accompanied by differences in the rate of major adverse cardiac events (MACE) or bleeding events compared with patients who started antiplatelet treatment with a novel agent since their admission. Reports with prasugrel use are in the same line of evidence. In contrast, in-hospital switching in initially clopidogrel treated patients was accompanied by a higher risk of BARC type 1, type 2 and any type bleeding and less ischemic events, when compared to patients receiving clopidogrel only. Of note, the observed difference in BARC any type bleeding was driven by BARC type 1 bleeding events. Both findings are in agreement with the described higher anti-ischemic and bleeding potential of prasugrel and ticagrelor compared to clopidogrel. Having 3 oral P2Y12 inhibitors to select for clinical use in addition to aspirin in patients with acute coronary syndromes (ACS) undergoing PCI, in-hospital switching

represents a common clinical practice. Clinical factors and regional practice differences seem to affect the choice of this strategy, while in-hospital switching to a novel P2Y12 inhibitor may be associated with an increased risk of bleeding up to one month post treatment initiation (Alexopoulos et al, ***Am Heart J*** 2014;167:68-76).

Monitor Detects AF in Cryptogenic Stroke

An implanted cardiac monitor was much more effective at picking up atrial fibrillation (AF) than standard monitoring in patients with cryptogenic stroke in the CRYSTAL-AF trial. Because AF is one of the most important risk factors for stroke and the risk can be reduced greatly with anticoagulation therapy, such monitoring could bring about a significant reduction in recurrent stroke rates. Approximately 30% of strokes are labeled as cryptogenic, meaning no known cause. But patients with stroke of unknown etiology should not settle for this diagnosis after just 1 round of tests. Many will have AF, and finding it can prevent them from having a recurrent stroke. This idea of needing to pick up undiagnosed AF is not restricted to this 1 device, but we would say long-term cardiac monitoring is definitely coming into play, but how exactly we are going to do this is still very much open to question. We have to consider costs and logistics. If we did not have an effective treatment for AF, then this study would not be relevant, but we do have an effective treatment. Anticoagulation is the single most effective stroke prevention there is, having been shown to prevent about 70% of strokes, so the potential for benefit is huge. This is a very interesting device. There are many patients who have had a stroke, and we do a full workup and still cannot figure out why. This device picks up AF, which is a treatable cause of stroke; also, it could make a big difference. The CRYSTAL-AF trial included 441 patients who had had an unexplained stroke. All received at least 24 hours of standard cardiac monitoring within 90 days of the stroke, and half were then tracked with an insertable monitor (Reveal XT, Medtronic), which can provide data continuously for up to 3 years. The device, which is about the size of a USB stick, is inserted under the skin with a minimally invasive 15- to 30-min outpatient procedure under local anesthetic. Results showed a far greater detection of AF in the group receiving the monitor vs the control group. Among patients in the study who were found to have AF, oral anticoagulants were prescribed for 97% of cases. There were numerically fewer strokes in the device arm, but this study was not powered to show a reduction in stroke. The benefits of the insertable device far outweigh risks, noting that 2.4% of the devices had to be removed in the study because of complications, and the patients had no long-term problems. Results showed that in the control group, there were 121 ECGs, 32 24-hour Holter recordings, and 1 event recorder, but all these picked up only 4 cases of AF in 1 year in 220 patients, while 29 new cases were found in the device group. This shows how inadequate current methods of detecting AF are (International Stroke Conference - ISC 2014. Abstract LB11. Presented February 14, 2014).

Aldosterone-Antagonist did not Reduce Mortality and Morbidity in Heart Failure (HF) Patients with Preserved Ejection Fraction.

A randomized clinical trial in patients with HF with preserved ejection fraction (HFPEF) has its researchers and some experts hopeful that there may finally be a drug for the disorder that can improve clinical outcomes. The study was negative, all agree: patients who took the aldosterone inhibitor **spironolactone** failed to show benefit for the clinical composite primary end point. But they did have significantly fewer heart-failure hospitalizations, a part of the primary end point, over the average follow-up of 3.3 years in the trial, called Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist **(TOPCAT).** Overall, all-cause hospitalizations and all-cause mortality did not seem to be meaningfully impacted by this drug. And we have to acknowledge that, minus the careful [creatinine and serum potassium] monitoring that occurred in the clinical trial, the prevalence of worsening renal function and hyperkalemia would likely be more common in clinical practice. When physicians use a mineralocorticoid antagonist in patients with HFPEF, they agree on the importance of good safety monitoring, especially for renal function, and look carefully for any other reason that would further corroborate the decision to give any aldosterone antagonist, like hypertension, for example. TOPCAT randomized 3445 heart-failure patients at least aged 50 with an LVEF>45% at 270 sites in 6 countries to receive the aldosterone antagonist or placebo. Spironolactone was titrated up to 30 to 45 mg/day. There were no significant differences in adverse events, except, more hyperkalemia with spironolactone and more hypokalemia on placebo; there were no hyperkalemia-related deaths (Shah et al, ***Circ Heart Fail*** 2014;7:104-115).

Cardiac Resynchronization Therapy (CRT) in Mild Heart Failure Patients

Patients with mild – heart failure symptoms, left ventricular dysfunction and left bundle branch block (LBBB), early intervention with CRT-D was associated with a significant long term survival benefit. The MADIT-

CRT trial showed that at 7 years of follow up, the cumulative rate of death from any cause among patients with LBBB was 18% among patients randomly assigned to CRT-D, as compared with 29% among those randomly assigned to defibrillator (D) therapy alone. The survival difference corresponded to 9 patients who would need to be treated with CRT-D to save one life within 7 years. The long-term survival benefit of CRT-D in patients with LBBB did not differ significantly according to sex, cause of cardiomyopathy (ischemic or nonischemic), or QRS duration. In contrast, CRT-D was not associated with any clinical benefit and possibly with harm in patients without LBBB. The lack of survival benefit associated with CRT-D in patients without LBBB was consistent among those with a longer (≥150 ms) or a shorter QRS duration (<150 ms), and among patients with QRS morphologic findings showing RBBB or intra-ventricular conduction delay. The final study sample included the 1818 patients from MADIT-CRT for whom baseline ECG data were available (Goldenberg et al, ***N Engl J Med***, Epub 2014 Mar 30).

Is there a Place for Evolocumab in the Age of Statins?

LAPLACE-2 is a study evaluating the investigational drug evolocumab. Evolocumab is a monoclonal antibody in the new PCSK9 inhibitor class. The purpose of the LAPLACE-2 study was to look at the efficacy and safety of adding evolocumab to moderate- or high-intensity statin therapy and to compare it with ezetimibe. This was a large, phase 3 trial with more than 1800 participants who were randomly assigned to receive atorvastatin 80 mg or rosuvastatin 40 mg for high-intensity statin therapy or to atorvastatin 10 mg, rosuvastatin 5 mg, or simvastatin 40 mg for moderate-intensity statin therapy. The primary finding was that the dose of statin did not matter. There was an additional 65% reduction in low-density lipoprotein cholesterol (LDL-C) when evolocumab was added to moderate- or high-intensity statin therapy, and that was in comparison with a 20%-25% reduction in LDL-C when ezetimibe was added to moderate- or high-intensity statin therapy. The other thing that was very interesting about the LAPLACE-2 study is that it reported, for the first time, achieved LDL-C levels. Those who received a moderate-intensity statin started out with a little bit lower LDL-C level than the high-intensity group, but at the end of the day, both groups achieved a fairly similar LDL-C level: 35-40 mg/dL in the high-intensity group compared with 35-45 mg/dL in the moderate-intensity group. We are achieving, for the first time, very low LDL-C levels. It is exciting to contemplate the added efficacy in terms of reducing heart attack and stroke from achieving very dramatic additional LDL reductions. LAPLACE-2 was only a 12-week study and it did not address that question, but it is basically the model for the design of the ongoing FOURIER trial which is testing whether evolocumab will further reduce heart attack and stroke events in optimally statin-treated patients. That trial will be completed circa 2018. In the meantime, we all hope that these PCSK9 inhibitors will be available to treat our patients who need additional LDL lowering -- such as people with genetic hypercholesterolemia whose LDL-C levels are still very high on a high-intensity statin, or people who are statin-intolerant and are either not able to tolerate a statin at all or can only tolerate a suboptimal statin dose. It would be very nice to have something to add to further lower their LDL-C levels in the meantime (ACC 2014 Scientific Sessions; Washington, DC; March 29-31, 2014. Session 402-10).

Radiofrequency Ablation vs Antiarrhythmic Drugs

The Radiofrequency Ablation vs Antiarrhythmic Drugs as First-Line Therapy of Atrial Fibrillation (RAAFT 2) trial showed that radiofrequency catheter ablation with pulmonary vein isolation could be successfully performed as first-line therapy in patients with atrial fibrillation (AF). Most important, when the results are analyzed with other data, the study reinforces the conclusion that AF ablation for most patients is not a curative procedure. This trial and others make it clear that symptomatic and asymptomatic recurrences of AF are not uncommon following AF ablation and that the efficacy of this procedure, even in optimal candidates, is modest: 54.5% of patients with persistent or paroxysmal AF treated with first-line ablation therapy experienced a documented atrial tachyarrhythmia lasting more than 30 sec over the 24-month follow-up period. In comparison, 72.1% of patients treated with antiarrhythmic medication experienced an atrial tachyarrhythmia. This translated into a 44% lower risk of symptomatic or asymptomatic AF, atrial flutter, or atrial tachycardia over the 2-year period. Recurrent arrhythmias were documented by electrocardiogram, Holter, transtelephonic monitor, or rhythm strip. Regarding secondary end points in the 127-patient trial conducted at 16 centers in Europe and North America, 59% of patients treated with antiarrhythmic medication had a recurrence of symptomatic AF, atrial flutter, or atrial tachycardia at 2 years compared with 47% of patients treated with first-line catheter ablation therapy. There were no deaths or stroke in the ablation arm, but 4 cases of cardiac tamponade were documented. Quality of life was improved with both treatments. The RAAFT-2 trial results show that ablation is not without its risks. The overall complication rate in the trial was 9%, and the rate of cardiac tamponade was 6%. These rates are higher than those reported in a recent worldwide survey of AF-ablation procedures. RAAFT-2

reinforces the recommendations of the 2012 HRS/EHRA consensus statement and the 2012 ESC updated AF guidelines. Catheter ablation is class 1 recommendation (A level of evidence) in patients with paroxysmal AF who have failed at least one antiarrhythmic drug. It is only a class 2 recommendation (B level of evidence) for paroxysmal AF patients who have not yet failed drug therapy. In clinical practice, it is uncommon to find a patient who is eager to undergo catheter ablation without at least one trial of an antiarrhythmic medication. This is especially true after a thorough discussion of the risks of the procedure, the fact that 30%-50% of patients require a repeat procedure, and consideration that the techniques and tools used for catheter ablation continue to improve. The one subgroup of patients that might benefit from immediate ablation of AF comprises those with paroxysmal AF and significant sinus-node dysfunction. The data suggest the procedure can help control AF and eliminate the need for a pacemaker in this patient subgroup (Morillo et al, ***JAMA*** 2014; 311:692-699 & JAMA 2014;311: 679-680).

Heparin versus Bivalirudin in STEMI

One trial at the American College of Cardiology 2014 Scientific Sessions took heat like no other: the How Effective Are Antithrombotic Therapies in Primary PCI (HEAT-PPCI) trial. The single-center randomized trial of unfractionated heparin vs bivalirudin (Angiomax, the Medicines Company) (with bailout GPIIb/IIIa inhibitors) in ST elevation myocardial infarction (STEMI) patients surprised by showing a significantly lower rate of major adverse cardiac events (MACE) in the heparin-treated patients at 28 days and no differences in bleeding complications. The trial recruited 1829 patients over a 22-month period at a single UK hospital with 14 interventional cardiologists participating in the study. In the heparin group, patients received a bolus dose of 70 units/kg preprocedure, while bivalirudin was given as a bolus of 0.75 mg/kg, followed by infusion of 1.75 mg/kg per hour for the duration of the procedure. At four weeks, the primary efficacy end point (MACE, defined as all-cause mortality, cerebrovascular accident, reinfarction, or unplanned target lesion revascularization [TLR]) had occurred in 8.7% of bivalirudin-treated patients and in 5.7% of heparin-treated patients, an absolute increased risk of 3%. Definite or probable stent thrombosis was 3.4% in the bivalirudin group and 0.9% in the heparin group. Minor bleeds, as well as major/minor bleeds, were no different between groups. Bailout glycoprotein-GP IIb/IIIa-inhibitor use was similar in both groups, at 13.5% in the bivalirudin group and 15.5% in the heparin-treated patients. In the HORIZONS trial, bivalirudin alone was compared with heparin plus routine GPIIb/IIIa-inhibitor use. EuroMAX, the only large randomized trial that studied bivalirudin vs heparin (low-molecular-weight or unfractionated) with bailout GPIIb/IIIa-inhibitor use in both arms, also showed an increase in stent thrombosis in the bivalirudin group, although bleeding risk was lower. In REPLACE 2, bleeding was lower with bivalirudin, but the comparator arm was heparin plus GPIIb/IIIa inhibitors. In ACUITY, bleeding rates were lower for the bivalirudin-monotherapy group but were equivalent in the other two trial arms where routine GPIIb/IIIa inhibitors were used on top of either heparin/enoxaparin or bivalirudin (Shahzad A. Presented at the American College of Cardiology/i2 Annual Scientific Session. March 31, 2014. Washington, DC).

Transcatheter Aortic-Valve Replacement with a Self-Expanding Prosthesis vs Surgical Aortic Valve Replacement

A total of 795 patients with severe aortic stenosis and an increased risk of death during surgery, underwent randomization at 45 centers in the United States. In the as-treated analysis, the rate of death from any cause at 1 year was significantly lower in the TAVR (self-expanding transcatheter aortic-valve bioprosthesis) than in the surgical group (14.2% vs. 19.1%). In the TAVR group there were more vascular complications, the same strokes and fewer bleedings and renal dysfunctions compared with the surgical group. In a hierarchical testing procedure, TAVR was noninferior with respect to echocardiographic indexes of valve stenosis, functional status, and quality of life. Exploratory analyses suggested a reduction in the rate of major adverse cardiovascular and cerebrovascular events and no increase in the risk of stroke. In the TAVR group more than 20% of the patients required implantation of a permanent pacemaker vs 10% of the surgical group. In addition, more patients had paravalvular leak at 1 year (6.1% vs 0.5%). CoreValve has already indication in the USA in patients who are not candidates for operation and will ask to have indication for patients with severe aortic stenosis and an increased risk of death during surgery (Adams et al, ***N Engl J Med*** 2014; doi: 10.1056/NEJMoa1400590. Epub 2014 Mar 29.).

Renal Denervation

SYMPLICITY HTN-3 trial was the first randomized control trial of renal denervation, where patients with therapy-resistant hypertension were randomized in a 2-to-1 fashion to renal denervation (active treatment) or to a sham procedure. Patients were blinded to whether they received renal denervation or only renal arteriography. Office systolic blood pressure tended to be lower in the renal denervation group, but this was far away from

reaching statistical significance, and the 24-hour blood pressure lowering was not significant between both groups. There was no significant difference between both groups 6 months after treatment. (Bhatt et al, ***N Engl J Med*** 2014; doi: 10.1056/NEJMoa1402670. Epub 2014 Mar 29).

Beta-Blockers vs ACE Inhibitors in Dialysis Patients

Dr Agarwal recently published in the *Nephrology, Dialysis, and Transplant* journal that beta-blockers are better than angiotensin converting enzyme (ACE) inhibitors in patients on dialysis. This study looked at people with left ventricular hypertrophy and compared lisinopril vs atenolol, with cardiovascular mortality, myocardial infarction, and stroke as endpoints. Atenolol was really working well in these individuals. The primary endpoint was regression of left ventricular hypertrophy or change in left ventricular mass index from baseline to 12 months. The trial was terminated early due to a strong signal favoring atenolol in terms of cardiovascular event rate and all-cause hospitalizations. Many patients in the lisinopril group were hospitalized, and they were hospitalized more frequently. The same was true for cardiovascular event rates. More patients in the lisinopril group had myocardial infarctions, strokes, heart failure hospitalizations, and cardiovascular-related death. Everything looked better for atenolol. There is a whole literature promulgated by the cardiologists about the fact that beta-blockers really do not do a good job on left ventricular mass regression, whereas ACE inhibitors, angiotensin receptor blockers, and even calcium channel blockers (CCBs) are better; but in the COSMOS trial, where the investigators actually randomly assigned people to ACE inhibition or beta blockade using carvedilol, the key factor was blood pressure control. It did not matter what drug you used; if the blood pressure was controlled, you actually saw left ventricular mass regression. Many people do not appreciate that beta-blockers reduce blood pressure by renin inhibition, not by their effects on the sympathetic system. They do affect the sympathetic system, but that is not the mechanism through which they reduce blood pressure. The advantage in dialysis patients is that the renin angiotensin system is almost nonexistent in most of those patients because the kidneys are pretty much not functioning. The sympathetic nervous system is playing a role, however. The ACE inhibitors are essentially worthless for blood pressure control in dialysis patients because their target is not really functional, whereas the beta-blockers are better at lowering blood pressure. Not only that, but many of these people on dialysis are prone to atrial fibrillation and other arrhythmias, and the beta-blockers have a role in controlling atrial fibrillation (Agarwal et al, ***Nephrol Dial Transplant*** 2014;29:672-681).

Cryoballoon Ablation vs Radiofrequency Ablation of Atrial Fibrillation

Junxia Xu et al sought to undertake a meta-analysis with special emphasis on comparing the efficacy and safety between cryoballoon and radiofrequency ablations by synthesizing published clinical trials. Articles were identified by searching the MEDLINE and EMBASE databases before September 2013, by reviewing the bibliographies of eligible reports, and by consulting with experts in this field. Pulmonary vein isolation (PVI) via catheter ablation has become the recommended choice of treatment for patients with drug-refractory paroxysmal or persistent atrial fibrillation (AF). Conventionally radiofrequency current is the preferred source of energy for ablation procedures, whereas its application has been limited by disrupting tissues due to excess heating or generation of inhomogeneous lesions. An alternative energy source, cryothermal energy, has recently been developed to overcome this limitation. The most noteworthy of this study was that there was greater improvement in fluoroscopic time and total procedure duration in patients referred for cryoballoon ablation than those for radiofrequency ablation in PVI of AF. Moreover, success rate of PVI, the percentages of recurrence of AF and major complications were comparable between the two procedures. To our knowledge, this is so far the first comprehensive meta-analysis comparing cryoballoon ablation with radiofrequency ablation in terms of the efficacy and safety for electrical isolation of pulmonary veins. There were respectively 469 and 635 patients referred for cryoballoon and radiofrequency ablation procedures in PVI for the treatment of AF. Distributions of age, AF duration, left ventricular ejection fraction, previous percutaneous ablation, coronary artery disease, hypertension and diabetes were comparable between patients referred for cryoballoon and radiofrequency ablations ($P>0.05$). There were more males for radiofrequency ablation (79.2%) than cryoballoon ablation (72.0%) ($P = 0.0284$). Left atrium diameter was slightly elevated for radiofrequency ablation (42.96% vs 41.89% for cryoballoon ablation, $P = 0.0212$). By contrast, there were more patients with paroxysmal AF referred for cryoballoon ablation (87.36%) than radiofrequency ablation (71.91%) ($P = 0.0076$). Pooling the results of all qualified trials observed that cryoballoon ablation significantly reduced fluoroscopic time and total procedure time by a weighted mean of 14.13 ($P = 0.014$) minutes and 29.65 ($P = 0.006$) minutes compared with

radiofrequency ablation, respectively (Xu et al, ***PLoS One*** 2014;9:e90323).

Increased Risk for Cardiovascular Disease Early and Late After a Diagnosis of Giant-Cell Arteritis According to a Cohort Study

Involvement of large arteries is well-documented in giant-cell (or temporal) arteritis (GCA). An observational cohort study evaluated the risks for incident myocardial infarction (MI), cerebrovascular accident (CVA), and peripheral vascular disease (PVD) in 3408 patients with GCA in comparison with 17,027 age- and gender-matched control individuals without baseline cardiovascular disease (MI, CVA, or PVD). Data were taken from electronic medical records. Among the 3408 patients with GCA (73% female; mean age, 73 years), the incidence rates of MI, CVA, and PVD were 10.0, 8.0, and 4.2 events per 1000 person-years, respectively, vs 4.9, 6.3, and 2.0 events per 1000 person-years, respectively, among controls. The hazard ratios-HRs were 1.70 for the combined outcome, 2.06 for MI, 1.28 for CVA, and 2.13 for PVD. The HRs were higher in the first month after GCA diagnosis (combined HR, 4.92; HR for MI, 11.89; HR for CVA, 3.93; HR for PVD, 3.86). A major limitation was the missing information on temporal artery biopsies The authors concluded that giant-cell arteritis is associated with increased risks for MI, CVA, and PVD (Tomasson G, et al, ***Ann Intern Med*** 2014;160:73-80).

ADJUST-PE Study: Age-Adjusted D-Dimer Cutoff Levels Better Rules Out Pulmonary Embolism (PE)

Among 3346 patients presenting to the emergency department with clinically suspected PE, the prevalence of PE was 19%. Patients with a D-dimer value between the conventional cutoff of 500 µg/L and their age-adjusted cutoff, defined as age × 10 in patients >50 years, did not undergo computed tomography pulmonary angiography and were left untreated. Among the 2898 patients with nonhigh or unlikely probability, 817 patients (28.2%) had a D-dimer level <500 µg/L and 337 patients (11.6%) had a D-dimer between 500 µg/L and their age-adjusted cutoff. The 3-month failure rate in patients with a D-dimer level >500 µg/L but below the age-adjusted cutoff was 1 of 331 patients (0.3%). Among the 766 patients >75 years, of whom 673 had a nonhigh clinical probability, using the age-adjusted instead of the 500 µg/L cutoff increased the proportion of patients in whom PE could be excluded on the basis of D-dimer from 43 of 673 patients (6.4%) to 200 of 673 patients (29.7%), without any additional false-negative findings. The authors concluded that compared with a fixed D-dimer cutoff of 500 µg/L, the combination of pretest clinical probability assessment with age-adjusted D-dimer cutoff was associated with a larger number of patients in whom PE could be considered excluded with a low likelihood of subsequent clinical thromboembolism (Righini M, et al, ***JAMA*** 2014;311:1117-1124).

Catheter Ablation is Superior to Drugs for Maintaining Sinus Rhythm in Patients with Persistent AF

Patients (n=146; aged 55±9 years) with persistent AF were randomly assigned to catheter ablation (CA) or antiarrhythmic drugs (AD). After a 3-month blanking period, 69 of 98 patients (70.4%) in the CA group and 21 of 48 patients (43.7%) in the AD group were free of arrhythmia (>24h) recurrence (P=0.002); an absolute risk difference of 26.6% in favour of CA. The proportion of patients free of any recurrence (>30 s) was higher in the CA than in the AD group (60.2 vs. 29.2%; P < 0.001) and cardioversion was less frequent (34.7 vs 50%; P = 0.018). The authors concluded that catheter ablation is superior to medical therapy for the maintenance of sinus rhythm in patients with persistent AF at 12-month follow-up (Mont L, et al, ***Eur Heart J*** 2014;35:501-507).

Important Review and Other Articles

TASER devices causing cardiac arrest (Zipes DP, *Circulation* 2014;129:101-111), Assessment of aortic stenosis (Saikrishnan N et al, *Circulation* 2014;129:244-253), Thrombophilia (Cohoon KP & Heit JA, *Circulation* 2014;129:254-257), Heart disease & stroke statistics 2014 (Go AS et al, *Circulation. 2014;129:399-410*), Risk stratification for sudden cardiac death (Goldberger JJ et al, *Circulation* 2014;129:516-526), Nonsteroidal anti-inflammatory drugs and the heart (Patrono C & Baigent C, *Circulation* 2014;129:907-916), Fibromuscular dysplasia (Olin JW et al, *Circulation* 2014;129:1048-1078), Lomitapide & Mipomersen **(**Rader DJ & Kastelein JJP **(***Circulation* 2014;129:1022-1032), Endovascular therapy for stroke (Sun C et al, *Circulation* 2014;129:1152-1160), Chronic hypertension in pregnancy (Seely EW & Ecker J, *Circulation* 2014;129:1254-1261), Depression as a risk factor in acute coronary syndrome (Lichtman JH et al, *Circulation* 2014;129:1350-1369), Atrial autonomic innervation (Linz D et al, *J Am Coll Cardiol* 2014;63:215-224), Left atrial appendage occlusion (Holmes DR et al, *J Am Coll Cardiol* 2014;63:291-298), Left atrial size & function (Hoit BD, *J Am Coll Cardiol* 2014;63:493-505), Performance measures for PCI (Nallamothu BK et al, *J Am Coll Cardiol* 2014;63:722-745), Frailty assessment (Afilalo J et al, *J Am Coll Cardiol* 2014;63:747-762), Transcatheter therapies for mitral regurgitation (O'Gara PT et al, *J Am Coll Cardiol* 2014;63:840-852), AF in cancer (Farmakis D et al, *J Am Coll Cardiol* 2014;63:945-953), Cardiac MRI (*J Am Coll Cardiol* 2014;63:1031-1045 & 1046-1047), Biomarkers and ACS (Mueller C, *Eur Heart J*, 2014;35:552-556).