Cardiology News / Recent Literature Review / Last Quarter 2018

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ACC.19 Meeting: New Orleans, LA, USA, 16-18/3/2019

EHRA Congress: Lisbon, 17-19/3/2019

HRS Meeting: San Francisco, CA, USA, 8-11/5/2019

EuroPCR: Paris, 21-24/5/2019

ESC Meeting: Paris, 31/8-4/9/2019

TOTAL Trial: Although High Thrombus Burden Was an Important Predictor of Outcome in STEMI, Routine Thrombus Aspiration Did Not Improve Outcomes at 1 Year and Was Associated With an Increased Rate of Stroke

Among 10,732 patients with STEMI randomized to routine manual thrombectomy versus PCI alone, the primary outcome of cardiovascular (CV) death, MI, cardiogenic shock, or heart failure at 1 year was similar with thrombus aspiration in patients with high (8.1% vs. 8.3% thrombus aspiration; hazard ratio - HR: 0.97) or low thrombus burden (% vs. 5% thrombus aspiration; HR: 1.22; interaction p=0.41). However, among patients with high thrombus burden, stroke at 1 month was more frequent with thrombus aspiration (31 / 0.7% thrombus aspiration vs 16 / 0.4% PCI alone, HR: 1.90). In the high thrombus burden group, thrombus aspiration did not improve 1-month (HR: 0.78; p=0.06) and 1-year CV mortality (HR: 0.88; p=0.25). Irrespective of treatment assignment, high thrombus burden was an independent predictor of death (HR: 1.78) (Jolly SS et al, *J Am Coll Cardiol* 2018;72: 1589–96).

Meta-Analysis: Catheter Ablation of Atrial Fibrillation (AF) in Patients with Heart Failure (HF) was Superior to Conventional Drug Therapy in Improving All-Cause Mortality, HF Hospitalizations, LVEF, 6-Minute Walk Test Distance, VO_2max, and Quality of Life, With an Increase, Albeit Non-significant, in Adverse Events

Meta-analysis of 6 RCTs involving 775 patients indicated that compared with drug therapy, AF ablation reduced all-cause mortality (9% vs 17.6%; risk ratio -RR, 0.52) and HF hospitalizations (16.4% vs 27.6%; RR, 0.60). Ablation improved left ventricular ejection fraction (LVEF) (mean difference, 6.95%), 6-minute walk test distance (mean difference, 20.93 m), peak oxygen consumption (VO_2max) (mean difference, 3.17 mL/kg per minute), and quality of life (mean difference in Minnesota Living with Heart Failure Questionnaire score, −9.02 points). Serious adverse events were more common in the ablation groups (7.2% vs 3.8%; RR, 1.68) (Turagam MK et al, *Ann Int Med* 2018, Dec 25).

The Mitral Annulus Disjunction (MAD) Arrhythmic Syndrome

Mitral annulus disjunction (MAD) is an abnormal atrial displacement of the mitral valve leaflet hinge point. MAD has been associated with mitral valve prolapse (MVP) and sudden cardiac death. Among 116 patients with MAD (age 49 ± 15 years; 60% female), palpitations were the most common symptom (71%), while severe arrhythmic events occurred in 14 (12%) patients. Patients with severe arrhythmic events were younger (age 37 ± 13 years vs 51 ± 14 years; p=0.001), had lower ejection fraction (51 ± 5% vs 57 ± 7%; p=0.002) and had more frequently papillary muscle fibrosis (4 or 36% vs 6 or 9%; p=0.03). MVP was evident in 90 (78%) patients and was not associated with ventricular arrhythmia (Dejgaard LA et al, *J Am Coll Cardiol* 2018;72:1600-9).

In Atrial Fibrillation (AF) Patients With Myocardial Infarction (MI) and/or After PCI, Non-Vitamin K Oral Anticoagulant (NOAC) in Combination With Dual Antiplatelet Therapy (DAPT) was Associated With a Significantly Decreased Risk of Bleeding and Similar Thromboembolic Protection Compared With Vitamin K Antagonist (VKA) in Combination With DAPT

Among 3,222 patients, of whom 875 (27%) were treated with VKA+single antiplatelet therapy (SAPT), 595 (18%) with NOAC+SAPT, 1,074 (33%) with VKA+ DAPT, and 678 (22%) with NOAC+DAPT, at 3 months, there was a significant difference in the absolute risk of MI associated with NOAC+SAPT compared with VKA+ SAPT (3-month absolute risk difference-ARD: −1.53%), with no significant differences found regarding bleeding, ischemic stroke, and all-cause mortality. Compared with VKA+DAPT, NOAC+DAPT was associated with a significantly reduced risk of bleeding (3-month ARD: −1.96%), with no significant difference in the absolute risk of all-cause mortality, stroke, or MI (p< 0.0001) (Sindet-Pedersen C et al, *J Am Coll Cardiol* 2018; 72:1790-800)

Home Monitoring for Fetal Heart Rhythm (FHRM) During Anti-Ro Pregnancies

Fetal atrioventricular block (AVB) occurs in 2-4% of anti-Ro antibody–positive pregnancies between 18 and 26 weeks and can develop in <24 h. Outcome of anti-Ro pregnancies was surveilled with twice-daily home fetal heart rhythm monitoring (FHRM) and surveillance echocardiography. Most mothers (273 of 315, 87%) completed the monitoring protocol. Abnormal FHRM was

detected in 21 mothers (6.7%) who sought medical attention >12h (n=7), 3-12h (n=9), or <3h (n=5) after abnormal FHRM; 18 fetuses had benign rhythms, and 3 had second- or third-degree AVB. Treatment with oral dexamethasone and IV immunoglobulin of second-degree AVB<12h after abnormal FHRM restored sinus rhythm, but failed in 2 fetuses with complete AVB. Four fetuses had first-degree AVB diagnosed by echocardiography; none progressed to second-degree AVB (Cuneo et al, *J Am Coll Cardiol* 2018; 72:1940-51).

Single-Stage, Complete Multivessel Percutaneous Revascularization is Associated With Better Long-Term Survival Than Culprit Vessel–Only Revascularization in Patients With NSTEMI

A total of 21,857 patients (58.3%) presented with NSTEMI and multivessel disease, of whom 11,737 (53.7%) underwent single-stage complete revascularization during PCI. Those undergoing complete revascularization were older and more likely to be male, diabetic, have renal disease and a history of previous MI/revascularization compared with the culprit-only revascularization group. Over a median of 4.1 years, in-hospital major adverse cardiac event rates were similar (5.2% vs 4.8%; p=0.462), but mortality rates differed: 22.5% complete revascularization vs 25.9% culprit vessel intervention (p=0.0005) (hazard ratio-HR: 0.90 by multivariate analysis and 0.89 by propensity matching (Rathod KS et al, *J Am Coll Cardiol* 2018; 72:1989-99).

SURTAVI: In Patients With Symptomatic Severe Aortic Stenosis (AS) of Intermediate Surgical Risk, 30-Day Rates of Stroke and Encephalopathy Were Higher After Surgical Valve Replacement (AVR) than After (TAVI) and Were Associated With Higher Mortality by 1 Year After Either Type of Procedure

Among 1,660 intermediate risk AS patients, 864 had TAVI and 796 AVR. The rates of early (30-day) stroke and post-procedural encephalopathy were higher after AVR vs TAVI (5.4% vs 3.3%, p=0.031; 7.8% vs 1.6%, p< 0.001, respectively). At 1 year, the rate of stroke was not different (6.9% vs 5.2%; p=0.136). Early stroke and early encephalopathy resulted in increased mortality at 1 year in both groups. Quality of life after an early stroke was lower in AVR at 30 days and similar at 6 and 12 months (Durko AP et al, *J Am Coll Cardiol* 2018;72:2109-19).

PARTNER: The Risk of Major Stroke Within 30 Days was Higher after Surgical AVR than TAVI, while the Risk of Any Stroke or TIA was Similar

Among matched 1,204 pairs of patients with severe aortic stenosis treated with AVR vs transfemoral (TF) TAVI, 30-day stroke (5.1% vs 3.7%; p=0.09) was similar, but 30-day major stroke (3.9% vs. 2.2%; p=0.018) was lower after TF-TAVI than AVR. In both groups, risk of stroke peaked in the first post-procedure day, followed by a near-constant low-level risk to 4 years. Major stroke was associated with a decline in quality of life at 1 year in both and TF-TAVI (Kapadia SR et al, *J Am Coll Cardiol* 2018;72:2415-26).

CIRT Trial: Negative Results / Methotrexate Did Not Reduce MACE in Patients with Stable CAD and DM and/or Metabolic Syndrome

Among patients randomized (1:1) to low-dose methotrexate 15-20 mg/w (n=1,716) or placebo (n=1,695), all receiving folic acid 1 mg, the primary outcome of major adverse cardiac events (MACE) was 3.4/100 person-years for methotrexate vs 3.4/100 person-years for control (hazard ratio 1.01, p = 0.91). MACE plus hospitalization for unstable angina requiring revascularization was 4.1% vs 4.3%, p=0.67. Methotrexate did not reduce interleukin (IL)-1β, IL-6, hsCRP, or CV events compared with placebo among patients with established CAD and either diabetes or metabolic syndrome or both. Despite using a low dose, patients receiving methotrexate had a higher incidence of side effects such as transaminitis, leucopenia, anemia, and infections (Ridker et al, *N Engl J Med* 2018 Nov 10; doi: 10.1056/NEJMoa1809798).

TAVI: Paravalvular Leak and High Molecular Weight Multimers Defect of Von Willebrand Factor Detected by ADP Closure Time (CT-ADP) are Predictors of Major Hemorrhage Occurring > 30 Days After TAVI

Among 372 TAVI patients surviving 30 days, the impact of ongoing primary hemostasis disorders on late major/life-threatening bleeding was evaluated by CT-ADP, a surrogate marker of high molecular weight von Willebrand multimers proteolysis, defined as CT-ADP >180 s. Major bleeding occurred in 42 patients (11.3%) at a median of 383 days, was mainly gastrointestinal (42.8%) and was associated with increased overall mortality (hazard ratio - HR: 5.66; p< 0.001) and cardiac mortality (HR: 11.62; p< 0.001). A 2.5-fold higher bleeding rate was noted in patients with a CT-ADP > 180 s (27.4% vs 11.5%; p< 0.001). Regression analysis identified paravalvular leak (HR: 6.31; p< 0.0001) and CT-ADP > 180 s (HR: 3.08; p=0.0005) as predictors of major bleeding (Kibler M et al, *J Am Coll Cardiol* 2018;72: 2139-48).

Soluble Suppression of Tumorigenesis-2 (sST2) is an Independent Predictor for All-Cause & CV Mortality, and Heart Failure (HF) Hospitalization in Chronic HF

Soluble suppression of tumorigenesis-2 (sST2) is a biomarker related to inflammation and fibrosis. In 4,268 HF patients (median age 68 years, 75% males, 65% with ischemic HF, 87% with LVEF<40%), median NT-proBNP, hs-TnT, and sST2 were 1,360 ng/l, 18 ng/l, and

27 ng/l, respectively. Over a median of 2.4 years, among the 4,118 patients (96%) with available data, 1,029 (24%) were hospitalized at least once for worsening HF over 2.2 years. The best sST2 cutoff for the prediction of all-cause and CV death and HF hospitalization was 28 ng/ml. In multivariate analysis, the risk of all-cause death, CV death, and HF hospitalization increased by 26%, 25%, and 30%, respectively, per each doubling of sST2, which was an independent prognosticator (Emdin M et al, *J Am Coll Cardiol* 2018;72:2309–20).

GUIDE-IT: Guiding Therapy in Patients With Chronic HF and Reduced Ejection Fraction by Measurements of Plasma NT-proBNP Does Not Improve Clinical or Patient-Reported Outcomes and May Increase Cost

Baseline variables were well balanced in the 446 patients randomized to the NT-proBNP–guided therapy and 448 to usual care. Quality of life (QOL) measures improved over the first 6 months, but no evidence was found for a strategy-related difference at 2 years of follow-up. Total winsorized costs averaged $5,919 higher in the biomarker-guided strategy over 15-month median follow-up (Mark DB et al *J Am Coll Cardiol* 2018;72:2551–62).

Framingham Heart Study Offspring Cohort: Rising Plasma Levels of *Galectin-3* (Gal-3) are Associated With Incident Heart Failure (Both HFpEF and HFrEF), Cardiovascular Disease (CVD), and All-Cause Mortality in Community-Dwelling Individuals

Among 2,477 participants the following clinical correlates were associated with greater longitudinal increases in Gal-3 levels: age, female sex, hypertension, diabetes, body mass index, interim development of chronic kidney disease, and HF ($p< 0.0001$ for all). Change in Gal-3 was associated with future HF (hazard ratio - HR: 1.39 per 1-SD increase), CVD (HR: 1.29), and all-cause mortality (HR: 1.30). Change in Gal-3 was associated with both HF, HFpEF & HFrEF ($p< 0.05$ for both) (Ghorbani A et al, *J Am Coll Cardiol* 2018;72:3246–54).

CoreValve U.S. Pivotal High-Risk Trial: In High-Risk Patients With Aortic Stenosis, TAVI With Self-Expanding Bioprosthesis is Associated With Survival, Safety and Functional Outcomes at 5 Years Similar to Those With Surgical AVR

A total of 797 patients were randomized, of whom 750 underwent an attempted implant (TAVI=391, AVR=359). The overall mean age was 83 years, and the STS score was 7.4%. All-cause mortality rates at 5 years were 55.3% for TAVI and 55.4% for AVR. Major stroke rates were 12.3% for TAVI and 13.2% for AVR. Mean aortic valve gradients were 7.1 ± 3.6 mmHg for TAVI and 10.9 ± 5.7 mmHg for AVR. No clinically significant valve thrombosis was observed. Freedom from severe valve degeneration was 99.2% for TAVI and 98.3% for AVR (p=0.32), and freedom from valve reintervention was 97% for TAVI and 98.9% for AVR (p=0.04). A pacemaker was implanted in 33% of TAVI and 19.8% of AVR patients at 5 years (Gleason TG et al, *J Am Coll Cardiol* 2018;72:2687-96).

COMMANDER-HF: Rivaroxaban (2.5 mg bid) Was Not Associated With a Lower Rate of Death, MI, or Stroke than Placebo Among Patients With Worsening Chronic Heart Failure (HF), Reduced LVEF, Coronary Artery Disease (CAD), and No AF

Among 5022 patients with chronic HF, a LVEF of ≤40%, CAD, and elevated natriuretic peptides and who did not have AF, randomly assigned to rivaroxaban (2.5 mg bid) or placebo in addition to standard care, over a median of 21.1 months, the primary end point (death, MI, stroke) occurred in 25% vs 26.2%) (hazard ratio-HR; P=0.27). No significant difference in mortality was noted between the rivaroxaban and the placebo group (21.8% and 22.1%, respectively; HR, 0.98). The principal safety outcome occurred in 18 patients who took rivaroxaban and in 23 who took placebo (HR, 0.80; P=0.48) (Zannad F et al, *N Engl J Med* 2018; 379:1332-42).

Brugada Syndrome (BrS): Structural and Electrical Defects in the RVOT with Inflammation Playing a Crucial Role in These Changes and in the Evolution of the Arrhythmic Substrate

Low-voltage areas (LVAs) were observed in 93% (unipolar map) and 50% (bipolar map) of BrS patients, with unipolar LVAs always larger than bipolar LVAs, always colocalized, and in all cases including the RVOT. RVOT histology was pathologic in 75% (80% myocardial inflammation). Among patients with abnormal bipolar map submitted to endomyocardial biopsy, 9 (81%) showed evidence of myocardial inflammation. Conversely, bipolar map was abnormal in 83% of patients with myocardial inflammation. Gene mutations were detected in 10 (33%) patients. Programmed ventricular stimulation was positive in 16 cases (53%). Myocardial inflammation was also more prevalent among inducible patients (83% vs 25% in noninducible; p=0.032) (Pieroni M et al, *J Am Coll Cardiol* 2018;72:2747–57).

ASPREE: Low-Dose Aspirin as Primary Prevention Strategy in Older Adults Increased Bleeding and Did Not Result in Lower Risk of Cardiovascular Disease

Among 19,114 persons, 9525 assigned to aspirin and 9589 to placebo, after a median of 4.7 years, the rate of cardiovascular disease was 10.7 events per 1000 person-years in the aspirin group and 11.3 events per 1000 person-years in the placebo group (hazard ratio-HR, 0.95). The

rate of major hemorrhage was 8.6 events per 1000 person-years and 6.2 events per 1000 person-years, respectively (HR, 1.38; P<0.001) (McNeil JJ et al, *N Engl J Med* 2018; 379:1509-18).

ASPREE: Higher All-Cause Mortality Among Healthy Older Adults Who Received Daily Aspirin vs Placebo, Attributed Primarily to Cancer-Related Death

Among 19,114 persons, 9525 assigned to aspirin and 9589 to placebo, a total of 1052 deaths occurred over a median of 4.7 years. The risk of death was 12.7 events per 1000 person-years in the aspirin group and 11.1 events per 1000 person-years in the placebo group (hazard ratio-HR, 1.14). Cancer was the major contributor to the higher mortality in the aspirin group, accounting for 1.6 excess deaths per 1000 person-years (3.1% vs 2.3%; HR 1.31) (McNeil JJ et al, *N Engl J Med* 2018; 379:1519-28).

ASCEND: Aspirin Prevented Serious Vascular Events in Persons with Diabetes and no Evident CV Disease, Albeit with Increased Bleeding

Among 15,480 randomized participants, over a mean of 7.4 years, serious vascular events occurred in a lower percentage of participants in the aspirin group than in the placebo group (8.5% vs 9.6%; rate ratio, 0.88; P=0.01). In contrast, major bleeding events occurred in 4.1% vs 3.2% (rate ratio, 1.29; P=0.003), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There was no significant difference between groups in the incidence of gastrointestinal tract cancer (2% vs 2.0%) or all cancers (11.6% vs 11.5%) (ASCEND study group, *N Engl J Med* 2018; 379:1529-39).

MAIN-COMPARE: In Patients With Left Main (LM) Disease, PCI, Compared With CABG, Had Similar Rates of Death and Serious Composite Outcomes, But a Higher Rate of Target-Vessel Revascularization at 10 Years / However, in the Late Cohort Comparing DES and Concurrent CABG, CABG Showed Lower Mortality and Serious Composite Outcome Rates Compared With DES Especially After 5 Years

Among 2,240 patients with unprotected LM disease who underwent PCI (n=1,102) or CABG (n=1,138), there was no significant difference in adjusted risks of death and the composite outcome between the groups up to 10 years. The risk of target-vessel revascularization was higher in the PCI group. In the cohort comparing DES and concurrent CABG, the 2 study groups did not differ significantly in the risks of death and the composite outcome at 5 years. However, after 5 years, DES were associated with higher risks of death (hazard ratio-HR: 1.35) and the composite outcome (HR: 1.46) compared with CABG (Park D-W et al, *J Am Coll Cardiol* 2018;72:2813–22).

Favorable Long-Term Survival After Echo-Guided Alcohol Septal Ablation in Symptomatic Patients With Hypertrophic Obstructive Cardiomyopathy (HOCM)

Alcohol injection (2.1±0.4 cc) was performed in 952 HOCM patients (age 55.7±14.9 years; 59.2% men; 73.3% NYHA class III or IV; 50.3% syncope; 10.3% sudden cardiac death in family). Maximal creatine kinase rise was 872±489 U/l. Two (0.21%) patients died 3 and 33 days after ablation. Pacemaker was implanted in 100 (10.50%) patients. Echo gradients were acutely reduced from 63.9 ± 38.2 mmHg to 33.6 ± 29.8 mmHg at rest and from 104.6 ± 44.0 mmHg to 56.5 ± 41.0 mmHg at Valsalva (p< 0.0001, each). Over 6±5 years, 164 (17.2%) patients underwent reablation due to the planned staged procedure, 18 (1.9%) underwent surgical myectomy, and 49 (5.10%) underwent ICD implantation. Death occurred in 70 patients: non-cardiovascular (CV) in 50, stroke-related in 6, and cardiac in 14 patients. Estimated 5-, 10- and 15-year survival was 95.8/88.3/79.7%, survival free of CV events was 98.6/96.5/92.3%, and survival free of cardiac events was 98.9/97/96.5% (Batzner A et al, *J Am Coll Cardiol* 2018;72:3087–94).

PADIT Trial: Compared With Conventional Antibiotic Prophylaxis With Preprocedural Cefazolin in Patients Undergoing Implantation of Cardiac Electronic Devices (CIEDs), a More Aggressive Multicomponent Antibiotic Regimen Provided No Significant Efficacy Advantage in Preventing Device-Related Infections

Conventional treatment was pre-procedural cefazolin (IV); incremental treatment was pre-procedural cefazolin plus vancomycin, intraprocedural bacitracin pocket wash, and 2-day post-procedural oral cephalexin. Among 19,603 patients having a device, infection occurred in 99 patients (1.03%) receiving conventional treatment, and in 78 (0.78%) receiving incremental treatment (odds ratio-OR: 0.77; p=0.10). In high-risk patients, hospitalization for infection occurred in 1.23% receiving conventional and in 1.01% receiving incremental antibiotics (OR: 0.82; p=0.26). Subgroup analysis did not identify relevant patient or site characteristics with significant benefit from incremental therapy (Krahn AD et al, *J Am Coll Cardiol* 2018;72:3098–3109).

Elevated Baseline and On-Statin Lipoprotein(a) Has an Independent Relation With Cardiovascular (CV) Risk

Analyses of 7 statin trials (29,069 patients) (mean age 62 years, 28% women) indicated that initiation of statin therapy reduced LDL cholesterol (mean change −39%) without a significant change in lipoprotein(a) – Lp(a).

Associations of baseline and on-statin treatment Lp(a) with CV disease risk were approximately linear, with increased risk at Lp(a) values of ≥30 mg/dL for baseline Lp(a) and ≥50 mg/dL for on-statin Lp(a). For baseline Lp(a), adjusted hazard ratios - HRs were 1.04 for 15-30 mg/dL, 1·11 for 30-50 mg/dL, and 1.31 for ≥50 mg/dL; respective HRs for on-statin Lp(a) were 0.94, 1.06, and 1.43. HRs were almost identical after further adjustment for other risk factors. The association of on-statin Lp(a) with CV disease risk was stronger than for on-placebo Lp(a) (interaction p=0.010) and was more pronounced at younger ages (interaction p=0.008) without effect-modification by any other patient-level or study-level characteristics (Willeit P et al, *Lancet* 2018;392:1311-1320).

ARISTOTLE Trial: Biomarkers, High-Sensitivity Troponin T (hsTnT), Growth Differentiation Factor-15 (GDF-15), N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP), and Interleukin-6 (IL-6) Were Some of the Strongest Predictors of Cause-Specific Death and May Improve the Ability to Discriminate Among Patients' Risks for Different Causes of Death

Biomarkers were measured at randomization in 14,798 of 18,201 AF patients randomized to apixaban or warfarin. Over a median of 1.9 years, 1272 patients died: 652 (51%) cardiovascular (CV), 32 (3%) bleeding, and 588 (46%) non-CV/nonbleeding deaths. Among CV deaths, 255 (39%) were sudden cardiac deaths, 168 (26%) heart failure deaths, and 106 (16%) stroke/systemic embolism deaths. Biomarkers were the strongest predictors of cause-specific death: a doubling of hsTnT was most strongly associated with sudden death (hazard ratio -HR, 1.48; *P*<0.001), NT-proBNP with heart failure death (HR, 1.62; *P*<0.001), and GDF-15 with bleeding death (HR, 1.72; *P*=0.028). Prior stroke/systemic embolism (HR, 2.58; *P*>0.001) followed by hsTnT (HR, 1.45; *P*<0.0029) were the most predictive for stroke/ systemic embolism death (Sharma A et al, *Circulation* 2018;138:1666–1676).

Cooper Center Longitudinal Study: In a Low 10-Year Risk Cohort With Long-Term Follow-Up, LDL-Cholesterol and Non–HDL-Cholesterol ≥160 mg/dl Were Independently Associated With a 50-80% Increased Relative Risk of CVD Mortality

Among 36,375 participants (72% men, median age 42) followed for a median of 26.8 years, 1086 CVD and 598 CAD deaths occurred. Compared with LDL-C <100 mg/dL, LDL-C categories 100 to 129 mg/dL (HR 1.4), 130 to 159 mg/dL (HR 1.3), 160 to 189.9 mg/dL (HR 1.9), and ≥190 mg/dL (HR 1.7) were associated with a significantly higher risk of CVD death and mean reductions in years free of CVD death of 1.8, 1.1, 4.3, and 3.9, respectively. After adjustment for CV risk factors, LDL-C categories 160 to 189 mg/dL and ≥190 mg/dL remained independently associated with CVD mortality, with HRs of 1.7 and 1.5, respectively. In multivariable-adjusted models using non–HDL-C <130 mg/dL as the reference, non–HDL-C 160 to 189 mg/dL (HR 1.3), 190 to 219 mg/dL (HR 1.8), and ≥220 mg/dL (1.5) were significantly associated with CVD death (Abdullah SM et al, *Circulation* 2018;138:2315–25).

FRANCE-2 Registry: Good Durability of TAVI at 5 Years

Among 4201 patients the 5-year vital status was available for 95.5%; 88.1% had clinical evaluation or died. At 5 years, all-cause mortality was 60.8% (n=2478). The majority of CV events occurred in the first month after TAVI; incidence remained low thereafter, at <2% per year up to 5 years, except for heart failure rate which was 14.3% at 1 year, then decreased over time to <5% per year. The rate of severe structural valve deterioration (SVD) at 5 years was 2.5% and of moderate/ severe SVD 13.3%. Mortality did not differ between patients with or without severe SVD (hazard ratio, 0.71; *p*=0.1). Among those with severe SVD, 1 patient (1.7%) experienced a stroke, and 8 patients presented ≥1 heart failure event (13.3%) (Didier R et al, *Circulation* 2018;138:2597–2607).

HEART Pathway (History, ECG, Age, Risk Factors, and Initial Troponin) is an Accelerated Diagnostic Protocol Designed to Identify Low-Risk Emergency Department (ED) Patients With Chest Pain for Early Discharge Without Stress Testing or Angiography

Among 8474 adult ED patients with possible acute coronary syndrome (3713 pre-implementation and 4761 post-implementation cohorts), the HEART pathway identified 30.7% as low risk; 0.4% of these patients experienced death or MI within 30 days. Hospitalization at 30 days was reduced by 6% in the post-implementation vs pre-implementation cohort (55.6% vs 61.6%; odds ratio-OR, 0.79). During the index visit, more MIs were detected in the post-implementation cohort (6.6% vs 5.7%; OR, 1.36). Rates of death or MI during follow-up were similar (1.1% vs 1.3%; OR, 0.88) (Mahler SA et al, *Circulation* 2018;138: 2456–68).

Harmony Outcomes: In Patients With Diabetes and Cardiovascular (CV) Disease, Albiglutide was Superior to Placebo Regarding Major Adverse CV Events

Among 9463 patients randomized to albiglutide (n=4731) or placebo (n=4732), over a median of 1.6 years, the primary outcome (CV death, MI or stroke) occurred in 7% vs 9% at an incidence rate of 4.6 vs 5.9 events per 100 person-years (hazard ratio -HR 0.78), which indicated that albiglutide was superior to placebo (p<0.0001 for non-inferiority; p=0.0006 for superiority). The incidence of

acute pancreatitis (10 vs 7 patients), pancreatic cancer (6 vs 5 patients), thyroid carcinoma (0 patients in both groups), and other serious adverse events did not differ between the two groups. There were 3 (<1%) deaths in the placebo group that were assessed to be treatment-related and two (<1%) deaths in the albiglutide group (Hernandez AF et al, *Lancet* 2018;392:1519-29).

HFpEF: Not Just a Disease of the Elderly / It Also Occurs in Younger Patients Who are Often Obese, Have Fewer Comorbidities vs the Older, Yet Similar Filling Pressures and LVH / Better Quality of Life and Mortality, Yet Much Worse Mortality Compared With Matched Controls

Among 1203 patients with heart failure with preserved ejection fraction (HFpEF), 37% were <65 years of age, more often male and obese (BMI ≥30 kg/m^2; 36% in very young (<55 years) vs 16% in elderly) together with less renal impairment, AF, and hypertension (all P<0.001). Left ventricular filling pressures and prevalence of LVH were similar in very young and elderly HFpEF. Quality of life was better and death and heart failure hospitalization at 1 year occurred less frequently (P<0.001) in the very young (7%) compared with elderly (21%) HFpEF. Compared with control subjects, very young HFpEF had a 3-fold higher death rate and twice the prevalence of hypertrophy (Tromp J et al, *Circulation* 2018;138:2763–73).

CULPRIT-SHOCK: Among Patients With Acute MI and Cardiogenic Shock, the Risk of Death or Renal-Replacement Therapy at 30 Days Was Lower With Culprit-Lesion-Only PCI Than With Immediate Multivessel PCI, While Mortality was Similar at 1 Year

Among 706 patients randomly assigned to culprit-lesion-only PCI or immediate multivessel PCI, at 30 days, the primary end point (death or renal failure) occurred in 45.9% vs 55.4% (P=0.01). At 1 year, death rate was 50% vs 56.9% (relative risk-RR, 0.88). The rate of recurrent MI was 1.7% vs 2.1% (RR, 0.85), and the rate of a composite of death or recurrent MI was 50.9% vs 58.4% (RR, 0.87). Repeat revascularization occurred more frequently with culprit-lesion-only PCI (32.3% vs 9.4%; RR, 3.44), as did rehospitalization for heart failure (5.2% vs 1.2%; RR, 4.46) (Thiele H et al, *N Engl J Med* 2018; 379:1699-1710.

LEADER: In Patients With Type 2 Diabetes (DM) and High Cardiovascular (CV) Risk, Liraglutide Reduced CV Outcomes Both in Patients With a History of MI/ Stroke and in Those With Established CV Disease Without MI/ Stroke, While it was Neutral in Patients With CV Risk Factors Alone

Of the 9340 patients with DM and high CV risk randomized to liraglutide (1.8 mg or maximum tolerated dose) vs placebo with a median follow-up of 3.8 years. , 3692 (39.5%) had a history of MI/stroke, 3083 (33.0%) had established atherosclerotic CV disease without MI/stroke, and 2565 (27.5%) had CV risk factors alone. Major adverse cardiovascular events (MACE) occurred in 18.8% of patients with a history of MI/stroke (incidence rate, 5.0 per 100 patient-years), 11.6% of patients with established CV disease without MI/stroke (incidence rate, 3.0 per 100 patient-years), and 9.8% of patients with CV risk factors alone (incidence rate, 2.6 per 100 patient-years). Liraglutide reduced MACE in patients with a history of MI/stroke (17.3% vs 20.4%; hazard ratio-HR, 0.85) and in those with established CV disease without MI/stroke (10.3% vs 12.9%; HR, 0.76) compared with placebo. In patients with risk factors alone, the HR for liraglutide vs placebo was 1.08 (p=NS) (Verma S et al, *Circulation*. 2018;138:2884-94).

LEADER Trial: Liraglutide Added to Standard of Care Reduced the Risk for Major Cardiovascular Events (MACE) and All-Cause Mortality in Patients With Diabetes and Chronic Kidney Disease (CKD)

In patients with eGFR <60 mL/min/1.73 m^2 (n=2158) risk reduction for the primary composite cardiovascular (CV) outcome with liraglutide was greater (hazard ratio - HR, 0.69) vs those with eGFR ≥60 mL/min/1.73 m^2 (n=7182) (HR, 0.94; *p*=0.01). Risk reductions in those with eGFR <60 vs ≥60 mL/min/1.73 m^2 were as follows: for nonfatal mi, HR, 0.74 vs HR, 0.93; for nonfatal stroke, HR, 0.51 vs HR, 1.07; for CV death, HR, 0.67 vs HR, 0.84; for all-cause mortality, HR, 0.74 vs HR, 0.90. Risk reduction for the primary composite CV outcome was not different for those with vs without baseline albuminuria (Mann JFE et al, *Circulation* 2018;138:2908–2918).

ODYSSEY OUTCOMES: Among Patients With Prior Acute Coronary Syndrome (ACS) Receiving High-Intensity Statin Therapy, the Risk of Recurrent Ischemic CV Events Was Lower Among Those Who Received Alirocumab vs Placebo

Among 18,924 ACS patients receiving high-intensity statin and having LDL-cholesterol >70 mg/dl, randomly assigned to s.c. alirocumab (75 mg/2 weeks, n=9462) or placebo (n=9462), over a median of 2.8 years, a composite primary end-point event (CV death, MI, stroke, unstable angina) occurred in 9.5% vs 11.1% (hazard ratio-HR, 0.85; P<0.001). Death rate was 3.5% vs 4.1% (HR, 0.85). The absolute benefit of alirocumab with respect to the composite primary end point was greater among patients who had a baseline LDL cholesterol level of ≥100 mg/dl vs a lower baseline level. The incidence of adverse events was similar in the two groups, with the exception of local injection-site reactions (3.8% in the alirocumab group vs.

2.1% in the placebo group) (Schwartz GG et al, *N Engl J Med* 2018; 379:2097-2107).

MITRA-FR: MitraClip Conferred No Benefit in Patients With Severe Secondary Mitral Regurgitation, Regarding Death or Unplanned Hospitalization for Heart Failure at 1 Year

Among randomly assigned patients with severe secondary mitral regurgitation, a left ventricular ejection fraction 15-40%, and symptomatic heart failure, in a 1:1 ratio, to MitraClip (n=152) or medical therapy alone (n=152), at 1 year, the rate of the primary outcome (death or unplanned hospitalization for heart failure) was 54.6% in the intervention group and 51.3% in the control group (odds ratio-OR, 1.16; P=0.53). The rate of death from any cause was 24.3% vs 22.4% (hazard ratio-HR, 1.11). The rate of unplanned hospitalization for heart failure was 48.7% vs 47.4% (HR, 1.13) (Obadia J-F et al, *New Engl J Med* 2018;379:2297-2306).

PURE Study: Dairy Consumption Was Associated With Lower Risk of Mortality and Major Cardio-vascular (CV) Disease Events in a Diverse Multi-national Cohort

Among 136,384 individuals aged 35–70 years enrolled from 21 countries, higher intake of total dairy (>2 servings per day compared with no intake) was associated with a lower risk of the composite outcome of mortality or major CV events (CV death, MI, stroke, or heart failure) (HR 0.84; p_{trend}=0.0004), total mortality (0.83; p_{trend}=0.0052), non-CV mortality (0.86; p_{trend}=0.046), CV mortality (0.77; p_{trend}=0.029), major CV disease (0·.8; p_{trend}=0.0001), and stroke (0.66; p_{trend}=0.0003). No significant association with MI was observed (HR 0.89; p_{trend}=0.163). Higher intake (>1 serving *vs* no intake) of milk (HR 0.90; p_{trend}=0.0529) and yogurt (0.86; p_{trend}=0.0051) was associated with lower risk of the composite outcome, whereas cheese intake was not significantly associated with the composite outcome (0.88; p_{trend}=0.1399). Butter intake was low and was not significantly associated with clinical outcomes (HR 1.09; p_{trend}=0.4113) (Dehgan M et al, *Lancet* 2018;392:2288-97).

Maternal Use of β-Blockers in the First Trimester is Not Associated With a Large Increase in the Risk for Overall Malformations or Cardiac Malformations

First-trimester exposure to β-blockers was assessed in 682 of 3577 (19.1%) women with hypertensive pregnancies in a Nordic cohort and 1668 of 14,900 (11.2%) in a U.S. cohort. The pooled adjusted relative risk (RR) and risk difference per 1000 persons exposed (RD_{1000}) associated with β-blockers were 1.07 and 3.0, respectively, for any major malformation; 1.12 and 2.1 for any cardiac malformation; and 1.97 and 1.0 for cleft lip or palate. For CNS malformations, the adjusted RR was 1.37 and the RD_{1000} was 1.0 (based on U.S. cohort data only). (Bateman BT et al, *Ann Intern Med* 2018; 169:665-673).

Comparative Safety and Effectiveness of Direct Oral Anticoagulants (DOACs): At Least as Effective and Safe as Warfarin for Patients With Nonvalvular AF

Analysis of data from 220 articles indicated that dabigatran and apixaban were superior and rivaroxaban and edoxaban were similar to warfarin in preventing stroke or systemic embolism. Apixaban and edoxaban were superior and rivaroxaban and dabigatran were similar to warfarin in reducing the risk for major bleeding. Treatment effects with dabigatran were similar in patients with renal dysfunction (interaction $P > 0.05$), and patients <75 years had lower bleeding rates with dabigatran (interaction $P < 0.001$). Apixaban had a consistent treatment benefit in many subgroups (renal impairment, diabetes, and prior stroke) (interaction $P > 0.05$ for all). The greatest bleeding risk reduction was observed in patients with a glomerular filtration rate <50 mL/min/1.73 m^2 ($P = 0.003$). Similar treatment effects were observed for rivaroxaban and edoxaban in patients with prior stroke, diabetes, or heart failure (interaction $P > 0.05$ for all) (*Lowenstern* A et al, *Ann Intern Med* 2018;169:774-787).

An Increased Risk for Venous Thromboembolism (VTE) in Patients With Rheumatoid Arthritis (RA), Psoriasis and Psoriatic Arthritis (PsA) and this Risk Remained Elevated After Adjustment for Established VTE Risk Factors in RA and Mild Psoriasis

Among patients with PsA ($n = 12,084$), RA ($n = 51,762$), psoriasis ($n = 194,288$) and matched controls ($n = 1,225,571$), patients with RA (with and without a disease modifying anti-rheumatic drug - DMARD prescription) and patients with mild psoriasis had significantly elevated risks of VTE (HR 1.35, 1.29, and 1.07, respectively) after adjusting for traditional risk factors. Severe psoriasis and PsA prescribed a DMARD had an elevated, but not statistically significant, risk for VTE. Findings were similar for deep vein thrombosis. The risk of pulmonary embolism was elevated in RA, severe psoriasis and PsA patients prescribed a DMARD (Ogdie A et al, *Eur Heart J* 2018;39:3608-14).

Sudden Death Represents the Largest Proportion of Cardiovascular (CV) Deaths After 30 Days Among Patients Enrolled in CV Clinical Trials With Non-ST Elevation Acute Coronary Syndromes (NSTE-ACS)

Of the 2606 patients (82.8%) with known modes of death among 66,252 patients with NSTE-ACS, over a median of ~1 year, 75.1% were related to CV event, 3%

were related to a bleeding event (including intracranial hemorrhage), and 21.8% were related to a non-CV/non-bleeding event. The most common modes of CV death were sudden death (SD) and recurrent myocardial infarction (MI) (36.4% and 23.4%, respectively, of CV deaths). The proportion of CV deaths related to recurrent MI was higher in the first 30 days than afterwards (30.6% vs. 18.7%), whereas the proportion of SD was lower in the first 30 days (21.6% vs. 46.2%) (Berg DD et al, *Eur Heart J* 2018;39:3810-20).

BIOSTATCHF: The Presence of Atrial Fibrillation (AF) is Associated With a Homogeneously Elevated Cardiovascular Risk Marker Profile in Patients With HFrEF, Whereas in HFpEF, the Presence of AF is Associated With a More Scattered Risk Marker Profile, Suggesting Differences in Pathophysiological Mechanisms of AF in These Two HF Groups

Among 2152 patients with heart failure (HF) with reduced ejection fraction (EF) (HFrEF) (EF< 40%), of whom 1419 were in sinus rhythm (SR) and 733 had AF, and 524 patients with HF with preserved EF (HFpEF) (EF ≥50%), of whom 286 in SR and 238 with AF, the circulating risk marker pattern observed in HFrEF was different than the pattern in HFpEF. In HFrEF, AF was associated with higher levels of 77 of 92 (84%) risk markers compared to SR; whereas in HFpEF, many more markers were higher in SR than in AF. Over a median follow-up of 21 months, AF was associated with increased mortality risk (hazard ratio - HR of 1.27, P= 0.002); there was no significant interaction between heart rhythm and EF group on outcome (Santema BT et al, *Eur Heart J* 2018;39:3867-75).

AF Prevalence Increases With Increasing Ejection Fraction (EF) but its Association With Worse Cardiovascular Outcomes, Remained Significant in Patients with HFpEF & HFmrEF, but not in Those with HFrEF

Among 14,964 HF patients (age 66 ± 13 years, 67% male; 53% HFrEF, 21% HFmrEF, 26% HFpEF), the prevalence of AF was 27% in HFrEF, 29% in HFmrEF, and 39% in HFpEF, associated with older age, lower functional capacity, and heightened physical signs of HF. Crude rates of mortality and HF hospitalization were higher in patients with AF compared to SR, in each EF subtype. The hazard ratio of AF for HF hospitalizations was: 1.036 ($P = 0.652$) in HFrEF, 1.430 ($P = 0.011$) in HFmrEF, and 1.487 ($P < 0.001$) in HFpEF; and for combined all-cause death or HF hospitalizations: 0.957 ($P = 0.502$), 1.302 ($P = 0.014$), and 1.365 ($P < 0.001$), respectively. In patients with HFrEF, AF was not associated with worse outcomes in those presenting with either an acute or a chronic presentation of HF (Zafrir B et al, *Eur Heart J* 2018;39:4277-84).

An Increased Risk of Ischemic Stroke or TIA Was Observed in Patients With Electrical Isolation of the Left Atrial Appendage (LAA)

In 39 patients with LAA isolation, a higher rate of ischemic stroke or TIA was observed, compared to those without LAA isolation (n=2313) (log-rank, P <0.001; hazard ratio – HR 23.6; P < .001). There were significant differences in the baseline characteristics of the 2 groups, including type of AF (87.2% vs 39.4% patients with and without LAA isolation had nonparoxysmal AF). LAA isolation was found to be a significant risk factor for ischemic stroke or TIA (HR 11.3; P < .001). Propensity score–matched analysis also revealed an increased risk of ischemic stroke or TIA in patients with LAA isolation compared with those without LAA isolation (log-rank, P = 0.001). The LAA flow velocity of post-LAA isolation status was similar in the 2 groups indicating that it is not a reliable marker to predict future ischemic events (Kim YG et al, *Heart Rhythm* 2018;15:1746-53).

Anti-Desmoglein-2 (DSG2) Antibodies: a Sensitive & Specific Biomarker for Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Among ARVC patients and controls evaluated for antibodies to cardiac desmosomal cadherin proteins, anti-desmoglein-2 (DSG2) antibodies were identified in 12/12 and 25/25 definite ARVC cohorts and 7/8 borderline subjects. Antibody was absent in 11/12, faint in 1/12, and absent in 20/20 of two controls. Anti-DSG2 antibodies were present in 10/10 Boxer dogs with ARVC, and absent in 18/18 without. In humans, the level of anti-DSG2 antibodies correlated with the burden of PVCs ($r = 0.70$), and antibodies caused gap junction dysfunction, a common feature of ARVC, *in vitro*. Anti-DSG2 antibodies were present in ARVC patients regardless of whether a mutation was identified, or which mutation was present. A disease-specific DSG2 epitope was identified (Chatterjee D et al, *Eur Heart J* 2018;39:3932-44).

BRUISE CONTROL-2: Either a Continued or an Interrupted DOAC Management Strategy Seems Reasonable at the Time of Device Implantation

A total of 590 AF patients with CHA_2DS_2-VASc score ≥2 planned for elective device (pacemaker or defibrillator) surgery, were randomly assigned to continued (12h median time between pre- and post-operative DOAC doses) vs interrupted DOAC (dabigatran, rivaroxaban, or apixaban) (72h median time). Clinically significant hematoma occurred in of 7 of 328 (2.1%)

patients in the continued DOAC arm and 7 of 334 (2.1%) patients in the interrupted DOAC arm ($P = 0.97$). Complications were uncommon, and included one stroke and one symptomatic pericardial effusion in each arm (Birnie DH et al, *Eur Heart J* 2018;39:3973-79).

Higher Overall and Major Complication Rates than Previously Reported for AF Ablations in Germany in 2014/Inordinately High Rates of Life-Threatening Complications for Atrial Flutter Ablations

Among 33,353 cases undergoing ablation for atrial fibrillation and atrial flutter in Germany in 2014, for left atrial ablations (n=19,514), the overall complication rate ranged from a mean of 11.7% to 13.8% depending on type and site of applied energy, including major complications ranging from 3.8% to 7.2%. Complication rates were lower for atrial flutter ablations (n=13,871, 10.5%; $P < 0.001$), however, major complications occurred more frequently (7.4%; $P < 0.001$) with a 4-fold more common in-hospital death following right than left atrial ablations (47 vs 18 cases, 0.34% vs 0.09%; $P < 0.001$). Fewer complications occurred in centers performing >100 vs ≤100 left atrial ablations annually (12.7% vs 16.4%; $P < 0.002$) (Steinbeck G et al, *Eur Heart J* 2018;39:4020-29).

Important Review and Other Articles

● 2018 ACC/AHA ***Cholesterol*** Guidelines (Grundy SM et al, J Am Coll Cardiol. 2018 Nov 8. pii: S0735-1097(18)39034-X. doi: 10.1016/j.jacc.2018.11.003. [Epub ahead of print])

● 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of ***Sudden Cardiac Death*** (Al-Khatib SM et al, *Circulation. 2018;138: e272-e391.*)

● ACC/AHA ***Hypertension*** Guidelines (Whelton PK et al, Circulation. 2018;138:e484-e594)

● ACC/AHA ***Bradycardia*** Guidelines (Kusumoto FM et al, Circulation. 2018 Nov 6: CIR0000000000000628. doi: 10.1161/CIR.0000000000000628. [Epub ahead of print])

● Comparison of American and European Guidelines on **Dual Antiplatelet Therapy** (Capodanno D et al, *J Am Coll Cardiol* 2018;72:2915-31)

● Stress cardiomyopathy (Medina de Chazal H et al, *J Am Coll Cardiol* 2018;72:1955-71)

● Air pollution and cardiovascular disease (Rajagopalan S et al, *J Am Coll Cardiol* 2018;72:2054-70)

● Arrhythmic mitral valve prolapse (Miller MA et al, *J Am Coll Cardiol* 2018;72:2904-14)

● LBBB (Auffret V et al, *J Am Coll Cardiol* 2018;72:3177-88)

● Modernized Classification of Antiarrhythmic Drugs (Lei M et al, *Circulation* 2018; 138:1879–1896)

● Thrombogenic & arrhythmogenic roles of left atrial appendage in AF (Di Biase L et al, *Circulation* 2018; 138:2036–50)

● 2018 AHA Focused Update on ACLS Use of Antiarrhythmic Drugs During and Immediately After Cardiac Arrest (Panchal AR et al, *Circulation* 2018; 138:e740–e749)

● 2018 ILCOR Statement on CPR (Soar J et al, *Circulation* 2018; 138: e714–e730)

● 2018 AHA Focused Update on Pediatric ALS (Duff JP et al, *Circulation* 2018; 138: e731–e739)

● Left ventricular assist devices (Han JJ et al, *Circulation.* 2018; 138:2841–2851)

● European recommendations for participation in competitive sports of athletes with arterial hypertension (Niebauer J et al, *Eur Heart J* 2018; 39:3664-71)

FDA News (2018)

18/4/2018: The US FDA gave full approval to Boehringer Ingelheim's idarucizumab (*Praxbind*) to reverse the anticoagulant effect of dabigatran (*Pradaxa*) in the event of urgent surgery or life-threatening or uncontrolled bleeding. The FDA had granted accelerated approval to idarucizumab in October 2015, with continued approval contingent upon the results of the recently completed RE-VERSE AD trial.

4/5/2018: The FDA approved *andexanet alpha (Andexxa, Portola Pharmaceuticals)* (coagulation factor Xa (recombinant) inactivated-zhzo) to reverse the anticoagulation effects of factor Xa inhibitors when needed due to life-threatening or uncontrolled bleeding

18/7/2018: The FDA keeps updating health care professionals and consumers following an FDA press release about voluntary recalls of several drug products containing *valsartan*. The recalled products contain an impurity, cancer-causing N-nitrosodimethylamine (NDMA), in the drug manufactured by Zhejiang Huahai Pharmaceuticals, Linhai, China.

27/11/2018: FDA alerted patients and health care professionals to Teva Pharmaceuticals' voluntary recall of *valsartan*-containing products manufactured by Mylan Pharmaceuticals.

12/12/2018: The FDA has updated its testing methods to detect NDMA and NDEA impurities –These methods were validated with respect to *valsartan* drug substances and drug products

19/12/2018: FDA is publishing interim acceptable intake levels of nitrosamine impurities in angiotensin II receptor blockers (ARBs) for manufacturers to use to ensure their finished drug products are safe for patients.

20/12/2018: An FDA review found that *fluoroquinolone* antibiotics can increase the occurrence of rare but serious events of aortic dissections, or ruptures of an aortic aneurysm

20/12/2018: FDA is alerting patients and health care professionals to Torrent Pharmaceuticals' voluntary recall of two lots of losartan potassium 100 mg tablets due to N-Nitroso-diethylamine (NDEA) in the *losartan* active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.