

Cardiology News /Recent Literature Review / Second Quarter 2014

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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

20th Annual Boston AF Symposium: Orlando, 8-10/1/15

HCS Working Groups Seminar: Ioannina, 2/2015

ACC: San Diego, 14-16/3/15

HRS: Boston, 13-16/5/15

EuroPCR: Paris, 19-22/5/15

Europace: Milan, 21-24/6/15

ESC: London, 29/8-2/9/15

Short QT Syndrome is Highly Lethal

A total of 62 out of 73 short QT syndrome (SQTS) patients (84% male; mean age, 26 ± 15 years; corrected QT interval, 329 ± 22 ms) were followed for 60 ± 41 months. Cardiac arrest (CA) was the most frequent presenting symptom (40% of probands). There was an age dependency in the susceptibility to arrhythmias, with a peak in the occurrence of CA in the first year of life (4%) and a second peak (1.3%) between 20 and 40 years of age; the probability of a first occurrence of CA by 40 years of age was 41%. Despite the male predominance, female patients had a similar risk profile. Familial disease was present in 44% of kindreds, but the yield of genetic screening was low (14%). A history of CA was the only predictor of recurrences at follow-up ($p < 0.0000001$). Arrhythmias occurred mainly at rest. The authors concluded that SQTS is highly lethal with CA often as the first manifestation of the disease with a peak incidence in the first year of life; survivors of CA have a high CA recurrence rate; implantation of a defibrillator is strongly recommended (Mazzanti A et al, *J Am Coll Cardiol* 2014;63:1300-1308).

Inferior Vena Cava (IVC) Filters in Patients With Acute Symptomatic Venous Thromboembolism (VTE) and a Significant Bleeding Risk Lower Pulmonary Embolism Mortality but Increase Risk of Recurrence

In a prospective cohort study of patients with acute VTE identified from the RIETE (Computerized Registry of Patients With Venous Thromboembolism), the investigators assessed the association between IVC filter

insertion due to significant bleeding risk and the 30-day outcomes [all-cause mortality, pulmonary embolism (PE)-related mortality, and VTE rates]. Of 40,142 patients who had acute symptomatic VTE, 371 received an IVC filter. A total of 344 patients treated with a filter were matched with 344 patients treated without a filter. There was a non-significant trend toward lower risk of all-cause death for filter insertion (6.6% vs 10.2%; $p = 0.12$). The risk adjusted PE-related mortality rate was lower for filter insertion than no insertion (1.7% vs 4.9%; $p = 0.03$). Risk-adjusted recurrent VTE rates were higher for filter insertion than for no insertion (6.1% vs 0.6%; $p < 0.001$). The authors concluded that in patients presenting with VTE and a significant bleeding risk, IVC filter insertion compared with anticoagulant therapy was associated with a lower risk of PE-related death and a higher risk of recurrent VTE (Muriel et al, *J Am Coll Cardiol* 2014;63:1675-1683).

Three-Year Follow-up of CONFIRM trial: FIRM-Guided Ablation is More Effective than Conventional Ablation Alone at Preventing AF Recurrences

Source (focal impulse and rotor modulation [FIRM]) ablation ($n = 27$) was compared with conventional ablation (pulmonary vein isolation-PVI) ($n = 65$) of atrial fibrillation (AF). FIRM mapping revealed a median of 2 rotors or focal sources in 97.7% of patients during AF. At 3 years, patients receiving FIRM-guided ablation, compared to FIRM blinded therapy, maintained higher freedom from AF after 1.2 ± 0.4 procedures (median 1) (77.8% vs 38.5%, $p = 0.001$) and a single procedure ($p < 0.001$) and higher freedom from all atrial arrhythmias ($p = 0.003$). The authors concluded that FIRM-guided ablation is more durable than conventional trigger-based ablation in preventing 3-year AF recurrence (Narayan et al, *J Am Coll Cardiol* 2014;63:1761-1768).

Successful Catheter Ablation of Atrial Fibrillation (AF) May Last a Decade in the Majority of Patients

A prospectively identified group of 445 patients who demonstrated freedom from AF for at least 1 year post-ablation (single procedure in 87.9%) was followed for 66.0 ± 34.0 months. At 40.7 ± 27.0 months postablation, 97 (21.8%) patients experienced at least 1 episode of recurrent AF. The majority of events were symptomatic. There was a steady attrition rate reaching 16.3% at 5 years and 29.8% at 10 years. In 29 patients (29.5%) recurrences were self-limited; the remainder required either medical therapy or repeat ablation. By multivariate analysis, persistent AF (hazard ratio-HR 3.08; $P < 0.0001$) and hypertension (HR 1.08; $P = 0.009$) were independent risk factors for the recurrence of AF; presence of both factors led to recurrence in 37.6% at 5 years and 68.8% at 10 years. The authors concluded that at 10 years after a successful

ablation of AF, most patients continue to demonstrate freedom from AF. Hypertension and prior persistent AF predict recurrences (Steinberg et al, *Heart Rhythm* 2014;11:771-776).

EMBRACE: 30-Day Event – Triggered Recorder Better Detects Atrial Fibrillation in Patients with Cryptogenic Stroke

A total of 572 patients ≥ 55 years of age, without known atrial fibrillation (AF), who had had a cryptogenic ischemic stroke or transient ischemic attack (TIA) within the previous 6 months were randomly assigned to undergo ambulatory ECG monitoring with either a 30-day event-triggered recorder or a conventional 24-hour monitor. AF lasting ≥ 30 s was detected in 16.1% in the event recorder group vs 3.2% in the control group ($P < 0.001$; number needed to screen, 8). AF lasting ≥ 2.5 min was present in 9.9% in the longer monitored group vs 2.5% in the control group ($P < 0.001$). By 90 days, oral anticoagulant therapy had been prescribed for more patients in the event monitor group than in the control group (18.6% vs 11.1%; $P = 0.01$). The authors concluded that among patients with a recent cryptogenic stroke or TIA ≥ 55 years of age, paroxysmal AF was common. Noninvasive ambulatory ECG monitoring for 30 days significantly improved the detection of AF by a factor of > 5 and nearly doubled the rate of anticoagulant treatment (Gladstone et al, *N Engl J Med* 2014; 370:2467-2477).

CRYSTAL AF: Insertable Loop Monitor Better Detects Atrial Fibrillation (AF) in Patients With Cryptogenic Stroke

A total of 441 patients (≥ 40 years old) with cryptogenic stroke were randomized to an insertable cardiac monitor (ICM) or conventional follow-up to assess detection of AF. By 6 months, AF was detected in 8.9% of patients in the ICM group (19 patients) vs 1.4% of patients in the control group (3 patients) (hazard ratio, 6.4; $P < 0.001$). By 12 months, AF was detected in 12.4% of patients in the ICM group (29 patients) vs 2.0% of patients in the control group (4 patients) (hazard ratio, 7.3; $P < 0.001$). The authors concluded that ECG monitoring with an ICM was superior to conventional follow-up for detecting AF after cryptogenic stroke (Sanna et al, *N Engl J Med* 2014; 370:2478-2486).

Pharmacologic Rate- and Rhythm-Control Therapies are Comparable, but Ablation is Better in Patients With Atrial Fibrillation

A total of 200 articles (162 studies) involving 28 836 patients were reviewed comparing rate- and rhythm-control strategies. Strength of evidence (SOE) was moderate supporting comparable efficacy with regard to all-cause mortality (odds ratio-OR, 1.34), cardiac mortality

(OR, 0.96), and stroke (OR, 0.99) in older patients with mild AF symptoms. For rhythm-control therapies in reducing AF recurrence, SOE was high favoring pulmonary vein isolation vs antiarrhythmic drugs (OR, 5.87) and the surgical maze procedure done during other cardiac surgery vs other cardiac surgery alone (OR, 7.94). The authors concluded that pharmacologic rate- and rhythm-control strategies have comparable efficacy in older patients with mild AF symptoms. Pulmonary vein isolation is better than antiarrhythmic medications at reducing recurrences of AF in younger patients with paroxysmal AF and mild structural heart disease (Al-Khatib et al, *Ann Intern Med.* 2014;160:760-773).

Colchicine May Reduce One-Year Postablation AF Recurrence

Among patients with paroxysmal atrial fibrillation (AF) who had a single ablation, those who then received a short course of colchicine were less likely to have AF recurrence and more likely to have higher quality of life a year later, researchers report. The mid-term results from the current study were impressive. Only 6 patients needed to be treated to avoid one AF recurrence. The generic drug colchicine—used for a long time, is approved for gout and familial Mediterranean fever, and has been studied for resistant pericarditis—"seems to be a rather simple and powerful approach to reducing subsequent effects" in people with paroxysmal AF. The study showed that colchicine "is a durable, long-lasting, preventive measure associated with isolated pulmonary vein ablation". What's really incredible is that it's a really cheap addition to a very expensive procedure. According to current consensus, the first 3 months after ablation is considered a "blanking" period—that is, any AF or atrial flutter during this time is considered "early recurrence" and is not considered as part of "AF recurrence." The researchers hypothesized that colchicine might help reduce inflammation after ablation and thus decrease AF recurrence. In fact, an earlier study did demonstrate "proof of principle". There was a significant reduction in the incidence of early AF recurrence and smaller increases in the proinflammatory biomarkers C-reactive protein (CRP) and interleukin-6 (IL-6) in patients who had received colchicine compared with those who received placebo after ablation for AF. The primary outcome in the current study was efficacy at 12 months after the blanking period. The secondary outcome was change in scores for physical and psychological health in the World Health Organization Quality of Life scale at 3 and 12 months compared with baseline. The researchers analyzed data from 206 patients with paroxysmal AF who were seen in 3 centers in Europe and randomized to undergo pulmonary vein isolation followed by 0.5-mg

colchicine bid for 3 months or placebo. The patients were younger than 80 (with a mean age of 62.2), and 70% were men. They had no severe liver or kidney disease, since about 80% of the drug is metabolized in the liver and about 20% is excreted in the urine. Each patient had an average of 13.8 Holter recordings. After a median of 15 months, 32 of 103 patients (31.1%) in the colchicine group vs 51 of 103 patients (49.5%) in the control group had AF recurrence ($p=0.01$), a 37% reduction in relative risk. These significant differences were seen even when the blanking period was not excluded. Most recurrences occurred within the first 6 months after ablation. CRP and IL-6 levels were strongly associated with subsequent recurrences. Diarrhea and nausea were the most frequently reported adverse events. Diarrhea was reported in 10 of 103 patients (9.7%) in the treatment group vs 2 of 103 patients (1.9%) in the control group. However, only 5 cases in the colchicine group and one case in the control group lasted more than one week. Nausea was reported by 6 patients taking colchicine (5.8%) vs 3 patients taking placebo (2.9%). Physical- and psychological-health quality-of-life scores increased in both groups, but the improvement was greater in the patients who had received colchicine. On the whole, colchicine has a potent anti-inflammatory effect, and, even more important, it is probably the only medication with anti-inflammatory action that can be used safely for a relatively long period of time in patients with cardiovascular disease, given the well-known and feared cardiovascular adverse effects of other anti-inflammatory classes, including corticosteroids and nonsteroidal anti-inflammatory drugs. Before this use of colchicine becomes part of clinical practice, funding is needed to conduct further studies to determine the optimal dose and length of treatment and to conduct a large-scale clinical trial that could lead to regulatory approval (Deftereos et al, *Heart Rhythm* 2014;11:620-628).

Athlete-Specific ECG Criteria Proposed for Sports Screening

The current study, presented at the Heart Rhythm Society-HRS 2014 Scientific Sessions, suggests that the history and physical may not be that good for picking up abnormalities that could put these athletes at risk of sudden death. We need to be looking at further screening methods such as an ECG to determine what best way to prevent sudden death in these young people. In the current study, 4812 teenaged athletes were screened at US high schools from October 2010 through June 2013. All completed a questionnaire with personal and family history screening questions like those recommended by the AHA and underwent 12-lead ECG, with additional echocardiography for anyone with an abnormality in the

other tests. The ESC criteria for interpreting ECGs of athletes were used for the first two-thirds of the cohort and the Seattle criteria for the latter one-third. Women made up 46% of the group; 65% were white, 10% Asian, and 6% were African American. The screening process identified "significant abnormalities requiring further evaluation" in 23 of the subjects, or about 0.5% of the cohort; they included 9 cases of Wolff-Parkinson-White syndrome, 4 anomalous coronary arteries, 3 dilated aortic roots or aneurysms, 3 long-QT syndromes, 2 of hypertrophic cardiomyopathies, one with ventricular arrhythmia, and one with short-QT syndrome. An abnormal history or physical pointed to the diagnoses in 61% of cases and an abnormal ECG in 70%. The rate of false-positive diagnoses was 50% for the initial history and physical (which improved to 32% after physician review), 4% for the ECG, and 35% for the postreview history and physical considered with the ECG. Abnormalities pointing to possibly increased sudden-death risk in the Seattle criteria include:

- T-wave inversion (defined as >1 mm in depth in ≥ 2 leads V2-V6, II and aVF, or I and aVL).
- Long QT interval (corrected QT-QTc >470 ms in men, >480 ms in women).
- Short QT interval (QTc <320 ms).
- ST-segment depression (>0.5 mm in ≥ 2 leads).
- Pathologic Q waves (>3 mm in depth or >40 ms in duration in ≥ 2 leads, excluding III and aVR).
- Left atrial enlargement (P-wave duration >120 ms in leads I or II with negative portion of the P wave >1 mm in depth and >40 ms in duration in lead V1).
- Right ventricular hypertrophy ($R-V_1 + S-V_5 >10.5$ mm plus right axis deviation $>120^\circ$).
- Complete LBBB or any QRS >140 ms.
- Mobitz type II 2° AV block or complete heart block.
- Ventricular preexcitation (PR interval <120 ms with a delta wave and QRS >120 ms).
- Profound sinus bradycardia defined as <30 beats per minute or sinus pauses >3 s.
- Atrial tachyarrhythmias (supraventricular tachycardia or atrial fibrillation or flutter).
- PVCs (>2 per 10-sec tracing), ventricular arrhythmias (couplets, nonsustained VT).
- Type 1 Brugada pattern.

(HRS 2014 Scientific Sessions; Abstract PO01-194).

COMPARE Trial: Performing Catheter Ablation for AF Without Warfarin Discontinuation Reduces Occurrence of Stroke and/or Minor Bleeding When Compared to Bridging With Heparin

The "COMPARE" Randomized Trial is the first randomized study showing that performing catheter

ablation of AF without warfarin discontinuation reduces the occurrence of peri-procedural stroke and minor bleeding complications when compared to bridging with low molecular weight heparin (LMWH). “COMPARE” was a prospective, randomized, parallel-group, multicenter study assessing the role of continuous warfarin therapy in preventing periprocedural thromboembolic (TE) events after radiofrequency catheter ablation. Inclusion criteria were: age 18 or above, INR in the range of 2.0-3.0 in the last 3-4 weeks prior to ablation and CHADS2 score >1 or CHADS score=1. A total of 1584 patients were randomly assigned (1:1 ratio) to anticoagulation strategy of either discontinued warfarin (group I) or continuous warfarin (group II). Periprocedural symptomatic TE events occurred in 39 (4.9%) patients in group I [29(3.7%) stroke and 10 (1.3%) TIA] and only in 2 (0.25%) patients (both stroke) in group II ($p < 0.001$). Compared to group I, patients in group II had significantly lower risk for periprocedural TE; the unadjusted relative risk was 0.051, with a relative risk reduction of 95% in favor of the uninterrupted warfarin. Eighty-five percent of all the TE events (35/41) occurred in the long standing-persistent (LSP) AF population. In the off warfarin population (group I), one TIA and one stroke were reported in PAF, 2 TIAs and 2 strokes in persistent AF patients, while 7 TIAs and 26 strokes were reported in LSP AF patients. In group II patients, both events occurred in LSP AF patients. Both patients had subtherapeutic INR the day of the procedure (1.6 and 1.7 respectively). Both patients had a TEE that did not show thrombus and did not receive LMWH. Significant reduction in TE risk in the “on” warfarin group, as compared to the “off” warfarin, was consistently observed across 6 major subgroups- female gender, age >75 years, diabetes, coronary artery disease, and prior history of cerebrovascular accident (CVA) and or /TIA, and CHADS2 score. No statistical differences between groups were found for major bleeding. Although not statistically different, group II (on warfarin) had a relative risk reduction for major bleedings of 50% when compared to group I (off warfarin). Of great clinical interest is the fact that in case of tamponade no major differences in the patients’ management were found between groups with the exception of more fluid aspirated and more protamine utilized in group II. In group II, besides protamine to reverse the effect of i.v. heparin, fresh frozen plasma was necessary to reverse the effect of warfarin. Minor bleeding complications were significantly higher in the off warfarin group. Of note is the fact that all procedures were performed under intracardiac echo (ICE) guidance. The use of ICE could help reducing bleeding complication, in addition to facilitate transseptal access, confirm ablation

catheter contact and improve anatomical orientation (Di Biase et al, *Circulation* 2014;129:2638-2644).

Predicting Coronary Plaque Rupture

The “napkin-ring sign”, a feature seen on coronary computed-tomography angiography (CCTA) can help identify coronary plaques at risk of rupture. In *Nature Reviews Cardiology*, Dr Pál Maurovich-Horvat and colleagues argue that there is a role for CCTA that goes beyond ruling out coronary stenosis. Some of the CCTA plaque features are more important than others to identify high-risk plaques and to predict adverse cardiovascular events. Low CT attenuation, positive remodeling, and the napkin-ring sign indicate a 5- to 20-fold increase in the risk of suffering acute coronary syndrome (ACS). To further improve the prognostic value of CCTA to identify high-risk plaques, however, it is necessary to combine different quantitative and qualitative plaque characteristics—for example, plaque volume and napkin-ring sign—with functional information, such as fractional flow reserve (FFR) or endothelial shear stress, or preventive therapies based on patient-specific information. Large plaque burden with high-risk features might warrant intensified statin therapy. Combining functional and morphological features could lead to a vulnerable plaque score that could help predict the likelihood of plaque rupture and sudden luminal thrombosis (Maurovich-Horvat et al, *Nat Rev Cardiol* 2014; DOI:10.1038/nrcardio.2014.60. Epub 2014 Apr 22).

Prophylactic Implantable Cardioverter-Defibrillators (ICDs) Confer Improved Survival in Patients With Left Ventricular Ejection Fraction (LVEF) Between 30% and 35%

A retrospective cohort study of Medicare beneficiaries in the National Cardiovascular Data Registry ICD registry compared 3120 patients with an LVEF between 30% and 35% (816 in matched cohorts) who received an ICD during a heart failure hospitalization with similar patients with no ICD. The analysis was repeated for 4578 patients (2176 in matched cohorts) with an LVEF <30%. There were no significant differences in the baseline characteristics of the matched groups ($n = 408$ for both groups). Among patients with an LVEF between 30% and 35%, there were 248 deaths in the ICD Registry group, within a median follow-up of 4.4 years and 249 deaths in the control group, within a median follow-up of 2.9 years. The risk of all-cause mortality in patients with an LVEF between 30% and 35% and an ICD was significantly lower than that in matched patients without an ICD (3-year mortality rates: 51.4% vs 55.0%; hazard ratio-HR, 0.83; $P = 0.04$). Presence of an ICD also was associated with better survival in patients with an LVEF <30% (3-year mortality rates: 45% vs

57.6%; HR, 0.72; $P < 0.001$) ($P = \text{NS}$ for interaction). The authors concluded that among Medicare beneficiaries hospitalized for heart failure and with an LVEF between 30% and 35% and $< 30\%$, survival at 3 years was better in patients who received a prophylactic ICD than in comparable patients with no ICD (Al-Khatib et al, *JAMA*. 2014;311:2209-2215).

CRT-D Better than ICD in Older than 65 Years Old Patients

7090 propensity-matched patients older than 65 years with reduced left ventricular ejection fraction (< 0.35) and prolonged QRS duration on electrocardiography (≥ 120 ms) were treated with CRT-D or ICD implantation. At the 3-year follow-up period, compared with ICD therapy, CRT-D was associated with lower risks for mortality (cumulative incidence, 25.7% vs 29.8%; adjusted hazard ratio-HR, 0.82), all-cause readmission (cumulative incidence, 68.6% vs 72.8%; adjusted HR, 0.86), cardiovascular readmission (cumulative incidence, 45.0% vs 52.4%; adjusted HR, 0.80), and heart failure readmission (cumulative incidence, 24.3% vs 29.4%, HR 0.78). It was also associated with greater risks for device-related infection (cumulative incidence, 1.9% vs 1.0%). The lower risks for heart failure readmission associated with CRT-D compared with ICD therapy were most pronounced among patients with left bundle branch block or a QRS duration at least 150 ms and in women. In older patients with reduced left ventricular ejection fraction and prolonged QRS duration, CRT-D was associated with lower risks for death and readmission than ICD therapy alone (Masoudi et al, *Ann Intern Med* 2014;160:603-611).

Safe and Effective Transcatheter Aortic Valve Implantation (TAVI) Using a Self-Expanding Bioprosthesis in Patients With Severe Aortic Stenosis at Very High Risk for Surgery

A prospective, multicenter, nonrandomized study evaluated the safety and efficacy of self-expanding TAVI in patients ($n=489$) with symptomatic severe aortic stenosis with prohibitive risks for surgery at 41 US sites. All-cause mortality or major stroke occurred in 26% vs expected 43% at 12 months ($p < 0.0001$). Individual 30-day and 1-year events included all-cause mortality (8.4% and 24.3%, respectively) and major stroke (2.3% and 4.3%, respectively). Procedural events at 30 days: life-threatening bleeding (12.7%), major vascular complications (8.2%), and need for permanent pacemaker placement (21.6%). Moderate or severe paravalvular aortic regurgitation was lower 12 months after self-expanding TAVI (4.2%) than at discharge (10.7%; $p = 0.004$). The authors concluded that TAVI with a self-expanding bioprosthesis was safe and effective in patients with

symptomatic severe aortic stenosis with a prohibitive risk for surgery (Popma et al, *J Am Coll Cardiol* 2014;63:1972-1981).

Transcatheter Aortic-Valve Replacement with a Self-Expanding Prosthesis Superior to Surgery in Patients at Increased Surgical Risk

This study compared transcatheter aortic-valve implantation (TAVI), using a self-expanding aortic-valve bioprosthesis, with surgical aortic-valve replacement in 795 patients with severe aortic stenosis and an increased risk of death during surgery. In the as-treated analysis, the rate of death from any cause at 1 year was significantly lower in the TAVI group than in the surgical group (14.2% vs 19.1%) ($P < 0.001$ for noninferiority; $P = 0.04$ for superiority). The results were similar in the intention-to-treat analysis. The authors concluded that in patients with severe aortic stenosis who are at increased surgical risk, TAVI compared to surgery was associated with a significantly higher rate of survival at 1 year (Adams et al, *N Engl J Med* 2014; 370:1790-1798).

CHOICE Trial: Balloon-Expandable Superior to Self-Expandable Valves in Patients Undergoing TAVI

A total of 241 patients undergoing transcatheter aortic valve implantation (TAVI) were randomly assigned to receive a balloon-expandable valve (Edwards Sapien XT) ($n=121$) or a self-expandable valve (Medtronic CoreValve) ($n=120$). Device success was 95.9% in the balloon-expandable valve group and 77.5% in the self-expandable valve group (relative risk -RR, 1.24, $P < .001$), due to a significantly lower frequency of residual more-than-mild aortic regurgitation (4.1% vs 18.3%; RR, 0.23; $P < .001$) and a less frequent need for implanting more than 1 valve (0.8% vs 5.8%, $P=0.03$) in the balloon-expandable valve group. Cardiovascular mortality at 30 days was comparable (4.1% vs 4.3%, RR, 0.97; $P = \text{NS}$), as well as bleeding and vascular complications. Need for a permanent pacemaker was less frequent in the balloon-expandable valve group (17.3% vs 37.6%, $P = 0.001$). The authors concluded that among patients with high-risk aortic stenosis undergoing TAVI, the use of a balloon-expandable valve resulted in a greater rate of device success than use of a self-expandable valve (Abdel-Wahab et al, *JAMA* 2014;311:1503-1514).

ARISTOTLE Trial: Major Bleeding in Patients With Atrial Fibrillation is Less in Patients Receiving Apixaban than Warfarin

The on-treatment safety population in the ARISTOTLE trial included 18,140 patients. The rate of major hemorrhage among patients in the apixaban group was 2.13% per year compared with 3.09% in the warfarin group (hazard ratio -HR 0.69; $p < 0.001$). The most

frequent sites of major hemorrhage were gastrointestinal (31%; n= 248), intracranial (22%; n= 171), and soft tissue (10%; n= 75). Compared with warfarin, apixaban-related major extracranial bleeding led to reduced hospitalization, medical or surgical intervention, transfusion, or change in antithrombotic therapy. Fatal major hemorrhage within 30 days occurred half as often with apixaban than warfarin (HR 0.50; p< 0.001). Older age, prior hemorrhage, prior stroke or transient ischemic attack, diabetes, lower creatinine clearance, decreased hematocrit, aspirin therapy, and nonsteroidal anti-inflammatory drugs were independently associated with an increased risk. The authors conclude that apixaban, compared with warfarin, was associated with fewer intracranial hemorrhages, less adverse consequences following extracranial hemorrhage, and a 50% reduction in fatal hemorrhage at 30 days (Hylek et al, *J Am Coll Cardiol* 2014;63:2141-2147).

MENDEL-2: Anti-PCSK9 Inhibitor Most Effective for Hypercholesterolemia

This study comprised 614 patients (18-80 years old) with fasting low-density lipoprotein cholesterol (LDL-C) >100 and <190 mg/dl and Framingham risk scores >10%, randomized (1:1:1:1:2:2) to oral placebo and subcutaneous (SC) placebo biweekly; oral placebo and SC placebo monthly; ezetimibe and SC placebo biweekly; ezetimibe and SC placebo monthly; oral placebo and evolocumab 140 mg biweekly; or oral placebo and evolocumab 420 mg monthly. Evolocumab, a human monoclonal antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9), significantly reduced LDL-C from baseline, on average, by 55% to 57% more than placebo and 38% to 40% more than ezetimibe (p < 0.001 for all). Therapy-related adverse events (AEs), muscle-related AEs, and laboratory abnormalities were comparable across treatment groups. The authors concluded that evolocumab significantly reduced LDL-C compared with placebo or ezetimibe and was well tolerated in patients with hypercholesterolemia (Koren et al, *J Am Coll Cardiol* 2014;63:2531-2540).

GAUSS-2: Evolocumab is Promising for High-Risk Statin-Intolerant Hypercholesterolemic Patients

GAUSS-2 (Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects) trial was a 12-week, double-blind study comprising 307 patients, aged 62±10 years with LDL-C 193±59 mg/dl, (2:2:1:1) randomized to evolocumab 140 mg every 2 weeks (Q2W) or evolocumab 420 mg once monthly (QM) both with daily oral placebo or subcutaneous placebo Q2W or QM both with daily oral ezetimibe 10 mg. Evolocumab reduced LDL-C from baseline by 53-56%, differences of 37-39% vs ezetimibe (p <0.001). Muscle adverse events occurred

in 12% with evolocumab vs 23% with ezetimibe. Treatment-related adverse events and laboratory abnormalities were comparable among treatment groups. The authors concluded that evolocumab is a promising therapy for high-risk patients with high cholesterol who are statin intolerant (Stroes et al, *J Am Coll Cardiol* 2014;63:2541-2548).

DESCARTES: A Successful 52-Week Placebo-Controlled Trial of Evolocumab in Hyperlipidemia

A total of 901 patients with hyperlipidemia were started on diet alone or diet plus atorvastatin at a dose of 10 mg daily, atorvastatin at 80 mg daily, or atorvastatin at 80 mg daily plus ezetimibe at 10 mg daily, for a run-in period of 4 to 12 weeks. Patients with an LDL cholesterol (LDL-C) level of ≥75 mg/dl were then randomly assigned in a 2:1 ratio to receive either evolocumab (420 mg) or placebo every 4 weeks. Evolocumab reduced LDL-C by 57.0±2.1% (P<0.001). Evolocumab treatment also significantly reduced levels of apolipoprotein B, non-high-density lipoprotein cholesterol, lipoprotein(a), and triglycerides. The most common adverse events were nasopharyngitis, upper respiratory tract infection, influenza, and back pain. The authors concluded that at 52 weeks, evolocumab added to diet alone, to low-dose atorvastatin, or to high-dose atorvastatin with or without ezetimibe significantly reduced LDL-C levels in patients with a range of cardiovascular risks (Blom et al, *N Engl J Med* 2014; 370:1809-1819).

LEADLESS Trial: Implantation of Permanent Leadless Cardiac Pacemakers is Feasible and Safe

This study tested the safety and performance of a novel, self-contained leadless cardiac pacemaker in 33 patients (aged 77±8 years), mostly (67%) for complete AV block in the setting of permanent atrial fibrillation (AF). The implant success rate was 97% (n=32); 5 patients (15%) required >1 devices. One patient died after developing cardiac tamponade and stroke. The overall complication-free rate was 94% (31/33). After 3 months of follow-up, the measures of pacing performance (sensing, impedance, and pacing threshold) either improved or remained stable. The authors concluded that a single-chamber leadless cardiac pacemaker is safe and feasible, representing a paradigm shift in cardiac pacing (Reddy et al, *Circulation* 2014; 129: 1466-1471).

French Registry (FAST-MI Trial): In a Real-World Setting, in Patients With STEMI, a Pharmacoinvasive strategy (Thrombolysis With Subsequent PCI) is a Valid Alternative to Primary PCI, with Equivalent 5-Year Survival

Although primary percutaneous coronary intervention (pPCI) is the preferred reperfusion method for ST-

segment-elevation myocardial infarction (STEMI), it remains difficult to implement. Five-year mortality was assessed in 1492 patients with STEMI of whom 447 (30%) received fibrinolysis (66% prehospital; 97% with subsequent angiography, 84% with subsequent PCI), 583 (39%) had pPCI, and 462 (31%) received no reperfusion. Five-year survival was 88% for fibrinolysis, 83% for pPCI, and 59% for no reperfusion, with hazard ratios of 0.73 for fibrinolysis vs pPCI, 0.57 for prehospital fibrinolysis vs pPCI, and 0.63 for fibrinolysis vs pPCI. In propensity score-matched populations, survival rates were not significantly different for fibrinolysis and pPCI, both in the whole population (88% lysis, 85% pPCI) and in the population seen early (87% fibrinolysis, 85% pPCI beyond 90 minutes from call). The authors concluded that in a real-world setting, on a nationwide scale, a pharmaco-invasive strategy is a valid alternative to pPCI, with an equivalent 5-year survival to that of thrombolysis (Danchin et al, *Circulation* 2014;129:1629-1636).

SORT OUT III study: Superiority of Sirolimus-Eluting Stent at 1 year over Zotarolimus-Eluting Stent is Lost at 5 Years

A total of 2332 patients were randomly assigned to the zotarolimus-eluting Endeavor Sprint stent (ZES) (Medtronic, Santa Rosa, CA, USA) (n=1162) or the sirolimus-eluting Cypher Select Plus stent (SES) (Cordis, Johnson & Johnson, Warren, NJ, USA) (n=1170). At 5-year follow-up, rates of major adverse cardiac events were similar in patients treated with both types of stents (ZES 17% vs SES 15.6%; odds ratio-OR 1.10; p=NS). This finding contrasted with results for rates of major adverse cardiac events at 1-year follow up (zotarolimus 8% vs sirolimus 3.9%; OR 2.13; p<0.0001) compared with those at follow-up between 1 and 5 years (9% vs 11.6%; OR 0.78; p=0.071). At 1-year follow-up, definite stent thrombosis was more frequent after implantation of the ZES (1.1%) than the SES (0.3%; OR 3.34; p=0.036), whereas the opposite finding was recorded for between 1 and 5 years' follow-up (ZES 0.1% vs SES 1.8%, OR 0.05; p=0.003). 30% target lesion revascularisations in the ZES group occurred between 1 and 5 years' follow-up, whereas 77% of those in the SES group occurred during this follow-up period. The authors concluded that the superiority of SES compared with ZES at 1-year follow-up was lost after 5 years (Maeng et al, *Lancet* 2014;383(9934):2047-2056).

PEITHO: Fibrinolysis Prevented Hemodynamic Compromise but Increased Risk of Major Hemorrhage and Stroke in Intermediate Risk Patients for Pulmonary Embolism

Tenecteplase plus heparin was compared with placebo plus heparin in normotensive patients with intermediate-

risk pulmonary embolism. Of 1006 patients who underwent randomization, 1005 were included in the intention-to-treat analysis. Death or hemodynamic compromise occurred in 13 of 506 patients (2.6%) in the tenecteplase group and 28 of 499 (5.6%) in the placebo group (odds ratio, 0.44; P=0.02). Between randomization and day 7, a total of 6 patients (1.2%) in the tenecteplase group and 9 (1.8%) in the placebo group died (P=0.42). Extracranial bleeding occurred in 32 patients (6.3%) in the tenecteplase group and 6 patients (1.2%) in the placebo group (P<0.001). Stroke occurred in 12 patients (2.4%) in the tenecteplase group and was hemorrhagic in 10 patients; 1 patient (0.2%) in the placebo group had a stroke, which was hemorrhagic (P=0.003). At 1 month, death rate was 2.4% in the tenecteplase group and 3.2% in the placebo group (P=0.42). The authors concluded that in patients with intermediate-risk pulmonary embolism, fibrinolysis prevented hemodynamic decompensation but increased risk of major hemorrhage and stroke (Meyer et al, *N Engl J Med* 2014; 370:1402-1411).

RELAX-AHF Trial: Serelaxin is Effective in Acute Heart Failure Patients with Preserved Left Ventricular Ejection Fraction

RELAX-AHF randomized 1161 acute heart failure (AHF) patients to 48-h serelaxin (30 mg/kg/day) or placebo within 16 h from arrival; drug effects were compared between preserved ($\geq 50\%$) (HFpEF) and reduced ($< 50\%$, HFrEF) ejection fraction heart failure. HFpEF was present in 26% of patients. Serelaxin induced a similar dyspnea relief in HFpEF vs HFrEF patients. No differences were encountered in the effect of serelaxin on short- or long-term outcome between HFpEF and HFrEF patients regarding cardiovascular death or hospitalization for heart/renal failure at 2 months, cardiovascular death and all-cause death at 3 months. Similar safety and changes in biomarkers were found in both groups. The authors concluded that in AHF patients with HFpEF compared with those with HFrEF, serelaxin was well tolerated and effective in relieving dyspnea and had a similar effect on short- and long-term outcome, including survival benefit (Filipatos et al, *Eur Heart J* 2014; 35: 1041-1050).

TOPCAT: Spironolactone for Heart Failure with Preserved Ejection Fraction

A total of 3445 patients with symptomatic heart failure and a left ventricular ejection fraction of $\geq 45\%$ were assigned to receive either spironolactone (15 to 45 mg daily) or placebo. At a mean follow-up of 3.3 years, the primary outcome (composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure) occurred in 18.6% of patients in the spironolactone group and 20.4% 351 of patients in

the placebo group (hazard ratio, 0.89; P=0.14). Hospitalization for heart failure had a significantly lower incidence in the spironolactone group (12% vs 14%; hazard ratio, 0.83; P=0.04). Neither total deaths nor hospitalizations for any reason were significantly reduced by spironolactone. Treatment with spironolactone was associated with increased serum creatinine levels and a doubling of the rate of hyperkalemia (18.7%, vs 9.1%) but reduced hypokalemia. With frequent monitoring, there were no significant differences in the incidence of serious adverse events, a serum creatinine level of 3 mg/dl (265 μmol/L) or higher, or dialysis. The authors concluded that in patients with heart failure and a preserved ejection fraction, treatment with spironolactone did not significantly reduce the incidence of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure (Pitt et al, *N Engl J Med* 2014; 370:1383-1392).

Effective Combination Therapy With Statin and Another Agent vs Intensified Statin Monotherapy for Patients Intolerant of or Unresponsive to Statins

According to a review of 36 trials, for patients intolerant of or unresponsive to statins, low-intensity statin plus bile acid sequestrant decreased LDL cholesterol level 0-14% more than mid-intensity monotherapy among high-risk hyperlipidemic patients. Mid-intensity statin plus ezetimibe decreased LDL cholesterol level 5-15% and 3-21% more than high-intensity monotherapy among patients with atherosclerotic heart disease and diabetes, respectively. Evidence was insufficient to evaluate LDL cholesterol for fibrates, niacin, and ω-3 fatty acids, or to assess long-term clinical outcomes, adherence, and harms for all regimens. The authors concluded that clinicians could consider using lower-intensity statin combined with bile acid sequestrant or ezetimibe among high-risk patients intolerant of or unresponsive to statins; however, this strategy should be used with caution given the lack of evidence on long-term clinical benefits or harms (Gudzone et al, *Ann Intern Med* 2014;160:468-476).

CORP-2: Colchicine is Effective and Safe for Treatment of Multiple Recurrences of Pericarditis

Adult patients with multiple recurrences of pericarditis (≥2) were randomly assigned (1:1) to placebo (n=120) or colchicine (n=120) (0.5 mg bid for 6 months for those weighing >70 kg or 0.5 mg qd for weight ≤70 kg) in addition to conventional anti-inflammatory treatment with aspirin, ibuprofen, or indomethacin. The proportion of patients who had recurrent pericarditis was 21.6% in the colchicine group and 42.5% in the placebo group (relative risk 0.49; p=0.0009; number needed to treat 5). Adverse

effects and discontinuation of study drug occurred in similar percentages in each group. The most common adverse events were gastrointestinal intolerance (9 patients in each group) and hepatotoxicity (3 vs 1). No serious adverse events were reported. The authors concluded that colchicine added to conventional anti-inflammatory treatment significantly reduced the rate of subsequent recurrences of pericarditis in patients with multiple recurrences (Imazio et al, *Lancet* 2014;383(9936):2232 – 2237).

Important Review and Other Articles

Obesity & cardiovascular disease (Lavie et al, *J Am Coll Cardiol* 2014;63:1345-1354), Subcutaneous defibrillator (Aziz et al, *J Am Coll Cardiol* 2014;63:1473-1479), Coronary artery calcification (Madhavan et al, *J Am Coll Cardiol* 2014;63:1703-1714), Lone AF (Wyse et al, *J Am Coll Cardiol* 2014;63:1715-1723), Severe hypercholesterolemia (Sniderman et al, *J Am Coll Cardiol* 2014;63:1935-1947), Percutaneous mitral valve repair (Feldman & Young, *J Am Coll Cardiol* 2014;63:2057-2068), Micro-RNAs in cardiovascular disease (Condorelli et al, *J Am Coll Cardiol* 2014;63:2177-2187), 2014 AHA/ACC Guideline for the management of patients with valvular heart disease (Nishimura et al, *J Am Coll Cardiol* 2014;63:2438-2488 63 & e57-e185; *Circulation* 2014;129:2440-2492), In-stent restenosis (Alfonso et al, *J Am Coll Cardiol* 2014;63:2659-2673), Mitral regurgitation & TAVI (Nombela-Franco et al, *J Am Coll Cardiol* 2014;63:2643-2658), 2013 ACC/AHA Guidelines for treating hypercholesterolemia (Stone et al, *J Am Coll Cardiol* 2014; 63:2889-934), Bicuspid aortic valve (Michelena et al, *Circulation* 2014;129:2691-2704), heart failure with preserved ejection fraction (Komajda & Lam, *Eur Heart J* 2014; 35: 1022-1032), Complications after cardiac implantable electronic device implantations Kirkfeldt et al, *Eur Heart J* 2014; 35: 1186-1194), Risk of proarrhythmia by psychotropic medications (Fanoe et al, *Eur Heart J* 2014; 35: 1306-1315), Depression and cardiovascular disease (Hare et al, *Eur Heart J* 2014;35:1365-1372), HIV infection and cardiovascular disease (Hemkens & Bucher, *Eur Heart J* 2014;35: 1373-1381), Aortic dilatation in bicuspid aortic valve (Verma & Siu, *N Engl J Med* 2014; 370:1920-1929), Cardiovascular remodelling (Heusch et al, *Lancet* 2014; 383 (9932): 1933 – 1943).