

CARDIOLOGY CORNER

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DAPT Study: Continuation of Dual Antiplatelet Therapy After PCI in Patients With and Without Acute Myocardial Infarction (MI) Beyond 1 Year Reduced Ischemic Events, but Increased Bleeding Compared With Treatment With Aspirin Alone

Among 11,648 randomized patients (9,961 treated with drug-eluting stents, 1,687 with bare-metal stents), 30.7% presenting with MI, between 12 and 30 months, continued thienopyridine reduced stent thrombosis compared with placebo in patients with and without MI at presentation (MI group, 0.5% vs 1.9%, $p < 0.001$; no MI group, 0.4% vs 1.1%, $p < 0.001$). The reduction in major adverse cardiovascular and cerebrovascular events (MACCE) for continued thienopyridine was greater for patients with MI (3.9% vs 6.8%; $p < 0.001$ for MI; 4.4% vs 5.3%; $p = 0.08$ for no MI). In both groups, continued thienopyridine reduced MI (2.2% vs 5.2%, $p < 0.001$ for MI; 2.1% vs 3.5%, $p < 0.001$ for no MI) but increased bleeding (1.9% vs 0.8%, $p = 0.005$ for MI; 2.6% vs 1.7%, $p = 0.007$ for no MI). The authors concluded that extended dual antiplatelet therapy reduced the risk of stent thrombosis and MI in patients with and without MI, but increased bleeding (Yeh RW et al, *J Am Coll Cardiol* 2015;65:2211-2221).

Metaanalysis: Dual Antiplatelet Therapy (DAPT) is Associated With Protection Against Stent Thrombosis but Increases Risk of Bleeding in Patients With Drug Eluting Stents (DES) / Benefit of Extended DAPT for Patients With First-Generation DES, but not for Second-Generation DES

Metaanalysis of 10 randomized controlled trials (N=32,135) indicated that compared to longer duration DAPT (L-DAPT;

mean exposure time 20.3 months for second-generation DES and 28 months for first-generation DES), shorter duration DAPT (S-DAPT; mean exposure time 7.8 months for second-generation DES and 10.9 months for first-generation DES) had an overall higher rate of stent thrombosis (odds ratio - OR: 1.71; $p = 0.001$). The effect of S-DAPT on stent thrombosis was attenuated with the use of second-generation DES (OR: 1.54) compared with first-generation DES (OR: 3.94; p for interaction=0.008). S-DAPT had an overall significantly lower risk of bleeding (OR: 0.63; $p < 0.001$). Finally, a numerically lower all-cause mortality rate was observed with S-DAPT (OR: 0.87; $p = 0.073$). The authors concluded that S-DAPT had overall lower rates of bleeding, yet higher rates of stent thrombosis compared with L-DAPT; the latter effect was significantly attenuated with the use of second-generation DES. All-cause mortality was higher (not statistically) with L-DAPT (Giustino G et al, *J Am Coll Cardiol* 2015;65:1298-1310).

ISAR-TRIPLE Trial: Antithrombotic Therapy in Patients with Indications for Oral Anticoagulation Undergoing Implantation of DES is Problematic / A Shorter (6-week) Course of Triple Therapy was not Superior to a Longer (6-Month) Course for Major Bleeding and Ischemic Events

A total of 614 patients receiving concomitant aspirin and oral anticoagulant (OAC) were randomized to either 6-week (n=307) or 6-month clopidogrel therapy (n=307). The primary endpoint (composite of death, myocardial infarction - MI, stent thrombosis, stroke, or TIMI major bleeding at 9 months) occurred in 30 patients (9.8%) in the 6-week group compared with 27 patients (8.8%) in the 6-month group (hazard ratio - HR: 1.14; $p = 0.63$). There were no significant differences for the secondary combined ischemic endpoint of cardiac death, MI, stent thrombosis, and ischemic stroke or the secondary bleeding endpoint of TIMI major bleeding. The authors concluded that 6 weeks of triple therapy was not superior to 6 months with respect to net clinical outcomes (Fiedler KA et al, *J Am Coll Cardiol* 2015; 1819-1629).

SYMPPLICITY-3: 6-Month Negative Results of Renal Denervation Remain Negative at 12 Months

The SYMPPLICITY HTN-3 trial confirmed safety but not efficacy of renal denervation for treatment-resistant hypertension at 6 months. The 12-month results, available for 319 of 361 denervation subjects and 48 of 101 non-crossover subjects, showed that in denervation subjects, the office systolic BP (SBP) change was greater than that observed at 6 months (-15.5 ± 24.1 mmHg vs -18.9 ± 25.4 mmHg, respectively; $p=0.025$), but the 24-h SBP change was not significantly different at 12 months ($p=0.229$). The non-crossover group office SBP decreased by -32.9 ± 28.1 mmHg at 6 months, but this response was reduced to -21.4 ± 19.9 mmHg ($p=0.01$) at 12 months, increasing to 11.5 ± 29.8 mmHg. The authors concluded that there was no further reduction in office or ambulatory blood pressure after 1-year follow-up, while there was loss of blood pressure reduction in the non-crossover group, probably reflecting decreased medication adherence (Bakris G et al, *J Am Coll Cardiol* 2015;65:1314-1321).

Low-Risk AF Patients, i.e., CHA₂DS₂-VASc=0 (Male), =1 (Female) Have a Low Risk for Stroke, Cerebral and Major Bleeding / With 1 Additional Stroke Risk Factor, i.e., CHA₂DS₂-VASc=1 (Male), =2 (Female), there is a Significant Increase in Event Rates, Including Mortality, if Non-anticoagulated

According with a Danish study of 39,400 patients discharged with diagnosis of nonvalvular atrial fibrillation (AF) with 0 or 1 CHA₂DS₂-VASc risk factor, 23,572 were not treated, 5,353 were on aspirin, and 10,475 received warfarin. Stroke event rates for untreated low-risk patients (CHA₂DS₂-VASc=0 [male], 1 [female]) were 0.49 per 100 person-years at 1 year and 0.47 per 100 person-years at full follow-up. Bleeding event rates among untreated low-risk patients were 1.08 per 100 person-years at 1 year and 0.97 at full follow-up. The presence of 1 additional stroke risk factor, i.e. CHA₂DS₂-VASc=1 (male), =2 (female) among untreated patients increased the stroke rate at 1 year to 1.55 per 100 person-years, representing a 3-fold increase. At 1-year, bleeding increased 2.35-fold, and death increased 3.12-fold. The authors concluded that low-risk patients, i.e. CHA₂DS₂-VASc=0 (male), 1 (female) have a truly low risk for stroke and bleeding. With 1 additional stroke risk factor, i.e. CHA₂DS₂-VASc=1 (male), =2 (female), there was a significant increase in event rates (particularly mortality) if non-anticoagulated (Lip G et al, *J Am Coll Cardiol* 2015;65:1385-1394).

EFFORTLESS Trial: The Subcutaneous ICD (S-ICD) Showed High Shock Efficacy for Ventricular Arrhythmias and a Decreasing Incidence of Inappropriate Shocks With Acceptable Complication Rate and Low Mortality Rate Extended at 2 Years

Among 882 patients who received a S-ICD followed for

a mean of 2 years, arrhythmia events ($n=111$) were treated in 59 patients; 100 (90.1%) events were terminated with 1 shock, and 109 events (98.2%) within the 5 available shocks. The estimated 3-year inappropriate shock rate was 13.1%, and all-cause mortality 4.7%, with 26 deaths (2.9%). Device-related complications occurred in 11.1%; there were no electrode failures, and no S-ICD-related endocarditis or bacteremia. Three devices (0.3%) were replaced for right ventricular pacing. The 6-month complication rate decreased by quartile of enrollment (Q1: 8.9%; Q4: 5.5%), and there was a trend toward a reduction in inappropriate shocks (Q1: 6.9% Q4: 4.5%). The authors concluded that the S-ICD demonstrated high efficacy; rates of complications and inappropriate shocks were reduced consistently with strategic programming and as operator experience increased (Burke MC et al, *J Am Coll Cardiol* 2015;65:1605-1615).

Leadless Cardiac Pacemakers Exhibit Stable Electrical Performance Without Device-Related Adverse Events at 1 Year in a Small Cohort of 31 Patients

Follow-up of 31 of 33 patients (aged 76 ± 8 years; 65% male) from the LEADLESS trial who received a leadless VVI pacemaker indicated that between 3 and 12 months of follow-up, there were no pacemaker-related adverse events reported. The pacing performance remained stable, with adequate rate response observed in all (61%) patients in whom it was activated. The authors concluded that the leadless pacemaker demonstrates very stable performance and good safety results at 1 year (Knops RE et al, *J Am Coll Cardiol* 2015; 1497-1504).

LEGACY Study: Sustained Weight Loss Reduces AF Burden and Maintains Sinus Rhythm Probably Related to Favorable Changes in the Cardiometabolic Risk Factor Profile, Inflammatory State, and Cardiac Remodeling

Among 3 groups based on weight loss achieved ($\geq 10\%$, 3-9%, and $< 3\%$) of 355 obese (body mass index ≥ 27 kg/m²) patients with atrial fibrillation (AF), offered weight management, AF burden and symptom severity decreased more in group 1 compared with groups 2 and 3 ($p < 0.001$ for all). Arrhythmia-free survival regardless of rhythm or rate control strategies was also greatest in group 1 ($p < 0.001$ for both). Weight loss and weight fluctuation were independent predictors of outcomes ($p < 0.001$). Weight loss $\geq 10\%$ resulted in a 6-fold ($p < 0.001$) greater probability of arrhythmia-free survival. Weight fluctuation $> 5\%$ partially offset this benefit, with a 2-fold ($p=0.02$) increased risk of arrhythmia recurrence. The authors concluded that long-term sustained weight loss is associated with significant reduction of AF burden and maintenance of sinus rhythm (Pathak RK et al, *J Am Coll Cardiol* 2015;65:2159-2169).

German Aortic Valve Registry (GARY, 2011-2013): Incidence of Severe Vital Complications (SVCs) and Technical Procedural Complications (TCOs) Decreased Significantly From Year to Year, but Remained at ~4% With no Changes in Need for Sternotomy (~1.2%) and In-Hospital Death (~5%)

Among 15,964 transcatheter aortic valve replacement (TAVR) procedures (mean patient age 81 ± 6 years, 54% women, median logistic Euroscore I 18.3), overall in-hospital mortality was 5.2%, whereas SVCs occurred in 5%. Independent predictors for SVCs were female gender, pre-operative NYHA functional class IV, ejection fraction $<30\%$, pre-operative intravenous inotropes, arterial vascular disease, and higher degree of calcifications. TCOs occurred in 4.7% and decreased significantly from 2011 to 2013. An emergency sternotomy was performed in 1.3% of the patients. The authors concluded that TAVR had good outcomes and a regression in complications. Survival of patients who experienced SVCs or who required sternotomy was ~60% (Walther T et al, *J Am Coll Cardiol* 2015;65:2173-2180).

Nordic Aortic Valve Intervention (NOTION) Trial: Comparing Transcatheter (TAVR) With Surgical Aortic Valve Replacement (SAVR) in an All-Comers Patient Cohort, no Significant Differences were Found Regarding the Primary Outcome (Death, Stroke, or MI) or the Exploratory Outcomes of Cardiovascular Mortality or Prosthesis Reintervention After 1 Year

Among 280 (mean age 79 years; 82% considered low-risk) patients randomized to TAVR or SAVR, no significant difference in the primary endpoint (death, stroke, or MI) was found (13.1% vs 16.3%). No difference in the rate of cardiovascular death or prosthesis reintervention was found. TAVR led to more pacemakers due to conduction abnormalities, larger improvement in effective orifice area, more total aortic valve regurgitation, and higher NYHA functional class at 1 year. SAVR patients had more major or life-threatening bleeding, cardiogenic shock, acute kidney injury, and new-onset or worsening atrial fibrillation at 30 days. The authors concluded that no significant difference between TAVR and SAVR was found for the composite rate of death from any cause, stroke, or MI after 1 year (Thyregod HG et al, *J Am Coll Cardiol* 2015;65:2184-2194).

PRECOMBAT Study: No Difference Over 5 Years in MACCE Between PCI With Sirolimus Eluting Stents and CABG for Patients Treated for Unprotected Left Main Coronary Artery Stenosis

Among 600 patients with unprotected left main coronary artery stenosis undergoing PCI with a sirolimus-eluting stent ($n=300$) or CABG ($n=300$), at 5 years, the primary endpoint (major adverse cardiac or cerebrovascular events - MACCE:

a composite of death from any cause, MI, stroke, or ischemia-driven target vessel revascularization) occurred in 52 patients in the PCI group and 42 patients in the CABG group (event rates of 17.5% and 14.3%, respectively; hazard ratio - HR: 1.27; $p=0.26$). The 2 groups did not differ significantly in terms of death from any cause, MI, or stroke as well as their composite (8.4% and 9.6%; HR, 0.89; $p=0.66$). Ischemia-driven target vessel revascularization occurred more frequently in the PCI group than in the CABG group (11.4% and 5.5%, respectively; HR: 2.11; $p=0.012$) (Ahn JM et al, *J Am Coll Cardiol* 2015;65:2198-2206).

Therapeutic Manipulation of miRNA to Reduce In-Stent Restenosis / in Pig, Mouse, and in Vitro Models, miR-21 Promotes Vascular Inflammation and Remodeling After Stenting and May be a Therapeutic Target to Enhance Wound Healing After Vascular Injury

A subset of inflammatory miRNAs was documented which was activated after stenting in pigs, including the miR-21 stem loop miRNAs. Genetic ablation of the miR-21 stem loop attenuated neointimal formation in mice post-stenting. This occurred via enhanced levels of anti-inflammatory M2 macrophages coupled with an impaired sensitivity of smooth muscle cells to respond to vascular activation. The authors concluded that miR-21 plays a prominent role in promoting vascular inflammation and remodeling after stent injury and may be a therapeutic target to enhance wound healing after vascular injury (McDonald RA et al, *J Am Coll Cardiol* 2015;65:2314-2327).

Meta-Analysis: Fewer Hemorrhagic Strokes, Cardiovascular Death, and Nonprocedural Bleeding, Similar All-cause Strokes or Systemic Embolism, but More Ischemic Strokes With LAA Closure Compared With Warfarin

A meta-analysis of PROTECT AF and PREVAIL trials, and their registries indicated that at a mean follow-up of 2.69 years, patients receiving left atrial appendage closure (LAAC) with the Watchman device had fewer hemorrhagic strokes (hazard ratio - HR: 0.22; $p=0.004$), cardiovascular/unexplained death (HR: 0.48; $p=0.006$), and nonprocedural bleeding (HR: 0.51; $p=0.006$) compared with warfarin. All-cause stroke or systemic embolism was similar, but there were more ischemic strokes in the device group (HR: 1.95 and 0.22, respectively; $p=0.05 / 0.004$) (Holmes DR et al, *J Am Coll Cardiol* 2015;65:2614-2623).

Safe Full-Body MRI in Patients With a Specifically Designed Implantable Cardioverter-Defibrillator (ICD) System: First-in-Human Randomized Study

A total of 275 patients (76% male, age 60.4 ± 13.8 years)

received an MRI-safe single- or dual-chamber ICD (Evera MRI ICD, Medtronic) designed for full-body imaging. Patients were randomly assigned 2:1 to undergo full-body MRI (MRI group, n=175; 1.5-T) or to undergo a 1-h waiting period without MRI (control group, n=88) 9 to 12 weeks after implant. A subset of MRI patients underwent ventricular fibrillation induction testing post-MRI to characterize defibrillation function. The safety endpoint was met with 100% freedom from the composite endpoint (MRI-related events: occurrence of sustained ventricular tachyarrhythmia during MRI exposure, complication within 30 days related to the MRI, or loss of capture within 30 days of MRI; $p<0.0001$). A total of 34 ventricular tachyarrhythmia/ventricular fibrillation episodes (20 induced; 14 spontaneous) occurred in 24 patients post-MRI, with no observed effect on sensing, detection, or treatment. The authors concluded that this ICD system designed for full-body MRI at 1.5-T is safe and the MRI scan does not adversely affect electrical performance or efficacy (Gold MR et al, *J Am Coll Cardiol* 2015;65:2581-2588).

Review & Metaanalysis: Strong Evidence of the Safety of Remote Monitoring (RM) of ICDs, with the Suggestion of a Potential Mortality Benefit

Data from 9 randomized controlled trials (RCTs) reporting clinical outcomes of 6,469 ICD patients who did (n=6,469) or did not undergo RM (n=3,496), indicated clinical outcomes of RM comparable with office follow-up for all-cause mortality (odds ratio - OR: 0.83; $p=0.285$), cardiovascular mortality (OR: 0.66; $p=0.103$), and hospitalization (OR: 0.83; $p=0.196$). However, a reduction in all-cause mortality was noted in the 3 trials using home monitoring (OR: 0.65; $p=0.021$) with daily verification of transmission. Also the odds of inappropriate shock were reduced in RM patients (OR: 0.55; $p=0.002$) (Parthiban N et al, *J Am Coll Cardiol* 2015;65:2591-2600).

CARDIA Study: Cumulative Blood Pressure (BP) Exposure in Early Adulthood Leads to Cardiac Dysfunction in Middle Age

At the year 25 examination of 2,479 participants, cumulative BP measures were not related to LV ejection fraction; however, high cumulative exposure to systolic blood pressure (SBP) and diastolic blood pressure (DBP) were associated with lower longitudinal strain rate (both $p<0.001$). For diastolic function, higher cumulative exposures to SBP and DBP were associated with low early diastolic longitudinal peak strain rate (Kishi S et al, *J Am Coll Cardiol* 2015;65:2679-2687).

Digoxin Use in Registry Patients with AF had a Neutral Association with Outcomes Under Most Circumstances

Among 9,619 patients with atrial fibrillation (AF) and serial follow-up every 6 months for up to 3 years, 2,267 (23.6%)

received digoxin at enrollment, 681 (7.1%) during follow-up, and 6,671 (69.4%) never took digoxin. Digoxin use at registry enrollment was not associated with subsequent onset of symptoms, hospitalization, or mortality. Incident digoxin use during follow-up was not associated with subsequent death in patients with heart failure, but was associated with subsequent death in those without heart failure (hazard ratio-HR: 1.99) (Allen LA et al, *J Am Coll Cardiol* 2015;65:2691-2698).

ROCKET AF: Retrospective Analysis Indicated that Digoxin Treatment was Associated With a Significant Increase in All-Cause Mortality, Vascular Death, and Sudden Death in Patients With Atrial Fibrillation (AF)

Retrospective analysis of 5,239 (37%) out of 14,171 randomly assigned patients, receiving digoxin, more likely female (42% vs 38%) and having a history of heart failure (73% vs 56%), diabetes (43% vs 38%), and persistent AF (88% vs 77%; $p<0.0001$), showed that digoxin was associated with increased all-cause mortality (5.41 vs 4.30 events per 100 patients-years; hazard ratio - HR 1.17; $p=0.0093$), vascular death (3.55 vs 2.69 per 100 patient-years; HR 1.19; $p=0.0201$), and sudden death (1.68 vs 1.12 events per 100 patient-years; HR 1.36; $p=0.0076$). These data indicate that a randomized trial of digoxin in treatment of AF patients with and without heart failure is needed (Washam JB et al, *Lancet* 2015;385(9985):2363-2370).

TTM Trial: Comparable Cognitive Function in Survivors of Out-of-Hospital Cardiac Arrest After Target Temperature Management at 33°C vs 36°C

Among 652 cardiac arrest survivors randomized to temperature control at 33°C or 36°C, survival until 180 days after the arrest was 52% (33°C, n=178/328; 36°C, n=164/324). A total of 287 cardiac arrest survivors (33°C, n=148/36°C, n=139) were assessed with tests for memory, executive functions, and attention/mental speed and compared with a control group (n=119). Half of the cardiac arrest survivors had cognitive impairment, which was mostly mild. Cognitive outcome did not differ ($P>0.30$) between the 2 temperature groups (33°C/36°C). Compared with control subjects, attention/mental speed was more affected among cardiac arrest patients, but results for memory and executive functioning were similar (Lilja G et al, *Circulation* 2015;131: 1340-1349).

Some Chronic Heart Failure Patients Without Atrial Fibrillation (AF) are at High Risk for Stroke

Pooled data from 2 heart failure trials, the CORONA and the GISSI-HF, comprising 9585 patients, of whom 6054 did not have AF, indicated stroke occurrence in 165 patients (4.7%) with AF and in 206 patients (3.4%) without AF. Independent predictors of stroke in patients without AF included age (hazard ratio-HR, 1.34 per 10 years), New York Heart Association

class (HR 1.60, class III/IV vs II), insulin-treated diabetes mellitus (1.87), body mass index (0.74, per 5 kg/m² up to 30), and previous stroke (1.81). N-terminal pro B-type natriuretic peptide (n=2632 patients) was also an independent predictor of stroke (HR, 1.31; per log unit) when added to this model (Abdul-Rahim AH et al, *Circulation* 2015;131:1486-1494).

ARIC Study: Atrial Fibrillation (AF) Confers Increased Risk of Non–ST-Segment–Elevation Myocardial Infarction (NSTEMI)

The association between AF and incident MI was examined in 14462 participants (mean age, 54 years; 56% women; 26% blacks) who were free of coronary heart disease at baseline. Over a median follow-up of 21.6 years, 1374 MI events occurred (829 NSTEMIs, 249 STEMIs, 296 unclassifiable MIs). AF (n=1545) was associated with a 63% increased risk of MI (hazard ratio, 1.63), specifically NSTEMI (hazard ratio, 1.80) but not STEMI (hazard ratio, 0.49; *P* for hazard ratio comparison=0.004). The association between AF and MI, total and NSTEMI, was stronger in women than in men (Soliman EZ et al, *Circulation* 2015;131:1843-1850).

Most Cardiotoxicity of Anthracycline Occurs Within the First Year and is Associated With Anthracycline Dose and LVEF at the End of Treatment / Early Detection and Prompt Therapy Appear Crucial for Recovery

In a cohort of 2625 patients receiving anthracycline-containing therapy, cardiotoxicity occurred in 9% (n=226) at a median time of 3.5 months after the end of chemotherapy, and in 98% of cases (n=221), it occurred within the first year. Twenty-five (11%) patients had full and 160 (71%) partial recovery. End-chemotherapy LVEF (hazard ratio - HR, 1.37; for each percent unit decrement) and cumulative doxorubicin dose (HR, 1.09; for each 50 mg/m² increment) were independent correlates of cardiotoxicity (Cardinale D et al, *Circulation* 2015;131:1981-1988).

Oxygen Commonly Administered to Patients With STEMI May Increase Myocardial Injury Due to Coronary Vasoconstriction and Heightened Oxidative Stress

In a multicenter, prospective, randomized, controlled trial comparing oxygen (8 L/min) with no supplemental oxygen in 441 patients with ST-elevation–myocardial infarction (STEMI), mean peak troponin was similar in the oxygen and no oxygen groups (57.4 vs 48.0 µg/L; ratio, 1.20; *P*=0.18). However, there was a significant increase in peak creatine kinase (1948 vs 1543 U/L; means ratio, 1.27; *P*=0.01), in the rate of recurrent MI (5.5% vs 0.9%; *P*=0.006) and in frequency of cardiac arrhythmia (40.4% vs 31.4%; *P*=0.05) in the oxygen group.

At 6 months, the oxygen group had an increase in MI size on cardiac magnetic resonance (n=139; 20.3 vs 13.1 g; *P*=0.04). The authors concluded that supplemental oxygen therapy in patients with STEMI but without hypoxia may increase early myocardial injury and cause larger infarct size assessed at 6 months (Stub D et al, *Circulation* 2015;131:2143-2150).

STROKESTOP Study: Mass Screening in a 75- to 76-Year-Old Population Identifies a Significant Proportion (3%) of Participants With Untreated Atrial Fibrillation (AF)

Systematic screening using intermittent ECG recordings over 2 weeks among 7,173 75- to 76-year-old individuals without a previous diagnosis of AF uncovered 218 (3%) to have previously unknown AF, and of these, AF was found in 37 (0.5% of the screened population) on their first ECG. The use of intermittent ECGs increased new AF detection 4-fold. AF was previously diagnosed in 9.3% (n=666). Total AF prevalence in the screened population was 12.3%. Of participants with known AF, 149 (2.1%) had no oral anticoagulant (OAC) treatment. In total, 5.1% of the screened population had untreated AF; screening resulted in initiation of OAC treatment in 3.7%, with >90% of the participants with previously undiagnosed AF accepting initiation of OAC treatment (Svensberg E et al, *Circulation* 2015;131:2176-2184).

In Symptomatic Patients With Suspected Coronary Artery Disease (CAD), a Strategy of Initial Computed Tomography Coronary Angiography (CTA), Compared With Functional Testing, did not Improve Clinical Outcomes Over a Median of 2 Years

A total of 10,003 patients (aged 61±8) with symptoms suggestive of CAD (88% chest pain or dyspnea on exertion), and pretest likelihood of CAD 53±21%, were randomized to a strategy of computed tomographic coronary angiography (CTA) or to functional testing (exercise electrocardiography, nuclear stress testing, or stress echocardiography). Over median follow-up of ~2 years, a primary end-point event (death, myocardial infarction, hospitalization for unstable angina, or major procedural complication) occurred in 164 of 4996 patients in the CTA group (3.3%) and in 151 of 5007 (3%) in the functional-testing group (*P*=NS). CTA was associated with fewer catheterizations showing no obstructive CAD (3.4% vs 4.3%, *P*=0.02), although more patients in the CTA group underwent catheterization within 90 days after randomization (12% vs 8%). Median cumulative radiation exposure was lower in the CTA group (10 vs 11 mSv), but 32.6% of the patients in the functional-testing group had no exposure, thus overall exposure was higher in the CTA group (mean, 12 mSv vs 10 mSv; *P*<0.001) (Douglas PS et al, *N Engl J Med* 2015; 372:1291-1300).

TOTAL Trial: In Patients With STEMI Undergoing Primary PCI, Routine Manual Thrombectomy did not Reduce Cardiovascular Death, Recurrent MI, Cardiogenic Shock, or NYHA Class IV Heart Failure at 6 Months, But Conferred More Strokes at 1 Month

Among 10,732 patients with STEMI undergoing primary PCI randomized to manual thrombectomy vs PCI alone, the primary outcome (death from cardiovascular causes, recurrent MI, cardiogenic shock, or NYHA class IV heart failure) occurred in 347 of 5033 patients (6.9%) in the thrombectomy group vs 351 of 5030 patients (7%) in the PCI-alone group (P=NS). The rates of cardiovascular death (3.1% vs 3.5%) and primary outcome plus stent thrombosis or target-vessel revascularization (9.9% vs 9.8%) were also similar. Stroke within 30 days occurred in 33 patients (0.7%) in the thrombectomy group vs 16 patients (0.3%) in the PCI-alone group (hazard ratio, 2.06; P=0.02) (Jolly SS et al, *N Engl J Med* 2015;372:1389-1398).

Added Atrial Fibrillation (AF) Ablation to Mitral-Valve Surgery Led to Higher Rate of Freedom from AF at 1 Year Among Patients With Persistent or Long-Standing Persistent AF, but Increased the Risk for a Permanent Pacemaker

A total of 260 patients with persistent or long-standing persistent AF who required mitral-valve surgery were randomized to undergo either concomitant surgical ablation (ablation group), either via pulmonary vein isolation or biatrial maze procedure, or no ablation (control group), all with closure of the left atrial appendage. More patients in the ablation group than in the control group were free from AF at both 6 and 12 months (63% vs 29%, P<0.001). There was no significant difference between patients who underwent pulmonary-vein isolation and those who underwent biatrial maze procedure (61% and 66%). One-year mortality was 6.8% in the ablation group and 8.7% in the control group (P=NS). Ablation was associated with more implantations of a permanent pacemaker (21.5 vs 8.1 per 100 patient-years, P=0.01) (Gillinov AM et al, *N Engl J Med* 2015;372:1399-1409).

OSLER Studies: Over 1 Year, Use of Evolocumab Plus Standard Therapy, Compared With Standard Therapy Alone, Reduced LDL Cholesterol and Cardiovascular Events

A total of 4465 patients who had completed 1 of 12 phase 2 or 3 studies ("parent trials") of evolocumab, were randomly assigned in a 2:1 ratio to receive either evolocumab (140 mg every 2 weeks or 420 mg monthly) plus standard therapy or standard therapy alone. Over 11.1 months, evolocumab reduced LDL cholesterol by 61%, from a median of 120 to 48 mg/dl (P<0.001). Most adverse events occurred with similar frequency in the two groups, although neurocognitive events were reported more frequently in the evolocumab group. The rate of cardiovascular events at 1 year was reduced from 2.18%

in the standard-therapy group to 0.95% in the evolocumab group (hazard ratio, 0.47; P=0.003) (Sabatine MS et al, *N Engl J Med* 2015;372:1500-1509).

ODYSSEY LONG TERM Trial: Over 78 Weeks, Alirocumab, When Added to Statin Therapy at Maximum Tolerated Dose, Significantly Reduced LDL Cholesterol, with Evidence of Reduction in Cardiovascular Events With Alirocumab

A total of 2341 patients at risk for cardiovascular events with LDL \geq 70 mg/dl (1.8 mmol/L) receiving treatment with statins at the maximum tolerated dose, with or without other lipid-lowering therapy, were randomly assigned in a 2:1 ratio to receive alirocumab (150 mg) or placebo as a 1-ml subcutaneous injection every 2 weeks for 78 weeks. At week 24 and through 78 weeks, the difference between the alirocumab and placebo groups in the mean percentage change from baseline in LDL cholesterol level was -62% points (P<0.001). The alirocumab group had higher rates of injection-site reactions (5.9% vs 4.2%), myalgia (5.4% vs 2.9%), neurocognitive events (1.2% vs 0.5%), and ophthalmologic events (2.9% vs 1.9%). Major adverse cardiovascular events (death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was lower with alirocumab than with placebo (1.7% vs 3.3%; hazard ratio, 0.52; P=0.02) (Robinson JG et al, *N Engl J Med* 2015;372:1489-1499).

PEGASUS-TIMI 54: In Patients with >1 Year History of MI, Ticagrelor Reduced the Risk of Cardiovascular Death, MI, or Stroke and Increased the Risk of Major Bleeding

Over a median of 33 months, among 21,162 patients with prior myocardial infarction (MI) randomized to ticagrelor 90 mg bid or 60 mg bid, or placebo on top of low-dose aspirin, the two ticagrelor doses each reduced, as compared with placebo, the rate of the primary efficacy end point (cardiovascular death, MI, or stroke) to 7.85%, 7.77%, and 9.04% respectively (hazard ratios 0.85, P=0.008 and 0.84; P=0.004 for the two ticagrelor doses vs placebo). Rates of TIMI major bleeding were higher with ticagrelor (2.6% and 2.3%) than with placebo (1.06%) (P<0.001); the rates of intracranial hemorrhage or fatal bleeding in the three groups were 0.63%, 0.71%, and 0.60%, respectively (Bonaca MP et al, *N Engl J Med* 2015; 372:1791-1800).

STAR AF II: Addition of Linear Ablation or Ablation of Complex Fractionated Electrograms to Pulmonary Vein Isolation did not Reduce Recurrences Among Patients with Persistent Atrial Fibrillation (AF)

Among 589 patients with persistent AF, randomized in a 1:4:4 ratio to ablation with pulmonary-vein isolation (PVI) alone (n=67), PVI plus ablation of electrograms showing complex fractionated activity (n=263), or PVI plus additional

linear ablation across the left atrial roof and mitral valve isthmus (n=259), procedure time was shorter for PVI alone (P<0.001). At 1.5 years, 59% of patients assigned to PVI alone were free from recurrent AF, as compared with 49% assigned to PVI plus complex electrogram ablation and 46% assigned to PVI plus linear ablation (P=NS). There were no significant differences among the 3 groups for freedom from AF after 2 ablation procedures and freedom from any atrial arrhythmia. Complications included tamponade (3 patients), stroke or transient ischemic attack (3 patients), and atriopharyngeal fistula (1 patient) (Verma A et al, *N Engl J Med* 2015;372:1812-1822).

THAPCA Trial: In Comatose Children Who Survived Out-Of-Hospital Cardiac Arrest, Therapeutic Normothermia is Equivalent With Therapeutic Hypothermia, Regarding Survival With a Good Functional Outcome at 1 Year

Within 6 hours after return of circulation, 295 comatose patients (aged 2 days to 18 years) were randomly assigned to therapeutic hypothermia (target temperature, 33°C) or therapeutic normothermia (target temperature, 36.8°C). Analysis of data in 260 patients indicated no significant difference in the primary outcome (survival at 12 months with good functional outcome) between the hypothermia and the normothermia group (20% vs 12%; relative likelihood, 1.54; P=0.14). The groups had similar incidences of infection and serious arrhythmias, use of blood products and 28-day mortality (Moler FW et al, *N Engl J Med* 2015;372:1898-1908).

Swedish Study: Early Cardiopulmonary Resuscitation (CPR) (Bystander CPR Before EMS Arrival) in Out-of-Hospital Cardiac Arrest was Associated with a 30-Day Survival Rate >2-Fold Higher Than That Associated with no CPR Before EMS Arrival

Analysis of 30,381 witnessed out-of-hospital cardiac arrests indicated that CPR was performed before the arrival of Emergency Medical Services (EMS) in 15,512 cases (51.1%) and was not performed before the arrival of EMS in 14,869 cases (48.9%). The 30-day survival rate was 10.5% when CPR was performed before EMS arrival vs 4% when CPR was not performed before EMS arrival (P<0.001). Thus, CPR before the arrival of EMS was associated with an increased 30-day survival rate (odds ratio, 2.15) (Hasselqvist-Ax I et al, *N Engl J Med* 2015;372:2307-2315).

VADT Trial: 10-Year Follow-Up of Patients With Type 2 Diabetes Who Had Been Randomized to Intensive Glucose Control for 5.6 Years Had 8.6 Fewer Major Cardiovascular Events per 1000 Person-Years Than Those Assigned to Standard Therapy, but no Improvement in Overall Survival

The initial VADT had shown that intensive glucose low-

ering, compared with standard therapy, did not reduce the rate of major cardiovascular events among 1791 military veterans at a median of 5.6 years. The difference in glycated hemoglobin levels between the 2 groups averaged 1.5% points during the trial and declined to 0.2 to 0.3% points by 3 years after the trial ended. At extended follow-up at ~10 years, the intensive-therapy group had a significantly lower risk of the primary outcome (major cardiovascular event) than did the standard-therapy group (hazard ratio, 0.83; P=0.04), with an absolute risk reduction of 8.6 major cardiovascular events per 1000 person-years, but did not have a reduced cardiovascular mortality (hazard ratio, 0.88; P=NS). No reduction in total mortality was evident (Hayward RA et al, *N Engl J Med* 2015;372:2197-2206).

SWIFT PRIME: Stent-Retriever Thrombectomy Within 6 Hours, in Addition to i.v. t-PA, Improved Functional Outcomes at 90 Days in Stroke Due to Occlusions in the Proximal Anterior Intracranial Circulation

Patients (N=196) with stroke due to occlusions in the proximal anterior intracranial circulation, were randomized to thrombectomy with use of a stent retriever within 6 hours, in addition to intravenous t-PA (n=98), or to t-PA alone (n=98). The study was stopped early because of efficacy. In the intervention group, the median time from qualifying imaging to groin puncture was 57 min, and the rate of substantial reperfusion at the end of the procedure was 88%. Thrombectomy with the stent retriever plus i.v. t-PA reduced disability at 90 days (P<0.001). The rate of functional independence was higher in the intervention group than in the control group (60% vs 35%, P<0.001). There were no significant between-group differences in 90-day mortality (9% vs 12%, P=NS) or symptomatic intracranial hemorrhage (0% vs 3%, P=NS) (Saver JL et al, *N Engl J Med* 2015;372:2285-2295).

REVASCAT Trial: Anterior Circulation Stroke Treated Within 8 Hours After Symptom Onset, With Stent Retriever Thrombectomy Had Reduced Severity of Post-Stroke Disability and Increased Rate of Functional Independence

Over 2 years, 206 patients who could be treated within 8 hours after the onset of symptoms of acute ischemic stroke and had confirmed proximal anterior circulation occlusion and absence of a large infarct on neuroimaging, were randomized to receive either medical therapy (including i.v. alteplase) and endovascular therapy with the Solitaire stent retriever (thrombectomy group) or medical therapy alone (control group). Thrombectomy reduced the severity of disability and led to higher rates of functional independence. At 90 days, the rates of intracranial hemorrhage were 1.9% in both groups, and rates of death 18.4% and 15.5%, respectively (P=NS) (Jovin TG et al, *N Engl J Med* 2015;372:2296-2306).

IMPROVE-IT: Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes Confers Incremental Lowering of LDL and Improved Cardiovascular Outcomes / Lowering LDL to Levels Below Previous Targets Provided Additional Benefit

A total of 18,144 patients hospitalized for acute coronary syndrome within the preceding 10 days and having LDL cholesterol levels of 50 - 100 mg/dl (1.3 to 2.6 mmol/L) if they were receiving lipid-lowering therapy or 50 - 125 mg/dl (1.3 to 3.2 mmol/L) if they were not receiving lipid-lowering therapy, were randomized to combination of simvastatin (40 mg) and ezetimibe (10 mg) (simvastatin–ezetimibe) or simvastatin (40 mg) and placebo (simvastatin monotherapy). Median LDL cholesterol level during the study was 53.7 mg/dl (1.4 mmol/L) in the simvastatin–ezetimibe group, vs 69.5 mg/dl (1.8 mmol/L) in the simvastatin-monotherapy group ($P < 0.001$). The event rate for the primary end point (cardiovascular death, nonfatal MI, unstable angina requiring rehospitalization, coronary revascularization ≥ 30 days after randomization, or nonfatal stroke) at 7 years was 32.7% in the simvastatin–ezetimibe group vs 34.7% in the simvastatin-monotherapy group (hazard ratio, 0.936; $P = 0.016$). Rates of prespecified muscle, gallbladder, and hepatic adverse effects and cancer were similar in the two groups (Cannon CP et al, *N Engl J Med* 2015;372:2387-2397).

PREPIC 2: In Patients with Severe Acute Pulmonary Embolism who Can be Treated with Anticoagulation, Use of a Retrievable Inferior Vena Cava Filter is not Supported as it did not Reduce the Risk of Recurrent Pulmonary Embolism at 3 Months

Hospitalized patients with acute, symptomatic pulmonary embolism associated with leg vein thrombosis and at least 1 criterion for severity were assigned to retrievable inferior vena cava filter implantation plus anticoagulation (filter group; $n = 200$) or anticoagulation alone with no filter implantation (control group; $n = 199$). The filter was successfully inserted in 193 patients and was retrieved as planned in 153 of the 164 patients. By 3 months, recurrent pulmonary embolism had occurred in 6 patients (3%; all fatal) in the filter group and in 3 patients (1.5%; 2 fatal) in the control group ($P = \text{NS}$). Results were similar at 6 months. Filter thrombosis occurred in 3 patients (Mismetti P et al, *JAMA* 2015;313:1627-1635).

Fewer than 1 in 10 Eligible Medicare Patients With Low Ejection Fraction (EF) Received an ICD Within 1 Year After MI, Although ICD Implantation was Associated With Lower Mortality at 2 Years

According to an observational study of 10,318 Medicare beneficiaries with an EF of $\leq 35\%$ after MI, the cumulative 1-year ICD implantation rate was 8.1% ($n = 785$). Patients with ICD implantation were more likely to have prior coronary artery bypass graft procedures (31% vs 20%; hazard ratio - HR, 1.49), higher peak troponin levels, in-hospital cardiogenic shock (13%

vs 8%; HR, 1.57), and cardiology follow-up within 2 weeks after discharge (30% vs 20%; adjusted HR, 1.64) relative to patients who did not receive an ICD within 1 year. Implantation of ICD was associated with lower 2-year mortality (15.3 events per 100 patient-years / 128 deaths in 838 patient-years vs 26.4 events per 100 patient-years / 3033 deaths in 11,479 patient-years; HR, 0.64) (Pokorney SD et al, *JAMA* 2015;313:2433-2440).

Bioprosthetic Mitral Valve Replacement May be a Reasonable Alternative to Mechanical Prosthetic Valve Replacement in Patients Aged 50 - 69 Years, but the 15-Year Follow-Up in this Study is Insufficient to Fully Assess Lifetime Risks, Including Reoperation

Analysis of 3433 patients (aged 50-69 years) who underwent mitral valve replacement indicated no survival difference between mechanical prosthetic and bioprosthetic mitral valves. Actuarial 15-year survival was 57.5% after mechanical vs 59.9% after bioprosthetic valve replacement (hazard ratio -HR, 0.95, $P = \text{NS}$); the 15-year cumulative incidence of stroke was higher after mechanical valve replacement (65 strokes, 14% vs 41 strokes; 6.8%; HR, 1.62); reoperation rate was lower for mechanical valves (28 reoperations, 5% vs 47 reoperations, 11.1%; HR, 0.59). The 15-year cumulative incidence of a bleeding event was higher for mechanical valves (72 events, 14.9% vs 49 events, 9%; HR, 1.50) (Chikwe J et al, *JAMA* 2015;313:1435-1442).

ENGAGE AF-TIMI 48: Edoxaban Had Greater Efficacy than Warfarin in Patients who were VKA Naive than VKA Experienced / It Also Significantly Reduced Major Bleeding Regardless of Prior VKA Exposure

In a subgroup of the ENGAGE AF-TIMI 48 trial which randomized 21,105 patients with atrial fibrillation (AF) to edoxaban vs warfarin, over 2.8 years, higher-dose edoxaban significantly reduced the risk of stroke or systemic embolism in patients who were vitamin K antagonist (VKA) naive (hazard ratio - HR 0.71) and was similar to warfarin in the VKA experienced. Lower-dose edoxaban was similar to warfarin for stroke or systemic embolism prevention in VKA naive patients (HR 0.92), but was inferior to warfarin in those who were VKA experienced (HR 1.31; $P = 0.019$). Both higher-dose and lower-dose edoxaban regimens significantly reduced the risk of major bleeding regardless of prior VKA experience (P interaction = 0.90 and 0.71, respectively) (O'Donoghue ML et al, *Eur Heart J* 2015;36:1470-1477).

MATRIX: In Patients With Acute Coronary Syndrome, Radial Compared With Femoral Access Reduces Net Adverse Clinical Events, Through a Reduction in Major Bleeding and All-Cause Mortality

A total of 8404 patients with acute coronary syndrome, with or without ST-segment elevation, were randomly assigned to radial (4197) or femoral (4207) access for coronary angiography

and percutaneous coronary intervention (PCI). 369 (8.8%) patients with radial access had major adverse cardiovascular events, vs 429 (10.3%) patients with femoral access (rate ratio - RR 0.85; $p=0.0307$). 410 (9.8%) patients with radial access had net adverse clinical events compared with 486 (11.7%) patients with femoral access (0.83; $p=0.0092$). The difference was driven by major bleeding (1.6% vs 2.3%, RR 0.67; $p=0.013$) and all-cause mortality (1.6% vs 2.2%, RR 0.72; $p=0.045$) (Valgimigli M et al, *Lancet* 2015;385(9986):2465–2476).

PARTNER 1: Similar 5-Year Outcomes of Transcatheter and Surgical Aortic Valve Replacement for High Surgical Risk Patients With Aortic Stenosis

The PARTNER trial has shown that mortality at 1, 2, and 3 years of transcatheter aortic valve replacement (TAVR) is comparable to surgical aortic valve replacement (SAVR) for high-risk patients with aortic stenosis. The 5-year outcomes were similar. Among 3105 patients, of whom 699 were enrolled (348 assigned to TAVR, 351 assigned to SAVR; mean STS Predicted Risk of Mortality score 11.7%), at 5 years, risk of death was 67.8% in the TAVR group compared with 62.4% in the SAVR group (hazard ratio 1.04; $p=NS$). There was no structural valve deterioration requiring surgical valve replacement in either group. Moderate or severe aortic regurgitation occurred in 40 (14%) of 280 patients in the TAVR group and 2 (1%) of 228 in the SAVR group ($p<0.0001$), and was associated with increased 5-year mortality in the TAVR group (72.4% for moderate or severe aortic regurgitation vs 56.6% for mild aortic regurgitation or less; $p=0.003$). Thus, TAVR as an alternative to surgery for patients with high surgical risk results in similar clinical outcomes (Mack MJ et al, *Lancet* 2015;385(9986):2477–2484).

5-Year Outcomes of PARTNER 1: Transcatheter Aortic Valve Replacement (TAVR) is More Beneficial Compared With Standard Treatment For Patients With Inoperable Aortic Stenosis

Of 3015 patients, of whom 358 were enrolled (mean age 83 years, STS Predicted Mortality Risk 11.7%, 54% female), 179 were assigned to TAVR treatment and 179 were to standard treatment. 20 patients crossed over from the standard treatment group and 10 withdrew from study, leaving only 6 patients at 5 years, of whom 5 had AVR treatment outside of the study. Mortality at 5 years was 71.8% in the TAVR group vs 93.6% in the standard treatment group (hazard ratio 0.50; $p<0.0001$). At 5 years, 42 (86%) of 49 survivors in the TAVR group had NYHA class 1 or 2 symptoms compared with 3 (60%) of 5 in the standard treatment group. Echocardiography after TAVR showed durable hemodynamic benefit (aortic valve area 1.52 cm² and mean gradient 10.6 mmHg at 5 years), with no evidence of structural valve deterioration. Thus, TAVR is more beneficial than standard treatment for

treatment of inoperable aortic stenosis (Kapadia SR et al, *Lancet* 2015;385(9986):2485–2491).

HYPITAT-II Trial: for Women with Non-Severe Hypertensive Disorders at 34–37 Weeks of Gestation, Immediate Delivery Might Reduce the Already Small Risk of Adverse Maternal Outcomes Compared to Expectant Monitoring With Delivery at 37 Weeks, But it Increases the Risk of Neonatal Respiratory Distress Syndrome

Women (N=703) with non-severe hypertensive disorders of pregnancy between 34 and 37 weeks of gestation were randomly allocated to either induction of labour or caesarean section within 24 h (immediate delivery, 352) or a strategy aimed at prolonging pregnancy until 37 weeks of gestation (expectant monitoring, 351). The composite adverse maternal outcome (thromboembolic disease, pulmonary edema, eclampsia, HELLP syndrome, placental abruption, or maternal death), occurred in 4 (1.1%) women having immediate delivery vs 11 (3.1%) women allocated to expectant monitoring (relative risk - RR 0.36; $p=0.069$). Respiratory distress syndrome was diagnosed in 20 (5.7%) neonates in the immediate delivery group vs 6 (1.7%) of 351 neonates in the expectant monitoring group (RR 3.3; $p=0.005$). No maternal or perinatal deaths occurred. Thus, routine immediate delivery does not seem justified and a strategy of expectant monitoring until the clinical situation deteriorates can be considered (Broekhuijsen K et al, *Lancet* 2015;385(9986):2492–2501).

DENERHTN Trial: Optimum and Stepped Care Standardized Antihypertensive Treatment (SSAHT) With Renal Denervation for Resistant Hypertension Decreases Ambulatory Blood Pressure More Than the Same SSAHT Alone at 6 Months

Eligible patients aged 18–75 years received indapamide 1.5 mg, ramipril 10 mg (or irbesartan 300 mg), and amlodipine 10 mg daily for 4 weeks to confirm treatment resistance by ambulatory blood pressure monitoring. Patients (106 of 1416 screened) were then randomly assigned (1:1) to receive either renal denervation plus an SSAHT regimen (renal denervation group, 53) or the same SSAHT alone (control group, 53). For SSAHT, after randomization, spironolactone 25 mg per day, bisoprolol 10 mg qd, prazosin 5 mg qd, and rilmenidine 1 mg qd were sequentially added from months 2 to 5 in both groups if home blood pressure was $\geq 135/85$ mmHg. The mean change in daytime ambulatory systolic blood pressure at 6 months was -15.8 mmHg in the renal denervation group and -9.9 mmHg in the group receiving SSAHT alone, a baseline-adjusted difference of -5.9 mmHg (-11.3 to -0.5; $p=0.0329$). The number of antihypertensive drugs and drug-adherence at 6 months were similar between the two groups. Three minor renal denervation-related adverse events were noted (lumbar

pain in 2 patients and mild groin hematoma in 1 patient). A mild and similar decrease in estimated glomerular filtration rate from baseline to 6 months was observed in both groups. Thus, in patients with well defined resistant hypertension, renal denervation plus an SSAHT decreases ambulatory blood pressure more than the same SSAHT alone at 6 months (Azizi M et al, *Lancet* 2015;385(9981):1957–1965).

ROX CONTROL HTN Study: Central Arteriovenous (AV) Anastomosis Significantly Reduced Blood Pressure and Hypertensive Complications in Patients With Uncontrolled Hypertension

Eligible patients (83 or 43% of 195 screened) with baseline office systolic blood pressure of ≥ 140 mmHg and average daytime ambulatory blood pressure of $\geq 135/85$ mmHg despite antihypertensive treatment were randomly assigned in a 1:1 ratio to undergo implantation of an AV coupler device (central iliac AV anastomosis, 44) plus current drug treatment or to maintain current treatment alone (control, 39). Mean office systolic blood pressure reduced by 26.9 ± 23.9 mmHg in the AV coupler group ($p < 0.0001$) and by 3.7 ± 21.2 mmHg in the control group ($p = 0.31$). Mean systolic 24 h ambulatory blood pressure reduced by 13.5 ± 18.8 mmHg ($p < 0.0001$) in AV coupler recipients and by 0.5 ± 15.8 mmHg ($p = 0.86$) in controls. Late ipsilateral venous stenosis occurred in 12 (29%) of 42 patients and was treatable with venoplasty or stenting. Thus, this approach might be a useful adjunctive therapy for patients with uncontrolled hypertension (Lobo MD et al, *Lancet* 2015;385(9978):1634–1641).

Stanford University Study: Proton Pump Inhibitor (PPI) Usage is Associated With Increased Risk of Myocardial Infarction in the General Population

Via a novel “data-mining” approach for pharmacovigilance on multiple electronic medical record datasets and a prospectively followed clinical cohort, the investigators explored the association of PPIs with cardiovascular risk in the general US population (2.9 million individuals). They found gastroesophageal reflux disease (GERD) patients exposed to PPIs to have a 1.16 fold increased association with myocardial infarction (MI). Survival analysis in a prospective cohort found a two-fold ($HR = 2.00$; $P = 0.031$) increase in association with cardiovascular mortality. This association was independent of clopidogrel use. Contrariwise, H2 blockers were not associated with increased cardiovascular risk. The authors concluded that their findings support the association of PPI exposure with risk for MI in

the general population, probably by adversely impacting vascular function (Shah NH et al, *PLoS One* 2015;10:e0124653). (Editor’s note/N.B.: Some initial criticism indicates that the risk of PPIs, if real, is still quite small; importantly, this was not a prospective and not a formal epidemiological study evaluating known risk factors, which would have had more power to demonstrate a causal relationship between PPIs and cardiovascular disease; patients with significant GERD may have concomitant multiple risks of comorbid diseases and thus there is the possibility for stratification bias; in addition, it cannot be determined whether PPIs were prescribed for chest pain, thus including patients with coronary disease. Most clinicians still believe that the benefits of PPIs outweigh their risks, but further research will be needed to clarify any real association) (<http://www.jwatch.org/fw110298/2015/06/12/proton-pump-inhibitors-associated-with-increased-mi-risk/>) / (http://www.gastro.org/news_items/2015/6/11/interpretation-of-study-on-ppi-heart-attack-risk).

Important Review and Other Articles

Practical management of anticoagulation in AF (Kovacs RJ et al, *J Am Coll Cardiol* 2015;65:1340-1360), Management of pulmonary hypertension (McLaughlin VV et al, *J Am Coll Cardiol* 2015;1976-1997), AHA/ACC/ASH Scientific Statement on treatment of hypertension in patients with coronary artery disease (Rosendorff C et al, *J Am Coll Cardiol* 2015;65:1998-2038), 2015 SCAI/ACC/HFSA/STS Clinical Expert Consensus Statement on the Use of Percutaneous Mechanical Circulatory Support Devices (Rihal CS et al, *J Am Coll Cardiol* 2015;65:2140-2141), Bleeding avoidance strategies during PCI (Singh M, *J Am Coll Cardiol* 2015;65:2225-2238), Functional tricuspid regurgitation (Dreyfus GD et al, *J Am Coll Cardiol* 2015;65:2331-2336), Left atrial appendage occlusion (Alli O et al, *J Am Coll Cardiol* 2015;65:2337-2344), Cardio-pulmonary-renal interactions (Husain-Syed F et al, *J Am Coll Cardiol* 2015;65:2433-2448), Left ventricular assist devices (Mancini D & Colombo PC, *J Am Coll Cardiol* 2015;65:2542-2555), PCSK9 inhibitors (Giugliano RP & Sabatine MS, *J Am Coll Cardiol* 2015;65:2638-2651), Percutaneous interventions in aortic disease (Aranson NJ & Watkins MT, *Circulation* 2015;131:1291-1299), Revised Jones criteria for rheumatic fever (Gewitz MH et al, *Circulation* 2015;131:1806-1818), Stroke prevention in AF (Lip G & Lane D, *JAMA* 2015;313:1950-1962), Acute stroke prevention (Prabhakaran S et al, *JAMA* 2015;313:1451-1462), Statin associated muscle problems (Stroes ES et al, *Eur Heart J* 2015;36:1012-1022), Management of valvular disease in pregnancy (Sliwa K et al, *Eur Heart J* 2015;36:1078-1089).