Cardiology News / Recent Literature Review / Second Quarter 2018

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EASEL Study: Sodium Glucose Cotransporter 2 Inhibitors (SGLT2i) Confer a Lower Rate of All-Cause Mortality, Hospitalization for Heart Failure (HF), and Major Adverse Cardiovascular Events (MACE)

After propensity matching, 25 258 patients were followed for a median of 1.6 years. Compared with non-SGLT2i, initiation of SGLT2i was associated with a lower rate of all-cause mortality and hospitalization for HF (1.73 vs 3.01 events per 100 person-years; HR, 0.57) and MACE (2.31 vs 3.45 events per 100 person-years; HR, 0.67). SGLT2i initiation was also associated with an ≈2-fold higher risk of below-knee lower extremity amputation (0.17 vs 0.09 events per 100 person-years; HR, 1.99). Because of the disproportionate canagliflozin exposure in the database, the majority of amputations were observed on canagliflozin (Udell JA et al, *Circulation* 2018;137:1450-9).

In Most Young Patients Who Experienced Sudden Cardiac Arrest (SCA), Sports was a Trigger in a Minority of Cases, while Standard Cardiovascular Risk Factors were Found in Over Half of them

Among 186 SCAs in the young (ages 5-34 years) (5% of all SCAs), overall prevalence of warning signs before SCA was low (29%), and 26 (14%) were associated with sports as a trigger. The remainder (n=160) occurred in other settings categorized as non-sports. Sports-related SCAs accounted for 39% of SCAs in patients aged ≤18, 13% of SCAs in patients aged 19 to 25, and 7% of SCAs in patients aged 25 to 34. Sports-related SCA cases were more likely to present with shockable rhythms, and survival from cardiac arrest was 2.5-fold higher in sports-related vs non-sports SCA (28% vs 11%; *P*=0.05). Overall, the most common SCA-related conditions were sudden arrhythmic death syndrome (31%), coronary artery disease (22%), and hypertrophic cardiomyopathy (14%). There was an unexpectedly high overall prevalence of established cardiovascular risk factors (obesity, diabetes mellitus, hypertension, hyperlipidemia, smoking) with ≥1 risk factors in 58% of SCA cases (Jayaraman R et al, *Circulation* 2018;137:1561-1570).

Although Second Arterial Conduit Use May be Low and Declining, Arterial Grafts are Associated With Lower Mortality and Fewer Cardiovascular Events / A Right Internal Mammary Artery (IMA) Graft Offers no Benefit Over That of a Radial Artery, But did Increase Risk of Sternal Wound Infection / Thus, the Radial Artery May be the Preferred Second Conduit

The study included patients who received second arterial (right IMA or radial artery, n=5866) or a venous conduit (n=53 566). Propensity score matching yielded 5813 matched sets. Subgroup analysis compared outcomes between propensity score–matched recipients of a right IMA (n=1576) or a radial artery (n=4290). Use of second arterial conduit use decreased from 10.7% in 2006 to 9.1% in 2011 (*P*<0.0001). However, receipt of a second arterial conduit was associated with lower mortality (13.1% vs 10.6% at 7 years; hazard ratio-HR, 0.79), and lower risks of MI (HR, 0.78) and repeat revascularization (HR, 0.82). In comparison with radial artery grafts, right IMA grafts were associated with similar mortality rates (10.3% vs 10.7% at 7 years; HR, 1.10) and individual risks of cardiovascular events, but the risk of sternal wound infection was increased (risk difference, 1.07%) (Goldstone AB et al, *Circulation* 2018;137:1698-1707).

RADIAL: Use of Radial-Artery vs Saphenous Vein Grafts (SVG) for CABG Resulted in a Lower Rate of Adverse Cardiac Events and a Higher Rate of Patency at 5 Years of Follow-Up

Analysis of 6 trials comprising 1036 patients (534 with radial-artery grafts and 502 with SVGs) indicated that over 5±2.5 years, adverse cardiac events were fewer with radial-artery grafts than with SVGs (hazard ratio-HR, 0.67; p=0.01). At follow-up angiography, use of radial-artery grafts was associated with a lower risk of occlusion (HR, 0.44; p<0.001). Use of radial-artery grafts was associated with a lower incidence of MI (HR, 0.72; p=0.04) and of repeat revascularization (HR, 0.50; p<0.001) but not of death from any cause (HR, 0.90; p=0.68) (Gaudino M et al, *N Engl J Med* 2018; 378:2069-77).

CREATIVE Trial: In Patients With Low Responsiveness to Clopidogrel (According to Thromboelastography), Adjunctive Use of Cilostazol Improved Clinical Outcomes Without Increasing Risk of Major Bleeding / Decreased Trend of Negative Outcomes With Double Dosage of Clopidogrel

Using thromboelastography, 1078 patients undergoing percutaneous coronary intervention (PCI) at high

thrombotic risk were selected and the intensified antiplatelet therapies with standard antiplatelet therapy were compared. The primary end point (major adverse cardiac and cerebrovascular events at 18 months after PCI) occurred in 52 patients (14.4%) in the standard (conventional strategy) group, 38 patients (10.6%) in the double (double-dose clopidogrel) group, and 30 patients (8.5%) in the triple (adjunctive cilostazol) group (hazard ratio-HR, 0.72, double vs standard; HR, 0.55, triple vs standard). No significant difference in the rates of major bleeding was found in the double group (3.34% vs 1.93% in standard, *P*=0.133) and the triple group (2.53% vs 1.93% in standard, *P*=0.240). The rate of minor bleeding increased in the double group (27.4% vs 20.3% in standard, *P*=0.031), but not in the triple group (23.6% vs 20.3% in standard, *P*=0.146) (Tang Y-D et al, *Circulation* 2018;137:2231-2245).

MOMENTUM 3: A Fully Magnetically Levitated Centrifugal-Flow Pump was Superior to a Mechanical-Bearing Axial-Flow Pump With Regard to Survival Free of Disabling Stroke or Reoperation to Replace or Remove a Malfunctioning Device

Of 366 patients with advanced heart failure, 190 were assigned to the centrifugal-flow pump group and 176 to the axial-flow pump group. In the intention-to-treat population, the primary end point (survival at 2 years free of disabling stroke or of reoperation to replace or remove a malfunctioning device) occurred in 151 patients (79.5%) in the centrifugal-flow pump group and in 106 (60.2%) in the axial-flow pump group (P<0.001 for noninferiority; hazard ratio-HR, 0.46; P<0.001 for superiority]). Reoperation for pump malfunction was less frequent in the centrifugal-flow pump group than in the axial-flow pump group (3 patients or 1.6% vs 30 patients or 17%; HR, 0.08; P<0.001). The rates of death and disabling stroke were similar in the two groups, but the overall rate of stroke was lower in the centrifugal-flow pump group than in the axial-flow pump group (10.1% vs 19.2%; HR, 0.47, P=0.02). (Mehra MR et al, *N Engl J Med* 2018;378:1386-95).

CABANA: Catheter Ablation for Atrial Fibrillation (AF) Not Superior to Drug Therapy

Among 2,204 AF patients (median age 68 years), randomized to drugs (n=1096, 49.7%) or pulmonary vein isolation (PVI) (n=1108), over a median of ~4 years, in an intention-to-treat analysis, the primary endpoint (death, disabling stroke, serious bleeding, or cardiac arrest) occurred in 89 patients (8%) randomized to ablation and 101 patients (9.2%) randomized to drugs (hazard ratio-HR 0.86, p=NS). Also, none of the components of the primary endpoint differed significantly (www.acc.org/latest-in-cardiology/clinical-trials/2018/05/10/15/57/cabana).

REPRISE III: Lotus (a Mechanically Expanded) Valve Had Significantly Greater Freedom from Moderate or Severe Paravalvular Leak and Smaller Valve Area / Higher Gradients than (Self-Expanding) Corevalve, but with no Clinical Differences in the Composite End Point (Mortality, Disabling Stroke, and Moderate Paravalvular Leak) or in Quality of Life at 1 Year

Among 912 patients with extreme- and high-risk aortic stenosis (median age 84, 51% women, STS score 6.8±4.1) randomly assigned (2:1 ratio; 607 Lotus:305 CoreValve), CoreValve demonstrated lower gradients and larger aortic valve area and Doppler velocity index than Lotus at discharge; the difference decreased in subsequent follow-up up to a year (all p<0.01). Lotus had lower rates of paravalvular leak that persisted over time (*p*<0.05). Similar outcomes were seen when comparing each valve type by size group (small, medium, large). These differences did not translate into worse clinical outcomes (Asch FM et al, *Circulation* 2018:137:2557-67).

Elderly ACS 2: Elderly Patients With Acute Coronary Syndromes (ACS) Showed no Difference in the Primary End Point Between Reduced-Dose (5 mg) Prasugrel and Standard-Dose Clopidogrel

Among 1443 elderly (>74 years) ACS patients undergoing PCI enrolled in a study (interrupted early because of futility) comparing a once-daily maintenance dose of prasugrel 5 mg with the standard clopidogrel 75 mg, the primary end point (mortality, MI, disabling stroke, and rehospitalization for cardiovascular causes or bleeding) occurred in 121 patients (17%) with prasugrel and 121 (16.6%) with clopidogrel (hazard ratio, 1.007; p=0.955). Definite/probable stent thrombosis rates were 0.7% with prasugrel vs 1.9% with clopidogrel (odds ratio-OR, 0.36; p=0.06). Bleeding rates were 4.1% with prasugrel vs 2.7% with clopidogrel (OR, 1.52; *p*=0.18). (Savonitto S et al, *Circulation* 2018;137:2435-45).

SWAP-4: De-Escalation from Ticagrelor to Clopidogrel is Associated with an Increase in Platelet Reactivity / The Use of a Loading Dose Before the Initiation of a Maintenance Dose of Clopidogrel Mitigates these Observations

This study was conducted in patients on maintenance dosing (MD) of aspirin (81 mg/d) and clopidogrel (75 mg/d). After a 7-day run-in with ticagrelor (180 mg loading dose [LD] followed by 90 mg bid MD), patients (n=80) were randomized into 1 of 4 groups: group A, clopidogrel 600 mg LD 24 h after the last MD of ticagrelor (C-600 mg-24h); group B, clopidogrel 600 mg LD 12 h after the last MD of ticagrelor (C-600 mg-12h); group C, clopidogrel 75 mg/d MD 24 h after the last MD of

ticagrelor (C-75 mg-24h); and group D, ticagrelor 90 mg bid MD (T-90 mg twice daily). MD of the randomized treatment was maintained for 10±3 days. Pharmacodynamic assessments were performed by VerifyNow.

T-90 mg bid led to lower platelet reactivity than any clopidogrel regimen. $P2Y_{12}$ reaction unit levels were similar between the C-600 mg-24h (group A) and the C-75 mg-24h (group C) (p=0.29), including at 48 hours. $P2Y_{12}$ reaction unit levels were lower with C-600 mg-12h (group B) than with C-75 mg-24h (group C; p=0.024). Maximal platelet aggregation over time was lower with both C-600 mg-24h (group A; p=0.041) and C-600 mg-12h (group B; P=0.028) compared with C-75 mg-24h (group C). There were no pharmacodynamic differences for all tests between C-600 mg-24h (group A) and C-600 mg-12h (group B). In group C (C-75 mg-24h), platelet reactivity increased compared with baseline as early as 24 hours, reaching statistical significance at 48 and 72 hours and up to 10 days. These pharmacodynamic findings were delayed and blunted in magnitude with the administration of an LD. (Franchi F et al, *Circulation* 2018;137:2450-62).

Registry Data: Use of VF Conversion Testing (CT) after Subcutaneous (S-ICD) Implantation, Performed in ~71%, was not Associated With a Composite of In-hospital Complications or Death / Insufficient Safety Margin (ISM) was Relatively Uncommon (~7%)

Ventricular fibrillation (VF) conversion testing (CT) was performed in 70.7% (n=5624) of 7960 patients with S-ICDs. Although deferral of CT was associated with several patient characteristics, the facility effect was comparatively more important. An insufficient safety margin (ISM) (defined as VF conversion energy >65J) during testing, occurred in 6.9% (n=336) of 4864 patients without a prior ICD and was more common among white patients and those with ventricular pacing on the preimplant ECG, higher preimplant blood pressure, larger body surface area, higher body mass index, and lower ejection fraction. A risk score was able to identify patients at low (<5%), medium (5% to 10%), and high risk (>10%) for ISM. CT testing was not associated with a composite of inhospital complications including death (Friedman DJ et al, *Circulation* 2018;137:2463-77).

Ambulatory Blood-Pressure (BP) Measurements: A Stronger Predictor of All-Cause and Cardiovascular (CV) Mortality than Clinic BP Measurements / White-Coat Hypertension Not Benign / Masked Hypertension Associated with a Greater Risk of Death than Sustained Hypertension

Analyzed data from a registry-based, multicenter, national cohort including 63,910 adults followed-up for 4.7 years (3808 deaths from any cause / 1295 of these from CV causes), indicated that 24-hour systolic BP was more strongly associated with all-cause mortality (hazard ratio-HR, 1.58 per 1-SD increase in BP) than the clinic systolic BP (HR, 1.02). Corresponding hazard ratios per 1-SD increase in pressure were 1.55 for nighttime ambulatory systolic BP and 1.54 for daytime ambulatory systolic BP. These relationships were consistent across subgroups of age, sex, and status with respect to obesity, diabetes, cardiovascular disease, and antihypertensive treatment. Masked hypertension was more strongly associated with all-cause mortality (HR, 2.83) than sustained hypertension (HR, 1.80) or white-coat hypertension (HR, 1.79). Results for CV mortality were similar to those for all-cause mortality (Banegas JR et al, *N Engl J Med* 2018; 378:1509-20).

EXTEND-IA TNK: Tenecteplase Before Thrombectomy is Associated With a Higher Incidence of Reperfusion and Better Functional Outcome Than Alteplase Among Patients With Ischemic Stroke Treated Within 4.5 Hours After Symptom Onset

Among 202 stroke patients, 101 assigned to receive tenecteplase and 101 to alteplase, the primary outcome (reperfusion of >50% of the involved ischemic territory or an absence of retrievable thrombus at time of initial angiographic assessment) occurred in 22% of tenecteplase patients vs 10% of alteplase patients (p=0.002 for noninferiority; p=0.03 for superiority). Tenecteplase resulted in a better 90-day functional outcome than alteplase (p=0.04). Symptomatic intracerebral hemorrhage occurred in 1% of patients in each group (Campbell BCV et al, *N Engl J Med* 2018; 378:1573-1582).

NAVIGATE ESUS: Rivaroxaban is not Superior to Aspirin in the Prevention of Recurrent Stroke After an Initial Embolic Stroke of Undetermined Source (ESUS) and is Associated With Higher Risk of Bleeding

Among 7213 patients with recent ischemic stroke (ESUS), 3609 randomly assigned to rivaroxaban (15 mg qd) and 3604 to aspirin (100 mg qd), over a median of 11 months, the primary efficacy outcome (first recurrence of ischemic or hemorrhagic stroke or systemic embolism) occurred in 172 patients in the rivaroxaban group (annualized rate, 5.1%) and in 160 in the aspirin group (annualized rate, 4.8%) (hazard ratio - HR, 1.07; p=0.52). Recurrent ischemic stroke occurred in 158 patients in the rivaroxaban group (annualized rate, 4.7%) and in 156 in the aspirin group (annualized rate, 4.7%). Major bleeding occurred in 62 patients in the rivaroxaban group (annualized rate, 1.8%) and in 23 in the aspirin group

(annualized rate, 0.7%) (HR, 2.72; p<0.001) (Hart RG et al, *N Engl J Med* 2018; 378:2191-2201).

GARY Registry: The Incidence of Pacemaker Implantation and Disabling Stroke Was Higher With Rapid (RDVs) vs Conventional Deployment Valves (CBVs), With no Beneficial Effect on In-Hospital Mortality / The 3 RDVs Presented Different Complication Profiles With Regard to Pacemaker Implantation and Transvalvular Gradients

Among 22,062 patients undergoing isolated surgical aortic valve replacement (AVR), 20,937 patients received a CBV, whereas 1,125 patients were treated with an RDV with significantly reduced procedure with use of RDV (160 vs 150 min; p< 0.001), cardiopulmonary bypass (83 vs 70 min; p< 0.001), and aortic cross clamp times (60 vs 44 min; p< 0.001), but RDVs showed significantly elevated rates of pacemaker implantation (3.7% vs 8.8%; p< 0.001) and disabling stroke (0.9% vs 2.2%; p< 0.001), whereas in-hospital mortality was similar (1.7% vs 2.2%; p=0.22). These findings persisted after 1:1 propensity score matching. Comparison of the 3 RDVs, the self-expanding, nitinol-based 3F Enable valve (Medtronic) (n=162) (has been withdrawn from the market), the balloon expandable INTUITY valve (Edwards) (n=466), and the Perceval sutureless valve (Sorin/LivaNova) (n=900), revealed nonsignificant different pacemaker rates (~8-14%) and significantly different post-operative transvalvular gradients (21% of Perceval with gradient >20 mmHg) (Ensminger S et al, *J Am Coll Cardiol* 2018;71:1417–28).

Delayed Coronary Obstruction (DCO) Following TAVI is a Rare (0.22%) Phenomenon, Mostly Occurring Within 24h but Also ≥2 Months, More Commonly After Valve-in-Valve Procedures & with the Self-Expanding Valves, & Associated With High In-Hospital Mortality Rate

38 DCO (incidence 0.22%) cases were identified from a total of 17,092 TAVR procedures, occurring more commonly after valve-in-valve procedures (0.89% vs. 0.18%; p< 0.001) and if self-expandable valves were used during the index procedure (0.36% vs. 0.11% balloon expandable; p< 0.01). DCO was most likely to occur ≤24h after the TAVI procedure (47.4%; n=18); 6 (15.8%) cases occurred between 24h and ≤7 days, with the remaining 14 (36.8%) at ≥60 days. The most frequent presentation was cardiac arrest (31.6%; n=12), followed by STEMI (23.7%; n=9). The left coronary artery was obstructed in most cases (92.1%; n=35). PCI was attempted in the majority of cases (74.3% left main; 60% right coronary), and stent implantation was successful in 68.8%. Overall in-hospital death rate was 50% (n=19), higher if DCO occurred ≤7 days from the index procedure (62.5% vs 28.6%; p=0.09) (Jabbour RJ et al, *J Am Coll Cardiol* 2018;71:1513–24).

RELEXAO Registry: Thrombus Formation on the Device is not Uncommon in Patients With AF Who Are Treated by LAA Closure, Strongly Associated With a Higher Risk of Ischemic Stroke During Follow-Up

Among 339 imaged patients of 469 AF patients who underwent LAA closure (272 Watchman and 197 Amplatzer devices), there were 98 major adverse events (26 thrombi on devices, 19 ischemic strokes, 2 transient ischemic attacks, 18 major hemorrhages, 33 deaths) recorded in 89 patients over 13 ± 13 months. The incidence of device-related thrombus in patients with LAA imaging was 7.2% per year. Older age (hazard ratio - HR: 1.07 per 1-year increase; p=0.02) and history of stroke (HR: 3.68; p=0.03) were predictors of thrombus formation on the devices, whereas dual antiplatelet therapy (HR: 0.10; p=0.03) and oral anticoagulation at discharge (HR: 0.26; p=0.02) were protective factors. Thrombus on the device (HR: 4.39; p=0.04) and vascular disease (HR: 5.03; p=0.01) were independent predictors of ischemic strokes and TIAs during follow-up (Fauchier L et al, *J Am Coll Cardiol* 2018;71:1528-36).

LAA Occlusion: A Reasonable Option for Stroke Prevention in High-Risk Patients With Atrial Fibrillation Ineligible for Anticoagulation, but Procedural Complication Rates are not Insignificant, and Patients Remain at Risk of Serious Adverse Events and Death Even After Successful Implant

Of 143 referrals, 83 patients (aged 76±8 years, 32.5% female, mean $CHAD_2S_2$-VASc score 4±1) were offered LAA occlusion with 80 (95.3%) having had previous major bleeding (59% intracranial). LAA occlusion with an Amulet device was successful in 82 (98.8%), with periprocedural major adverse events occurring in 5 (6%) patients (2 device embolizations including 1 death, 2 major bleeds). Cardiac imaging in 75 (94%) patients at 2 months showed device-related thrombus in 1 case (1.3%) and minor (<5mm) device leaks in 13 (17.1%). Over a median of 12 months, 3 (3.8%) ischemic strokes, 2 (2.5%) hemorrhagic strokes and 5 (6.3%) major extracranial bleeds occurred. All-cause mortality was 10%, with most deaths (7, 87.5%) due to non-cardiovascular causes (Masood A et al, *Heart* 2018;104:594-9).

Brugada Syndrome: Dynamic Substrate Variability / Substrate Size Independently Associated With Arrhythmia Inducibility /Substrate Ablation Confers ECG Normalization & No Arrhythmia Reinducibility

Among 191 patients with (group 1; n=88) and without (group 2; n=103) Brugada syndrome–related symptoms

undergoing electrophysiological study and substrate mapping or ablation, before ajmaline testing, 53.4% of patients had ventricular tachyarrhythmia inducibility, more frequent in group 1 (65.9%) than in group 2 (42.7%; p< 0.001). Larger substrates with more fragmented long-duration ventricular potentials were found in patients with inducible arrhythmias than in patients without inducible arrhythmias (p< 0.001). After ajmaline, patients without arrhythmia inducibility had arrhythmia inducibility without a difference in substrate characteristics between the 2 groups. The substrate size was the only independent predictor of inducibility (odds ratio: 4.51, p< 0.001). A substrate size of 4 cm^2 best identified patients with inducible arrhythmias. Substrate ablation prevented ventricular tachyarrhythmia re-inducibility (Pappone C et al, *J Am Coll Cardiol* 2018;71:1631-46).

Multicenter Registry: Myocarditis After Immune Checkpoint Inhibitor (ICI) Therapy May Be More Common Than Appreciated, Occurs Early After Starting Treatment, Has a Malignant Course, and Responds to Higher Steroid Doses

Of all 964 patients started on ICI, there were 35 patients with ICI-associated myocarditis (aged 65±13 years, 29% female, 54% with no other immune-related side effects), who were compared to a random sample of 105 ICI-treated patients without myocarditis. The prevalence of myocarditis was 1.14% with a median time of onset of 34 days after starting ICI. Relative to controls, combination ICI (34% vs 2%; p< 0.001) and diabetes (34% vs 13%; p=0.01) were more common in cases. Over a median of 102 days, 16 (46%) developed major adverse cardiovascular events (MACE) (cardiovascular death, cardiogenic shock, cardiac arrest, and hemodynamically significant complete heart block); 38% of MACE occurred with normal ejection fraction. There was a 4-fold increased risk of MACE with troponin T of ≥1.5 ng/ml (hazard ratio: 4.0; p=0.003). Steroids were administered in 89%, and lower steroids doses were associated with higher residual troponin and higher MACE rates (Mahmood SS et al, *J Am Coll Cardiol* 2018;71:1755-64).

Electrical Storm (ES) in ICD Patients: The Combination of IV Amiodarone and Oral Propranolol is Safe, Effective, and Superior to the Combination of IV Amiodarone and Oral Metoprolol

Among 60 ICD patients (45 men, age 65.0 ± 8.5 years) with ES, randomized to either propranolol (160 mg/24h, Group A) or metoprolol (200 mg/24h, Group B), combined with IV amiodarone for 48h, those on propranolol (n=30) presented a 2.67 times decreased incidence rate (rate ratio: 0.375; p=0.001) of ventricular arrhythmic events and a 2.34 times decreased rate of ICD discharges (rate ratio: 0.428; p=0.004) during the ICU stay, after adjusting for age, sex, ejection fraction, NYHA class, heart failure type, arrhythmia type, and arrhythmic events before ICU admission. At the end of the first 24-h treatment period, 27 of 30 (90%) patients in group A, while only 16 of 30 (53.3%) patients in group B were free of arrhythmic events (p=0.03). The termination of arrhythmic events was 77.5% less likely in Group B compared with Group A (hazard ratio: 0.225, p< 0.001). Time to arrhythmia termination and length of hospital stay were significantly shorter in the propranolol group (p< 0.05 for both) (Chatzidou S et al, *J Am Coll Cardiol* 2018;71:1897-1906).

CECCY Trial: With a Lower Than Expected Incidence of Anthracycline Cardiotoxicity With Contemporary Moderate to High Doses, Prophylactic Carvedilol Had no Impact on the Incidence of Early Onset of LVEF Reduction / However, Carvedilol Significantly Reduced Troponin and Diastolic Dysfunction

Among 200 patients with HER2-negative breast cancer and normal left ventricular ejection fraction (LVEF) referred for anthracycline therapy (240 mg/m^2), who were randomized to carvedilol or placebo until chemotherapy completion, the primary endpoint (prevention of a ≥10% reduction in LVEF at 6 months) occurred in 14 patients (14.5%) in the carvedilol group and 13 patients (13.5%) in the placebo group (p=1.0). No differences in changes of LVEF or B-type natriuretic peptide were noted between groups. A significant difference existed between groups in troponin I levels over time, with lower levels in the carvedilol group (p=0.003). Additionally, a lower incidence of diastolic dysfunction was noted in the carvedilol group (p=0.039) (Avilla MS et al, *J Am Coll Cardiol* 2018;71:2281-90.

Genetic Etiology for Alcoholic Cardiomyopathy (ACM): Titin Truncating Variants (TTNtv) Represent a Prevalent Genetic Predisposition for ACM, Associated With a Worse LVEF

Among 141 ACM cases, 716 dilated CM (DCM) cases, and 445 healthy volunteers, variants in well-characterized DCM-causing genes were more prevalent in patients with ACM than control subjects (13.5% vs 2.9%; $p=1.2\times10^{-5}$), but similar between patients with ACM and DCM (19.4%; p=0.12) and with a predominant burden of titin truncating variants (TTNtv) (9.9%). Separately, an interaction was identified between *TTN* genotype and excess alcohol consumption in a cohort of DCM patients not meeting ACM criteria. On multivariate analysis, DCM patients with a TTNtv who consumed excess alcohol had an 8.7% absolute reduction in ejection fraction (LVEF) (p< 0.007) compared with those without TTNtv and excess alcohol consumption. The presence of TTNtv did not predict

phenotype, outcome, or functional recovery on treatment in ACM patients (Ware JS C et al, *J Am Coll Cardiol* 2018;71:2293-2302.

Better Clinical Outcomes of His Bundle Pacing (HBP) Compared to Right Ventricular Pacing (RVP)

HBP was successful in 304 of 332 (92%) consecutive patients (92%), whereas 433 patients underwent RVP. The primary endpoint of death, heart failure hospitalization (HFH), or upgrade to biventricular pacing (BiVP) was significantly reduced in the HBP group (25% vs 32%; hazard ratio -HR: 0.71; p=0.02). This difference was observed primarily in patients with ventricular pacing >20% (25% in HBP vs 36% in RVP; HR: 0.65; p=0.02). The incidence of HFH was significantly reduced in HBP (12.4% vs 17.6%; HR: 0.63; p=0.02). There was a trend toward reduced mortality in HBP (17.2% vs 21.4%, p=0.06) (Abdelrahman M et al, *J Am Coll Cardiol* 2018;71:2319-30).

DEFENSE-PFO: PFO Closure in Patients With High-Risk PFO Characteristics Resulted in a Lower Rate of the Primary Endpoint as Well as Stroke Recurrence

Among 120 patients with cryptogenic stroke (mean age: 51.8 years) randomized to PFO closure or medical therapy, the primary endpoint (stroke, vascular death, or major bleeding during 2 years of follow-up) occurred exclusively in the medication-only group (6 of 60 patients; 2-year event rate: 12.9%, p=0.013; 2-year rate of ischemic stroke: 10.5%, p=0.023). The events in the medication-only group included ischemic stroke (n=5), cerebral hemorrhage (n=1), major bleeding (n=2), and TIA (n=1). Nonfatal procedural complications included development of atrial fibrillation (n=2), pericardial effusion (n=1), and pseudoaneurysm (n=1) (Lee PH et al, *J Am Coll Cardiol* 2018;71:2335-42).

Risk of Endocarditis: Several Invasive Nondental Medical Procedures are Associated With a Markedly Increased Risk for Infective Endocarditis / Health Care Professionals Performing Particularly Risk-Prone Procedures Should Consider Every Possible Preventive Measure to Decrease the Excess Risk

Analysis of 7,013 cases of infective endocarditis in Sweden indicated that among others, several cardiovascular procedures, especially coronary artery bypass grafting (CABG); procedures of the skin and management of wounds; transfusion; dialysis; bone marrow puncture; and some endoscopies, particularly bronchoscopy, were strongly associated with an increased risk for infective endocarditis. For example, the relative risk (RR) was 6 for arterial puncture, 16 for bronchoscopy, 4.4 for cystoscopy, 4.2 for coronary angiography, 3.5 for PCI, ~10 for other CV procedures (EPS, IVUS), ~14 for CABG, etc. (Janszky I et al, *J Am Coll Cardiol* 2018; 71:2744-52).

CVD-REAL: Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2i) Conferred Lower Risk of Death and Heart Failure (HF) Regardless of Pre-Existing Cardiovascular Disease (CVD)

Among153,078 propensity score matched patients with diabetes (T2D) (13% with established CVD), initiation of an SGLT-2i was associated with lower risk of death in patients with and without CVD compared to other glucose-lowering drugs (HR: 0.56 and 0.56, respectively). There were also associations between SGLT-2i and lower risk of heart failure (HF) (HR: 0.72 and 0.61, respectively) and the composite of HF or death (HR: 0.63 and HR: 0.56, respectively) observed in patients with and without established CVD (Cavender MA et al, *J Am Coll Cardiol* 2018;71:2497-2506)

CVD-REAL 2: Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2i) in Patients with Diabetes (T2D) Conferred Lower Risk of Cardiovascular (CV) Events

After propensity-matching, there were 235,064 episodes of treatment initiation in each group; ~27% had established CV disease. Dapagliflozin, empagliflozin, ipragliflozin, canagliflozin, tofogliflozin, and luseogliflozin accounted for 75%, 9%, 8%, 4%, 3%, and 1% of exposure time in the SGLT-2i group, respectively. Use of SGLT-2i vs old glucose-lowering drugs (oGLDs) was associated with a lower risk of death (HR: 0.51, p< 0.001), heart failure hospitalization (HHF) (HR: 0.64, p=0.001), death or HHF (HR: 0.60, p< 0.001), MI (HR: 0.81, p< 0.001), and stroke (HR: 0.68, p< 0.001). Results were directionally consistent across both countries and patient subgroups, including those with and without CV disease (Kosiborod M et al, *J Am Coll Cardiol* 2018;71:2628-39).

Cocaine and/or Marijuana Use is Present in 10% of Patients With an MI at Age≤50 Years and is Associated With Worse All-Cause and Cardiovascular Mortality

Among 2,097 MI patients (age 44.0±5.1 years, 19.3% female, 73% white), cocaine and/or marijuana was used by 224 (10.7%); cocaine by 99 (4.7%), and marijuana by 125 (6.0%). Individuals with substance use had significantly lower rates of diabetes (14.7% vs 20.4%, p=0.05) and hyperlipidemia (45.7% vs 60.8%, p< 0.001), but they were significantly more likely to use tobacco (70.3% vs 49.1%, p< 0.001). Over a median of 11.2 years, use of cocaine and/or marijuana was associated with significantly higher cardiovascular mortality (hazard ratio-HR: 2.22, p=0.005) and all-cause mortality (HR: 1.99, p=0.001) (DeFilippis EM et al, *J Am Coll Cardiol* 2018;71:2540-51)

MANAGE Trial: Among Patients who Had Myocardial Injury after Non-Cardiac Surgery (MINS), Dabigatran 110 mg bid Lowered Risk of Major Vascular Complications, with no Significant Increase in Major Bleeding

Among 1754 patients with MINS randomly assigned to dabigatran (n=877) or placebo (n=877) (556 also randomized to omeprazole), the composite primary efficacy outcome (major vascular complication) occurred in fewer patients randomized to dabigatran than placebo (11% *vs* 15%; hazard ratio - HR 0.72, p=0.0115). The primary safety composite outcome (major bleeding) occurred in 3% in the dabigatran and 4% in the placebo group (HR 0.92, p=0.76) (Devereaux PJ et al, *Lancet* 2018;391:2325-34).

RADIANCE-HTN SOLO: Compared With a Sham Procedure, Endovascular Ultrasound Renal Denervation Reduced Ambulatory Blood Pressure at 2 Months in Patients With Combined Systolic–Diastolic Hypertension in the Absence of Medications

Among 146 patients randomized to undergo renal denervation (n=74) or a sham procedure (n=72), the reduction in daytime ambulatory systolic blood pressure was greater with renal denervation (−8.5±9.3 mmHg) than with the sham procedure (−2.2±10 mmHg; baseline-adjusted difference between groups: −6.3 mmHg, p=0.0001). No major adverse events were reported in either group (Azizi M JL et al, *Lancet* 2018;391:2335-45).

SPYRAL HTN-ON MED*:* Renal Denervation in the Main Renal Arteries and Branches Significantly Reduced Blood Pressure (BP) Compared With Sham Control With no Major Safety Events / Incomplete Medication Adherence was Common

Among 80 patients randomly assigned to renal denervation (n=38) and sham control (n=42), office and 24 h ambulatory BP decreased significantly from baseline to 6 months in the renal denervation group (mean baseline-adjusted treatment differences in 24 h systolic BP −7.0 mm Hg, p=0.0059, 24 h diastolic BP −4.3 mmHg, p=0.0174, office systolic BP −6.6 mm Hg, p=0.0250, and office diastolic BP −4.2 mm Hg, p=0.0190). The change in BP was significantly greater at 6 months in the renal denervation group than the sham-control group for office systolic BP (difference −6.8 mm Hg, p=0.0205), 24 h systolic BP (difference −7.4 mmHg, p=0.0051), office diastolic BP (difference −3·5 mmHg, p=0.0478), and 24 h diastolic BP (difference −4·1 mm Hg, p=0.0292). Evaluation of hourly changes in 24 h systolic and diastolic BP showed BP reduction throughout 24 h for the renal denervation group. 3-month BP reductions were not significantly different between groups. Medication adherence was about 60% and varied for individual patients throughout the study. No major adverse events were recorded in either group (Kandzari DE et al, *Lancet* 2018;391:2346-55).

DIVA Trial: In Patients Undergoing Stenting of Saphenous Vein Graft (SVG) Lesions, no Significant Differences in Outcomes Between DES and BMS at 1 Year / The Lower-Cost BMS Can be Used in SVG Lesions Without Compromising Safety or Efficacy

Among 597 patients (aged 68.6±7.6 years, 99% men) randomly assigned to drug eluting stents (DES) (n=292) or bare metal stents (BMS) (n=305), at 1 year, the incidence of target vessel failure was 17% in the DES group vs 19% in the BMS group (adjusted hazard ratio 0.92, p=0.70). Between-group differences in the components of the primary endpoint, serious adverse events, or stent thrombosis were not significant. Enrolment was stopped before the revised target sample size of 762 patients was reached (Brilakis ES et al, *Lancet* 2018; 391:1997-2007).

Meta-Analysis: In Selected Patients With Cryptogenic Stroke, PFO Closure is Superior to Medical Therapy for Prevention of Further Stroke, Particularly so for Patients With Moderate-To-Large Shunts

Meta-analysis of 5 studies (3440 patients: 1829 randomized to device closure and 1611 to medical therapy) indicated that across all patients, PFO closure was superior to medical therapy for prevention of stroke (hazard ratio - HR 0.32, p= 0.018, $I^2 = 73.4\%$). The risk of AF was significantly increased with device closure (risk ratio - RR 4.68, $p<0.001$, heterogeneity $I^2 = 27.5\%$). In patients with large shunts, PFO closure was associated with a significant reduction in stroke (HR 0.33; $p = 0.005$), whilst there was no significant reduction in stroke in patients with a small shunt (HR 0.90, $p = 0.712$). There was no effect from the presence or absence of an atrial septal aneurysm on outcomes ($P = 0.994$) (Ahmad Y et al, *Eur Heart J* 2018;39:1638-49).

Meta-Analysis: PFO Closure Confers Significant Reduction in Risk of Stroke vs Medical Management at the Expense of Increased Risk of Atrial Arrhythmias

Pooled analysis of 5 RCTs investigating 3630 PFO patients with cryptogenic stroke revealed that device closure compared to medical management was associated with a significant reduction in stroke (RR=0.3). There was, however, a significant increase in atrial arrhythmias with device therapy (RR=4.8). There was no increase in bleeding (RR=0.80), death (RR=0.76) or "any adverse events" (RR=1.02) with device therapy. Sub-group analysis revealed that device closure significantly reduced the incidence of the composite primary endpoint among

patients who had moderate to large shunt sizes (RR=0.22) (Riaz H et al, *Am Heart J* 2018;199:44-50).

Meta-Analysis: Compared with Triple (TAT), Double Antithrombotic Therapy (DAT) Shows a Reduction in Bleeding by 47% with Comparable Outcomes of MACE / DAT May be a Better Option than TAT in Many Patients with AF Following PCI

Meta-analysis of 4 trials including 5317 patients with AF undergoing PCI, of whom 3039 (57%) received DAT, showed that compared with the TAT arm, TIMI major or minor bleeding showed a reduction by 47% in the DAT arm (4.3% vs 9%; hazard ratio-HR 0.53, $I^2 = 42.9\%$). In addition, there was no difference in major adverse cardiac events (MACE) (10.4% vs 10%, HR 0.85, $I^2 = 58.4\%$), or in individual outcomes of all-cause mortality, cardiac death, MI, stent thrombosis, or stroke between the two arms (Golwala HB et al, *Eur Heart J* 2018;39:1726-35a).

Meta-Analysis: Outcomes in Patients with Angina Without Obstructive CAD are Worse in Patients With a Higher Burden of Cardiovascular Risk Factors, 'Some' Coronary Atherosclerosis, Typical Angina, and Well-Documented Myocardial Ischemia

Meta-analysis of 54 studies, reporting outcomes in overall 35,039 patients (mean age 56, male/female ratio 0.51) with angina and no obstructive CAD, showed that after a median of 5 years, the pooled incidence of the primary outcome (death and MI) was 0.98/100 person-years, with considerable heterogeneity among studies ($I^2 = 91\%$, $p < 0.001$). The primary outcome was associated with prevalent dyslipidemia ($P = 0.016$), diabetes ($P = 0.035$), and hypertension ($P = 0.016$). Studies enrolling patients with less-than-obstructive CAD showed a higher incidence of the primary outcome (1.32/100 person-years) compared with studies including only patients with 'entirely normal' coronary arteries (0.52/100 person-years, respectively; $p < 0.01$). Ischemia documented by non-invasive imaging techniques was associated with a higher incidence of events ($p = 0.02$). Overall, these patients, however, suffered from a high incidence of recurrent hospitalization (Radico F et al, *Eur Heart J* 2018;39:2135-46).

Patients with Heart Failure with Reduced Ejection Fraction (HFrEF) Taking Carvedilol Had Improved Survival as Compared to Metoprolol

A total of 43,941 metoprolol patients were matched with as many carvedilol patients. The adjusted hazard ratio of mortality for metoprolol succinate compared to carvedilol was 1.069 ($p < 0.001$). At 6 years, the survival probability was higher in the carvedilol group compared to the metoprolol group (55.6% vs 49.2%, $p < 0.001$). The sub-group analyses show that the results hold true separately for male, over or under 65 years old, therapy duration >3 months and non-diabetic patients (Ajam T et al, *Am Heart J* 2018;199:1-6).

Important Review and Other Articles

● 2018 ESC Guidelines for the diagnosis and management of ***syncope*** (Brignole M et al, *Eur Heart J* 2018;39:1883-1948)

● Cardiovascular imaging for the ***athlete's heart*** (Pelliccia A et al, *Eur Heart J* 2018;39: 1949-69)

● Expert Consensus Document on ***Takotsubo*** syndrome, Part I & II (Ghadri J-R et al, *Eur Heart J* 2018;39:2032-62)

● Acute Coronary Syndromes with Normal or Non-Obstructive Coronary Arteries (ACSNNOCA) (Manolis AS et al, *Trends Cardiovasc Med* 2018 May 23; doi: 10.1016/j.tcm.2018.05.006)

● Obesity (Gadde KM et al, *J Am Coll Cardiol* 2018;71:69-84)

● Ultrasound for lower extremity deep venous thrombosis (Needleman L et al, *Circulation* 2018;137:1505-1515

● Leptin-Aldosterone-Neprilysin Axis (Packer M, *Circulation* 2018;137:1614–1631)

● Thyroid hormones and cardiovascular function and diseases (Razvi S et al, *J Am Coll Cardiol* 2018;71:1781-96)

● Cerebrovascular events after cardiovascular procedures (Devgun JK et al, *J Am Coll Cardiol* 2018;71:1910-20)

● Psychopharmacology and cardiovascular disease (Pina IL et al, *J Am Coll Cardiol* 2018;71:2346–59)

● Chronic thromboembolic pulmonary hypertension (Mahmud E et al, *J Am Coll Cardiol* 2018;71:2468-86)

● 2018 ACC/HRS/NASCI/SCAI/SCCT Expert Consensus on Optimal Use of Ionizing Radiation in Cardiovascular Imaging: Best Practices for Safety and Effectiveness (Hirshfeld JW et al, *J Am Coll Cardiol* 2018;71: e283–351)

● Anthracycline cardiotoxicity (Henriksen PA, *Heart* 2018:104:971-77)

● ECG screening in athletes (Lampert R, *Heart* 2018;104:1037-43)

● Myocardial biopsy (Francis R & Lewis C, *Heart* 2018;104:950-8)

● Constrictive pericarditis (Welch TD, *Heart* 2018;104:725-31)

● PCSK-9 inhibitors (Landmesser U et al, *Eur Heart J* 2018;39:1131-43)

● 2018 EHRA Guide on use of NOACs in AF patients (Steffel J et al, *Eur Heart J* 2018;39:1330-93)

● Electrical cardiac injuries (Waldmann V et al, *Eur Heart J* 2018;39:1459-65)

● High altitude exposure (Parati G et al, *Eur Heart J* 2018;39:

● Re-innervation post-heart transplantation (Grupper A et al, *Eur Heart J* 2018;39:1799-1806)