Cardiology News / Recent Literature Review / Third Quarter 2019

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Rhythmos 2019;14(4):80-86.

HCS 40th Cardiology Congress: Ioannina, 17-19/10/2019

AHA Meeting: Philadelphia, PA, USA, 16-18/11/2019

HCS Working Groups: Thessaloniki, 20-22/2/2020

ACC Meeting: Chicago, IL, USA, 28-30/3/2020

EHRA Meeting: Vienna, 29-31/3/2020

HRS Meeting: San Diego, 6-9/5/2020

EuroPCR: Paris, 19-22/5/2020

ESC Meeting: Amsterdam, 29/8-2/9/2020

Carpal Tunnel Syndrome (CTS) is Associated With Amyloidosis, Heart Failure (HF), and Adverse Cardiovascular (CV) Outcomes

Among 56,032 patients from the Danish registries who underwent surgical treatment for CTS, compared with a sex- and age-matched cohort, CTS was associated with a future diagnosis of amyloidosis (hazard ratio-HR: 12.12), and a higher incidence of HF, (HR 1.54). Risk of other adverse outcomes was also associated with CTS ($p<0.0001$ for AF, AV block, and pacemaker implantation) (Fosbel EL et al, *J Am Coll Cardiol* 2019; 74:15-23).

MI Risk Stratification with a Single Measurement of High-Sensitivity Cardiac Troponin: an optimized threshold of <5 ng/l safely identified almost one-half of all patients as low risk at presentation, with hs-cTnI ≥120 ng/l identifying high-risk patients

Among 2,212 patients admitted for chest pain, acute MI occurred in 12%. Two assays of high-sensitivity cTnI had excellent sensitivities (98.6-99.6%) and negative predictive values (NPVs) (range 99.5-99.8%) for acute MI or death at 30 days across both assays. An optimized threshold of <5 ng/l identified almost one-half of all patients as low risk, with sensitivities of 98.6% and NPVs of 99.6% for acute MI or death at 30 days across both assays. For high-risk patients, hs-cTnI ≥120 ng/l resulted in positive predictive values for acute MI of ≥70% (Sandoval Y et al, *J Am Coll Cardiol* 2019; 74:271-82).

AG10, a Selective Transthyretin (TTR) Stabilizer, Appears a Safe and Effective Treatment for Patients With Amyloid TTR Cardiomyopathy (ATTR-CM)

Patients (n=49) with ATTR-CM (NYHA class II-III) were randomized 1:1:1 to AG10 400 mg, AG10 800 mg, or placebo bid for 28 days. AG10 is a selective, oral TTR stabilizer under development for ATTR-CM that mimics a protective TTR mutation. AG10 treatment was well-tolerated, achieved target plasma concentrations and achieved near-complete stabilization of TTR. TTR stabilization was more complete and less variable at the higher dose. Average serum TTR increased by 36 ± 21% and 51 ± 38% at 400 and 800 mg, respectively (both $p<0.0001$ vs placebo). Baseline serum TTR in treated subjects was below normal in 80% of mutant and 33% of wild-type subjects. AG10 treatment restored serum TTR to the normal range in all patients (Judge DP et al, *J Am Coll Cardiol* 2019; 74:285-95).

IMPULSE/PEFCAT: Pulsed Field Ablation (PFA) is a New Promising Mode Allowing Ultra-Rapid PV Isolation

During PFA, subsecond electric fields creating microscopic pores in cell membranes (electroporation) are particularly applicable to cardiomyocytes which have among the lowest thresholds to these fields, potentially permitting preferential myocardial ablation. Safety and effectiveness of catheter-PFA was assessed in 2 first-in-human trials in 81 patients with paroxysmal atrial fibrillation (AF). All PVs were acutely isolated by monophasic (n=15) or biphasic (n=66) PFA with ≤3 min elapsed delivery/patient, skin-to-skin procedure time of 92.2 ± 27.4 min, and fluoroscopy time of 13.1 ± 7.6 min. With successive waveform refinement, durability at 3 months improved from 18% to 100% of patients with all PVs isolated. There was only 1 procedure-related pericardial tamponade, with no additional adverse events over the 120-day median follow-up. The 12-month Kaplan-Meier estimate of freedom from arrhythmia was 87.4 ± 5.6% (Reddy VY et al, *J Am Coll Cardiol* 2019;74: 315-26).

Applying the ESC 0/1-Hour Algorithm in Patients With Suspected MI Leads to Short Time to Emergency Department (ED) Discharge, and Low Rate of 30-Day MACE

The ESC recommends the 0/1-h algorithm for rapid triage of patients with suspected NSTEMI based on high-sensitivity cardiac troponin (hs-cTn) concentrations at presentation and their absolute 1-h changes. Among 2,296 patients, NSTEMI prevalence was 9.8%. In median, 1-h blood samples were collected 65 min after the 0-h blood draw. Median ED stay was 2 h and 30 min. The ESC 0/1-h algorithm triaged 62% of patients toward rule-out, and 71% of all patients underwent outpatient management. Proportion of patients with 30-day MACE was 0.2% in the rule-out group and 0.1% in outpatients. Very low MACE

rates were confirmed in multiple subgroups, including early presenters (Twerenbold R et al, *J Am Coll Cardiol* 2019;74:483-94).

Cardiac Evaluation of Children With a Family History of Sudden Death (SD): The Strongest Predictors for a Successful Diagnosis Were an Abnormal ECG (Odds Ratio-OR 24.2) and a First-Degree Relationship to the Nearest Affected Relative (OR 18.8)

Among 419 pediatric relatives of 256 SD decedents, 27% had findings: 9.3% had a heritable cardiac disease, 5.5% had a nonheritable cardiac disease and 12.4% (n=52) had findings of uncertain significance, including abnormal electrophysiological test results (41 of 52) or imaging test results (11 of 52). Among patients diagnosed with a heritable cardiac disease, the nearest affected relative was almost always a first-degree relative (37 of 39, 95%). The strongest predictors for a successful diagnosis in the patient were an abnormal ECG and a first-degree relationship to the nearest affected relative (Webster G et al, *J Am Coll Cardiol* 2019; 74:759-70).

Physiologic Pacing via Biventricular (BiVP) or His Bundle Pacing (HisBP): Both Methods Appear to Mitigate the Deleterious Structural and Functional Effects of Right Ventricular Pacing (RVP) / Patients With Chronic AF and a Rapid Ventricular Rate Who Undergo AV Node Ablation Receive Most Benefit / Patients With LVEF 36-52% May be More Likely to Receive Clinical Benefit

Evidence from 8 studies (N=679) indicates that among patients who received physiologic pacing with either BiVP or HisBP, the LV end-diastolic and end-systolic volumes were significantly lower (mean duration of follow-up: 1.64 years; –2.77 mL; p=0.001; and –7.09 mL; p=0.0009) and LVEF remained preserved or increased (mean duration of follow-up: 1.57 years; 5.33%; p<0.0001). There was no effect on mortality. Patients with LVEF >35% but ≤52% were more likely to receive benefit from physiologic pacing. Patients with chronic AF who underwent AV node ablation and pacemaker implant demonstrated clear improvement in LVEF with BiVP or HisBP vs RVP (Slotwiner DJ H et al, *J Am Coll Cardiol* 2019; 73:988-1008).

Loss of Contractility Leading to Stasis of Blood Flow Following Left Atrial Appendage Electrical Isolation (LAAEI) Leads to Thrombus Formation

Among 1,854 consecutive post-LAAEI patients, the transesophageal echocardiography (TEE) performed at 6 months revealed preserved LAA velocity, contractility, and consistent A waves in 336 (18%; remained off OAC/ had no stroke events) and abnormal parameters in the remaining 1,518 (82%) patients, of whom 1,086 remained on OAC, and the incidence of stroke/TIA was 1.7%, whereas the number of TE events in the off-OAC patients (n=432) was 72 (16.7%); p <0.001. Of the 90 patients with stroke, 84 received left atrial appendage occlusion (LAAO) devices. At median 12.4 months of device implantation, 2 (2.4%) patients were on OAC because of high stroke risk or personal preference, whereas 81 discontinued OAC after LAAO without any TE events (Di Biase L et al, *J Am Coll cardiol* 2019; 74:1019-28).

ODYSSEY OUTCOMES: Alirocumab in Patients With Polyvascular Disease and Recent Acute Coronary Syndrome (ACS) Confers Large Risk Reductions, Including Those With CABG Preceding the ACS Event

Of 18,924 patients, 17,370 had monovascular CAD with MACE occurring in 10%, 1,405 had polyvascular disease in 2 beds (coronary and peripheral artery or cerebrovascular) with 22.2% MACE, and 149 had polyvascular disease in 3 beds (coronary, peripheral artery, cerebrovascular) with 39.7% MACE over a median of 2.8 years. With alirocumab, the corresponding absolute risk reduction was 1.4%, 1.9%, and 13%. With placebo, the incidence of death by respective vascular categories was 3.5%, 10%, and 21.8%; the absolute risk reduction with alirocumab was 0.4%, 1.3%, and 16.2% (Jukema JW et al, *J Am Coll Cardiol* 2019; 74:1167-76).

When patients were categorized by CABG status, i.e. no CABG (n=16,896); index CABG after qualifying ACS, but before randomization (n=1,025); or CABG before the qualifying ACS (n=1,003), in each CABG category, hazard ratios for MACE (no CABG 0.86, index CABG 0.85, prior CABG 0.77) and death (0.88, 0.85, 0.67, respectively) were consistent with the overall trial results (0.85 and 0.85, respectively). Absolute risk reductions differed across CABG categories for MACE (no CABG 1.3%, index CABG 0.9%, prior CABG 6.4%) and for death (0.4%, 0.5%, and 3.6%) (Goodman SG et al, *J Am Coll Cardiol* 2019; 74:1177-86).

ODYSSEY: Alirocumab Added to Intensive Statin Therapy Has the Potential to Reduce Death After ACS, Particularly if Treatment is Maintained for ≥3 Years, if Baseline LDL-Cholesterol is ≥100 mg/dl, or if Achieved LDL-C is Low

In 18,924 patients who had an acute coronary syndrome (ACS) 1-12 months previously and elevated cholesterol despite intensive statin therapy, alirocumab dose was blindly titrated to target achieved LDL cholesterol (LDL-C) between 25 and 50 mg/dL. Over a median of 2.8 years, death occurred in 334 (3.5%) and 392 (4.1%) patients, respectively, in the alirocumab and

placebo groups (hazard ratio -HR, 0.85; *P*=0.03). This resulted from nonsignificantly fewer CV (2.5% vs 2.9%; HR, 0.88; *P*=0.15) and non-CV (1% vs 1.3%; HR, 0.77; *P*=0.06) deaths with alirocumab. In a prespecified analysis of 8242 patients eligible for ≥3 years follow-up, alirocumab reduced death (HR, 0.78; *P*=0.01). Patients with nonfatal CV events were at increased risk for CV and non-CV deaths (*P*<0.0001). Alirocumab reduced total nonfatal CV events (*P*<0.001). A post hoc analysis found that, compared to patients with lower LDL-C, patients with baseline LDL-C ≥100 mg/dL had a greater absolute risk of death and a larger mortality benefit from alirocumab (HR, 0.71; $P_{interaction}$=0.007). In the alirocumab group, all-cause death declined with achieved LDL-C at 4 months of treatment, to a level of ~30 mg/dL (adjusted *P*=0.017 for linear trend) (Steg PG et al, *Circulation* 2019;140:103–112).

Anticoagulation (AC) After Surgical or Transcatheter Bioprosthetic Aortic Valve Replacement (AVR): In the Short Term, Early AC did not Result in Adverse Clinical Events, did not Significantly Affect Aortic Valve Hemodynamics, and Conferred Lower Rates of Stroke After SAVR (but not After TAVI)

Among 4,832 patients undergoing bioprosthetic AVR (TAVI, n=3,889 and surgical AVR - SAVR, n=943), there was no significant difference in aortic valve mean gradients or aortic valve areas between patients discharged on AC vs those not discharged on AC, for either TAVI or SAVR cohorts. A significantly greater proportion of patients not discharged on AC had an increase in mean gradient >10 mmHg from 30 days to 1 year, compared with those discharged on AC (2.3% vs 1.1%, p=0.03). There was no independent association between AC after TAVI and adverse outcomes, whereas AC after SAVR was associated with significantly fewer strokes (hazard ratio-HR: 0.17; p=0.006) (Chakravarty t et al et al, *J Am Coll Cardiol* 2019;74:1190-1200).

Spontaneous Coronary Artery Dissection (SCAD) and STEMI: Primary PCI is Successful in Most STEMI-SCAD Patients, With Low 3-Year Mortality

Among 5,208 STEMI patients, SCAD was present in 53 (1%; 93% female). SCAD prevalence was 19% in female STEMI patients aged ≤50 years. Compared with STEMI-atherosclerosis, STEMI-SCAD patients were younger (age 49 ± 10 years vs 63 ± 13 years), were more often female (93% vs 27%), and had more frequent cardiogenic shock (19% vs 9%) (all p≤ 0.03). In STEMI-SCAD, the culprit artery was more commonly left main (13% vs 1%) or LAD (47% vs 38%) (both p=0.003). Acute revascularization was lower in STEMI-SCAD (70% vs 97%; p<0.001) and included PCI in 33 (62%), or bypass in 4 (8%); PCI success was 91%. The 3-year survival was 98% for STEMI-SCAD vs 84% for regular STEMI (p<0.001) (Lobo AS et al, *J Am Coll Cardiol* 2019;74: 1290-1300).

Sleep Duration is a Potentially Causal Risk Factor for Myocardial Infarction (MI): Compared to Those With Favorable (6-9 h) Sleep Duration and the Least Difficulty Getting Up, Those With Unfavorable Sleep Duration (<6h or >9h) and Who Reported Hard Getting Up Had an 81% Higher Risk of Incident MI

In 461,347 UK Biobank (UKB) participants free of relevant CV disease, compared with sleeping 6-9 h/night, short sleepers had a 20% higher multivariable-adjusted risk of incident MI (HR: 1.20), and long sleepers had a 34% higher risk (HR: 1.34). Healthy sleep duration mitigated MI risk even among individuals with high genetic liability (HR: 0.82). Mendelian randomization was consistent with a causal effect of short sleep duration on MI (HR: 1.19/1.21) (Daghlas I et al, *J Am Coll Cardiol* 2019;74:1304–14).

Oral Fluoroquinolones (FQs) and Risk of Mitral and Aortic Regurgitation: The Risk is Highest With Current Use Followed by Recent Use

Recent studies have linked FQs to aortic dissection and aneurysm. The link of valvular (mitral and aortic) regurgitation with FQs was studied among 9,053,240 patients from a U.S. database. The reported odds ratio for the disproportionality analysis was 1.45 for valvular regurgitation. A total of 12,505 cases and 125,020 control subjects were identified in the case-control study. The adjusted RRs for current users of FQ compared with amoxicillin and azithromycin users were 2.40 and 1.75, respectively. The adjusted RRs for recent and past FQ users when compared with amoxicillin were 1.47 and 1.06, respectively. No risk was observed with past use of FQs (Etminan M et al *J Am Coll Cardiol* 2018;74:1444–50).

Meta-Analysis of 4 RCTs Comparing TAVI vs Surgical AVR in Low-Risk Patients: TAVI was Associated With Significantly Lower Risk of All-Cause Death and Cardiovascular (CV) Death at 1 Year

Meta-analysis of 4 RCTs that randomized 2,887 patients, 1,497 to TAVI and 1,390 to surgical AVR (mean age 75.4 years, mean STS-PROM score 2.3%) showed that compared with AVR, TAVI was associated with significantly lower risk of all-cause death (2.1% vs 3.5%; p=0.03; I^2=0%) and CV death (1.6% vs 2.9%; RR: 0.55; p=0.02; I^2=0%) at 1 year. Rates of new/worsening atrial fibrillation, life-threatening/disabling bleeding, and acute kidney injury stage 2/3 were lower, whereas those of permanent pacemaker implantation and moderate/severe

paravalvular leak were higher after TAVI vs AVR. There were no significant differences in major vascular complications, endocarditis, aortic valve re-intervention, and NYHA functional class ≥II (Kolte D et al, *J Am Coll Cardiol* 2018;74:1532–40).

Amyloid Transthyretin Cardiomyopathy (ATTR-CM) is a Belatedly Diagnosed, Progressive and Finally Fatal Cardiomyopathy Associated With Poor Quality of Life/ Improved Awareness and Wider Use of Recently Validated Diagnostic Imaging Methods are Needed to Benefit from Recent Therapeutic Developments

Among 711 patients with wild-type ATTR-CM, 205 with hereditary ATTR-CM associated with the V122I variant (V122I-hATTR-CM), and 118 with non-V122I-hATTR-CM, there was substantial diagnostic delay, with patients using hospital services a median of 17 times during the 3 years before diagnosis, by which time quality of life was poor; diagnosis of wild-type ATTR-CM was delayed >4 years after presentation with cardiac symptoms in 42% of cases. Patients with V122I-hATTR-CM were more impaired functionally (P<0.001) and had worse measures of cardiac disease (P<0.001) at the time of diagnosis, a greater decline in quality of life, and poorer survival (P<0.001) in comparison with the other subgroups (Lane T et al, *Circulation* 2019;140:16–26).

Three Public Health Interventions Could Save 94 Million Lives in 25 Years: Scaling Up Treatment of Hypertension to 70%, Reducing Sodium Intake by 30%, and Eliminating Artificial Trans Fatty Acids

The global mortality impact of 3 high-impact and feasible interventions was quantified: scaling up treatment of high blood pressure to 70%, reducing sodium intake by 30%, and eliminating the intake of artificial trans fatty acids. The combined effect of the 3 interventions delayed 94.3 million deaths during 25 years. Increasing coverage of antihypertensive medications to 70% alone would delay 39.4 million deaths, whereas reducing sodium intake by 30% would delay another 40.0 million deaths and eliminating trans fat would delay an additional 14.8 million. The estimated impact of trans fat elimination was largest in South Asia. Sub-Saharan Africa had the largest proportion of premature delayed deaths out of all delayed deaths (Kontis V et al, *Circulation* 2019;140:715–725).

EWTOPIA-75: LDL-C–Lowering With Ezetimibe Prevented CV Events, Suggesting The Importance Of LDL-C Lowering For Primary Prevention In Individuals Aged ≥75 Years With Elevated LDL-C

Among 3796 patients (>75 years) randomly assigned to ezetimibe (10 mg qd) vs control, over a median of 4.1 years, ezetimibe reduced the incidence of the primary outcome (sudden death, MI, revascularization or stroke) (HR, 0.66; P=0.002). Regarding the secondary outcomes, the incidences of composite cardiac events (HR, 0.60; P=0.039) and coronary revascularization (HR, 0.38; P=0.007) were lower in the ezetimibe than in the control group; however, there was no difference in the incidence of stroke, all-cause mortality, or adverse events between groups (Ouchi Y et al, *Circulation* 2019;140:992–1003).

External Cardioversion (CV) for Atrial Arrhythmias in Patients with ICDs is Superior for Restoration of Sinus Rhythm / Internal Cardioversion May Unmask Silent Lead Malfunction

In 230 ICD patients with atrial arrhythmias randomized to external vs internal CV, shock efficacy was 93% in the external CV group and 65% in the internal CV group (P<0.001). Clinically relevant adverse events caused by external or internal CV were not observed. Three cases of pre-existing silent lead malfunction were unmasked by internal shock, resulting in lead failure. Troponin release did not differ between groups (Luker J et al, *Circulation* 2019;140:1061–1069).

QT Prolongation and Torsade de Pointes (TdP) are a Risk in Men Receiving Enzalutamide and Other Androgen-Deprivation Therapies (ADTs)

Searching the pharmacovigilance database VigiBase for men (n=6,560,565 individual case safety reports) presenting with acquired long QT syndrome (aLQTS), TdP, or sudden death associated with ADT, we identified 184 cases of aLQTS (n=168) and/or TdP (n=68; 11% fatal), and 99 with sudden death. Of the 10 ADT drugs examined, 7 had a disproportional association (reporting odds ratio=1.4–4.7; P<0.05) with aLQTS, TdP, or sudden death. The minimum and median times to sudden death were 0.25 and 92 days, respectively. Enzalutamide was associated with more deaths (17%; P<0.0001) than other ADT used for prostate cancer (8.1%). In induced pluripotent stem cells, acute and chronic enzalutamide prolonged action potential durations (P<0.001), and generated afterdepolarizations and/or triggered activity in drug-treated cells. Enzalutamide acutely and chronically inhibited delayed rectifier potassium current, and chronically enhanced late sodium current. Dihydrotesto-sterone reversed enzalutamide EP effects (Salem J-E et al, *Circulation* 2019; 140:1070–1080).

PARTNER II: New LBBB Post-TAVI (15%) was Associated with Adverse Clinical Outcomes at 2 Years

In 2043 patients who had TAVI, clinical outcomes at 2 years were compared between patients with and without persistent, new-onset LBBB at hospital discharge. Among 1179 intermediate-risk patients, new-onset LBBB

occurred in 179 patients (15.2%). Patients with new LBBB were similar to those without, except for more frequent diabetes and treatment with SAPIEN 3 vs SAPIEN XT. At 2 years, new LBBB was associated with increased rates of all-cause mortality (19.3% vs 10.8%, $P = 0.002$), CV mortality (16.2% vs. 6.5%, $P < 0.001$), rehospitalization, and new pacemaker implantation. By multivariable analysis, new LBBB remained an independent predictor of 2-year all-cause (hazard ratio- HR 1.98; $P < 0.001$) and CV (HR 2.66; $P < 0.001$) mortality. New LBBB was also associated with worse LV systolic function at 1 and 2-year follow-up (Nazif TM et al, *Eur Heart J* 2019;40:2218–27).

Incident AF is Associated with Increased Risk of Dementia Independent of Stroke / Oral Anticoagulation Lowers Incidence of Dementia

The association of incident AF with incident dementia was assessed in 262,611 dementia- and stroke-free participants aged ≥60 years. During the observational period, the incidence of dementia was 4.1 and 2.7 per 100 person-years in the incident AF and propensity score-matched AF-free groups, respectively. After adjustment, the risk of dementia was significantly increased by incident AF with a hazard ratio-HR of 1.52, even after censoring for stroke (1.27). Incident AF increased the risk of both Alzheimer (HR 1.31) and vascular dementia (HR 2.11). Among patients with incident AF, oral anticoagulant use was associated with a preventive effect on dementia development (HR 0.61), and an increasing CHA_2DS_2-VASc score was associated with a higher risk of dementia (Kim D et al, *Eur Heart J* 2019;40: 2313–2323).

Older Atrial Fibrillation (AF) Patients Taking Oral Anticoagulation (OAC) Have Lower Risk of Dementia than Those Who do not use OAC

A retrospective of AF patients ($n = 91,254$) of whom 43% used OAC at baseline, showed that treatment with OAC was associated with lower risk of dementia after adjustment for death as a competing risk (subhazard ratio - sHR 0.62). Regarding the composite brain protection endpoint, OAC treatment was associated with an overall 12% lower risk (sHR 0.88). This apparent benefit was restricted to patients aged >65 years, whereas OAC treatment of patients <60 years of age without risk factors appeared to do more harm than good (Friberg L et al, *Eur Heart J* 2019;40: 2327–2335).

ELIMINATE-AF Trial: Uninterrupted Edoxaban Therapy Represents an Alternative to Uninterrupted VKA Treatment in Patients Undergoing AF Ablation

Among 553 AF patients undergoing ablation, randomized to endoxaban or VKA, major bleeds occurred in 0.3% (1 patient) on edoxaban and 2% (2 patients) on VKA (HR: 0.16). In the ablation population, the primary endpoint was observed in 2.7% of edoxaban (n= 10) and 1.7% of VKA patients ($n = 3$) between start and end of ablation. There were 1 ischemic and 1 hemorrhagic stroke, both in patients on edoxaban. Cerebral microemboli were detected in 13.8% (16) patients who received edoxaban and 9.6% (5) patients in the VKA group ($P = 0.62$) (Hohnloser SH et al, *eur Heart J* 2019;40: 3013–3021).

STITCH: Findings do not Support the Concept That Myocardial Viability is Associated With a Long-Term Benefit of CABG in Patients With Ischemic Cardiomyopathy / Presence of Viable Myocardium Was Associated With Improvement in Left Ventricular Systolic Function, Irrespective of Treatment, but Such Improvement was not Related to Long-Term Survival

Among 601 patients with LVEF ≤35% randomized to CABG plus medical therapy or medical therapy and followed for a median of 10.4 years, CABG plus medical therapy was associated with a lower incidence of death from any cause than medical therapy alone (adjusted hazard ratio, 0.73). However, no significant interaction was observed between the presence or absence of myocardial viability and the beneficial effect of CABG plus medical therapy over medical therapy alone (P=0.34 for interaction). An increase in LVEF was observed only among patients with myocardial viability, irrespective of treatment assignment. There was no association between changes in LVEF and subsequent death (Panza JA et al, *N Engl J Med* 2019; 381:739-748).

PIONEER 4: Oral Semaglutide was Non-Inferior to Subcutaneous Liraglutide and Superior to Placebo in Decreasing HbA_{1c}, and Bodyweight Compared With Both Liraglutide and Placebo at Week 26 / Safety and Tolerability of Oral Semaglutide Were Similar to Subcutaneous Liraglutide

Among 711 patients randomized to oral semaglutide (n=285), subcutaneous liraglutide (n=284), or placebo (n=142), mean change from baseline in HbA_{1c} at week 26 was −1.2% with oral semaglutide, −1.1% with subcutaneous liraglutide, and −0.2% with placebo. Oral semaglutide was non-inferior to subcutaneous liraglutide in decreasing HbA_{1c} and superior to placebo. Oral semaglutide had significantly greater decreases in HbA_{1c} than both subcutaneous liraglutide and placebo (p<0.0001) at week 26. Oral semaglutide resulted in superior weight loss compared with liraglutide. Adverse events were more frequent with oral semaglutide (80%) and subcutaneous liraglutide (74%) than with placebo (67%) (Pratley R et al, *Lancet* 2019;394:39-50)

PIONEER 6: In Patients With Type 2 Diabetes, the Cardiovascular (CV) Risk Profile of Oral Semaglutide was not Inferior to That of Placebo

A total of 3183 patients were randomized to oral semaglutide or placebo (mean age 66 years; 84.7% ≥50 years of age with CV or chronic kidney disease). Over a median of 15.9 months, major adverse CV events (MACE) occurred in 3.8% in the semaglutide group and 4.8% in the placebo group (hazard ratio-HR 0.79; P<0.001 for noninferiority); CV death in 0.9% vs 1.9% (HR, 0.49); nonfatal MI in 2.3% vs 1.9% (HR 1.18); and nonfatal stroke in 0.8% vs 1% (HR 0.74). Death from any cause occurred in 1.4% vs 2.8% (HR 0.51). Gastrointestinal adverse events leading to discontinuation of semaglutide or placebo were more common with oral semaglutide (Husain M et al, *N Engl J Med* 2019; 381:841-51).

A Polypill Strategy Led to Greater Reductions in Systolic Blood Pressure and LDL Cholesterol Than Were Observed With Usual Care in a Socioeconomically Vulnerable Minority Population

A total of 303 adults (96% black, 3/4 with annual income <$15,000, mean estimated 10-year CV risk 12.7%, baseline blood pressure 140/83 mm Hg, and baseline LDL cholesterol level 113 mg/dl) received a polypill (atorvastatin/amlodipine/losartan/thiazide; monthly cost $26). At 12 months, adherence to the polypill regimen was 86%. The mean systolic blood pressure decreased by 9 mmHg in the polypill group, as compared with 2 mmHg in the usual-care group (p=0.003). The mean LDL cholesterol level decreased by 15 mg/dl in the polypill group, as compared with 4 mg/dl in the usual-care group (p<0.001) (Munoz D et al, *N Engl J Med* 2019;381:1114-1123).

REWIND: Dulaglutide Could be Considered for the Glycemic Control in Middle-Aged and Older People With Type 2 Diabetes With Either Previous Cardiovascular (CV) Disease or CV Risk Factors

A total of 9901 participants (mean age 66.2 years, median HbA_{1c} 7.2%, 46.3% women) were randomized to dulaglutide (n=4949) or placebo (n=4952). During a median of 5.4 years, the primary composite outcome (MI, stroke or CV death) occurred in 12% in the dulaglutide group and 13.4% in the placebo group (hazard ratio-HR 0.88; p=0·026). All-cause mortality did not differ between groups (10.8% *vs* 12%; HR 0.90; p=0.067). Gastrointestinal adverse events were reported in 47.4% vs 34.1% (p<0.0001) (Gerstein H et al, *Lancet* 2019; 394:121-30).

DEBUT: PCI with Drug-Coated Balloon was Superior to Bare-Metal Stents in Patients at Bleeding Risk

208 patients were assigned to percutaneous coronary intervention (PCI) with drug-coated balloon (n=102) or bare metal stent (n=106). At 9 months, major adverse cardiac events (MACE) occurred in 1 patient (1%) in the drug-coated balloon group and in 15 (14%) in the bare-metal stent group (absolute risk difference −13.2 percentage points, risk ratio 0.07; p<0.00001 for non-inferiority and p=0.00034 for superiority). Two definitive stent thrombosis events occurred in the bare metal stent group but no acute vessel closures in the drug-coated balloon group (Rissanen TT et al, *Lancet* 2019; 394:230-9).

Polyran Study: Use of a Polypill was Effective in Preventing Major Cardiovascular (CV) Events

Among 6838 persons randomized to polypill (n=3421; hydrochlorothiazide 12.5 mg, aspirin 81 mg, atorvastatin 20 mg, and enalapril 5 mg or valsartan 40 mg for those with cough on enalapril) or to the minimal care group (n=3417), median adherence to polypill was 80.5%. At follow-up, 8.8% in the minimal care group had CV events compared with 5.9% in the polypill group (adjusted hazard ratio-HR 0.66). There was no significant interaction with the presence (HR 0.61) or absence of pre-existing CV disease. In the polypill group with high adherence, the reduction in the risk of CV events was even greater compared with the minimal care group (HR 0.43). The frequency of adverse events was similar between the two groups. 21 intracranial hemorrhages were reported over 5 years-10 participants in the polypill group and 11 participants in the minimal care group. There were 13 cases of upper GI bleeding in the polypill group and 9 in the minimal care group (Roshandel G et al, *Lancet* 2019;394:672-83).

THEMIS-PCI: In Patients With Diabetes, Stable Coronary Artery Disease, and Previous PCI, Ticagrelor Added to Aspirin Reduced Cardiovascular (CV) Death, Myocardial Infarction (MI), and Stroke, Although With Increased Major Bleeding

Among 11,154 patients with a previous PCI, over a median of 3.3 years, fewer patients receiving ticagrelor had a primary efficacy outcome (CV death, MI, stroke) event than in the placebo group (7.3% *vs* 8.6%; HR 0.85, p=0.013). The same effect was not observed in patients without PCI. The proportion of patients with CV death was similar (3.1% *vs* 3.3%; HR 0.96, p=0.68), as well as all-cause death (5.1% *vs* 5.8%; 0.88, p=0.11). TIMI major bleeding occurred in 2% vs 1.1% (HR 2.03, p<0.0001), and fatal bleeding in 0.1% of patients in each group (HR 1.13, p=0.83). Intracranial hemorrhage occurred in 0.6% and 0.6% patients (HR 1.21, p=0.45). Ticagrelor improved net clinical benefit: 9.3% vs 11%, HR=0.85, p=0.005, in contrast to patients without PCI where it did not. Benefit was present irrespective of time from most recent PCI (Bhatt DL et al, *Lancet* 2019; 394:1169-80).

Ten-Year AF Ablation Outcomes: Modest (58%) Efficacy of Single-Procedure / Enlarged Left Atrial Diameters Associated with More Recurrences

Among 176 (131 men, age 51.2 ± 12.1 years) patients with drug-refractory symptomatic PAF who underwent electroanatomic-guided PVI, after a mean of 10.8 ± 0.9 years, sinus rhythm was achieved in 102 (58%) patients after a single procedure (including 8% on antiarrhythmic drugs) and in 88% patients after multiple procedures (including 10% on antiarrhythmic drugs). Left atrial diameter (odds ratio 1.067; $P = 0.023$) was the predictor of recurrent AF after a single procedure. The single-procedure recurrence-free rates were similar between circumferential PVI and segmental PVI (59% and 50%; log-rank, p=0.251). The recurrence patterns of both groups regarding the role of non–PV and PV triggers were similar (Cheng W-H et al, *Heart Rhythm* 2019;16:1327-33)

Meta-Analysis: Vernakalant is Safe and Effective for Rapid and Durable Restoration of Sinus Rhythm in Patients With Recent-Onset AF

Meta-analysis of 9 (low quality) trials evaluating 1358 patients and comparing vernakalant with another drug (2 to ibutilide, 1 to amiodarone) or placebo (6), showed that for conversion within 90 min, vernakalant was superior to placebo (50% conversion, risk ratio - RR 5.15; $I^2 = 91\%$), whereas there was no significant difference in conversion when vernakalant was compared with an active drug (56% vs 24% conversion, RR 2.40; $I^2 = 94$). Sinus rhythm was maintained at 24 h in 85% with vernakalant. There was no difference in the risk of significant adverse events between vernakalant and comparator (RR 0.95; $I^2 = 0$, moderate quality evidence) (McIntyre WF et al, *Europace* 2019 Jul 10. pii: euz175. doi: 10.1093/europace/euz175. Epub ahead of print).

Important Review and Other Articles

2018 ACC/AHA/HRS **Guideline** on Evaluation & Management of Patients With **Bradycardia and Cardiac Conduction Delay** (Kusumoto FM et al, *J Am Coll Cardiol* 2019; 74:e51-e156)

● 2019 **ACC/AHA Guideline on the Primary Prevention of CV Disease** (Arnett DK et al, *J Am Coll Cardiol* 2019; 74: e177-e232 & *Circulation* 2019;140:e596–e646)

● 2019 AHA/ACC/HRS **Guideline** for the Management of Patients With **Atrial Fibrillation** (January CT et al, *Circulation* 2019;140:e125–e151)

● 2019 **ESC Guidelines** for the management of **SVT** (Brugada et al, *Eur Heart J* 2019; PMID: 31504425)

● **CAD & TAVI** (Faroux L et al, *J Am Coll Cardiol* 2019; 74:362-72)

● **Antithrombotic therapy in AF** patients undergoing **PCI** (Capodanno D et al, *J Am Coll Cardiol* 2019;74:83-99)

● **β-blockers** in CAD and heart failure (Joseph P et al, *J Am Coll Cardiol* 2019;74:672-82)

● **RAS inhibition** in CAD and heart failure (Leong DP et al, *J Am Coll Cardiol* 2019;74:683-98)

● **Antithrombotics** in CAD and AF (Verheugt FWA et al, *J Am Coll Cardiol* 2019;74:699-711)

● **AF and diabetes** (Wang A et al, *J Am Coll Cardiol* 2019;74:1107-15)

● Management of **conduction disturbances in TAVI** (Rodes-Cabau J et al, *J Am Coll Cardiol* 2019;74:1086-1106)

● Treatment of **type B Aortic Dissection** (Tadros RO et al, *J Am Coll Cardiol* 2019;74:1494-1504)

● **Vulnerable plaque** (Arbab-Zadeh A & Fuster V, *J Am Coll Cardiol* 2019;74:1582-93)

● **Plaque progression** (Ahmadi A et al, *J Am Coll Cardiol* 2019;74:1608-17)

● Expert consensus document on PCI for **chronic total occlusion (CTO)** (Brilakis ES et al, *Circulation* 2019;140:420–433)

● AHA Scientific statement on **diabetes and heart failure** (Dunlay SM et al, *Circulation* 2019;140:e294–e324)

● **Mitral valve prolapse**, ventricular arrhythmias and sudden death (Basso C et al, *Circulation* 2019;140:952–964)

● AHA advisory on omega-3 fatty acids for treatment of **hypertriglyceridemia** (Skulas-Ray AC et al, Circulation. 2019;140:e673–e691)

● Managing **cardiogenic shock** (Thiele H et al, Eur Heart J 2019;40:2671–2683)

● **Pheochromocytoma** and paraganglioma (Neumann HPH et al, *N Engl J Med* 2019; 381:552-565)

● **Adrenal crisis** (Rushworth RL et al, *N Engl J Med* 2019; 381:852-861)

● Treatment of **hypertension in patients with asthma** (Christiansen & Zuraw, *N Engl J Med* 2019;381:1046-1057)

● **Primary prevention of ischemic heart disease** (Gupta & Wood, *Lancet* 2019;394:685-696)

● **Thromboembolism** in the absence of AF (Smietana Jet al, *Am J Cardiol* 2019;124:303-311)

● **Cardiac amyloidosis** (Manolis AS et al, *Eur J Intern Med* 2019;67:1-13)

● 2019 HRS/EHRA expert consensus statement on catheter **ablation of ventricular arrhythmias** (Cronin EM et al, *EP Europace* 2019;21:1143)