

Cardiology News / Recent Literature Review / First Quarter 2018

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ICD in Children & Adolescents with Brugada Syndrome: ~1 in 4 Patients Receive Appropriate Life-Saving Interventions Over a Period of 7 Years, Although Inappropriate Shocks and Other Adverse Events Occur Relatively Frequently

Among 35 consecutive patients (aged 13.9±6.2 years) over a mean of 88 months, sustained ventricular arrhythmias were treated by the ICD in 9 patients (26%), including shocks in 8 (23%) and antitachycardia pacing in 1 patient (3%). Three patients (9%) died in an electrical storm. Seven patients (20%) experienced inappropriate shocks, and 5 (14%) had device-related complications. Aborted sudden cardiac death and spontaneous type I ECG were identified as independent predictors of appropriate shock occurrence (Gonzalez Corcia MC et al, *J Am Coll Cardiol* 2018;71: 148–57).

Cardiomyopathy (CM) Patients With LVEF≤35% and LBBB Demonstrate Significantly Less LV Functional Recovery With Medical Therapy Than Do Those With a Narrow QRS / Thus, They Would Benefit From Earlier Implantation of a CRT Device

Among 659 patients with CM, 111 having LBBB (17%), 59 wide QRS duration ≥120 ms but not LBBB (9%), and 489 narrow QRS duration (74%), adjusted mean increase in LVEF over 3-6 months in the 3 groups was 2.03%, 5.28%, and 8%, respectively (p<0.0001), with no different results for interim revascularization and myocardial infarction. The combined endpoint of heart failure hospitalization or mortality was highest for patients with LBBB (Sze et al, *J Am Coll Cardiol* 2017;71: 306-17).

1-Year Follow-Up of PRAGUE-18 Study: Among Patients With MI Undergoing Primary PCI, Antiplatelet Therapy With Prasugrel or Ticagrelor is Associated With Similar Outcomes / Economically Motivated, Early Post-Discharge Switch To Clopidogrel was not Associated With Increased Risk of Ischemic Events

Among 1,230 patients with acute myocardial infarction (MI) treated with primary PCI and randomized

to prasugrel or ticagrelor, the endpoint (cardiovascular death, MI, or stroke at 1 year) occurred in 6.6% of prasugrel patients and in 5.7% of ticagrelor patients (hazard ratio: 1.167; p = 0.503). No significant differences were found in: CV death (3.3% vs 3%), MI (3% vs. 2.5%), stroke (1.1% vs 0.7%), all-cause death (4.7% vs. 4.2%), definite stent thrombosis (1.1% vs. 1.5%), all bleeding (10.9% vs. 11.1%), and TIMI major bleeding (0.9% vs. 0.7%). The percentage of patients who switched to clopidogrel for economic reasons was 34.1% (n=216) for prasugrel and 44.4% (n=265) for ticagrelor (p=0.003). Patients who were economically motivated to switch to clopidogrel had (compared with patients who continued the study medications) a lower risk of major CV events; however, they also had lower ischemic risk (Motovska Z et al, *J Am Coll Cardiol* 2018;71:371-81).

DAWN Trial: Among Patients With Acute Stroke Who Had Last Been Known to be Well 6 - 24 Hours Earlier and Who Had a Mismatch Between Clinical Deficit and Infarct, Outcomes for Disability at 90 Days were Better With Thrombectomy Plus Standard Care Than With Standard Care Alone

206 ischemic stroke patients with occlusion of the intracranial internal carotid artery or proximal middle cerebral artery who had last been known to be well 6 -24 hours earlier and who had a mismatch between the severity of the clinical deficit and the infarct volume were enrolled (107 assigned to thrombectomy and 99 to controls). At 31 months, the mean score of disability on the utility-weighted modified Rankin scale at 90 days was 5.5 in the thrombectomy group as compared with 3.4 in the control group, and the rate of functional independence at 90 days was 49% in the thrombectomy group as compared with 13% in the control group (posterior probability of superiority, >0.999). The rate of symptomatic intracranial hemorrhage did not differ significantly between the two groups (6% vs 3%), nor did 90-day mortality (19% vs 18%) (Nogueira RG et al, *N Engl J Med* 2018; 378:11-21)

DEFUSE 3 Study: In Acute Ischemic Stroke Due to Large-Vessel Occlusion With Favorable Findings on Perfusion Imaging, Endovascular Therapy 6-16 Hours After Stroke Onset Resulted in Less Disability and a Higher Rate of Functional Independence at 3 Months

This trial was terminated early for efficacy after 182 patients had been randomized (92 to endovascular-therapy and 90 to medical-therapy). Endovascular therapy plus medical therapy, as compared with medical therapy alone, was associated with a favorable shift in the distribution of functional outcomes on the modified Rankin scale at 90 days (odds ratio, 2.77; P<0.001) and a higher percentage

of patients who were functionally independent (45% vs 17%, $P<0.001$). The 90-day mortality rate was 14% in the endovascular-therapy group and 26% in the medical-therapy group ($P=0.05$), and there was no significant between-group difference in the frequency of symptomatic intracranial hemorrhage (7% and 4%, respectively; $P=NS$) or of serious adverse events (43% and 53%, respectively; $P=NS$) (Albers GW et al, *N Engl J Med* 2018; 378:708-718).

CASTLE-AF: Catheter Ablation for Atrial Fibrillation (AF) in Patients with Heart Failure was Associated with a Significantly Lower Rate of a Composite End Point of Death From any Cause or Hospitalization for Worsening Heart Failure than was Medical Therapy

Among randomized patients to catheter ablation (179 patients) or medical therapy (184 patients) for AF, over a median of 37.8 months, the primary composite end point occurred in significantly fewer patients in the ablation group than in the medical-therapy group (51 patients or 28.5% vs 82 patients or 44.6%; hazard ratio-HR, 0.62; $P=0.007$). Significantly fewer patients in the ablation group died from any cause (24 or 13.4% vs 46 or 25%; HR, 0.53; $P=0.01$), were hospitalized for worsening heart failure (37 or 20.7% vs 66 or 35.9%; HR, 0.56; $P=0.004$), or died from cardiovascular causes (20 or 11.2% vs 41 or 22.3%; HR, 0.49; $P=0.009$) (Marrouche NF et al, *N Engl J Med* 2018; 378:417-427).

Significant Association Between Influenza Infection and Acute Myocardial Infarction (MI)

A total of 364 hospitalizations were identified for acute MI that occurred within 1 year before and 1 year after a positive test result for influenza. Of these, 20 (20 admissions per week) occurred during the risk interval and 344 (3.3 admissions per week) occurred during the control interval. The incidence ratio of an admission for acute MI during the risk interval as compared with the control interval was 6.05. No increased incidence was observed after day 7. Incidence ratio for acute MI within 7 days after detection of influenza B was 10.11, 5.17 for influenza A, 3.51 for respiratory syncytial virus, and 2.77 for other viruses (Kwong JC, *N Engl J Med* 2018; 378:345-353).

CABG had a Mortality Benefit Over PCI In Patients With Multivessel Disease, Particularly Those With Diabetes and Higher Coronary Complexity. No Benefit for CABG Over PCI was Seen in Patients With Left Main Disease

Analysis of 11 randomized trials involving 11 518 patients assigned to PCI ($n=5753$) or to CABG ($n=5765$) showed a 5-year all-cause mortality of 11.2% after PCI and 9.2% after CABG (hazard ratio -HR 1.20; $p=0.0038$). 5-

year all-cause mortality was significantly different between the interventions in patients with multivessel disease (11.5% after PCI vs 8.9% after CABG; HR 1.28; $p=0.0019$), including in those with diabetes (15.5% vs 10%; HR 1.48, $p=0.0004$), but not in those without diabetes (8.7% vs 8%; HR 1.08; $p=0.49$). SYNTAX score had a significant effect on the difference between the interventions in multivessel disease. 5-year all-cause mortality was similar between the interventions in patients with left main disease (10.7% vs 10.5%), regardless of diabetes status and SYNTAX score. (Head SJ A et al, *Lancet* 2018;391:939-948).

TASMINH4 Trial: Self-Monitoring, With or Without Telemonitoring, When Used by General Practitioners to Titrate Antihypertensive Medication in Individuals With Poorly Controlled Blood Pressure, Leads to Significantly Lower Blood Pressure Than Titration Guided by Clinic Readings

Among 1182 hypertensive patients, aged >35 years, with blood pressure >140/90 mmHg, randomly assigned to self-monitoring ($n=395$), telemonitoring ($n=393$), or usual care group ($n=394$), of whom 1003 (85%) were analyzed, after 12 months, systolic blood pressure was lower in both intervention groups compared with usual care (self-monitoring, 137 ± 16.7 mm Hg and telemonitoring, 136 ± 16.1 mm Hg vs usual care, 140.4 ± 16.5). No difference between the self-monitoring and telemonitoring groups was recorded. Results were similar in sensitivity analyses including multiple imputation. Adverse events were similar between all three groups (McManus RJ et al, *Lancet* 2018;391: 949-959).

Excess Mortality, Frequent Heart Failure and Undertreatment of Mitral Regurgitation (MR) in a Community Setting

Over 10 years, 1294 community residents (median age at diagnosis 77 years) were diagnosed with moderate or severe MR by Doppler (prevalence 0.46% overall; 0.59% in adults). Left-ventricular ejection fraction (LVEF) <50% was frequent (42%), and these patients had a slightly lower regurgitant volume than those with an LVEF of $\geq 50\%$. Post-diagnosis mortality was mainly cardiovascular in nature (51%) and higher than expected for residents of the county for age or sex (risk ratio -RR 2.23, $p<0.0001$). This excess mortality affected all subsets of patients, whether they had a LVEF <50% (RR 3.17, $p<0.0001$) or $\geq 50\%$ (1.71, $p<0.0001$) and with primary (RR 1.73, $p<0.0001$) or secondary MR (2.72, $p<0.0001$). Even patients with a low comorbidity burden combined with favourable characteristics such as LVEF of $\geq 50\%$ (RR 1.28, $p<0.0017$) or primary MR (1.29, $p=0.0030$) incurred

excess mortality. Heart failure was frequent (mean 64% at 5 years postdiagnosis), even in patients with LVEF of $\geq 50\%$ (49% at 5 years postdiagnosis) or in those with primary MR (48%). Mitral surgery was ultimately done in only 198 (15%) of 1294 patients, of which the predominant type of surgery was valve repair (75%). Mitral surgery was done in 28 (5%) of 538 patients with LVEF $< 50\%$ and in 170 (22%) of 756 patients with LVEF of $\geq 50\%$, and in 34 (5%) of 723 with secondary MR vs 164 (29%) of 571 with primary MR (Dziadzko V et al, *Lancet* 2018;391:960–9).

LAA Occlusion May be a Reasonable Option for Stroke Prevention in High-Risk Patients With Atrial Fibrillation (AF) Ineligible for Anticoagulation / However, Procedural Complication Rates are High, and Patients Remain at Risk of Serious Adverse Events and Death Even After Successful Implant of the Amplatzer Amulet LAA Occluder

Of 83 patients (age 76 ± 8 years, 32.5% female, mean CHAD₂S₂-VASc score 4 ± 1) offered LAA occlusion, 80 (95.3%) had previous major bleeding (intracranial in 59%). LAA occluder implantation 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 2 months later showed device-related thrombus in 1 (1.3%) and minor (< 5 mm) 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 (Masoud A et al *Heart* 2018;104:594–9).

Alarming Results for Left Atrial Appendage Closure with Lariat and Watchman Devices with Higher Complication Rates Reported Post-FDA Approval

Over 10 years (2006–2016) the Lariat® device was implanted in 4,889 patients and the Watchman™ in 5,849 patients (2,027 prior to FDA approval in March 2015 and 3,822 patients post-approval). The complication rate observed with Watchman was higher than what has been reported in recent registries, with higher point estimates for pericardial tamponade (0.5% higher), pericardial effusion (+0.15%), periprocedural stroke (+0.082%), device embolization (+0.28%), and death (+0.21%). In addition, the composite endpoint of stroke/TIA, pericardiocentesis, cardiac surgery, and death was higher with Watchman compared with Lariat (1.93% vs 1.15%, $P = 0.001$). The authors concluded that post-approval new technology adoption may be associated with increased complications

compared with premarket data (Jazayeri M-A et al, *J Cardiovasc Electrophysiol* 2018;29:5–13).

Meta-analysis of Chronic Total Occlusion (CTO) PCI Studies Identifies Predictors Associated With $> 20\%$ Reduction in Clinical/Technical Success: 5 Demographic Negative Predictors (History of MI/PCI/CABG, PVD and Stroke) / 8 Angiographic Predictors (Non-LAD CTO, Multivessel Disease, Bridging Collaterals, Moderate-to-Severe Calcification, $> 45^\circ$ Bending, Tortuous Vessel, Blunt Stump and Ostial Lesion)

Meta-analysis of 61 studies including 69 866 patients analyzing rates of CTO PCI success showed $\geq 20\%$ reduction in the odds of technical and clinical success with a prior history of MI, PCI, CABG, stroke/TIA and peripheral vascular disease (PVD). Angiographic factors were generally stronger predictors of reduced technical and clinical success: non-LAD CTOs, multivessel disease, presence of bridging collaterals, moderate-to-severe calcification, > 45 degree vessel bending, tortuous vessel, blunt stump and ostial lesions (Wang N et al, *Heart* 2018;104:517–24).

Pooled Analysis of β -Blocker Trials Demonstrates Reductions in All-Cause and Cardiovascular Mortality by 22% and 25%, Respectively, With no Pooled Effect Seen in ACE Inhibitor, ARB and MRA Trials in Patients With Heart Failure and Preserved Ejection Fraction ($\geq 40\%$) (HFpEF)

Data from 25 RCTs comprising 18,101 HFpEF patients showed that all-cause mortality was reduced with beta-blocker therapy compared with placebo (RR: 0.78, $p = 0.008$). There was no effect seen with ACE inhibitors, aldosterone receptor blockers, mineralocorticoid receptor antagonists and other drug classes, compared with placebo. Similar results were observed for cardiovascular mortality. No single drug class reduced heart failure hospitalization compared with placebo (Zheng SL et al, *Heart* 2018;104:407–415).

The Outcomes of Patients With Aortic Stenosis (AS) With an AVA of 0.8 – 0.99 cm² are Variable and are More Precisely Defined by Flow-Gradient Status / The Current AVA Cut-Off of 1 cm² is Inclusive of All Flow-Gradient AS Subtypes

Patients with isolated, severe AS and ejection fraction $\geq 55\%$ with an AVA of 0.8 – 0.99 cm² ($n = 105$) were compared with those with an AVA < 0.8 cm² ($n = 155$) and 1.0 – 1.3 cm² ($n = 81$). Patients with an AVA of 0.8 – 0.99 cm² group comprised predominantly normal-flow, low-gradient (NFLG) AS, while high gradients and low flow were more often observed with an AVA < 0.8 cm². The

frequency of symptoms was not significantly different between an AVA of 0.8–0.99 cm² and 1.0–1.3 cm². The combined endpoint (death or AVR at or before 3 years) was achieved in 71%, 52% and 21% of patients with an AVA of 0.8 cm², 0.8–0.99 cm² and 1.0–1.3 cm², respectively (p<0.001). Among patients with an AVA of 0.8–0.99 cm², NFLG AS was associated with a lower hazard (HR=0.40, p=0.001) of achieving the combined endpoint with outcomes similar to moderate AS in the first 1.5 years of follow-up. Patients with high-gradient or low-flow AS with an AVA of 0.8–0.99 cm² had outcomes similar to those with an AVA<0.8 cm² (Mehrotra P et al, *Heart* 2018;104:222-229).

Updated Meta-Analysis Demonstrates a Survival Benefit of ICD Therapy in Non-Ischemic Cardiomyopathy (NICM)

Meta-analysis of 6 primary prevention trials and 2 secondary prevention trials representing 3226 NICM patients revealed a 24% reduction in overall mortality with ICD therapy (RR 0.76) (Beggs SAS et al, *Heart* 2018;104:144-150).

High 30-Day Mortality Rate in Both Emergency Balloon Aortic Valvuloplasty (eBAV) (33%) and Emergency TAVI (eTAVI) Procedures (23.8%) Compared to 21.9% Mortality Rate for Elective TAVI After eBAV / Primary eTAVI May be a Viable Option, Albeit at Unexpected High Rate of Cerebral Events and Vascular Complications

In 5 German centers, 23 patients (logistic Euroscore 37.7%±18.1) underwent eTAVI and 118 patients underwent eBAV (logistic Euroscore 35.3%±20.8). In the eTAVI group, immediate procedural mortality was 8.7%, compared with 20.3% for the eBAV group (p=0.19). After 30 days, cardiovascular mortality for the eTAVI group was 23.8% and for the eBAV group 33% (p=0.40). Of note, the elective TAVI performed after eBAV (n=32, logistic Euroscore 25.9%±13.9) displayed an immediate procedural mortality of 9.4% and a cardiovascular mortality after 30 days of 15.6%. Major vascular complications were significantly more likely to occur after eTAVI (p=0.01) as well as stroke (p=0.01) (Bongiovanni D et al, *Heart* 2018;104:23-29).

Half of the Deaths Directly Related to a Heart Rhythm Disorder Management (HRDM) Procedure Were Among the Patients Undergoing Device Implantation Procedures, With Cardiac Tamponade Being the Most Common Cause of Death

Among 48 913 patients (age, 65.7±6.6 years; 64% male) who underwent a total of 62 065 HRDM procedures, the overall mortality and stroke rates in the cohort were

0.36% and 0.12%, respectively. Patients undergoing lead extraction had the highest overall mortality rate at 1.9% and stroke rate at 0.62%. Among patients undergoing HRDM procedures, 48% of deaths directly related to the HRDM procedure were among patients undergoing device implantation procedures. Overall, cardiac tamponade was the most frequent direct cause of death (40%), and infection was the most common indirect cause of death (29%). The overall 30-day mortality rate was 0.76%, with the highest being in lead extraction procedures (3.08%), followed by device implantation procedures (0.94%) (Lee JZ et al, *Circulation* 2018;137:24-33).

CANVAS: Canagliflozin Reduced Cardiovascular (CV) and Renal Outcomes in Diabetic Patients with High CV Risk

Primary prevention participants (N=3486; 34%) were younger (63 vs 64 years of age), more often female (45% vs 31%), and had a longer duration of diabetes mellitus (14 vs 13 years) compared with secondary prevention participants (N=6656; 66%). The primary end point (CV death, nonfatal MI & stroke) event rate was higher in the secondary prevention group (36.9 vs 15.7/1000 patient-years, P<0.001). In the total cohort, the primary end point was reduced with canagliflozin compared with placebo (26.9 vs 31.5/1000 patient-years; hazard ratio -HR, 0.86; P<0.001 for noninferiority, P=0.02 for superiority). Renal outcomes (HR, 0.59 vs HR, 0.63; interaction P value = 0.73) and heart failure hospitalization (HR, 0.68 vs HR, 0.64; interaction P value=0.91) were similarly reduced in the secondary and primary prevention cohorts. Lower extremity amputations were similarly increased in the secondary and primary prevention cohorts (HR, 2.07 vs HR, 1.52; interaction P value=0.63) (Mahaffey KW et al, *Circulation* 2018;137:323-34).

IRIS Trial: Pioglitazone Was Effective for Secondary Prevention of Ischemic Stroke in Nondiabetic Patients With Insulin Resistance

Among 3876 participants (mean age, 63 years; 65% male), 377 stroke events were observed in 319 participants over a median follow-up of 4.8 years. Pioglitazone was associated with a reduced risk for any stroke at 5 years (8% vs 10.7% for the placebo group; hazard ratio -HR, 0.75; log-rank P=0.01). Pioglitazone reduced risk for ischemic strokes (HR, 0.72; P=0.005) but had no effect on risk for hemorrhagic events (HR, 1; P=NS) (Yaghi S et al, *Circulation* 2018;137:455-463).

Takotsubo Cardiomyopathy (TC): Persistent Long-Term Changes (Heart Failure Phenotype)

Among 37 patients (middle-aged 64±11 women 97%) with history of TC 20 months earlier, the majority (88%)

of them had persisting symptoms compatible with heart failure (median of 13 in the Minnesota Living with Heart Failure Questionnaire) and cardiac limitation on exercise testing (reduced peak oxygen consumption, 24 ± 1.3 vs 31 ± 1.3 mL/kg/min, $P < 0.001$; increased VE/VCO₂ slope, 31 ± 1 vs 26 ± 1 , $P = 0.002$). Despite normal left ventricular ejection fraction and serum biomarkers, patients with prior TC had impaired cardiac deformation indices, increased native T1 mapping values, and impaired cardiac energetic status (Scally C et al, *Circulation* 2018;137:1039-48).

REDUCE LAP-HF 1: In Patients With Heart Failure (HF) and EF $\geq 40\%$, Implantation of an Interatrial Shunt Device (IASD) (8-mm Interatrial Communication) Unloaded the Left Atrium and Reduced Pulmonary Wedge Pressure (PWP) During Exercise to a Greater Extent Than a Sham Control Procedure

In 44 HF patients (aged 70 ± 9 years; 50% female) randomized to the IASD ($n=22$) and control ($n=22$) groups, at 1 month, the IASD resulted in a greater reduction in PWP compared with sham control ($P=0.028$). Peak PWP decreased by 3.5 ± 6.4 mm Hg in the treatment group vs 0.5 ± 5.0 mm Hg in the control group ($P=0.14$). There were no peri-procedural or 1-month major adverse cardiac, cerebrovascular, and renal events in the IASD group and 1 event (worsening renal function) in the control group ($P=NS$) (Feldman T et al; *Circulation* 2018;137:364-75).

Community-Based Framingham Heart Study: The Lifetime Risk of AF Was 37% After 55 Years of Age/ Estimation of Polygenic AF Risk is Feasible and Together With Clinical Risk Factor Burden Explains a Substantial Gradient in Long-Term AF Risk

Polygenic risk for AF was derived using a score of ≈ 1000 AF-associated single-nucleotide polymorphisms (SNPs). Clinical risk factor burden was calculated for each individual using a validated risk score for incident AF comprised of height, weight, systolic and diastolic blood pressure, current smoking status, antihypertensive medication use, diabetes mellitus, history of MI, and history of heart failure (CHARGE-AF score).

Among 4606 participants without AF at 55 years of age, 580 developed incident AF (median follow-up, 9.4 years). The lifetime risk of AF >55 years of age was 37.1% and was substantially influenced by both polygenic and clinical risk factor burden. Among individuals free of AF at 55 years of age, those in low-polygenic and clinical risk tertiles had a lifetime risk of AF of 22.3%, whereas those in high-risk tertiles had a risk of 48.2%. A lower clinical risk factor burden was associated with later AF onset after adjusting for genetic predisposition ($P < 0.001$) (Weng L-C et al, *Circulation* 2018;137:1027-38).

TOPAS-TAVI Registry: Patients With Low-Flow/Low-Gradient Aortic Stenosis (LFLG-AS), TAVI Was Associated With Good Early Outcomes, But $>1/3$ of the Patients Survived <2 Years / Pulmonary Disease, Anemia and Paravalvular Leaks Were Associated With Poorer Outcomes

Among 287 patients with LFLG-AS undergoing TAVI (median STS score 7.7%; mean LVEF $30.1 \pm 9.7\%$ and transvalvular gradient 25.4 ± 6.6 mmHg), the presence of contractile reserve was observed in 45% of patients at dobutamine stress echo (DSE), mortality rates were 3.8%, 20.1%, and 32.3% at 30 days, 1 year, and 2 years, respectively. On multivariable analysis, chronic obstructive pulmonary disease ($p=0.022$) and lower hemoglobin values ($p < 0.001$) were associated with all-cause mortality. Lower hemoglobin values ($p=0.004$) and moderate-to-severe aortic regurgitation post-TAVI ($p = 0.018$) were predictors of the composite of mortality and rehospitalization due to heart failure. LVEF increased by 8.3% at 1-year. The absence of contractile reserve at baseline DSE was not associated with any negative effect on clinical outcomes or LVEF changes at follow-up (Ribeiro HB et al, *J Am Coll Cardiol* 2018; 71:1297-308).

Abandoning Digoxin Long Overdue: Initiation of Digoxin in Patients With AF is Associated With Higher Mortality, Regardless of Heart Failure Status / In Patients With AF Already Taking Digoxin, Serum Levels should be Monitored, with Target <1.2 ng/ml

Among 17,897 participants in the ARISTOTLE trial, 5,824 (32.5%) patients were receiving digoxin. Baseline digoxin use was not associated with an increased risk of death, however, patients with a serum digoxin concentration ≥ 1.2 ng/ml had a 56% increased hazard of mortality compared with those not on digoxin. When analyzed as a continuous variable, serum digoxin concentration was associated with a 19% higher adjusted hazard of death for each 0.5-ng/ml increase ($p=0.0010$); these results were similar for patients with and without heart failure. Compared with propensity score-matched control participants, the risk of death (HR: 1.78) and sudden death (HR: 2.14) was significantly higher in new digoxin users (Lopes RD C et al, *J Am Coll Cardiol* 2018;71:1063-74).

Meta-Analysis: Compared With Medical Treatment, PFO Closure Prevents Recurrent Stroke and TIA But Increases Incidence of AF

Meta-analysis of 4 trials, involving 2531 patients, found that PFO closure reduced the risk for the main outcome of stroke or TIA (risk difference -RD, -0.029) and increased the risk for new-onset AF or AF_{fl} (RD,

0.033). The beneficial effect of PFO closure was associated with larger interatrial shunts ($P=0.034$) (De Rosa S et al, *Ann Intern Med* 2018;168:343-350.).

Meta-Analysis: In Patients With PFO and Cryptogenic Stroke, Transcatheter Device Closure Decreases Risk for Recurrent Stroke Compared With Medical Therapy Alone / Because Recurrent Stroke Rates are Low Even With Medical Therapy Alone and PFO Closure Might Affect AF Risk, Shared Decision Making is Crucial for this Treatment

Of 5 trials, 1 was excluded because it used a device that is no longer available due to high rates of complications and failure. Meta-analysis of 4 trials enrolling 2892 patients showed that PFO closure decreased the absolute risk for recurrent stroke by 3.2% (risk difference, -0.032) compared with medical therapy. The treatment strategies did not differ in rates of TIA or major bleeding. Closure of PFOs was associated with higher rates of new-onset AF than medical therapy alone in all trials, but this outcome had marked between-trial heterogeneity ($I^2=82.5\%$) (Shah R et al, *Ann Intern Med* 2018;168:335-42.).

Over the Last 8 Years, AF Recurrences after Ablation Almost Halved / Hypertension, Female Gender, Cardioversion 1 Year before Ablation, and AF Lasting >2 Years, Increased Risk of Recurrences / Fewer Recurrences with Lower CHA₂DS₂-Vasc Score / Patients with Diabetes, Chronic Kidney Disease, and Heart Failure Experienced No Improvement

According with Danish nationwide registers, among 5425 AF patients undergoing first-time ablation, between 2005 and 2014, the rates of recurrent AF decreased from 45% in 2005–2006 to 31% 2013–2014 with the relative risk of recurrent AF almost halved with an odds ratio of 0.57 in 2013–2014 compared with patients undergoing ablation in 2005–2006. Female gender, hypertension, AF duration >2 years, and cardioversion within 1 year prior to ablation were all associated with an increased risk of recurrent AF (Pallisaard JL et al, *Eur Heart J* 2018;39:442-9.).

CVD-REAL 2 Study: Gliflozins (SGLT2 inhibitors) Decreased the Risk of Cardiovascular (CV) Outcomes (Death, Heart Failure, MI, Stroke) in 408,807 Patients

In an international study, among 408,807 patients (~27% with established CVD), SGLT-2 inhibitors (SGLT-2i) were compared with other glucose-lowering drugs (oGLD) (235,064 episodes in each group). Use of SGLT-2i vs oGLDs was associated with 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 both across countries, and patient subgroups, including those with and without CVD (Kosiborod M et al, *J Am Coll Cardiol* 2018 March; doi: 10.1016/j.jacc.2018.03.009).

High Rho-Kinase Activity in Leucocytes Predicted Cardiac Events in Vasospastic Angina (VSA) Patients / A Rho-Kinase Activity Value of 1.24 was the Best Cut-off Level / Combination of the Japanese Coronary Spasm Association (JCSA) Risk Score and Rho-kinase Activity Further Improved Risk Stratification

Rho-kinase activity in circulating leucocytes is a useful biomarker for diagnosis and disease activity assessment of vasospastic angina (VSA). Among 174 patients with VSA and 50 non-VSA patients, in whom we measured Rho-kinase activity in circulating leucocytes, followed for a median of 16 months, cardiac events (cardiac death, non-fatal MI, and hospitalization for unstable angina) occurred in 10 VSA patients (5.7%) but in none of the non-VSA patients. Receiver-operating characteristic curve analysis showed that Rho-kinase activity value of 1.24 was the best cut-off level to predict cardiac events in VSA patients (hazard ratio-HR 11.19, $P=0.022$). Combination of the Japanese Coronary Spasm Association (JCSA) risk score and Rho-kinase activity significantly improved the prognostic impact in VSA patients as compared with either alone (Nihei T et al, *Eur Heart J* 2018; 39:952-9). (Editor's note: fasudil, a Rho-kinase blocker, widely used in patients with subarachnoid hemorrhage to prevent intracerebral vasospasm, has also been suggested for refractory VSA).

Less Dementia with Oral Anticoagulation in AF

Among 444,106 AF patients, those on anticoagulant had 29% lower risk of dementia (hazard ratio - HR 0.71). Direct comparison between new oral anticoagulants and warfarin showed no difference (HR 0.97) (Friberg L & Rosenqvist M, *Eur Heart J* 2018;39:453-60).

Important Review and Other Articles

- Obesity (Gadde KM et al, *J Am Coll Cardiol* 2018;71:69-84),
- 2017 ESC Guidelines for Peripheral Arterial Diseases (Aboyans V et al, *Eur Heart J* 2018;39:763-816),
- Out-of-hospital cardiac arrest (*Lancet* 2018; 391:970-9, 980-8, 989-98),
- Takotsubo cardiomyopathy (Dawson DK, *Heart* 2018;104:96-102),
- Non-surgical septal reduction in hypertrophic cardiomyopathy (Cooper RM et al, *Heart* 2018;104:73-83),
- Radial artery for PCI or surgery (Gaudino M et al, *J Am Coll Cardiol* 2018; 71:1167-75),
- Cryptogenic stroke and PFO (Mojadidi MK et al, *J Am Coll Cardiol* 2018;71:1035-43),