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HIGHLIGHTS FROM *JACC*

Highlights of the Year in *JACC* 2010

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As in past years, this Highlights article takes the place of the Editor's Page, and was assembled by the Associate Editors on the basis of the manuscripts that they perceived had or would have the greatest impact upon cardiology. Space constraints result in omitting many excellent manuscripts, and we apologize in advance to the authors.

Coronary Artery Disease

ST-segment elevation myocardial infarction (STEMI). Is the metric of door to balloon time (DBT) of great importance in patients who present late in the course of their STEMI? Theoretically, with less muscle to salvage, late presentations may negate the benefit of a short DBT. Using data from the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) and the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trials, Brodie et al. (1) document that in the subgroup of patients with late presentations (>90 min from onset of pain), long DBT was no longer associated with a lower mortality. Both high-risk and low-risk patients in the early presentation group benefited from a short DBT, but the absolute benefit was greatest in the high-risk patients (3.7% vs. 7.0% for short DBT vs. long DBT) compared with low-risk patients (0.8% vs. 1.5%).

One approach to reduce treatment delays is to initiate therapy in the pre-hospital setting. The On-TIME 2 (Ongoing Tirofiban in Myocardial Infarction Evaluation 2) trial evaluated the use of high-dose glycoprotein IIb/IIIA inhibitor tirofiban in the ambulance (2). The trial had an open label phase 1 followed by a double-blind phase 2; the primary endpoint of the pooled analysis was death, recurrent myocardial infarction (MI), and urgent target vessel revascularization (TVR) at 30 days. During the 3 years of the trial, 1,398 patients were treated, 414 in the open label phase and 984 in the double-blind phase. Major adverse cardiac events (MACE) at 30 days were significantly reduced by high-dose tirofiban (5.8% vs. 8.6%, $p = 0.043$) with a trend toward a reduction in mortality (2.25% vs. 4.1%, $p = 0.051$). There was no increase in bleeding noted.

While pre-hospital administration of lytics and adjunct therapies may improve time to reperfusion, patient delays in calling 911 still average more than 2 h. A novel approach to reduce this delay was reported by Fischell et al. (3), who implanted an intracardiac ST-segment monitoring device in 37 patients who were at high risk for acute coronary syndromes. The implanted device, similar to a pacemaker, continuously monitored the ST segments from the right ventricular apical lead. Patients were alerted with an alarm when ST-segment elevations were noted of 3 SDs or more of their regular daily range. Over a median follow-up of 1.52 years, 4 patients had appropriate alarms, which led to very rapid presentation to the hospital of 19.5 min. An additional 4 patients had alarms at elevated heart rates, which were determined to be related to flow-limiting lesions. Three patients had false positive alarms. This novel approach may be practical in patients already receiving a pacemaker/defibrillator.

Bleeding. Since bleeding during treatment of acute coronary syndrome (ACS), primarily invasive treatment, is a significant risk factor for mortality, it is important to predict the risk of this complication. Using data from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy Trial) and the HORIZONS-AMI trials, Mehran et al. (4) developed a simple 7-variable risk score consisting of female sex, advanced age, elevated serum creatinine and white cell count, anemia, non-STEMI, or STEMI, as well as the use of heparin plus a IIb/IIIa inhibitor. Moreover, the risk score identified patients at risk not only for 30-day rate of non–CABG-related major bleeding but also 1-year mortality. The score ranged from 0 (0.9% risk of major bleeding within 30 days) to 40 (43.5% bleeding risk). The risk score may allow for tailoring percutaneous coronary

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intervention (PCI) procedures (such as with the use of radial approach rather than femoral approach) to lower the bleeding risk. Whether such an approach would reduce mortality remains to be proven.

Risk factors and risk assessment. Optimal assessment of cardiovascular (CV) risk continues to be controversial. Where different studies have reached varying conclusions such as metabolic syndrome, the use of meta-analysis may be helpful. Mottillo et al. (5) performed a meta-analysis of 87 studies, involving 951,083 patients (approximately one-half using the 2001 National Cholesterol Education Program definition and half using the 2004 revised definition for the metabolic syndrome). The metabolic syndrome was found to be associated with a relative risk of 2.35 for CV disease, 2.02 for CV disease mortality, 1.58 for total mortality, 2.99 for MI, and 2.27 for stroke risk. Whether the risk associated with the metabolic syndrome is greater than the sum of its parts remains unclear.

Abdominal obesity is a key component of the metabolic syndrome. The question of whether a modest increase in abdominal fat is deleterious was assessed by Romero-Corral et al. (6) using the surrogate endpoint of endothelial dysfunction. They recruited 43 normal weight and healthy volunteers who were then randomly assigned to a weight gain group. Endothelial function measured by flow-mediated dilation decreased (9.1 ± 3% vs. 7.8 ± 3.2%, $p = 0.003$) with an average weight gain of 4.1 kg, but recovered when the subjects lost the weight again.

While low-density lipoprotein (LDL) cholesterol has been the primary lipid risk factor and target of therapy in various guidelines, increasing attention has been paid to other lipid parameters. Non–high-density lipoprotein (HDL) cholesterol is an attractive measure and target as it quantifies the cholesterol in all the known atherogenic cholesterol particles, including very low-density lipoprotein (VLDL), intermediate-density lipoprotein, and chylomicron remnants. Arsenault et al. (7) reported 21,488 men and women without diabetes mellitus or coronary disease between the ages of 45 and 79 years followed up for 11 years in the European Prospective Investigation Into Cancer and Nutrition-Norfolk population study. Even among subjects with low LDL cholesterol levels (<100 mg/dl), an elevated non-HDL cholesterol >130 mg/dl was associated with a hazard ratio (HR) of 1.84 compared with non-HDL cholesterol <130 mg/dl. Total cholesterol/HDL cholesterol and elevated triglycerides were also associated with increased risk.

Moderate alcohol consumption has been shown to be associated with reduced CV and overall mortality. Whether alcohol consumption has similar associations in secondary prevention populations is less clear. Costanzo et al. (8) performed a meta-analysis of 8 selected studies, which included 16,351 patients. They found that in a secondary prevention population there was a J curve with maximal protection for CV mortality by consuming 26 g/day, with a lower consumption in the range of 5 to 10 g/day having the lowest overall mortality.

The use of imaging to identify asymptomatic atherosclerosis and further risk stratify patients evaluated for primary prevention continues to generate intense interest as well as debate (9,10). Nambi et al. (11), reporting on data from the ARIC (Atherosclerosis Risk In Communities) study, assessed whether carotid intima-media thickness (CIMT) and carotid plaque, alone or in combination, improved risk stratification based on traditional coronary heart disease (CHD) risk factors. Of 13,145 subjects, close to a one-quarter were reclassified by adding CIMT plus plaque information, with an improvement in the area under the curve from 0.742 to 0.755. The net reclassification index was highest at 9.9% when both the CIMT and presence of plaque were added to the traditional CHD risk factors. The findings of the study add to an increasing body of literature supporting the incorporation of carotid imaging in intermediate risk patients, and are particularly timely given the upcoming National Cholesterol Education Program Adult Treatment Panel IV report (12).

While carotid imaging with intima media thickness (IMT) may play a role in baseline risk assessment, it has also been proposed as a surrogate endpoint for CV events in various intervention trials such as lipid-lowering therapy. Costanzo et al. (13), therefore, performed a meta regression analysis of randomized trials assessing IMT regression with reduction in CV effects. They included 41 trials enrolling 18,307 participants. Despite significant reduction in CV events and all-cause death with active treatments, surprisingly there was no significant relationship between IMT regression and CHD events. These findings raise doubt as to the suitability of IMT regression as a surrogate endpoint in CV trials.

Endothelial dysfunction is an early event in the progression of atherosclerosis, and therefore may also have a role in risk stratification. The traditional modality of brachial artery reactivity (flow-mediated dilation [FMD]) is technically challenging, however, and has not gained routine clinical use. Matsuzawa et al. (14), used a simpler and less user-operated commercial device, the Endopat 2000 (Itamar, Cesarea, Israel), which utilizes a finger plethysmograph rather than ultrasound measurement of the brachial artery. The reactive hyperemia peripheral artery tonometry (RH-PAT) measured by the device has been shown to correlate with FMD and with coronary endothelial dysfunction, and impaired RH-PAT was predictive of ischemic events in women. They further found that compared with the Reynolds Risk Score, RH-PAT was more predictive for nonobstructive coronary artery disease (CAD).

While smoking has been well recognized as a potent CV risk factor for decades, the impact of secondhand smoke (SHS) has been less well defined, and the associated mechanisms have not been fully understood. Hamer et al. (15) studied 13,443 subjects in England and Scotland and measured salivary cotinine, an objective marker of exposure

to SHS. Exposure to SHS was associated with all-cause mortality (HR: 1.21) and elevated C-reactive protein (CRP), linking inflammation as a mediator of SHS-related CV disease. Not all studies on smoking have confirmed an association with CRP. In a study from Japan, Tomiyama et al. (16) studied 2,054 subjects who were divided by their smoking status. Over a 5- to 6-year follow-up period, the continuous heavy smokers had significantly greater progression of arterial stiffening as judged by brachial-ankle pulse wave velocity. There was no relationship found, however, in that study with serum CRP levels.

The benefits of smoking cessation on vascular function was assessed by Johnson et al. (17) in a study of 1,504 smokers enrolled in various smoking cessation therapies. Among those who successfully quit smoking (36.2% of the cohort), there was a 1% improvement in FMD (6.2 ± 4.4% to 7.2± 4.2%), whereas those who continued smoking had no change in FMD.

Lipid-lowering therapy. While statins are likely to remain the cornerstone of lipid-lowering therapy, attempts to develop novel antilipidemic drugs continue. One approach is to inhibit the production of apolipoprotein B (apo-B), the carrier protein of atherogenic particles such as LDL. Akdim et al. (18) reported on the efficacy and safety of mipomersen, an antisense inhibitor of apo-B synthesis. In their phase 2 dose-escalation study, 74 subjects were enrolled into 6 dose cohorts, from 30 to 400 mg. The LDL cholesterol and apo-B were reduced by up to 52% and 54%, respectively. The drug, which is injected once weekly, caused some mild to moderate erythema. Importantly, there was a very high (50%) incidence of liver enzyme elevation in a group given the drug for 13 weeks.

The safety of statins, and particularly whether they may pose a cancer risk, has been the subject of much investigation and debate. Important additional data in this area were added by Gränsbo et al. (19), using a Swedish acute MI registry, with data on 21,410 patients 80 years of age and older. Using propensity analysis, they demonstrated a significant reduction in all-cause mortality without any increase in cancer mortality. These data are particularly interesting as it points to the benefit of statin treatment without increased cancer mortality in an elderly population with a high risk of cancer.

Platelets and antiplatelet therapies. The role of platelets in acute coronary syndromes and post-PCI complications as well as the complex area of response to clopidogrel and its interactions with other drugs (and the contribution of polymorphisms to these interactions) continued to generate great interest in 2010.

Whether a rebound phenomenon exists upon cessation of clopidogrel is a key question, as guidelines suggest discontinuing clopidogrel after 1 year of therapy after DES. Sibbing et al. (20) randomly assigned 65 patients about to have clopidogrel stopped to either a tapering regimen or abrupt discontinuation. The authors measured platelet aggregation using light transmission aggregometry and multiple electrode aggregometry. Adenosine diphosphate (ADP)-induced platelet aggregation was no different between the abrupt cessation and the tapering group, suggesting that rebound did not exist.

Lev et al. (21) identified 30 patients (of 485 initially screened) receiving 75 to 182 mg daily who were "aspirin resistant" and randomly allocated them to either 325 mg of aspirin or to the addition of omega-3 fatty acids. The patients were retested after 30 days. They found significant reductions in arachidonic acid and ADP-induced aggregation as well as in the VerifyNow score in both groups, with the majority in both groups no longer being aspirin resistant. Gajos et al. (22) similarly studied the effect of omega-3 fatty acids on platelet activation in patients on dual antiplatelet agents (aspirin and clopidogrel) undergoing PCI. After 1 month of treatment, platelet reactivity as assessed by 20 μmol/l ADP was reduced by 13.3% ($p = 0.026$).

One of the limitations of clopidogrel is that the drug is a prodrug, which requires activation through the cytochrome p450 system (CYP2C19) and is prone to polymorphisms. Prasugrel, while also a prodrug is more efficiently metabolized and produces greater, more rapid platelet inhibition, and reduced ischemic events but at an increased risk of bleeding. The pharmacodynamics of switching patients from clopidogrel to prasugrel was assessed in the SWAP (Switching Antiplatelet) study (23). The 139 patients with a recent ACS event were first treated with open label clopidogrel for 10 to 14 days, and were then randomly assigned to continued clopidogrel, prasugrel loading followed by maintenance prasugrel, or prasugrel maintenance only without a loading dose. Overall, prasugrel was more effective in achieving platelet inhibition than clopidogrel—the added platelet inhibition was evident at 1 week without a loading dose of prasugrel and within 2 h with a loading dose.

In ACS patients undergoing diagnostic angiography deemed to require coronary surgery, prior clopidogrel treatment may increase bleeding risk, prompting many surgeons to delay surgery for several days. Shim et al. (24) studied the use of a modified thromboelastography in predicting bleeding and need for transfusion in 100 recipients of clopidogrel awaiting coronary artery bypass graft surgery (CABG) within 5 days since their last dose of clopidogrel. They report that irrespective of time from last clopidogrel administration, high levels of platelet inhibition predicted increased blood loss and transfusion requirement after off-pump CABG, with a cut-off value of 70% for increased risk of transfusion. The use of the thromboelastography test may allow tailored timing of surgery to minimize bleeding risk and surgical delay.

Once a patient undergoes CABG is there a role for clopidogrel therapy? Gao et al. (25) randomly allocated 249 consecutive elective CABG patients to aspirin alone or to aspirin and clopidogrel therapy after CABG. Multislice coronary angiography was performed at 3 months. Vein graft patency was greater (91.6%) in the aspirin and clopi-

dogrel group than in the aspirin-alone group (85.7%, p = 0.043). Longer-term studies are now needed.

Assessment of high risk for CABG remains challenging. While frailty is a well-recognized risk factor for poor outcomes, its objective assessment is difficult. Afilalo et al. (26) conducted a multicenter prospective study of 131 elderly patients undergoing coronary bypass surgery and/or valve replacement. They tested the predictive value of slow gait speed, defined as a time taken to walk 5 m of ≥6 s. The primary endpoint was a composite of in-hospital postoperative mortality or major morbidity. Slow gait speed was an independent predictor of the composite endpoint even after adjusting for the Society of Thoracic Surgeons risk score (odds ratio [OR]: 3.05).

Hypertension and arterial stiffness. Pre-hypertension, defined as 120 to 139 systolic or 80 to 89 mm Hg diastolic, is common and increases with age. Whether changes in body composition, namely, weight gain or weight loss as well as fat gain or loss, influence the progression or regression of hypertension in pre-hypertensive persons was examined by Markus et al. (27) in a cohort of 1,145 subjects from the MONICA/KORA (Monitoring Trends and Determinants on Cardiovascular Diseases/Cooperative Research in the Region of Augsburg) cohort study. They followed up the group over 10 years. Subjects who had progression to hypertension (one-half the cohort) were characterized by weight gain, principally due to fat gain, while the small percentage (6.76%) who went from being hypertensive to pre-hypertensive were characterized by decrease in body weight and fat mass.

Resistant hypertension is a vexing problem in clinical care. Scheffers et al. (28) report on the use of a novel implantable device (Rheos System, CVRx, Inc., Minneapolis, Minnesota) that works by electrical stimulation of the carotid sinus, thereby causing baroreflex activation. Studying 45 patients with resistant hypertension, they report a reduction in mean blood pressure of 21/12 mm Hg at 3 months. Although the study was not randomized, when the device was turned off, there was a prompt increase in blood pressure. Further study is clearly warranted for such non-pharmacologic approaches, which may be practical for the most difficult to treat patients.

Various publications over the past year assessed the contribution of arterial stiffness to the prediction of CV events, as well as the utility of the various measurements reflective of arterial stiffness.

Vlachopoulos et al. (29) performed a systematic review and meta-analysis of studies looking at the predictive value of aortic pulse wave velocity (PWV) for CV events and all-cause mortality. Using data from 17 studies (total of 15,877 subjects followed up for a mean of 7.7 years), they showed that the pooled relative risks (RR) for clinical events increased in a linear fashion across tertiles of PWV, including an almost doubling of risk of total mortality. An increase of 1 SD in aortic PWV was associated with an increase in total CV events, CV mortality, and all-cause mortality of 47%, 47%, and 42%, respectively.

Benetos et al. (30) reported on a novel hemodynamic biomarker for CV risk, which they termed pulse pressure amplification. Normally central (carotid) pulse pressure is lower than brachial blood pressure. With aging, there is a disproportionate increase in central aortic stiffness, which puts an increased load on the heart. The result is an increase in central pulse pressure amplification compared with brachial. This parameter can be quantified as the carotid/brachial ratio. The authors first derived a normogram relating measured brachial and carotid pulse pressure. They then applied this model to a population of 125,151 subjects who were followed up for 12 years. They found that the carotid/brachial ratio was a strong predictor for both CV and total mortality (HR: 1.22, 95% confidence interval [CI]: 1.12 to 1.32, and HR: 1.41, 95% CI: 1.14 to 1.73, respectively).

Kidney disease. Widely accepted therapies such as antiplatelet agents and statins may have different risk/benefit profiles in patients with chronic kidney disease (CKD). One potentially novel mechanism was reported by Meyer et al. (31), who examined endothelial function in 14 hemodialysis patients. They measured FMD before and after dialysis and demonstrated a post-dialysis impairment of endothelial function, which correlated with release of hemoglobin (hemolysis). Moreover, the cell free hemoglobin led to a decrease in the bioavailability of free nitric oxide.

Jardine et al. (32) examined the effects of aspirin 75 mg daily versus placebo in patients with diastolic hypertension in the HOT (Hypertension Optimal Treatment) study who were stratified by glomerular filtration rate (GFR). The authors found an increasing benefit of aspirin treatment with decreasing renal function. Major CV events were reduced by 9%, 15%, and 66% in patients with baseline estimated GFR of ≥60, 45 to 59, and <45 ml/min/1.73 m^2 (p trend = 0.03); total mortality was similarly lowered, and major bleeding was nonsignificantly greater with lower eGFR. For every 1,000 patients with estimated GFR <45 ml/min/1.73 m^2 treated for 3.8 years, aspirin at 75 mg daily prevented 76 major CV events and 54 deaths, with only 27 excess major bleeds.

Diabetes and CKD often coexist. Diabetes is also a risk factor for high post-treatment platelet reactivity. Angiolillo et al. (33) examined 306 diabetic patients and compared the antiplatelet effects of dual antiplatelet therapy (aspirin and clopidogrel) in those with moderate and severe kidney dysfunction to those with normal kidney function. Patients with moderate/severe kidney disease were 3.8 times more likely to have high post-treatment platelet reactivity than were patients with normal function.

The long-term results of several landmark clinical trials regarding the treatment of ACS were reported this year. Damman et al. (34) reported the 5-year clinical outcomes of the ICTUS (Invasive Versus Conservative Treatment in Unstable Coronary Syndromes) trial. They randomly allo-

cated 1,200 patients to an early invasive or selective invasive strategy. At 5 years, cumulative death and MI rates were 22.3% and 18.1% in the early invasive and selective invasive groups, respectively ($p = 0.053$). However, no statistically significant differences were observed in either mortality or MI. Thus, at 5 years, patients with non–ST-segment elevation ACS and elevated troponin T did not manifest a long-term benefit from an early invasive strategy in reducing either death or MI. In an accompanying editorial, Bittl and Maron (35) point out that most patients in either arm underwent diagnostic angiography. They further opine that both early invasive and delayed selective invasive strategies have values and limitations; the greatest importance of the ICTUS trial is that it demonstrates that an individualized approach can be undertaken in patients with non-STEMI.

In a related paper dealing with the issue of non-STEMI, Fox et al. (36) performed an interesting meta-analysis that incorporated the findings not only of the ICTUS trial, but also the 5-year outcomes from the FRISC2 (Fragment and Fast Revascularization During Instability in Coronary Artery Disease) trial and the RITA3 randomized trial of the conservative treatment strategy versus an interventional treatment strategy for patients with unstable angina. The inclusion of 5,467 patients rendered significant as statistical power. Over 5 years, 14.7% of the patients randomly assigned to a routine invasive strategy experienced either CV death or nonfatal MI versus 17.9% in the selective invasive arm ($p < 0.002$). The greatest effect was upon a MI, and there was a substantial benefit attributed to patients in the highest risk category. Thus, when the results of the ICTUS trial was combined with those of 2 other similar studies, a routine invasive strategy appeared superior, although this was most dramatic in the highest-risk patients.

The role of plaque instability and thrombus formation in the production of MI continues to evolve. Kramer et al. (37) studied coronary lesions from 111 sudden death victims from the medical examiner. In this group, 65 of the lesions were ruptures, whereas 50 were erosions. Interestingly, 69% of all lesions associated with sudden death were found to have "late stage" organizing thrombi. These data suggest the sudden death may actually be a late stage complication of plaque instability and thrombosis, and perhaps may be related to microembolization. In an accompanying editorial, Levin (37a) comments that the distinction of plaque erosion and plaque rupture may allow for individualized therapy in patients with CAD.

Interventional Cardiology

Randomized Clinical Trials

The JETSTENT trial. The JETSTENT(AngioJet Rheolytic Thrombectomy Before Direct Infarct Artery Stenting in Patients Undergoing Primary PCI for Acute MI) trial (38), a multicenter, prospective study compared rheolytic thrombectomy before direct infarct artery stenting to direct stenting to improve myocardial reperfusion and MACE in 501 acute MI (AMI) patients with angiographic evidence of thrombus grade 3 to 5 and a reference vessel diameter ≥2.5 mm. Co-primary endpoints were early ST-segment resolution and 99mTc-sestamibi infarct size ($p < 0.05$ for both or $p < 0.025$ for 1 for significance). The ST-segment resolution was more frequent in the rheolytic thrombectomy versus the direct stenting alone arm (85.8% vs. 78.8%, $p = 0.043$). Although no differences were noted in the other surrogate endpoints, the 6-month MACE rate (11.2% vs. 19.4%, $p = 0.011$) and 1-year event-free survival rates (85.2 vs. 75.0, $p = 0.009$) were improved with rheolytic thrombectomy. The authors suggest that, although the primary efficacy endpoints were not met, the results support the use of rheolytic thrombectomy before infarct artery stenting in patients with AMI and evidence of coronary thrombus. However, an accompanying editorial suggested that in keeping with current guideline recommendations, thrombus extraction seems to be a useful adjunctive therapy for patients undergoing primary PCI for STEMI, and the modality of choice appears to be simple manual aspiration (39).

The ZEST trial. The ZEST (Comparison of the Efficacy and the Safety of Zotarolimus-Eluting Stent Versus Sirolimus-Eluting Stent and Paclitaxel-Eluting Stent for Coronary Lesions) trial (40), a single-blind, multicenter, prospectively randomized trial involving 2,645 patients undergoing PCI evaluated the relative efficacy and safety of zotarolimus-eluting stents (ZES), sirolimus-eluting stents (SES), and paclitaxel-eluting stents (PES) for a composite of MACE at 12 months. At 12 months, the ZES group showed noninferior rates of MACE compared with the SES group (10.2% vs. 8.3%, p for noninferiority = 0.01, p for superiority = 0.17) and significantly fewer MACE than the PES group (10.2% vs. 14.1%, p for superiority = 0.01). The incidence of death or MI was similar among the groups. The incidence of stent thrombosis was significantly lower in the SES group (ZES vs. SES vs. PES, 0.7% vs. 0% vs. 0.8%, respectively; $p = 0.02$). In this large-scale, practical randomized trial, the use of ZES resulted in similar rates of MACE compared with SES, and fewer MACE compared with PES at 12 months.

The EVA-AMI trial. The EVA-AMI (Efficacy of Eptifibatide Compared With Abciximab in Primary PCI for Acute ST Elevation MI) trial (41) randomly allocated 427 patients with STEMI <12 h and planned primary PCI to double-bolus eptifibatide followed by a 24-h infusion or single-bolus abciximab followed by a 12-h infusion. In this noninferiority trial, the primary endpoint was the incidence of complete (≥70%) ST-segment resolution 60 min after PCI. The incidence of complete ST-segment resolution at 60 min after PCI in the intention-to-treat analysis was 62.6% after eptifibatide and 56.3% after abciximab, and reinfarction was 0.4% versus 3.5%, respectively ($p = 0.03$). All-cause mortality, the combined endpoint of death, nonfatal reinfarction, TVR, after 6 months, and major bleeding complications after 30 days were similar. In conclusion, eptifibatide

as an adjunct to primary PCI is equally as effective as abciximab with respect to ST-segment resolution.

In the SCAAR (Swedish Coronary Angiography and Angioplasty Registry) study (42), 11,479 STEMI patients who underwent primary PCI and received either eptifibatide or abciximab were evaluated for the primary endpoint of death or MI during 1-year follow-up, with adjustment for baseline differences with a multivariate logistic regression analysis including propensity score. The combined endpoint occurred in 15% treated with eptifibatide and 15.7% treated with abciximab, the unadjusted OR was 0.95 (95% CI: 0.84 to 1.08). Multivariate adjustment and the adjusted secondary endpoints of death and MI separately also showed noninferiority. This large registry also supports that eptifibatide is noninferior to abciximab for patients with STEMI undergoing primary PCI.

The ISAR-DESIRE 2 trial. The ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) trial (43), randomly allocated, open-label, 450 patients with clinically significant in-SES restenosis to repeat SES versus PES. The primary endpoint was late lumen loss based on in-stent analysis at 6- to 8-month follow-up angiography. There were no differences between SES and PES in late loss, binary restenosis, target lesion revascularization (TLR), death/MI, and stent thrombosis, suggesting a comparable degree of efficacy and safety.

The ENDEAVOR IV trial. The ENDEAVOR IV (Randomized Comparison of Zotarolimus-Eluting and Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease IV) trial (44) evaluated the safety and efficacy of ZES (n = 773) compared with PES (n = 775) in a prospective, randomized, single-blind, controlled trial in patients with single de novo coronary lesions. The primary endpoint was noninferiority of 9-month target vessel failure (TVF) defined as cardiac death, MI, or TVR. At 9 months, ZES was noninferior to PES regarding TVF, and fewer had periprocedural MIs (0.5% vs. 2.2%; p = 0.007), although at 12 months there were no significant differences between groups in rates of cardiac death, MI, TVR, or stent thrombosis.

The LIPSIA-N-ACC trial. The LIPSIA-N-ACC (Myocardial Salvage and Contrast Dye Induced Nephropathy Reduction by N-Acetylcysteine) trial (45), a randomized, single-blind, controlled trial assessed *N*-acetylcysteine effects on contrast-induced nephropathy and reperfusion injury in 251 STEMI patients undergoing primary PCI with moderate contrast volumes. Patients were randomly allocated to either high-dose *N*-acetylcysteine (2 × 1,200 mg daily for 48 h) or placebo plus optimal hydration. The 2 primary endpoints were: 1) the occurrence of >25% increase in serum creatinine level <72 h after randomization; and 2) a reduction in reperfusion injury measured as myocardial salvage index by magnetic resonance imaging. The primary endpoint occurred in 14% of the *N*-acetylcysteine group and in 20% of the placebo group (p = 0.28). The myocardial salvage index was also not different. High-dose intravenous *N*-acetylcysteine does not provide an additional clinical benefit to placebo in nonselected patients undergoing PCI, although a larger study with more power may be indicated to define the role of *N*-acetylcysteine in PCI.

The NORDISTEMI trial. The NORDISTEMI (Norwegian Study on District Treatment of ST-Elevation MI) trial (46) compared immediate transfer for PCI with an ischemia-guided approach after thrombolysis in patients with very long transfer distances. A total of 266 patients with STEMI with >90-min transfer delays for PCI were treated with tenecteplase, aspirin, enoxaparin, and clopidogrel and randomly assigned to immediate transfer or to standard management in the local hospitals except clinical deterioration. The primary outcome, a composite of death, reinfarction, stroke, or new ischemia at 12 months, was reached in 21% patients in the early invasive group compared with 27% in the conservative group. (p = 0.19). The composite of death, reinfarction, or stroke at 12 months was significantly reduced in the early invasive compared with the conservative group (6% vs. 16%, p = 0.01). No significant differences in bleeding or infarct size were observed, perhaps because of the high rate of radial access (>80%). In conclusion, immediate transfer for PCI reduced the rate of death, reinfarction, or stroke at 12 months among patients with STEMI treated with thrombolysis and clopidogrel in areas with long transfer distances.

The ARMYDA-5 PRELOAD trial. The ARMYDA-5 PRELOAD (Antiplatelet therapy for Reduction of Myocardial Damage During Angioplasty) randomized trial (47) evaluated the safety and effectiveness of 600 mg clopidogrel in laboratory loading before PCI (in-laboratory, n = 205) versus 600 mg given 4 to 8 h before PCI (pre-load, n = 204). The primary endpoint, 30-day incidence of MACE, was similar between groups (8.8% in-laboratory vs. 10.3% pre-load), and no difference in bleeding or vascular complications was observed. Thus, when indicated, in-laboratory clopidogrel administration before PCI can be a safe alternative to routine pre-treatment given before knowing patients' coronary anatomy.

Follow-Up Studies of Randomized Clinical Trials

The FAME study. The FAME (Fractional Flow Reserve Versus Angiography in Multivessel Evaluation) study (48) investigated the relationship between angiographic and functional severity of coronary artery stenoses in 509 patients with multivessel CAD in the fractional flow reserve (FFR)-guided arm of the FAME study. Before FFR measurement, these lesions were categorized into 50% to 70% diameter stenosis (47% of all lesions), 71% to 90% diameter stenosis (39% of all lesions), and 91% to 99% diameter stenosis (15% of all lesions) by visual assessment. A total of 35%, 80%, and 96% stenosis were functionally significant (FFR ≤0.80) in the category 50% to 70%, 71% to 90%, and 90% to 91%, respectively. In stenoses, 96% were functionally significant. Of all 509 patients with angiographically defined multivessel disease, only 46% had functional multives-

sel disease by FFR. This study suggests that angiography is inaccurate in assessing the functional significance of a coronary stenoses in the 50% to 90% range.

The principle investigators of the FAME trial also reported their 2-year follow-up results comparing FFR versus angiography to guide PCI in patients with multivessel CAD (49). Combined rates of death and MI were 12.9% in the angiography-guided group and 8.4% in the FFR-guided group ($p = 0.02$). Differences between these approaches were not statistically significant when revascularization was added. Thus, these data indicate that routine measurement of FFR in patients with multivessel CAD undergoing PCI with drug-eluting stents reduces mortality and MI at 2 years compared with a standard angiography-guided PCI.

The DEDICATION trial. The DEDICATION (Drug Elution and Distal Protection in ST Elevation MI) trial (50) evaluated the long-term effects of distal protection during PCI for STEMI patients assigned to distal protection ($n = 312$) or conventional treatment ($n = 314$). The total number of stent thromboses was 11 in the distal protection group and 4 in the conventional treatment group ($p = 0.06$). In primary PCI for STEMI, the routine use of distal protection increased the incidence of definite stent thrombosis and clinically driven TLR/TVR during 15 months of follow-up. Although the events rates are low and the study needs to be confirmed, the results does suggest that additional vessel manipulation by distal protection devices may lead to increased MACE in native coronary vessels.

The SESAMI trial. The SESAMI (Sirolimus-Eluting Stent Versus Bare-Metal Stent In Acute MI) trial (51) investigated whether the reported favorable 1-year MACE incidence of SES versus BMS in 320 STEMI patients was maintained at 3-year follow-up. The 3-year incidence of MACE was lower in the SES group compared with the BMS group (12.7% vs. 21%, $p = 0.034$), as were TLR, TVR, and TVF rates. The 3-year survival rate free from MACE, TLR, and TVF was significantly higher in the SES group than in the BMS group. The lower incidence of adverse events in the SES group was driven by TLR reduction and achieved in the first year of follow-up. The cumulative incidence of death and recurrent MI, starting from clopidogrel discontinuation, was comparable in the 2 groups.

The ACUITY trial. The ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial (52) evaluated the impact of delay to PCI in 7,749 patients with non–ST-segment elevation ACS at a median of 19.5 h after presentation. Delay to PCI >24 h after clinical presentation was significantly associated with increased 30-day mortality, MI, and composite ischemia (death, MI, and unplanned revascularization). By multivariable analysis, delay to PCI of >24 h was a significant independent predictor of 30-day and 1-year mortality, and risk was greatest for high-risk patients. These findings suggest that angiography and triage to revascularization within 24 h should be a priority in non–ST-segment elevation ACS patients.

The SYNTAX trial. The SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus And Cardiac Surgery) trial in patients with symptomatic left main and/or 3-vessel disease demonstrated that bypass surgery and percutaneous intervention with Taxus stents yielded comparable results for death and MI, but a higher stroke rate for surgery and higher repeat revascularization rate for PCI. Banning et al. (53) reported the results of the Taxus trial in the pre-specified subgroup with diabetes mellitus. In 452 patients with diabetes, the 1-year major adverse cardiac and cerebral vascular event rate was higher when treated with paclitaxel stents than with bypass surgery, a difference due to a greater rate of repeat revascularization. However, the rate of hard events (death, MI, or stroke), was similar for the 2 treatment approaches. In an accompanying editorial, Dauerman (54) opines that these results indicate that, in diabetic patients with left main or triple-vessel disease, PCI with paclitaxel-eluting stents is not associated with increased mortality, as was true of bare metal stents, and may be undertaken in patients judged to be poor candidates for bypass surgery.

The HORIZONS AMI trial. The HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial randomly assigned >3,000 patients with STEMI to either paclitaxel-eluting stents or BMS (55). At 24 months of follow-up, TLR continued to be less with the PES than with BMS. Importantly, insulin-treated diabetes, reference vessel diameter <3.0 mm, and lesion length >30 mm were independent predictors of 12-month TLR with BMS. In patients with 2 or 3 of these risk factors, PES markedly reduced 12-month TLR, but no difference between PES and BMS existed for patients with no risk factors. Thus, in patients with STEMI, PES is of benefit in reducing TLR in patients with risk factors, but not in lower risk patients.

The ISAR-TEST 2 trial. Byrne et al. (56) reported the 2-year clinical and angiographic outcomes of the ISAR-TEST-2 (Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents) trial. In a randomized trial, they compared sirolimus, a new generation sirolimus and probucol-eluting stent, with zotarolimus-eluting stent (56). Probucol was added to sirolimus to target a different element of the restenotic process well as to retard the release of the sirolimus by virtue of lipophilicity. At 2-year follow-up, the drugs were found to have comparable safety profiles whereas the dual sirolimus/probucol stent manifested a greater reduction of TLR than the sirolimus stent, but comparable to that of the Endeavor instrument.

Registry Studies

The MAIN-COMPARE registry. The MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry (57)

evaluated 2,240 patients with unprotected left main coronary artery disease who received coronary stents (n = 1,102; 318 with BMS) or underwent CABG (n = 1,138) between 2000 and 2006, and for whom complete follow-up data were available for at least 3 to 9 years (median 5.2 years). After adjustment for differences in baseline risk factors with the inverse probability of treatment weighting, the 5-year risk of death (HR: 1.13; p = 0.35) and the combined risk of death, Q-wave MI, or stroke (HR: 1.07; p = 0.59) were not significantly different. The risk of TVR was significantly higher in the stenting group than in the CABG group (HR: 5.11; p < 0.001). Similar results were obtained in comparisons of BMS with concurrent CABG and of DES with concurrent CABG.

The ASAN-MAIN registry. The ASAN-MAIN (ASAN Medical Center–Left Main Revascularization) registry (58) evaluated the long-term safety and effectiveness of PCI compared with CABG for unprotected left main coronary artery disease in a 10-year clinical follow-up of 350 patients who underwent PCI with BMS or CABG (n = 250) and 5-year clinical follow-up of 395 patients with DES or CABG (n = 219). In the 10-year follow-up cohort of BMS and concurrent CABG, the adjusted risks of death and the composite of death, Q-wave MI, or stroke were similar between the 2 groups. The rate of TVR was significantly higher in the group that received BMS (HR: 10.34; p < 0.001). In the 5-year follow-up cohort of DES and concurrent CABG, there was no significant difference in the adjusted risk of death or the composite outcome. The rates of TVR were also higher in the DES group than the CABG group (HR: 6.22; p < 0.001). This registry of long-term outcomes of unprotected left main coronary artery disease suggests that PCI with stent implantation is associated with similar long-term mortality and rates of death, Q-wave MI, or stroke but higher rates of repeat revascularization than CABG for both BMS and DES.

The ARTS II study. The ARTS II (Arterial Revascularization Therapies Study II) study (59) compared the 5-year clinical outcomes, safety, and efficacy of SES with the outcomes of CABG and BMS from the ARTS I study. The ARTS I study was a randomized trial of 1,205 patients with multivessel disease comparing CABG and BMS. The ARTS II study was a nonrandomized trial with the SES, applying the same inclusion and exclusion criteria, endpoints, and protocol definitions. At 5 years, the death/stroke/MI event-free survival rate was 87.1% in the ARTS II SES cohort, versus 86.0% (p = 0.1) and 81.9% (p = 0.007) in the ARTS I CABG and BMS cohorts, respectively. The 5-year major adverse cardiac and cerebrovascular event rate in the ARTS II study (27.5%) was significantly higher than the ARTS I study CABG (21.1%, p = 0.02), and lower than in the ARTS I study BMS (41.5%, p < 0.001). The cumulative incidence of definite stent thrombosis was 3.8%. Thirty-two percent (56 of 176) of MACE at 5 years was related to possible, probable, or definite stent thrombosis.

The COBIS registry. The COBIS (Coronary Bifurcation Stenting) registry (60) compared the long-term clinical outcomes of 1,033 patients treated with SES and 562 patients treated with PES for coronary bifurcation lesions. Treatment with SES was associated with a lower incidence of MACE (HR: 0.53, p < 0.01) and TLR (HR: 0.55, p = 0.02), but not of cardiac death and cardiac death or MI. After propensity-score matching, patients with SES still had fewer MACE and lower TLR incidence than did patients with PES (HR: 0.52, p = 0.02, and HR: 0.48, p = 0.02, respectively). There was no significant difference in the occurrences of stent thrombosis between the groups (0.7%). In patients with bifurcation lesions, the use of SES resulted in better long-term outcomes than did the use of PES, primarily by decreasing the rate of repeat revascularization.

In a pathology study of 40 stented bifurcation lesions (21 BMS and 19 DES), plaque formation in native coronary bifurcations and neointimal growth after DES implantation was significantly less at the flow divider versus the lateral wall (61). A higher prevalence of late stent thrombosis in DES compared with BMS was associated with greater uncovered struts at flow divider sites, which is likely due to flow disturbances.

No-reflow phenomenon. Ndrepepa et al. (62) investigated the impact of no-reflow phenomenon by angiography on 5-year mortality among 1,406 patients with STEMI treated by primary PCI. Infarct size measured with single-photon emission computed tomography imaging 7 to 14 days after the acute event was 15.0% of the left ventricle in the no-reflow group versus 8.0% in the reflow group (p < 0.001). There were 59 deaths among patients with no-reflow and 73 deaths among patients with reflow (p < 0.001). The Cox proportional hazards model adjusting for infarct size among other variables identified the no-reflow phenomenon as an independent correlate of 5-year mortality (HR: 1.66, p = 0.004). The no-reflow phenomenon after PCI provides prognostic information that is independent of and beyond that provided by infarct size.

Cytochrome *CYP2C19* polymorphism and antiplatelet effects of clopidogrel. Hochholzer et al. (63) evaluated the impact of demographic and clinical variables versus the cytochrome P450 2C19 (*CYP2C19*) polymorphism on antiplatelet effects of clopidogrel in 760 patients undergoing elective PCI after loading with 600 mg of clopidogrel. Major independent predictors for an insufficient antiplatelet response to clopidogrel were *CYP2C19*2* carrier status (OR: 2.74), together with age (OR: 1.03), diabetes mellitus (OR: 1.75), and body mass index (BMI) (OR: 1.06). Classification and regression trees analyses demonstrated that *CYP2C19*2* carrier status followed by diabetes mellitus was the best discriminator between a sufficient and an insufficient antiplatelet response to clopidogrel. A full linear regression model including all these parameters could only explain 11.5% of the antiplatelet response (5.2% by *CYP2C19*2* carrier status alone). This study suggests that genotyping alone or in combination with clinical factors

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explains a very small portion of the antiplatelet response to clopidogrel.

Carotid and Peripheral Arterial Disease Stenting

Proximal endovascular occlusion for carotid artery stenting. Stabile et al. (64), in a single-center registry, evaluated proximal endovascular occlusion in 1,300 patients undergoing carotid artery stenting. Patients received an independent neurological assessment before the procedure and 1 h, 24 h, and 30 days after the procedure. Procedural success was achieved in 99.7% of patients. The 30-day stroke and death incidence was 1.38% (n = 19) and was greater in symptomatic patients (3.04% vs. 0.82%; $p < 0.05$). The 30-day stroke and death rate was similar among patients at high and average surgical risk. Operator experience, symptomatic status, and hypertension were found to be independent predictors of adverse events. If the remarkably low event rates in this study are reproduced, it may elevate proximal protection to a leading role in carotid stenting.

DES for below-the-knee critical limb ischemia. The PARADISE (Preventing Amputations Using Drug Eluting Stents) trial (65), a prospective registry of 106 patients (118 limbs), investigated the efficacy and safety of DES (n = 228) to prevent amputations in patients with below-the-knee critical limb ischemia. There were no procedural deaths, and 96% of patients were discharged within 24 h. The 3-year cumulative incidence of amputation was 6 ± 2%, survival was 71 ± 5%, and amputation-free survival was 68 ± 5%. Rutherford category, age, creatinine level, and dialysis ($p \leq 0.001$ to 0.04) were predictors of death but not amputation. Target limb revascularization occurred in 15% of patients, and repeat angiography in 35% of patients revealed a binary restenosis in 12%. Limb salvage and survival rates in patients treated with DES exceed those of historic controls. The authors conclude that treating below-the-knee critical limb ischemia with DES is an effective and safe means of preventing major amputation and relieving symptoms.

Late neointimal effects of BMS. Takano et al. (66) examined the neointimal characteristics of BMS by optical coherence tomography during the early (<6 months, n = 20) and late phases (≥5 years, n = 21) after implantation. Normal neointima proliferated homogeneously, and lipid-laden intima was not observed in the early phase. In the late phase, lipid-laden intima, intimal disruption, and thrombus frequently were found in comparison with the early phase. The appearance of intraintima neovascularization was more prevalent in the late phase than in the early phase (62% vs. 0%, respectively; $p < 0.01$) and in segments with lipid-laden intima than in nonlipidic segments (79% vs. 29%, respectively; $p = 0.026$). These remarkable optical coherence tomography finding suggest that neointima within the BMS often transforms into lipid-laden tissue and may explain some of the late adverse events noted with BMS.

Intravascular Ultrasound Predictors of Plaque Morphology and Progression

Kubo et al. (67) used virtual histology (VH) intravascular ultrasound (IVUS) to investigate the natural history of coronary lesion morphology by performing baseline and 12-month follow-up studies in 216 nonculprit lesions (plaque burden ≥40%) in 99 patients. Lesions were classified into pathological intimal thickening, thin-capped fibroatheroma (TCFA), thick-capped fibroatheroma (ThCFA), fibrotic plaque, and fibrocalcific plaque. At baseline, 20 lesions were VH TCFAs; during follow-up, 15 (75%) VH TCFAs "healed," 13 became ThCFAs, 2 became fibrotic plaque, and 5 (25%) VH TCFAs remained unchanged. Compared with VH TCFAs that healed, VH TCFAs that did not were located more proximally and had larger lumen, vessel, and plaque areas but not baseline VH IVUS plaque composition. Conversely, 12 new VH TCFAs developed; 6 were pathological intimal thickenings and 6 were ThCFAs at baseline. In addition, plaque area at minimum lumen sites increased significantly in all but fibrous or fibrocalcific plaque. This longitudinal study suggests novel insights into plaque progression, and by inference imaging of stable and active plaques, that will help guide future imaging and therapeutic trials using such techniques.

Bayturan et al. (68) evaluated 3,437 patients with CAD undergoing serial IVUS examination in 7 clinical trials. Patients who achieved an on-treatment LDL cholesterol level of ≤70 mg/dl (n = 951) were stratified as progressors (n = 200) or nonprogressors. Despite achieving LDL cholesterol ≤70 mg/dl, >20% of patients continued to progress. Progressors demonstrated higher baseline levels of glucose, triglycerides, and a smaller decrease of apo-B at follow-up. Multivariable analysis revealed that independently associated risk factors of progression included baseline percent atheroma volume, diabetes mellitus, increase in systolic blood pressure, less increase in HDL cholesterol, and a smaller decrease in apo-B levels, but not changes in CRP or LDL cholesterol. This study highlights the importance of residual risk factors, particularly LDL particle concentration, in the progression of atherosclerosis in patients who achieve very low LDL cholesterol levels.

In another IVUS study, Nicholls et al. (69) examined the relationship between IVUS measures and CV outcomes, by defining the relationship between baseline and change in percent atheroma volume (PAV) and total atheroma volume and total with MACE in 4,137 patients and 6 clinical trials. Greater baseline PAV was observed in patients with MI, coronary revascularization, or MACE. Importantly, each standard deviation increase in PAV with associated with a 1.32-fold greater likelihood of experiencing MACE. Thus, this study demonstrated a relationship between the burden and progression of coronary atherosclerosis as defined by IVUS and the occurrence of MACE. The investigators contended that their data support the use of IVUS as a

modality to predict beneficial effects of new antiatherosclerotic therapies.

Oxidation-Specific Biomarkers and Lipoprotein(a)

The relationship of a panel of oxidative biomarkers and lipoprotein(a) to CAD risk was determined in the prospective case-control study nested in the EPIC (European Prospective Investigation of Cancer)-Norfolk cohort of 45- to 79-year-old apparently healthy men and women followed up for ~6 years (70). After adjusting for conventional risk factors, the highest tertiles of oxidized phospholipids on apo-B-100 particles and lipoprotein(a) were associated with a significantly higher risk of CAD events (OR: 1.67 and 1.64, respectively; $p < 0.001$) compared with the lowest tertiles, which was significantly potentiated (approximately doubled) by the highest tertiles of secretory phospholipase A_2 activity and mass but less so for myeloperoxidase and lipoprotein-associated phospholipase A_2 activity. After taking into account the Framingham Risk Score, *c*-index values progressively increased when oxidative biomarkers were added to the model. This EPIC-Norfolk study links pathophysiologically related oxidation-specific biomarkers and lipoprotein(a) with CAD events and suggests that they provide cumulative predictive value when added to traditional CV risk factors.

A systematic review of 40 studies involving 58,000 participants measured apo(a) isoforms and determined their risk of vascular disease (71). Thirty-six studies used broadly comparable phenotyping and analytic methods to assess apo(a) isoform size. These studies yielded a combined relative risk for CHD of 2.08 for subjects with smaller versus larger apo(a) isoforms. There was substantial heterogeneity among these studies (I^2 = 85%, 80% to 89%), which was mainly explained by differences in the laboratory methods and analytic approaches used. In the 6 studies of ischemic stroke that used comparable phenotypic methods, the combined relative risk was 2.14. Thus, persons with smaller apo(a) isoforms have an approximately 2-fold higher risk of CHD or ischemic stroke than do those with larger proteins.

Alcohol Septal Ablation

Alcohol septal ablation represents an interventional therapy for hypertrophic cardiomyopathy. Agarwal et al. (72) performed a meta-analysis of 12 studies in an attempt to compare the efficacy of alcohol ablation versus surgical myectomy. No significant difference between alcohol ablation or surgical myectomy could be found in either short-term or long-term mortality or post-interventional functional status, functional class, ventricular arrhythmias, reinterventions, or mitral regurgitation. However, septal alcohol ablation did increase the risk of right bundle branch block, the need for a permanent pacemaker, and was associated with a significantly higher residual gradient in the left ventricular (LV) outflow track. In the absence of a randomized prospective clinical trial comparing these 2 therapeutic approaches, this meta-analysis suggests that septal alcohol ablation yields similar results to those for the treatment of hypertrophic obstructive cardiomyopathy.

Heart Rhythm Disorders

Mechanisms of atrial fibrillation. Recent studies have cast doubt on the hypothesis that paroxysmal atrial fibrillation (AF) progresses to persistent AF (73). De Vos et al. (73) studied the clinical correlates of patients in whom paroxysmal AF did and did not progress to persistent AF, to define a scoring system for progression. In 1,219 paroxysmal AF participants, AF progressed at 1 year in 15%. On multivariate analysis, HATCH (an acronym for heart failure, age, previous transient ischemic attack or stroke, chronic obstructive pulmonary disease [COPD], and hypertension) independently predicted AF progression. The researchers created a HATCH score for AF progression: half of patients with HATCH score = 5 but only 6% of patients with score = 0 progressed to persistent AF; HATCH thus had prognostic value. An accompanying editorial (74) agreed that the HATCH score may identify patients likely to progress to persistent AF and, if validated, may provide important bedside prognostic information.

Several studies have associated single nucleotide polymorphisms (SNPs) with AF, particularly those on chromosomes 4q25 and 16q22 (75,76). However, applying these data to clinical management has been unclear. A thought-provoking study in *JACC* by Husser et al. (77) showed that SNPs on chromosome 4q25 may identify patients with AF recurrence after ablation. In 195 AF patients undergoing ablation for drug, the authors studied SNPs rs2200733 and rs10033464 on chromosome 4q25 and prospectively assessed for AF recurrence per guidelines. Recurrent AF occurred in 37% within 7 days ("early"), and 21% at 3 to 6 months ("late"), and was not predicted by clinical characteristics. However, the presence of any variant allele (of identified SNPs) was strongly associated with early recurrence (OR: 1.994) and late recurrence (OR: 4.182). While calling for additional studies, an accompanying editorial (76) agreed that polymorphisms on chromosome 4q25 may modulate risk for AF recurrence after catheter ablation, pointing to a potential clinical role in risk stratification.

Ablation for persistent AF may involve extensive ablation to isolate the pulmonary veins (PV), ablate the left atrial roof, and interrupt circuits in other locations. However, the mechanistic rationale for each of these lesion sets is unclear. Nishida et al. (78) mapped canine AF circuits, then assessed the impact of the PV isolation and roof ablation of an extensive AF ablation procedure. The PV isolation failed to terminate AF, but did decrease AF vulnerability to single extrastimuli by increasing effective refractory periods. Conversely, left atrial roof ablation terminated AF in 67% of

dogs and reduced AF duration without affecting AF vulnerability. The authors conclude that PV isolation and left atrial roof ablations have beneficial but limited actions in this canine model, further emphasizing the need to systematically study individual step-wise components to refine AF ablation procedures.

The search for more effective pharmacological therapy for AF continues. Burashnikov et al. (79) used ex vivo canine perfused canine atrial, PV, and ventricular preparations to study the independent and concomitant effects of ranolazine and dronedarone on AF vulnerability (79). The authors found that low concentrations of ranolazine and dronedarone weakly suppressed AF, yet their combination potently depressed atrial-selective sodium channel activity and suppressed AF. This study supports future clinical trials.

Sinus nodal function. An elegant report by Fedorov et al. (80) used optical mapping of atria from human explanted hearts to define the functional sinoatrial node (SAN). Optical signals from the SAN region showed diastolic depolarization and multiple upstroke components, corresponding to the separate excitations of SAN and atrial layers. Excitation originated in the middle of the SAN, then spread slowly and anisotropically from it, to excite atrial myocardium via superior, middle, and/or inferior sinoatrial pathways. Notably, the oval SAN was functionally insulated from the atrium by connective tissue, fat, and coronary arteries, except for these pathways. The investigators conclude that these are the first data to show the location of the leading SAN pacemaker site, the pattern of excitation within the human SAN, and the conduction pathways into the right atrium. These findings have clinical significance in understanding the pathophysiology of atrial tachyarrhythmias.

Syncope. A definitive diagnosis for syncope is often difficult to achieve. The ROSE (Risk Stratification of Syncope in the Emergency Department) study, published by Reed et al. (81), prospectively developed a clinical decision rule to predict serious 1-month outcome and all-cause mortality among patients presenting to the emergency department with syncope. From this single-center, prospective, observational study was derived the ROSE rule and subsequently validated it in 550 patients each. Independent predictors of serious 1-month outcome or all-cause death that occurred in 7.3% patients were brain natriuretic peptide (BNP) concentration >300 pg/ml, positive fecal occult blood, hemoglobin <9 g/dl, oxygen saturation <94%, and Q-wave on electrocardiogram; and were similar in the validation cohort. The ROSE rule had a sensitivity and specificity of 87.2% and 65.5%, respectively, and a negative predictive value of 98.5%. Elevated BNP alone was a major predictor of serious CV outcomes (8 of 9 deaths, 89%). Thus, the ROSE rule (and particularly its BNP component) has excellent sensitivity and negative predictive value for identifying high-risk patients with syncope.

Sudden cardiac arrest and implantable cardioverter-defibrillator therapy. The automated external defibrillator (AED) has the potential to reduce mortality from sudden cardiac arrest (SCA) in high-risk public places. Weisfeldt et al. (82) reported the relationship of AED application (before emergency medical services) to survival to hospital discharge in a cohort with nontraumatic out-of-hospital SCA. From the Resuscitation Outcome Consortium, 4,403 out-of-hospital received bystander cardiopulmonary resuscitations (CPRs) without AED use, and 289 CPRs with AED were applied by health care workers (32%), lay volunteers (35%), police (26%), or others (7%). Survival was 9% (382 of 4,403) with bystander CPR without AED, 24% (69 of 289) with AED use, and 38% (64 of 170) with AED shock delivered. In multivariate analyses, AED use was associated with greater likelihood of survival (OR: 1.75; $p < 0.002$). Extrapolating the observed survival benefit from to the entire U.S. and Canadian population (330 million), AED application by bystanders might save 474 lives a year.

Kanoupakis et al. (83) tested the hypothesis that serum markers of collagen turnover, reflecting turnover in ventricular myocardium, may contribute to substrates for ventricular arrhythmias. In 70 patients with nonischemic cardiomyopathy, and an implantable cardioverter-defibrillator (ICD) for primary prevention, the authors measured serum C-terminal propeptide of collagen type-I, C-terminal telopeptide of collagen type-I, matrix metalloproteinase (MMP)-1, and tissue inhibitor of MMP-1. The authors found appropriate ICD therapies in 14 of 70 patients during 1-year follow-up. Pre-implantation serum levels of C-terminal telopeptide of collagen type-I were significantly baseline MMP-1 and tissue inhibitor of MMP-1 higher in patients with ICD therapy than without ICD therapy. The authors concluded that serum markers of collagen turnover, possibly reflecting altered extracellular matrix that influences the arrhythmogenic substrate in nonischemic cardiomyopathy, may predict arrhythmic events in ICD recipients.

Data continue to accrue on ICD risks. Lee et al. (84) reported complications from ICD insertion in a multicenter registry of 18 centers. The authors noted 45-day major complications in 4.1% of procedures. Implantation of a cardiac resynchronization defibrillator or dual-chamber device was associated with an increased risk of major complications, which were higher in women and when end-systolic dimension exceeded 45 mm. Major complications (excluding death) early after ICD insertion were associated with increased risk of death. Direct ICD-related complications were associated with higher risk for early death (HR: 24.89), whereas indirect complications increased the risk for near-term death (HR: 12.35). The authors concluded that major complications occurred in 4.1% of de novo ICD inserts, were strongly associated with device type, and were associated with increased risk of mortality.

Chung et al. (85) reported on compliance with, and efficacy of, the wearable cardioverter-defibrillator (WCD) for prevention of sudden death in patients whose risk for ventricular arrhythmias is being ascertained, or who temporarily cannot receive an ICD because of infection or other comorbidity. In 6,569 WCD recipients, daily use was >90%

of the day in 52% of patients, with <15% of patients discontinuing use because of discomfort or adverse reactions. Eighty sustained ventricular tachycardia/ventricular fibrillation (VT/VF) events were noted in 59 patients (1.7%). First-shock success was 100% for unconscious VT/VF and 99% for all events, and resulted in a 89.5% survival from VT/VF events. During WCD use, 3,541 of 3,569 patients (99.2%) survived overall. Using the Social Security Death Index, long-term mortality was not significantly different from first ICD implant patients. As editorialized by Verdino (86), wear time with the WCD was satisfactory and the WCD provided a survival from sudden death comparable to that with ICD, although asystole was not addressed by the WCD.

Ablation of ventricular tachycardia. Nakahara et al. (87) report a mapping study for substrates for VT, in cardiomyopathy patients with a particular focus on low voltage late potentials (LP) as targets for catheter ablation. In 33 cardiomyopathy patients referred for VT ablation, they mapped the endocardium (n = 33) and epicardium (n = 19) to identify LP, defined as electrograms <1.5 mV with onset after the QRS interval, and very late potentials (vLP), defined as onset >100 ms after the QRS. Sampling 564 ± 449 endocardial points and 726 ± 483 epicardial points in the left ventricle per patient, the authors found low voltage areas in the endocardium and epicardium. Patients with ischemic myopathy had a larger endocardial low voltage area and frequencies of vLP than nonischemic myopathy (NICM) patients. Notably, LP-targeted ablation was effective in ischemic myopathy patients (82% nonrecurrence at 12 months) but less in NICM patients (50% at 15 months). The authors concluded that the cause of signal types often targeted for VT ablation (LP and vLP) may differ between ischemic myopathy and NICM, and that approaches other than LP ablation, and pace-mapping may be required in NICM patients.

As suggested by the above study, epicardial mapping is increasingly used during VT ablation. Sacher et al. (88) examined the necessity and safety for this approach from VT ablation at 3 referral centers. Of 913 VT ablations, 156 procedures (17%) involved epicardial mapping and/or ablation, performed in 134 patients mostly after a previous VT ablation. Notably, 51 patients had ischemic cardiomyopathy, 39 had nonischemic cardiomyopathy, 14 had arrhythmogenic right ventricular cardiomyopathy, and 30 had other types of cardiomyopathy. Overall, 136 procedures were performed by percutaneous subxiphoid puncture, 14 by a surgical subxiphoid approach, and 6 during open-heart surgery. Epicardial ablation was performed in 121 of 156 procedures (78%) and was subsequently delivered endocardially in 21%. Twenty patients subsequently required repeat procedures, and the epicardium could be reaccessed in all but 1 patient. The authors observed a total of 8 (5%) major complications acutely, including 7 epicardial bleeding events and 1 coronary stenosis. After 23 ± 21 months of follow-up, 3 delayed complications included 1 major pericardial inflammatory reaction, 1 delayed tamponade, and 1 coronary occlusion after 2 weeks. Constrictive pericarditis or phrenic nerve injuries were not observed. An accompanying editorial (89) places these data in the context of prior studies, in which epicardial ablation was also more likely to be required in patients with nonischemic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy, and outlines future trends in VT ablation.

Long QT syndrome (LQTS). Several studies addressed the link between the LQTS and life-threatening ventricular arrhythmias. Viskin et al. (90) examined the utility of a simple bedside test to improve diagnosis: that is whether short-lived sinus tachycardia from the orthostatic response to standing exposes abnormal QT prolongation in patients with LQTS. The authors examined 68 patients with LQTS and 82 control subjects. In response to brisk standing, patients and control subjects responded with similar heart rate acceleration of 28 ± 10 beats/min (p = NS). However, the QT interval shortened in controls by 21 ms and lengthened in LQTS patients by 4 ms ($p < 0.001$), so that corrected QT interval increased by 50 ± 30 ms in controls and 89 ± 47 ms in LQTS patients ($p < 0.001$). The authors concluded that evaluating the QT-interval response to the brisk tachycardia induced by standing may aid in the diagnosis of LQTS.

Although syncope is highly predictive for future fatal arrhythmias in LQTS, few data exist to stratify such risk. Jons et al. (91) studied 1,059 LQTS patients from the International LQT registry with corrected QT interval >450 ms and syncope as a first symptom. The investigators found that the lowest risk for a "severe arrhythmic event" occurred with only 1 syncopal episode before beta-blocker therapy. In contrast, patients with syncope after starting beta-blocker therapy had a 3.6-fold increase in the risk of severe arrhythmic events compared to patients not treated with beta-blockers. The risk of syncope during beta-blocker therapy was high during childhood in both sexes but higher in women (HR: 2.3, $p < 0.001$). The authors concluded that patients with LQTS and syncope during beta-blocker therapy are at high risk of life-threatening events, and should be considered for ICDs.

Cardiac resynchronization therapy (CRT). There is increasing evidence that patient-tailored lead location may improve the hemodynamics of CRT (92). Spragg et al. (93) studied the impact of endocardial LV pacing site on the mechanical response to CRT in patients with ICM. The authors studied peak rate of LV pressure increase (dP/dt_{max}) at baseline, during VDD pacing at the right ventricular apex, and during biventricular pacing from the right ventricular apex and 51 LV endocardial sites in 11 patients with ICM. They used electroanatomic mapping to create color-coded maps of dP/dt_{max} within the ventricle. The authors found that endocardial biventricular pacing improved dP/dt_{max} over right ventricular apical pacing. In 7 patients with preexisting CRT leads, LV dP/dt_{max} was equivalent for endocardial and epicardial pacing, but dP/dt_{max} at the best

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endocardial site was higher than achieved with the pre-implanted CRT. An average of 2 optimal endocardial sites (yielding >85% of maximum dP/dt_{max}) were identified for each patient, located at the extreme basal lateral wall (8 of 11 patients) and elsewhere (9 of 11 patients). Standard mid-LV free wall pacing yielded suboptimal LV function in 73% of patients. Optimal pacing sites were typically located in LV territories remote from the infarct zone. An accompanying editorial emphasized that CRT delivered at the best LV endocardial sites for any given patient was more effective than by pre-implanted coronary sinus leads, confirming results of a paper published in the *Journal* in 2010 regarding patients with nonischemic cardiomyopathy, by Derval and Jais (94).

Defibrillator electrograms. Multiple configurations of ventricular tachycardias are typically inducible in patients in whom ICDs have been implanted. Yoshida et al. (95) set out to determine whether an electrogram recorded on the ICD could in fact differentiate the actual clinical arrhythmias occurring from others inducible at the time of testing (95). They found that electrograms stored on the ICD accurately identified clinical VTs from 98% of other VTs. By visual inspection of the ICD electrograms, 96% of clinical VTs were accurately differentiated from previously undocumented VTs. In addition, pace mapping based on ICD electrograms were found to be useful for identifying a VT exit site. This study validates the usefulness of defibrillator electrograms for recognizing clinical VTs. In an accompanying editorial, Almendral and Marchlinski (96) indicate that this work suggests that in the management of VT with catheterization ablation procedures, ICD electrograms could become the new "standard" link between spontaneous phenomena and induced arrhythmias.

Singh et al. (97) reviewed the clinical trials reported to date on the new antiarrhythmic drug developed for the treatment of AF. The authors summarized the DAFNE (Dronedarone Atrial Fibrillation Study after Electrical Cardioversion), EURIDIS (European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm), ADONIS (American-Australian-African Trial with Dronedarone in Patients with Atrial Fibrillation or Atrial Flutter for the Maintenance of Sinus Rhythm), and ATHENA (A Trial with Dronedarone to Prevent Hospitalization or Death in Patients with Atrial Fibrillation) trials and noted a modest antiarrhythmic drug efficacy of dronedarone compared with other antiarrhythmic drugs and placebo. Patients administered dronedarone had a recurrence rate of AF or atrial flutter of 43% compared with 54% in patients on placebo ($p < 0.0001$), comparable to quinidine. In the DIONYSIS (Efficacy and Safety of Dronedarone versus Amiodarone for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation) study, the composite endpoint of AF recurrence or premature drug discontinuation in patients on drug for at least 6 months was reached by 74% of patients on dronedarone versus 55% on amiodarone. Dronedarone was effective in reducing ventricular rate on AF compared with placebo. Dronedarone was found to increase mortality in the ANDROMEDA (European Trial of Dronedarone in Moderate to Severe Congestive Heart Failure) trial, in patients with moderate to severe CHF. This increased mortality rate appeared to be due largely to worsening of heart failure, predominately in those patients with recently decompensated heart failure. In contrast, in the ATHENA trial, in patients with compensated heart failure, there was a 24% reduction in combined risk of CV hospitalization and all-cause mortality compared with placebo at 21 months follow-up. The Food and Drug Administration approved dronedarone for treatment of AF/atrial flutter largely on the basis of the results of the ATHENA trial. The researchers note, however, that in a pooled analysis of these 6 studies, in a total of 6,771 patients, dronedarone treatment was not significantly different with respect to placebo in the incidence of all-cause mortality of CV hospitalization. With respect to side effects, dronedarone was noted in these studies to cause a slight increase in creatinine due to inhibition of renal tubular secretion. The main clinical side effects were diarrhea, nausea, and vomiting. Thus, the authors concluded that dronedarone was moderately effective in the treatment of AF/atrial flutter, it may reduce CV hospitalization and all-cause mortality, it had less toxicity than amiodarone, it should not be used in patients with decompensated heart failure, and it is most likely a second- or third-line agent. The researchers also noted that its high cost (as much as $9 per day) makes it uncertain if it will be cost effective compared with generic amiodarone.

Fein et al. (98), provide an important perspective on the use of CRT outside of the guidelines from the National Cardiovascular Data Registry (NCDR) ICD registry. More than 75% of hospitals nationally submit data to this registry. The authors examined a cohort of 45,392 CRT-defibrillator implants for primary prevention of sudden death. They defined "off-label" implants, however, as those in patients with an ejection fraction (EF) >35%, New York Heart Association (NYHA) functional class <III, or a QRS duration <120 ms. The investigators found that 23.7% of devices were implanted without meeting all 3 implant criteria, most often due to NYHA functional class <III or QRS duration <120 ms. Physician training and insurance payer were weakly associated with the likelihood of off-label use. Thus, nearly 25% of patients undergoing CRT therapy reported to the NCDR registry during the study time frame did not meet guideline-based indications for device implantation. While the investigators refrain from equating off-label use of CRT devices with inappropriate care, they do suggest that these apparently aberrant practices require careful scrutiny.

The effects of chronic stretch due to mitral valve stenosis and its reversal after mitral commissurotomy (MC) on the electrophysiological properties of the human atria were reported this year (99). Because atrial stretch due to mitral

stenosis is a known common cause of AF, studying the atrial electrophysiology before and after the relief of this stretch would appear to be good method to correlate electrophysiologic characteristics with a substrate known to predispose to AF. The researchers evaluated 21 patients with mitral stenosis undergoing MC, before and after intervention. They observed that, immediately after MC, there was significant increase in mitral valve area, with significant decrease in left atrial and pulmonary artery pressures and left atrial volume. That was associated with reduction in P-wave duration, an increase in conduction velocity and voltage in both the left atrium and right atrium, but no change in effective refractory period (ERP). Late after MC, mitral valve area remained improved, but there was an even further decrease in P-wave duration, associated with further increases in conduction velocity and voltage in the right atrium, and ERP decreased. They concluded that the atrial electrophysiologic and electroanatomic abnormalities that result from chronic stretch due to mitral stenosis do significantly reverse after MC, and that the substrate predisposing to atrial arrhythmias may therefore be reversed as well. The authors did not assess inducibility of AF or report on the incidence of AF late after MC. These observations suggest that abnormalities in conduction velocity and voltage may be more important in generating the substrate predisposing to AF than shortening of ERP, which, interestingly, was observed to shorten even further late after MC in these patients.

Tedrow et al. (100) evaluated the effects of BMI on the risk of new AF during nearly 13 years of follow-up in the Women's Health Study, to assess the relationship between changes in BMI and incident AF. They note that both obesity and AF are increasing public health problems, but the role of obesity in AF is uncertain. Over 12.9 ± 1.9 years of follow-up, 834 AF events were confirmed after chart review. The researchers determined that BMI was linearly associated with AF risk, with a 4.7% ($p < 0.0001$) increase in risk with each kg/m^2. When long-term measures of BMI were utilized to estimate dynamic risk, overweight (HR: 1.22, 95% CI: 1.02 to 1.45, $p = 0.03$) and obesity (HR: 1.65, 95% CI: 1.36 to 2.00, $p < 0.0001$) were associated with adjusted short-term elevations in AF risk. Participants becoming obese during the first 60 months had a 41% adjusted increase in risk of developing AF ($p = 0.02$) compared with those maintaining BMI <30 kg/m^2. The correlation between BMI and AF risk appeared strongest in women 60 years of age and younger, whereas this correlation was not observed in women older than 60 years at baseline. From their observations, the authors concluded that in this population of initially healthy, middle-aged, female healthcare professionals, elevated BMI was associated with both short- and long-term elevations in AF risk, accounting for a large proportion of incident AF independent of traditional risk factors.

Congenital Heart Disease

Starting with therapy from before birth, a paper by Jaeggi et al. (101) evaluated the level of maternal anti-Ro/SSA antibodies as prognostic markers for development of cardiac neonatal lupus, and especially complete atrioventricular (AV) block (101). Transplacental anti-inflammatory treatment with maternal steroids was indicated if complete AV block reduced contractility, with intravenous immunoglobulin given to the mother (70 g every 2 to 3 weeks) and to the newborn in a single dose (2 g/kg). Five percent of the 359 prospectively screened and treated pregnancies resulted in complete AV block. Anticipated is a large study with immunoglobulin treatment begun earlier, and in situations with high levels of maternal antibodies rather than just a presence with associated fetal tissue injury.

A study by Avis et al. (102) looks at the safety and efficacy of rosuvastatin therapy for children with familial hypercholesterolemia. Twenty milligrams per day reduced LDL cholesterol by 50%; but only 40% of the patients attained a consistent target of <110 mg/dl LDL cholesterol. Four patients had very high creatine kinase levels during the administration of rosuvastatin (2 each with 10 mg and 20 mg, respectively). Rosuvastatin was, in general, well tolerated.

A study by Kantor et al. (103) highlighted the impact of changing medical therapy on transplantation-free survival in pediatric patients with dilated cardiomyopathy. This single-center study included children with dilated cardiomyopathy, varying in severity and age at presentation. Lower EF at presentation and the absence of acute myocarditis were associated with poor outcome. There was only a transient survival associated with combined use of angiotensin-converting enzyme inhibitors and beta-blockers, and no obvious sustained improvement accompanying digoxin-based therapy. The investigators concluded that the etiology rather than the choice of therapy is most related to outcome, with cardiac transplantation remaining the most viable in the long term.

A study by Moulik et al. (104) sought to evaluate the prevalence and outcome of viral endomyocarditis infection after transplantation and the effect of treatment with hyper immune intravenous immunoglobulin. Ninety-four patients with a mean age at transplantation of 6.5 years had congenital heart disease (36%), dilated cardiomyopathy (35%), restrictive cardiomyopathy (14%), and retransplantation (13%). The investigators conclude that viral infection of the endomyocardium is common after pediatric heart transplant, and is an independent risk factor for graft loss. Outcomes suggest that adverse outcome may be delayed by using intravenous immunoglobulin, and hence polymerase chain reaction screening, surveillance, and biopsies for cardiotropic viruses is indicated. The viral genome itself was an independent risk factor for graft loss, and, therefore, the authors suggest that evaluation of other methods (interferon beta therapy, cellular immune therapy) may need to be

explored in these patients, because the outcome of their viral endomyocarditis is poor.

A paper by Apitz et al. (105) related to nonstructural congenital heart disease describes treatment of pulmonary hypertension with oral sildenafil. They studied 36 patients with a mean age 7.5 years, 8 of whom had idiopathic pulmonary hypertension, the remainder of whom had pulmonary hypertension associated with congenital heart disease. Hemodynamics and serum cyclic-guanosine monophosphate were monitored at baseline and after inhaled nitric oxide, and the same measurements and sildenafil levels were measured 30 min after sildenafil. The vasodilating ability of sildenafil was lower than that of inhaled nitric oxide—2.8% versus 11.6% reduction of pulmonary vascular resistance indexed for body surface area. For patients with detectable sildenafil levels, the vasodilating capability was not statistically different from inhaled nitric oxide. Higher sildenafil levels were found in the patients with idiopathic pulmonary hypertension, whereas no responses were frequently seen in pulmonary hypertension associated with congenital heart disease. Although sildenafil may be effective in some patients, suboptimal absorption of sildenafil occurs in almost half of the children undergoing acute hemodynamic testing.

Structural forms of congenital heart disease, therapy, and outcomes. Harrild et al. (106) examined exercise capacity, ventricular volumes, and function in 41 patients after balloon dilation for significant pulmonary stenosis, either native or residual. Most patients had a pulmonary regurgitation (PR) regurgitant fraction of <10%; 34% of the patients had PR >15%, and 17% had PR >30%. Higher regurgitant fraction was found by magnetic resonance imaging (MRI) in patients <1 year of age at time of valvuloplasty and with balloon to artery ratios >1.4. Only 2 patients had severe PR, regurgitant fraction >40%. Exercise capacity in patients with PR regurgitant fraction of <15% was significantly higher by VO_2.

The conclusions were that mild PR and right ventricular (RV) dilation were common in the long-term follow-up of balloon dilation. A PR >15% was associated with lower VO_2 and more often RV dilation and impaired exercise function in the aftermath of balloon valvuloplasty for pulmonary stenosis. The accompanying editorial, by Latson (107), points out that isolated pulmonary stenosis patients have greater preserved RV function and less RV dilation than patients who had surgery for tetralogy of Fallot.

Residual after Fontan operation for complex single ventricle and other disorders. Rathod et al. (108) studied 90 patients, 28% having significant positive late gadolinium enhancement, in whom the dominant ventricle had a lower EF (45%), increased mean end-diastolic volume, and increased ventricular mass. In the patients with significant late gadolinium enhancement, the median percent ranged from 3.3 to 9.8 of the myocardium. Most (64%) was observed in the wall of the primary ventricle, 36% in the free wall of the secondary ventricle, and 16% in the defective septum.

Patients with late gadolinium were much more likely (62% vs. 28%) to have regional wall motion abnormalities and associated dyskinesis. Distribution of gadolinium varied from completely subendocardial to patchy. In the exercise tests performed within 1 year of cardiac magnetic resonance imaging, the late gadolinium results were not associated with changes in exercise capacity. Patients with more gadolinium-enhancing area did have a higher incidence of nonsustained VT.

A multicenter study investigated the presence and clinical associations of arrhythmias in a Fontan cohort—7 centers and 520 patients total, from 6 to 18 years after Fontan (109). Supraventricular tachycardia was present in 9.6% and intra-atrial reentry tachycardia in 7.3%—lower in this cohort than previously reported. Lower functional status and aorticopulmonary connection and a paced rhythm were determined to be independently associated with intra-atrial re-entrant tachycardia (IART) after Fontan.

The IART increased with the age of patients and length since the time of Fontan and later childhood. Presence of IART was slightly higher in L-looping abnormalities. Neither the degree of AV valve regurgitation nor systemic ventricular EF was associated with IART, but post-protein losing enteropathy occurred in 7.9% of patients with IART compared with 2.9% of patients without IART. The presence of IART was lower than in previous reports, and independent associations of IART development include a paced rhythm, lower functional status, and an atrial-pulmonary connection.

An editorial comment by Van Hare (110) concludes that the fact that they are unable to avoid these serious atrial arrhythmias despite evolution of the procedure means that we may have to consider what is done at the time of Fontan completion. In his editorial, Van Hare (110) referred to a paper whose investigators strategically placed atrial incisions to avoid recurrence of flutter, and that some of the mapping and ablation in electrophysiology therapies should have provided information to help us understand the elements—the substrate for atrial arrhythmia—and to help develop and design more effective surgical techniques to avoid it in the first place.

A multicenter study for the Alliance for Adult Research in Congenital Cardiology (111) examined a not-surprising set of difficulties in the aftermath of Fontan—the status of lower extremities systemic venous health, the so-called CALF (Congenital Heart Disease in Adults Lower Extremity Systemic Venous Health in Fontan Patients) study. This study included 159 adults with Fontan physiology compared with age-matched controls. Significant venous abnormalities occurred in almost double the number (mean 60%) of the Fontan patients compared with age-matched healthy controls (mean 32%). Comorbidities included thromboembolism, heart failure, and interventions to improve hemodynamic conditions. A thoughtful editorial by Marelli (112) points out that Fontan patients have captured the imaginations of surgeons and cardiologists and that a

prospective study with a quantitative analysis on hemodynamics and ventricular function as well as ventricular type and morphology might be of further help.

Tobler et al. (113) reported 65 adults followed up in the Toronto Congenital Cardiac Centre for Adults, among 132 infants surviving operation for arterial switch before 1991. Of these 65 adults, 11 had at least 1 significant cardiac lesion, including ventricular dysfunction, valve dysfunction, or arrhythmia. Residual lesions were more common in patients who had cardiac reinterventions in childhood; 8 had arrhythmias requiring reoperation or pacemaker implantation. Intervention for aortic valve and aortic root was not observed, and exercise capacity was reduced in 82%.

Adults with surgical evaluation before arterial switch were more likely to have significant residua than were those who had primary arterial switch. Although further follow-up is needed, neoaortic valve regurgitation and aortic root dilation was not prominent in this group. Cardiac reinterventions after age 18 years mainly occurred for relief of RV outflow tract obstruction and pulmonary valve stenosis. This study highlights overall good outcomes in this early cohort, but the subgroups who needed further interventions in childhood are at higher risk for ventricular dysfunction, valve dysfunction, and arrhythmias.

The natural history of adult patients with bicuspid aortic disease—viewed previously as a relatively simple abnormality—has now come into question (114). A timely review points out that eventual abnormal shear stress leads to valve calcification and raises the risk of continuing aortic dilation, especially in patients >30 years of age with moderate to severe aortic stenosis or incompetence. The prevalence of aortic sinus dilation was 28% in a paper from Toronto, describing adults with a mean age of 35 ± 16 years. Aortic dissection occurs in 0.1% for patient-year follow-up. Because there is a risk of further root dilation, many surgeons consider reinforcing or replacing the ascending aorta at the top of valve surgery. Pregnancy also seems to accelerate the need for surgery in post-partum women with moderate or severe aortic stenosis. Guidelines suggest women with bicuspid aortic valve aortopathy, with ascending aortas >4.8 cm, be counseled against the high-risk pregnancy.

An important paper reviewing the Canadian experience discussed mortality in CHD and definitely shifted the emphasis away from infants toward adults, with an increase in age at death and a gradual decrease in mortality (115). There were 71,686 CHD patients from 1987 to 2005 in the Quebec population who were studied for 982,363 patient-years. Factors contributing to decreased mortality in older children and adolescents include earlier and more accurate diagnosis, and refinement of selection procedures for surgical or percutaneous interventions. The reduction in mortality observed in children over these years was not accompanied by an increased mortality rate in adults. The mortality rate in adults ages 18 to 64 years declined comparable to that of the general population, suggesting that adults with CHD benefited from the overall gains in population health.

This large study reports a reduction over time in infant mortality and decreasing mortality rates in children and adolescents. The population with congenital heart disease is, therefore, growing and aging, with the burden of healthcare transitioning away from the child and toward the adult, raising challenges that the healthcare community may need to be prepared for in the allocation of resources.

Heart Failure

Continuous flow left ventricular assist devices (LVAD) significantly improve outcomes in advanced heart failure patients. Rogers et al. (116) assessed the impact of a continuous flow device on functional capacity and heart failure-related quality of life using data from patients enrolled in the HeartMate II (HMII) LVAD bridge to transplantation (BTT [n = 281]) and destination therapy (DT [n = 374]) trials. Compared with baseline measurements, HMII patients experienced substantial improvements in mean 6-min walk distance in DT patients and sustained improvements from baseline in median Minnesota Living With Heart Failure and Kansas City Cardiomyopathy Questionnaire overall summary scores in both BTT and DT patients. In an accompanying editorial, Starling et al. (117) commented that LVAD therapy had entered a new phase with the introduction of continuous flow devices, while acknowledging that patients implanted with a continuous flow LVAD still experience significant functional impairment and increased risk from infection, device malfunction, and stroke. Bleeding believed to be related to anticoagulation therapy coupled with bleeding diathesis such as acquired von Willebrand syndrome is also frequently reported with continuous flow devices. To determine the prevalence of coagulation abnormalities, Uriel et al. (118) performed a retrospective study in all 79 HMII patients who underwent implantation over a 5-year period. Nearly half experienced significant bleeding episodes (with gastrointestinal bleeding being the most common event) at an average of 112 ± 183 days post-implantation. Compared with patients with a pulsatile device, transfusion requirements at heart transplantation were doubled in HMII patients. High molecular weight von Willebrand factor multimers were reduced in all 31 HMII patients in whom they were measured, with recovery demonstrated in a smaller number who were restudied post-transplant. These findings support the notion of altering anticoagulation therapy in HMII patents both during device support and before surgery. In an accompanying editorial, Miller (119) commented that the findings should lead to future trials assessing the effects on bleeding risk of monitoring von Willebrand factor levels in patients implanted with a continuous flow device.

Borlaug et al. (120) sought to determine mechanisms involved in exercise limitation and symptoms in patients with heart failure and preserved EF (HFpEF). They confirmed reduced exercise capacity and tolerance in HFpEF

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patients compared with hypertensive subjects without heart disease and compared with normotensive controls. The HFpEF patients had lower VO_2 and cardiac index at peak exercise and more severe dyspnea and fatigue at matched low-level workloads. Although endothelial function was impaired both in HFpEF patients and hypertensive subjects versus controls, blunted exercise-induced increases in chronotropy, contractility, and vasodilation and impaired dynamic ventricular-arterial coupling responses were seen only in the HFpEF population. Exercise capacity was correlated with abnormalities in each component of CV reserve function, and HFpEF patients were more likely to display multiple abnormalities in reserve. These findings provide evidence of depressed reserve capacity involving multiple domains of CV function in HFpEF patients. In an accompanying editorial, Paulus (121) noted that, while there is strong evidence for multiple causes of exercise intolerance in HFpEF patients, a steep LV diastolic pressure-volume relationship was likely the dominant mechanism involved.

Maeder et al. (122) also compared exercise responses in HFpEF patients and healthy controls. While resting pulmonary capillary wedge pressure (PCWP) was similar in HFpEF patients and controls, stroke volume index (SVI) was lower, and systemic vascular resistance index (SVRI) was higher in patients, and they stopped exercise at lower work rate. Although peak exercise PCWP was similar in both groups, peak SVI was lower and peak PCWP/work rate ratio and SVRI were higher in HFpEF patients. Notably, while resting E/e' from Doppler study was modestly elevated in HFpEF patients, peak exercise E/e' did not differ between the groups. Thus, HFpEF patients achieve a similar peak exercise PCWP to that of asymptomatic controls, at a much lower workload in the setting of higher SVRI. In a related paper, Penicka et al. (123) determined that, in patients with unexplained dyspnea, evidence of an elevated PCWP could be demonstrated in about two-thirds of patients during exercise, indicating the presence of HFpEF. Increased LV stiffness, dyssynchrony, and dynamic mitral regurgitation were the major mechanisms involved. In an accompanying editorial, Lam (124) noted that, while this study provided further evidence that HFpEF was a frequent cause of unexplained dyspnea, accurate diagnosis was only the first step in the management of the patient and new evidence-based therapies that improve the natural history of this condition are badly needed.

The role of pre-clinical diastolic dysfunction on echocardiogram in the development of heart failure in diabetics was examined by From et al. (125). They identified diabetic patients with a ratio of transmitral to mitral annular of velocities of >15 and followed them from 2001 to 2007. Of the 1,760 diabetic patients, 23 patients had evidence of pre-clinical diastolic dysfunction. They observed that for every 1 unit increase in the ratio of transmitral to a mitral annular Doppler velocities, there was a 3% increase in the incidence of heart failure ($p < 0.006$), and that this was independent of other traditional risk factors for heart failure. The cumulative probability of heart failure over 5 years for diabetic patients with diastolic dysfunction was 36.9% as compared with 16.8% for patients without ($p < 0.001$). In an accompanying editorial, Greenberg (126) comments that this study confirms the frequent presence of cardiac abnormalities in diabetic patients, and demonstrates their significance in leading to heart failure. However, he does not believe that this justifies the routine use of Doppler studies in diabetic patients, but rather argues strongly for very intensive treatment of heart failure risk factors in this population.

An additional paper dealing with diabetes related to the prevalence of cardiac events during different treatments of hypertension. Weber et al. (127) analyzed data from the ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension) study to determine whether the addition of amiodipine or hydrochlorothiazide to the angiotensin-converting enzyme blocker benazepril was more effective in decreasing CV events in diabetic patients. Comparable blood pressures were obtained in both groups, whereas events were experienced by 8.8% of amiodipine patients versus 11% of patients receiving diuretics ($p < 0.003$). Thus, as was true of the ACCOMPLISH trial in general, combining the calcium-channel blocker amiodipine with the angiotensin-converting enzyme inhibitor benazepril was superior to the combination with a diuretic for diabetic patients.

To determine whether differences in beta-receptor specificities affect lung or vascular function in CHF patients, Jabbour et al. (128) evaluated the respiratory, hemodynamic, and clinical effects of switching between beta-1-selective and nonselective beta-blockers in CHF patients and COPD (128). The 51 patients received dose-matched treatment with either carvedilol, metoprolol succinate, or bisoprolol for 6 weeks before resuming their original beta-blocker. They found that N-terminal pro-hormone brain natriuretic peptide and central augmented pressure were significantly lower with carvedilol than with metoprolol or bisoprolol, and returned to baseline level on resumption of the initial beta-blocker. In COPD patients, forced expiratory volume in 1 second was lowest with carvedilol and highest with bisoprolol. Thus, switching between beta-1-selective and the nonselective beta-blocker carvedilol, although well tolerated, resulted in demonstrable changes in airway function, which was most pronounced in COPD patients.

Cardinale et al. (129) evaluated anthracycline-induced cardiomyopathy (AC-CMP) and its response to heart failure therapy in 201 consecutive patients with left ventricular ejection fraction (LVEF) <0.45. They initiated enalapril, and if possible, carvedilol, promptly after detecting impaired LVEF. Patients were classified according to complete, partial, or no response in LVEF. Overall, 85 (42%) were responders, 26 (13%) were partial responders, and 90 (45%) were nonresponders. The likelihood of a favorable response progressively decreased as the time from chemo-

therapy end to the start of heart failure treatment increased; no complete recovery of LVEF was observed after 6 months. Responders also showed a lower rate of cumulative cardiac events. Thus, early initiation of neurohormonal-blocking therapy in patients having AC-CMP results in recovery of LVEF and a reduction in cardiac events.

Sezai et al. (130) compared the effects of infusing 0.02 μg/kg/min of human atrial natriuretic peptide (hANP) versus saline in patients with LVEF <0.35 undergoing CABG in the NU-HIT (Nihon University Working Group Study of Low-Dose Human ANP Infusion Therapy During Cardiac Surgery) study. While early post-operative mortality was not significantly affected by treatment, perioperative complications were significantly less frequent and cardiac death-free rate at 5 to 8 years post-operatively was significantly lower in the hANP group. Post-operative EF was also significantly higher, BNP levels significantly and renal function appeared better in hANP-treated patients in the first post-operative year. In their accompanying editorial, Voors and van Veldhuisen (131) note that while the NU-HIT study results were consistent with other previously published reports about the use of natriuretic peptides during surgery, definitive evidence of a favorable effect on renal function and clinical outcomes required a larger well-designed trial. They concluded that the favorable results presented in this article should provide the stimulus to proceed with such a trial.

A paper by Verhaert et al. (132) describes long-term (mean 3.6 years) clinical and echocardiographic follow-up in 313 patients who underwent CRT. In patients with event-free survival, left ventricular end-systolic volume index (LVESVI) decreased significantly in the first 6 months, whereas patients with adverse clinical outcomes had no change in LVESVI. These data demonstrate the value of measuring LVESVI at baseline and follow-up as a powerful predictor of event-free survival after CRT.

A study by Derval and Jais (133) sought to evaluate the relationship between LV pacing site and the hemodynamic response to CRT. The investigators assessed 11 predetermined pacing sites and assessed several measures of LV function for each site. Pacing at the optimal site significantly improved LV function compared with coronary sinus pacing, improving maximum dP/dT by >2.

Health Services Research

Risk adjustment is central to the concepts of score-carding and quality improvement, because some patients are sicker than others and would be expected to have worse outcomes irrespective of treatment. Clinicians have perennial concerns that the standard data elements used in risk adjustment scores might not fully capture how sick the patient really is. This is a particular issue for older patients, many of whom fail "the eyeball test." Chaudhry et al. (134) abstracted charts of older patients with heart failure to capture data on their mobility and cognitive function, 2 elements that are not available in discharge codes, and found that each significantly improved risk assessment when added to standard data elements from history, physical, and laboratory findings. These results are plausible, and suggest we need ways to capture a clinician's gestalt about the functioning of older patients in records of care.

Cardiac noninvasive tests have continued to increase faster than other forms of medical care. Serial testing to monitor patients over time constitutes a large fraction of test use. Shah et al. (135) studied patterns of cardiac stress testing after coronary revascularization procedure and found that most patients were tested at least once within 24 months after their procedure. Interestingly, test use spiked at 6 and 12 months post-procedure, suggesting these stress tests were done at a routine visit, not based on recurrent symptoms as recommended in appropriate use criteria.

In the mind of the public, stress and psychological factors lead to heart disease, but the relationship has been difficult to assess in epidemiologic studies. Long-term follow-up of men 18 to 20 years of age who had psychological tests done as part of a medical examination for compulsory military service in Sweden showed that anxiety disorders were independently associated with incident heart disease decades later, independent of other risk factors (136). A meta-analysis of 20 other epidemiologic studies also found that anxiety disorders increased the incidence of coronary disease over the subsequent 11 years (137). Whether these associations reflect a causal pathway, such as chronic sympathetic activation, or whether anxiety is merely a marker for other factors, is not established.

If anxiety is bad for the heart, might a glass of wine with dinner help reduce stress and risk of cardiac disease? The effect of alcohol on the heart has been controversial. A study based on the National Health Interview Study (138) suggests that light or moderate alcohol intake was associated with lower cardiac risk than either abstaining from alcohol on the one hand or heavy alcohol intake on the other (>7 drinks per week for women, >14 drinks per week for men). The U-shaped relationship between alcohol consumption and heart disease may make public health education tricky, but fits well with advice to drink in moderation.

A paper by Aboyans et al. (139) reports on the relationship between location of peripheral arterial disease (PAD) and MACE. The authors studies 400 PAD patients. Proximal PAD (aortoiliac disease) was associated with a significantly worse prognosis compared with distal PAD. Adjusted for comorbidities, proximal PAD patients were >3 times more likely to experience a MACE event compared with distal PAD patients. There was also a significantly higher rate of mortality in patients with proximal PAD.

Freeman et al. (140) examined the outcome for >330,000 patients who underwent an ICD implantation during the years 2000 to 2008, demonstrating a strong relationship between hospital ICD volume and procedural complications. The adjusted OR of any adverse event was 1.26 for hospitals in the lowest volume quartile compared with

hospitals in the highest volume quartile. This relationship was strongest for biventricular devices (OR: 3.22) but also significant for single-chamber ICD procedures (OR: 1.10). The authors suggest that implantation of these devices may be performed more safely at high-volume centers.

Coronary Calcium

A provocative manuscript and editorial reports by Gottlieb et al. (141) on the relationship between coronary calcium score and the presence or absence of obstructive coronary lesion in patients undergoing 64-slice multidetector coronary computed tomography angiography. Although patients with a calcium score of zero were less likely to have a coronary obstruction ≥50%, the absence of calcium by multidetector coronary computed tomography angiography did not rule out obstructive CAD. In the patients without coronary calcium, 19% had a least 1 lesion with >50% stenosis. In 64 totally occluded vessels, 20% had no calcium.

Few data are available regarding quality and outcome measures in patients with CV disease treated in the outpatient setting. Therefore, the American College of Cardiology established within the NCDR the PINNACLE (Practice Innovation and Clinical Excellence) program. The performance measures for the first nearly 15,000 patients enrolled were presented by Chan et al. (142) regarding CAD, heart failure, and AF. Compliance with performance measured in these 27 U.S. practices ranged from a low of 13.3% of CAD patients screened for diabetes to a high of 96.7% of heart failure patients with blood pressure assessment, and was moderate (70% to 90%) for most performance measures. Thus, this registry established for the first time the feasibility of assessing compliance with performance measures in the outpatient setting, and showed both moderate compliance as well as the opportunity for improvement. In an editorial, Rao (143) commented that it provided an opportunity to evaluate the quality of medical care in a longitudinal perspective over time.

With increasing emphasis upon performance measures, there is critical need to identify risk factors for PCI so as to assist in decision making, compare provider performance, and assist comparative effectiveness research. Peterson et al. (144) utilized data from the NCDR to develop risk score for PCI from 588,000 procedures (144). They found that clinical factors were significantly associated within hospital mortality, whereas angiographic factors provided only modest incremental information. They developed a simplified NCDR risk score based on 8 pre-procedural factors that had an excellence discrimination (see index 0.93). In an accompanying editorial, Kereiakes (145) commented that this simple 8-variable model accurately predicted the risk of death to 30 days PCI in Medicare patients, and should be very clinically applicable. However, he pointed out that the continuing development of interventional cardiology will require additional risk scores in the future.

Questions exist on whether long-term intensive endurance training can have adverse effects upon LV structural function. Therefore, Pelliccia et al. (146) participated in the extreme endurance conditioning necessary to compete uninterrupted in 2 to 5 consecutive Olympic games. No cardiac events or new CV conditions were diagnosed. In addition, global LV systolic function was unchanged, and wall motion abnormalities were absent. Thus, in this group of young Olympic athletes, long-term uninterrupted endurance training was not associated with deterioration of LV function. In an accompanying editorial, Bhella and Levine (147) commented that the possibility of "athletes heart" has been suspected in the past, and has been supported by the demonstration of post-exercise elevations and cardiac specific markers and changes in cardiac structure. However, they endorse that the report by Pelliccia et al. (146) is quite reassuring that any abnormalities incurred in intense prolonged endurance training are likely reversible and relatively benign.

Genetics/Genomics

If you are questioning whether to skip over this genetic section because you think it does not apply to your clinical practice, we ask you to reconsider. The *Journal* strives to publish significant findings in the area of CV genetics that make a difference in clinical practice. This year "The Best of *JACC*" focuses on how genetics improves patient care and management, and defines how genetic variants alter CV risk.

Hofman et al. (148) report a 12-year look at a clinical management of probands and relatives with congenital long QT syndrome (LQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT) in the context of genetic testing. First-degree relatives of an affected person with an inherited arrhythmia syndrome carry an ~50% risk of carrying the mutation (149). The risk of a lethal event with or without this specific mutation in an affected relative is less clear. Moreover, the response to therapy has been shown to be genotype specific for LQTS (2–4). Surprisingly, 59% of the patients in this retrospective analysis had a QTc <460 ms, and would have been missed for LQTS if genetic testing were not performed. These patients can be provided with a series of lifestyle instructions and a set of QT-prolonging drugs to be avoided.

CPVT does not have 100% penetrance (similar to LQTS). A negative exercise test does not rule out that the patient carries a mutation associated with CPVT. Thus again, genetic testing was informative (150). Mutations in SCN5a have been associated with BrS. However, these mutations in SCN5a account for roughly one-third of mutations associated with BrS. Unlike LQTS and CPVT, the treatment options for BrS are limited (151). Thus, the advantages and disadvantages of genetic testing for BrS are less clear. Schwartz (152) provides a well-written editorial

with a historical reminder that, in 1980, a hypothesis was presented that patients affected by LQTS had a normal QT interval. This 12-year retrospective study supports that hypothesis.

A second LQTS paper published highlights how a risk-conferring modifier gene in a large cohort of LQTS individuals increases the incidence of cardiac events (153). This work follows others showing modifier genes in the nitric oxide synthase (NOS) signaling pathway in persons with LQTS; NOS1AP encodes the protein CAPON, which is an adaptor protein linking neuronal NOS with scaffold and signaling ligands, including dystophins. Next-generation sequencing will be informative in identifying other modifier genes in the probands and families with inherited arrhythmic disorders. Identification of modifier genes for inherited arrhythmic disorders is a significant area of study to help identify risk of major CV events and death in these patients.

A selected meta-analysis from Benn et al. (154) showed that the loss of function 49L allele of proprotein convertase subtilisin/kexin type 9 (PCSK9) was associated with a reduction in LDL cholesterol of 11% to 16%. This loss of function allele is found in 2% to 3% of the general population. PCSK9 is a protease that reduces LDL receptor levels and thereby increases plasma LDL cholesterol. This study determined the effect of this loss of function allele in PCSK9 on LDL cholesterol and the risk of ischemic heart disease and mortality. A significant association between carriers of the risk allele and reduced risk of ischemic heart disease was identified in only 1 of the 3 cohorts studied, perhaps because of environmental differences between the cohorts, including statin use, and changes in risk factors that may have altered the effects of the loss of function PCSK9 risk allele on ischemic heart disease. This meta-analysis demonstrated that the influence of genotype on CV disease risk depends on modifiable risk factors, environment and pharmacological therapy. Newton-Cheh and Smith (155) provided an accompanying editorial that discusses how genetic associations can be used to judge whether a clinical trait is a causal factor in disease development. The pipeline of deoxyribonucleic acid variants in genes associated with altered lipid metabolism continues to expand exponentially (156).

A pharmacogenomics meta-analysis by Hulot et al. (157) showed that reduced CYP2C19 function exposes clopidogrel-treated patients to excess CV risk and mortality. Clopidogrel requires transformation to an active metabolite, which is regulated in part through CYP2C19. Risk for stent thrombosis increases by 3- to 6-fold with a genotype positive for loss of function mutations in the CYP2C19. The study also suggests that proton pump inhibitors increase risk for CV events when taken with clopidogrel, although the variability in the studies was high, suggesting that more information is needed in these studies including genotypes and severity of disease.

Continuing along the lines of CAD, Dandona et al. (158) report that the common variant in 9p21 predicts the severity of atheroma burden. This study provides evidence that gene dosage of the risk allele for rs1333049 (homozygosity vs. heterozygosity) was associated with severity of CAD in younger patients at the time of mitral catheterization and in a cohort of older persons. Importantly, no association was found between 9p21 and MI. The mechanisms that are responsible for increased risk of CV disease due to regions near 9p21 are still not understood, and this better defines the role of atherosclerosis burden and risk of MI. An editorial by Anderson and Horne (159) discusses the potential role of 9p21 as a potential initiator, promoter, or precipitator of CAD. The underlying mechanisms of the risk allele on the 9p21 locus are not likely linked to inflammation or rupture of a fibrous cap leading to MI.

A state-of-the-art review by Baird (160) points out that the underlying cause of >30% of ischemic strokes remains unknown, and the diagnosis for stroke is accurate only ~70% of the time. It is well known that stroke is heritable, and a family history of stroke increases one's risk by 2- to 3-fold (161). Monogenic disorders and causative genes/chromosomal locations associated with stroke are reviewed as well as findings from genome-wide association studies. The genome-wide association studies have identified loci that are associated with increased risk for stroke that also predispose risk for atrial fibrillation. Hope in the arena of improved diagnostic platforms for stroke may be near; messenger RNA and proteomic profiling to identify targets in the blood after ischemic stroke are reviewed.

The field of genetics is changing our overall understanding of dilated cardiomyopathy. Lakdawala et al. (162) reported that a mutation in alpha-tropomyosin in 2 unrelated families is associated with a distinct age-dependent dilated cardiomyopathy that can be lethal early in life. This is the first evidence to supporting a role for tropomyosin in dilated cardiomyopathy that provides multigenerational family data and contractility assays in vitro. Treatment with potential for improvement in a subset of affected infants increasingly moves the bar for improvement in quality patient care. The inclusion of state-of-the-art contractility assays in vitro build the evidence that this specific mutation leads to decreased functional properties of tropomyosin. Commentary on how deoxyribonucleic acid variants in sarcomeric proteins alter the structure and function of the sarcomeric protein to influence the final common pathway of hypertrophic cardiomyopathy versus dilated cardiomyopathy is expertly laid out for the clinician and scientist in an editorial by Tardiff (163).

The Z disc is a region that joins the contractile apparatus to the cytoskeleton. Using a genome-wide linkage approach in 4 families, Chiu et al. (164) provide evidence that mutations in alpha-actinin 2 are associated with hypertrophic cardiomyopathy. The mutations in alpha-actinin 2 are within a number of important functional domains. An accompanying editorial by Bos and Ackerman (165) points

out that clinical genetic testing currently includes a 9-panel screen for sarcomeric or myofilament genes, which explains roughly 65% of genetic hypertrophic cardiomyopathy. The discovery of new genes will improve the genetic screening for all and aid in our overall understanding of hypertrophic cardiomyopathy. They also point out that alpha-actinin 2 also binds to ion channels and serves as a bridge to calcium channels and mutations may also increase risk for other CV-related endpoints.

Girolami et al. (166) undertook a novel direct sequencing screening of 8 genes in 488 unrelated hypertrophic cardiomyopathy patients, showing that persons harboring triple sarcomeric gene mutations are rare, and that this led to a significantly increased risk of end-stage disease and ventricular arrhythmias. These findings alert us that multiple rare variants do modulate the CV phenotype, as pointed out in an accompanying editorial by Hershberger (167). Exome sequencing and the release of the 1,000 genomes data will provide more information on rare variants. How these variants may collectively influence disease and/or interact with the environment is an area nearly untapped in the field of CV medicine.

Arrhythmogenic right ventricular cardiomyopathy is believed to be inherited in a moderate percentage of cases. Multiple genes, primarily involving desmosomal proteins, have been believed to be causative in arrhythmogenic right ventricular cardiomyopathy. However, Xu et al. (168) identified 21 variants of plakophilin-2 in 38 of 198 probands (19%), in 9 of whom compound heterozygosity was present. In addition, digenic heterozygosity was identified in 16 of the 38 subjects. Accordingly, these data demonstrate that the genetic basis of arrhythmogenic right ventricular cardiomyopathy includes compound and digenic heterozygosity, and demonstrated that simple single gene analysis would be inappropriate in attempting to define the nature of the genetic and clinical basis of this disorder.

Achieving the optimal dose of warfarin without encountering either bleeding or thrombosis is often problematic. Polymorphisms in 2 genes regulating the effect of warfarin (CYP2C9 and VKORC1) have recently been identified. Epstein et al. (169) performed a clinical trial to document whether commercially available phenotype testing of warfarin patients for these 2 polymorphisms could enhance the clinical administration of this drug. They demonstrated 28% reduction in hospitalizations for bleeding or thromboembolism in the 6-month follow-up of patients receiving warfarin in whom the genotype had been determined and presented to the referring physician. Interpretation of these data was complicated by the historical control group, the genotype information was not conveyed until 3 months after starting therapy, and the physicians participating were aware that their treatment was being observed. In an accompanying editorial, Ginsburg et al. (170) indicate that, although this study has flaws, the results suggest that genotype-guided warfarin therapy may result in clinically meaningful reductions in patient outcomes in a "real world" setting.

A paper by Zhang et al. (171) describes the association between hypertension and a naturally occurring genetic variation in the promoter of chromogranin B, a 33-amino acid neuropeptide associated with catecholamine storage vesicles. The researchers conclude that this variation contributes substantially to the risk for human hypertension, primarily through responses to environmental stress and may also explain sex differences in the rate of hypertension.

Pre-Clinical Research

The role of specific cell subtypes in ventricular remodeling after MI. After MI, acute inflammatory responses and healing are regulated by a complex sequence of events involving multiple cell types. Dissecting out the components of these processes may provide new therapeutic targets to improve cardiac structure and function after acute MI.

Panizzi et al. (172) examined the role of 2 subsets of monocytes. They previously found inflammatory monocytes with the marker Ly-6C^{hi} predominate during the first 4 days after infarction, whereas Ly-6C^{lo} monocytes that are important for angiogenesis and repair are prevalent during the healing phase. Increasing baseline circulating levels of Ly-6C^{hi} monocytes in mice, causes persistent inflammation 5 days after MI, with increased expression of inflammatory genes, protease, and phagocytosis activity with worse MRI EF after 21 days. Adverse remodeling related to the subset of Ly-6C^{hi} monocytes may be a potential therapeutic target. Cardilo-Reis et al. (173) in an editorial, note there are similar subsets of monocytes in humans. The major subset in peripheral blood are CD14+CD16− monocytes, which are similar to the inflammatory Ly-6C^{hi} monocytes. These "inflammatory" monocytes are important for inflammation, phagocytosis and proteolysis. In contrast, CD14+CD16+ monocytes are similar to Ly-6C^{lo} monocytes, and are involved in healing, repair, collagen, and angiogenesis. It will be important to determine how switching between these subtypes of monocytes is regulated, which may lead to treatments that maximize their beneficial, while minimizing adverse effects after recovery from MI.

Cell therapy in MI continues to garner interest despite their mixed success in clinical studies. Dubois et al. (174) postulated varying efficacies of different progenitor cells. Pigs were randomly assigned to receive intracoronary autologous late-outgrowth endothelial progenitor cells (EPC), allogeneic mesenchymal stem cells (MSC), or vehicle (controls) 1 week after occlusion of the left circumflex coronary artery. Pigs receiving EPCs had improved LV remodeling with smaller end-systolic volumes by MRI after 6 weeks, with smaller transmural infarct size, higher angiogenic placental growth factors and increased vascular density in the border zone. The success of EPCs in this pre-clinical model may be related to better engraftment of EPCs (but not MSCs) late after infarction, and that late outgrowth EPCs are progenitors of endothelial cells, whereas early outgrowth EPCs used in most clinical studies are monocytic

progenitor cells. Although it was a small study with a single dose of EPCs, these results may have potential applications for treating chronic ischemic cardiomyopathy.

In the setting of pre-clinical translational biology, Kim et al. (175) published data to support a role for human peripheral blood-derived CD31+ cells in the treatment of ischemic peripheral vascular disease. The work by Kim et al. (175) shows clear improvements in capillary density, and circumvents ex vivo culture issues, given the abundance of CD31+ circulating cells in humans. Moreover, blood perfusion was improved and limb loss was attenuated. Thus, improvements in functional endpoints were attained along with an approach that appears feasible for translation to humans. Questions as to whether these cells are actually merging with the endothelium are not fully addressed, as pointed out by Simari and Gulati (176) in the accompanying editorial. Cell therapy success will depend not only on improvement of perfusion but also on manufacturing and delivery of these cells, as well as the potential to merge cells with systemic delivery of enhancing pharmacological agents.

Novel target sites for treating cardiomyopathy. PRECLINICAL STUDIES. Ogino et al. (177) examined the beneficial effects of erythropoietin (EPO) receptor activation in heart failure related to renal dysfunction. In mice undergoing 5/6 nephrectomy, renal dysfunction, anemia, cardiac hypertrophy, leukocyte infiltration, and oxidative damage with cardiac fibrosis developed after 8 weeks. These abnormalities progressively worsened from 8 to 12 weeks in rats given saline, but were attenuated in rats treated with either recombinant human erythropoietin (rhEPO) (5,000 IU twice a week for 4 weeks), or asialoerythropoietin (AsEPO), an EPO derivative that does not alter hemoglobin. Both EPO and AsEPO effectively attenuated nephrectomy-induced decreases in sarcomeric proteins and decreased inflammatory cytokines and lipid peroxidation. Thus, EPO receptor activation is cardioprotective to decrease inflammation, oxidative damage, and fibrosis independently of any effects on anemia. van der Meer et al. (178) discussed clinical studies that have shown adverse effects from treating anemia in chronic kidney disease with EPO. The increase in hemoglobin is associated hypertension, increased viscosity, and an increased risk for stroke and mortality. The development of AsEPO by removing sialic acid moieties increases clearance to attenuate hematopoiesis without losing tissue protective effects. This may provide an alternative and safer approach to activate EPO receptors while retaining the beneficial cardioprotective effects.

Rajesh et al. (179) examined a novel target to treat diabetic cardiomyopathy, in a mouse model of type I diabetes (intraperitoneal streptozotocin for 5 days). Cannabidiol, a nonpsychoactive constituent of marijuana with anti-inflammatory effects, improved LV function, decreased oxidative/nitrosative stress with decreased reactive oxygen species generation from mitochondria, decreased inflammation, cell death from apoptosis, and decreased cardiac fibrosis. This study is attractive because cannabidiol is nonpsychoactive, well tolerated, and safe in humans, and has been approved (in Canada) for the treatment of pain and spasticity for multiple sclerosis.

In another study, Zheng et al. (180) used the antibiotic doxycycline to target a novel site in a mouse model of desmin-related cardiomyopathy. Transgenic mice with cardiac overexpression of abnormal αB-crystallin form protein aggregates with LV hypertrophy, progressive heart failure, and increased mortality. Doxycycline added to the drinking water at 8 or 16 weeks of age resulted in decreases in hypertrophy, protein aggregates, and ubiquinated proteins. Villarreal and Lew (181), in an editorial comment, discuss the emergence of drugs to target misfolded proteins to prevent the formation of insoluble protein aggregates in conditions such as Alzheimer's disease and cardiomyopathies. The heart continuously synthesizes and degrades proteins with a turnover rate of ~2% per day. That can lead to the formation of damaged or misfolded proteins, which are identified and eliminated by the uniquitin-proteasome system (UPS). The finding by Zheng et al. (182) that doxycycline, a safe antibiotic, decreased cardiac protein aggregate formation to attenuate cardiomyopathy is intriguing.

Pathogenesis of atherosclerosis. There is a dearth of data on the long-term vascular effects of radiotherapy in humans. Halle et al. (183) compared arteries exposed to radiation treatment in 13 patients with nonradiated donor artery from the same person (183). There was evidence of sustained inflammation both early (4 to 7 weeks) and late (20 to 500 weeks) after radiation. Increased expression of several genes related to inflammation in radiated arteries was found and confirmed by immunohistochemistry. There was sustained activation nuclear factor-kappa B (NF-κB), suggesting a unique role of this transcription factor for sustaining inflammation. Although this was a small study, Weintraub et al. (184) note this provides the first direct evidence of chronic up-regulation of NF-κB in human arteries exposed to radiation. This raises several important questions, such as the mechanisms for radiation to up-regulate NF-κB, if this involves oxidative stress, and if changes in small conduit arteries also occur in larger sized arteries that underlie most CV events.

Gene therapy has been limited by finding safe and effective means for delivery without systemic effects. Suzuki et al. (185) used ultrasound microbubbles to deliver interfering ribonucleic acids (siRNA) targeting intercellular adhesion molecule (ICAM) -1 using a transducer placed directly over the injured femoral artery of mice that suppressed neointimal formation and inflammation without systemic effects. Kupatt (186), in an editorial, reviews the obstacles for in vivo gene therapy in atherosclerosis. This has included difficulties in achieving in vivo transfection of the endothelium, developing suitable viral vectors to produce long-term expression without integration into nontargeted sites with side effects, and limitations in transfection efficiency of liposomal delivery systems. He notes this study provided proof of principle that siRNA can be selectively

delivered with targeted ultrasound to injured endothelium, to attenuate inflammatory processes and intimal hyperplasia for up to 1 week after injury.

The genetic basis of atherosclerosis is intriguing but enigmatic. Gonzalez-Navarro et al. (187) found a mechanistic link between the *CDKN2a* gene that encodes tumor suppressor ARF and atherosclerosis. Deficiency in $p19^{ARF}$ increased aortic atherosclerosis 1.5-fold in association with decreased apoptosis in the atherosclerotic lesions in mice deficient for apolipoprotein E. This was not observed in less atherogenic regions. Macrophages and vascular smooth muscle cells from $p19^{ARF}$-deficient mice also showed decreased apoptosis in vitro, suggesting that gene is associated with the progression, rather than initiation of atherosclerosis by limiting apoptosis in the plaque. Wessely (188), in an editorial comment, notes the emerging understanding of the role of cyclin-dependent kinase, and the use of cyclin-dependent kinase inhibitors to inhibit cell cycle regulation in CV diseases (188). This study supports the hypothesis that cyclin-dependent kinase inhibitors may be useful for inhibiting vascular inflammation and proliferation in the progression of atherosclerosis.

Mechanisms of AF. Structural remodeling of the atrium with interstitial fibrosis increases conduction heterogeneity that may be a substrate for developing AF. Adam et al. (189) found increased interstitial fibrosis in the left atrial appendage of patients undergoing valvular surgery with AF compared with tissue from patients in sinus rhythm. There was up-regulation of connective tissue growth factor, and increases downstream of N-cadherin and connexin 43, which play important roles in the formation of gap junctions. Neonatal mouse myocyte and fibroblast studies supported the role for angiotensin II to activate connective tissue growth factor by Rac1 and NADPH oxidase, to increase gap junction proteins as a potential mechanism for atrial structural remodeling. Liao (190), in an editorial, notes Rac1 and connective tissue growth factor may provide an important link between atrial fibrosis and AF, and provide a rationale for angiotensin receptor blockers or statins to interrupt atrial remodeling and AF.

Biomarkers. It is well known that activation of the renin-angiotensin system is essential for maintaining arterial blood pressure within the normal range. Tomaschitz et al. (191) measured plasma aldosterone and plasma renin concentration in >3,000 Caucasian patients, one-third of whom had resistant hypertension. In the highest quartile of the aldosterone-renin ratio, 13% had elevations great enough to justify with a clinical workup of primary aldosteronism. The higher the decile, the more the rise in blood pressure, irrespective of confounders such as age and renal function. In an accompanying editorial by Bravo et al. (192), they believe this is the first study that demonstrates the relationship of aldosterone-renin ratio to central blood pressure, often now accepted as the "true" blood pressure. They suggest studies such as this will lead to consideration of a wider use of aldosterone antagonists in patients with hypertension.

Acute pulmonary embolism is a fairly frequent CV emergency that requires not only rapid diagnosis but also risk stratification as well. However, risk stratification of initially normotensive patients is lacking. Heart type fatty acid binding protein (HFABP) is a sensitive marker of myocardial necrosis that is released from damaged myocytes within 1 to 3 h. Dellas et al. (193) studied 126 normotensive pulmonary embolism patients, of whom 7% suffered a catastrophic event within 30 days. An elevated HFABP was associated with a 16-fold increased likelihood of a major complication at 30 days. It was more sensitive and specific than troponin and BNP. In an accompanying editorial, Goldhaber (194) suggests pairing the measurement of HFABP with troponin to create a large database, but believes that HFABP is an excellent addition to the armamentarium of clinical assessment, imaging, and biomarker evaluation of patients with pulmonary embolism.

McKie et al. (195) tackled the issue of screening healthy normal subjects and stage A/B heart failure patients for prognosis. The NT-proBNP was not predictive of death or CV events in the healthy normal subgroup. However, in patients with stage A/B heart failure, there was a strong association between these peptides and risk of death, heart failure, cerebrovascular accident, and MI. In an editorial by Ho and Levy (196), they make note of some limitations in the study regarding the healthy normal subgroup as not being quite the same as the general population—as the controls were referred to echocardiography. They go on to suggest that understanding the role of biomarkers as tools to identify high-risk patients will allow us to effectively target treatment strategies in the future.

Kalogeropoulos et al. (197) explored the Health ABC (Health, Aging, and Body Composition) and found that when added to the previous risk factor model, inflammatory biomarkers, especially interleukin-6, improved the model for predicting heart failure. The associations were similar across sex and race. In an accompanying editorial, Cohn et al. (198) speaks to the important issue of whether examination of statistical associations in population risk can be clinically useful. Thus far, there has been little evidence that the inflammation associated with these biomarkers is causative and needs to be treated. They conclude that it is time to initiate and document the effectiveness of efforts to identify early stages of CV disease in attempt to reduce overt manifestations of disease.

Clinical decision limits for cardiac troponins levels have moved progressively toward lower concentrations. Bonaca et al. (199) investigated the prognostic implications of low-level increases in cardiac troponin I using a current generation sensitive test in patients with suspected ACS. They applied decision limits at the 99th percentile of the reference limit (0.04 μg/l). These low level values above the 99th percentile were able to identify patients at higher risk of death/MI at 30 days. In an accompanying editorial, Jesse

(200) stated that in the "old days" when troponin was a limited assay, it was a great test because, when used in the appropriate context, it markedly improved diagnosing MI. As troponin assays have improved in threshold of detection, imprecision has also increased, and higher sensitivity has become a double edged-sword and created problems in specificity.

Kim et al. (201), as part of the Women's Health Initiative hormone trials sought to investigate whether multiple biomarkers contributed to improved CAD risk prediction in post-menopausal women compared with traditional risk factors. Eighteen biomarkers were tested in a nested case-control study that included 321 patients with CHF and 743 controls. The biomarker addition gave a net reclassification improvement of 6.45% over traditional risk factors. The 5 best biomarkers were interleukin-6, d-dimer, factor VII, von Willebrand factor, and homocysteine. C-reactive protein achieved only borderline significance. Wang (202) points out in an accompanying editorial that biomarkers that lead to refinement of risk estimates might aid treatment decisions. This does not, he goes on to say, mean we should use routine screening of a panel of biomarkers at the present time, as risk classification is unlikely to change significantly.

Ranolazine is believed to exert its anti-ischemic effects by reducing myocardial sodium and calcium overload and, consequently, ventricular wall stress. The BNP increases in response to increased wall stress and is a strong risk factor in ACS. To this end, Morrow et al. (203), in the MERLIN–TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary–Thrombolysis In Myocardial Infaction 36) trial, examined the interaction between BNP and the effect of ranolazine in patients with ACS as part of a randomized, blinded, placebo-controlled trial. There results indicated that ranolazine might work better in high-risk patients with ACS, identified by elevated BNP levels (>80 pg/ml). In an accompanying editorial, Califf et al. (204) comment that, while the report does not provide definitive evidence that ranolazine should be used in patients with ACS and elevated BNP levels, the findings do warrant a prospective clinical trial.

Accurate CV risk prediction is difficult in elderly people. deFilippi et al. (205) sought to determine whether serial measurement of NT-proBNP in community dwelling elderly people would provide additional information above traditional risk factors. The NT-proBNP was measured at baseline and 2 to 3 years later in almost 3,000 community-dwelling older adults free of heart failure. The NT-proBNP in the highest quintile (>267 pg/ml) was independently associated with greater risks of heart failure, with an inflection point of 190 pg/ml. Patients with an initially high NT-proBNP who had a >25% increase (40%) in a later sample, were at higher risk for heart failure.

Risk stratification of ACS is increasingly dependent on measurement of biomarkers. To this end, Weir et al. (206) studied soluble ST2, a member of the interleukin-1 receptor family, in 100 patients admitted with MI and LV dysfunction, randomly assigned to receive eplerenone or placebo. Using serial MRI scans, the authors were able to connect the fact that soluble ST2 concentrations at the time of enrollment were strongly predictive of future infract remodeling. Of note, a post-hoc observation suggesting that the anti-remodeling benefits of eplerenone were mainly restricted to patients with a high soluble ST2 concentration at the time of enrollment. As pointed out by Moore et al. (207) in an editorial, this work suggests the potential to use biomarkers to identify patients at highest risk for remodeling, who are the same patients most likely to respond to anti-remodeling therapies like eplerenone.

Questions continue regarding the ability to use natriuretic peptides to guide the treatment for chronic CHF. Lainchbury et al. (208) address this question in the BATTLESCARRED (NT-proBNP Assisted Treatment to Lessen Serial Cardiac Readmissions and Death) trial. They randomly assigned 364 patients to NT-proBNP–guided therapy, intensive clinical management, or usual care. One-year mortality was less with either NT-proBNP or clinically guided treatment over usual care (9.1 vs. 18.9; $p < 0.03$), but at 3 years, mortality was reduced with hormone-guided treatment only in patients <75 years of age. Thus, while demonstrating a benefit for natriuretic peptide-guided therapy at 1 year, this study showed value for this strategy at 3 years only for patients <75 years of age. In an accompanying editorial, Maisel (209) pointed out that the BATTLESCARRED trial shared all of the challenges confronting biomarker-guided therapy of heart failure; it appeared that future research would determine whether such a strategy would be ready for prime time clinical use.

Cardiac Imaging

Recent work has confirmed that coronary calcium scoring permits further risk stratification on top of risk engines such as the Framingham Risk Score (210). Min et al. (211) demonstrated that, in 25% of patients with normal calcium scan (score 0), an abnormal calcium scan developed over time; the time to conversion was 4.1 ± 0.9 years, suggesting that repeat scanning in patients with calcium score 0 is not needed within 4 years of the index scan (212). These findings would support risk factor modification and aggressive medical therapy in some patients, although prediction of conversion appeared difficult. In addition, a comprehensive literature review revealed that the currently available studies could not demonstrate regression of coronary artery calcium after medical interventions (e.g., statin therapy) (213).

Although calcium scans identify atherosclerosis, coronary atherosclerosis is frequently not associated with ischemia. Nuclear myocardial perfusion imaging with single-photon emission computed tomography (SPECT) is often used for assessment of ischemia, and with the modern, hybrid SPECT-CT systems, the coronary calcium score can be

derived from the CT part, whereas the SPECT part provides information on myocardial perfusion and ischemia (214). A drawback is that SPECT imaging with current systems is time consuming. Novel, high-speed SPECT systems have been developed that permit data acquisition of 4 min and 2 min for stress and rest images, respectively (215). A head-to-head comparison between conventional and high-speed SPECT in 63 patients demonstrated similar detection of ischemia by high-speed SPECT in one-seventh of the conventional acquisition time. The high reproducibility and quantitative nature makes high-speed SPECT a very attractive method to assess myocardial ischemia (216).

Although ischemia is mainly related to obstructive lesions in the large epicardial vessels, microvascular disease is also important, particularly in women. Pepine et al. (217) reported on the prognostic value of coronary microvascular reactivity. At 5.4 years of follow-up, reduced coronary flow reserve (<2.32, measured by Doppler flow wire and adenosine) was related to adverse outcome.

In patients presenting to the emergency room with the suspicion of an ACS, SPECT imaging was used with the novel tracer β-methyl-p-[123I]-Iodophenyl-pentadecanoic acid (BMIPP) (218). A total of 507 patients were enrolled in 50 centers; these patients received BMIPP within 30 h of onset of chest pain. The sensitivity for diagnosing an ACS was 71%; moreover, BMIPP SPECT added incremental value over the clinical data for diagnosis of an ACS at an early stage.

Integrated imaging with positron emission tomography (PET) and CT was explored for visualization of vascular inflammation (219). In this proof-of-concept study, 6 patients with active vasculitis and 9 asymptomatic control patients underwent PET-CT with [11C]-PK11195, a selective ligand for peripheral benzodiazepine receptors expressed in activated macrophages, which is used to visualize vascular inflammation. High tracer uptake in arterial walls (aorta, carotid arteries) was shown in the symptomatic subjects, but not in the asymptomatic subjects. Of interest, plasma levels of inflammatory biomarkers could not differentiate between symptomatic and asymptomatic subjects.

In patients with CAD and reduced LV function, prediction of long-term outcome is important. In 603 patients with previous infarction and LV dysfunction from the VALIANT (Valsartan in Acute Myocardial Infarction Trial) echo study, global systolic strain and strain rate were determined (220). Whereas longitudinal and circumferential strain rate were predictive for death or recurrent heart failure, only circumferential strain rate was predictive for LV remodeling. Possibly, strain imaging can also eventually be used for prediction of sudden cardiac death (221), which is important in post-infarction patients with reduced LV function. Currently, patients with LVEF <30% to 35% have a class I indication for an ICD. How often sudden cardiac death occurs in patients with LVEF >35% was evaluated in 4,865 patients who previously underwent myocardial perfusion SPECT imaging; the median LVEF was 56% (222). Over a median follow-up of 6.5 years, 161 (3.3%) sudden deaths occurred, and the extent of perfusion defects on SPECT was associated with sudden death; whether SPECT perfusion could be of value for benefit from ICD implantation in patients with LVEF >35% needs further study (223).

Although radionuclide myocardial perfusion imaging is a valuable diagnostic tool, the studies require considerable time. Chang et al. (224) studied whether a normal stress-only SPECT would retain its ability to predict prognosis. In that study, 8,034 patients underwent a stress-only SPECT protocol, and manifested a comparable annual mortality rate as another 8,000 patients who underwent rest and stress testing. In addition, the stress-only group received 61% lower pharmaceutical dosage. In an accompanying editorial, Iskandrian (225) opined that stress-only myocardial perfusion imaging represented a new paradigm in this diagnostic testing modality.

The increasing use of cardiac imaging has prompted the development of appropriate-use criteria, which were assessed in regard to SPECT by Hendel et al. (226) in a multicenter study. Six clinical sites enrolled data regarding patients undergoing SPECT into an online form, 93% of whom were successfully assigned an appropriate criteria. Inappropriate use of SPECT was found in 14.4% of patients, with women and younger patients more prevalent. Thus, this study showed that appropriate-use criteria could be readily applied in the clinical setting and would point out areas in which the selection of imaging could be improved.

The question of the prognostic value of CT angiography (CTA) remains uncertain. Chow et al. (227) followed up 2,076 consecutive patients who underwent cardiac CT. Multivariate analysis showed that CAD severity was a predictor of MACE in that LVEF had incremental value over this parameter. Thus, using CTA, CAD severity and LVEF and total plaque score have prognostic and incremental value over routine clinical prognosticators. In an accompanying editorial, Mark and Kong (228) commented that although the data from Chow et al. (227) are encouraging, the ability of CTA to provide "actionable" information will await the results of the major soon-to-be-undertaken PROMISE (Prospective Multi-Center Imaging Study for Evaluation of Chest Pain) trial.

Cardiovascular imaging in *JACC* this year was remarkable not only for the introduction to practicing cardiologists and translational CV investigators of methods that are ripe for use in discovery, but also for the publication of a series of important articles on myocardial injury characterization by MRI delayed enhancement and its potential utilization in state-of-the-art clinical cardiology. Indeed, in the last year, a series of articles defined the state of the art, in terms of measuring the area at risk by imaging the injured myocardial mass directly in addition to a full characterization of myocardial necrosis, microvascular damage, and obstruction in the setting of acute MI. In the first study (229). 100 consecutive patients with NSTE-ACS underwent MRI

with T2-weighted edema imaging. The authors showed that after adjustment for peak troponin, patients with edema were at higher risk of having CV events than patients without edema. They concluded that measuring myocardial edema identifies reversible injured myocardium and predicts worse outcome. In a similar study, Eitel et al. (230) measured the relationship between infarct size and area at risk by MRI as the myocardial salvage index, and report that the index correlates well with the prognosis of patients who suffered acute MI. Conversely, Larose et al. (231) document a strong relationship between infarct volume and late functional recovery. Indeed, infarct volume provided important incremental benefit for predicting late myocardial dysfunction, with an area under the curve of 0.92 ($p < 0.05$) when compared with traditional markers. The articles were accompanied by editorial comments by Klocke (232) and by reviews of infarct imaging by Kim et al. (233) and microvascular obstruction by Bekkers et al. (234) that define the present capabilities of this technology for the clinical phenotyping of acute MI.

The long-term effect of cyclosporine A on LV remodeling from the landmark study reported this year illustrates the power of the foregoing methods not only for the individual post-infarct patient, but also for testing of future strategies to reduce infarct size and improve ventricular remodeling. In that study, Mewton et al. (235) examined the effect of a single dose of cyclosporine administered at the time of reperfusion on LV remodeling and function by cardiac MRI performed 5 days and 6 months after infarction. The investigators demonstrate that the infarct-limiting effect of cyclosporine given at the time of reperfusion persists up to 6 months, highlighting the influence of inflammation and potential reperfusion injury on infarct size progression after coronary occlusion.

Along the same lines, *JACC* has been the main venue for the demonstration that myocardial damage associated with ventricular overload can be characterized and accurately quantified by MRI delayed enhancement. This year, an important study (235) fully demonstrated the prognostic importance of MRI delayed enhancement in patients with myocardial overload induced by aortic stenosis. The study shows that myocardial loss and replacement by fibrosis can be quantified by MRI delayed enhancement and relates directly to prognosis after aortic valve replacement. Indeed, Kaplan-Meier analyses revealed that higher degrees of fibrosis related to worse long-term all-cause mortality. Similar relationship could be shown for fibrosis measured by histopathology. The study also validates the MRI method against fibrosis measured by histopathology from biopsies obtained at the time of valve replacement.

Along similar lines, the relationship between myocardial damage as demonstrated by contrast-enhanced MRI and ventricular arrhythmias continues to feature among this year's *JACC* original publications as the knowledge body in this field augments. This year, Heidary et al. (236) published a significant article relating infarct morphology and characteristics by delayed enhanced MRI with CV outcomes. They studied 70 patients with low EF ($25 \pm 11\%$) being considered for defibrillator placement to characterize the infarct border zone by delayed enhanced MRI. They found that the size of the border zone was larger in the 29 patients who had CV events compared with patients who did not, whereas infarct core and all other parameters (including EF and LV end-diastolic volume and end-systolic volume) were not. They concluded that quantification of core and border zones by MRI are important in the prediction of events after automatic ICD insertion and might assist in the management of patients with ischemic cardiomyopathy. In a related paper, Aquaro et al. (237) reported an interesting relationship between right ventricle (RV) abnormalities detected by MRI in patients with very frequent premature ventricular contractions (PVCs) of left bundle branch block (LBBB) morphology and clinical outcomes. They enrolled 440 consecutive patients with >1,000 PVCs of LBBB morphology (minor diagnostic criterion for arrhythmogenic right ventricular cardiomyopathy/dysplasia) and evaluated RV size and function. They found that subjects with multiple RV abnormalities were at higher risk for CV events, suggesting that in subjects with frequent PVCs of LBBB morphology, cardiac MRI allows risk stratification. The emerging pattern from the results of these and other studies indicates that risk stratification efforts in patients with MI and nonischemic cardiomyopathies may be enriched or even in large part defined by myocardial damage characterized and quantified by MRI delayed enhancement.

Several important articles addressed the issue of prognosis during stress MRI imaging using dobutamine or adenosine as modalities. Until recently, the lack of data on prognosis represented 1 of the most important obstacles to the clinical implementation of these techniques. An article by Korosoglou et al. (238) examined myocardial wall motion abnormalities and perfusion in 1,493 patients undergoing stress MRI and demonstrated that abnormal wall motion or perfusion yielded independent prognostic value for both hard events and late revascularization, surpassing clinical findings and those derived from the rest MRI. An accompanying an editorial by Hundley et al. (239) concluded that the technique was reaching maturity for clinical use. Moreover, contributions from Patel et al. (240) and Neizel et al. (241) push the envelope in this field by studying the influence of perfusion quantification using Fermi deconvolution and regional dysfunction quantification using spatial encoded strain imaging, respectively. Both groups found that quantification of MRI parameters enhanced the MRI stress test, highlighting the cutting edge of this technology at the moment.

Finally, Langham et al. (242) describe a truly unique MRI technique of measuring oxygen saturation in the calf muscles of patients with PAD. The authors made direct measurements of oxygen saturation in the femoral/popliteal arteries and veins during cuff-induced reactive hyperemia

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with MR spectroscopy. They found a significantly longer washout time, and lower upslope of blood flow, in patients with peripheral vascular disease compared with healthy controls. The suggest that post-occlusive transient changes in venous blood oxygenation might provide a new measure of vascular competence found to be abnormal in patients with PAD.

In an editorial, Nagel (243) discusses the methodology and results of a multicenter study performed in Japan using coronary imaging by MRI. Kato et al. (244) uses a method that has been the focus of great interest for nearly 2 decades, but has faced important technologic limitations given the challenges of imaging such small moving targets by MRI. In that study, the investigators studied 138 patients with suspected CAD from 7 hospitals in Japan in comparison with conventional X-ray angiography. They found an encouraging area under the curve value for the patient-based analysis (0.87, 95% CI: 0.0.81 to 0.93) using whole-body MRA techniques without contrast. In the CT side, this year, the work of Gottlieb et al. (245), using data from the Core64 trial, highlighted the higher than expected prevalence of obstructive coronary lesions among symptomatic patients with calcium score zero. In that analysis, 291 patients were included, and of those, 72 patients had a calcium score of zero. Fourteen of these patients had at least 1 $\geq$50% stenoses by conventional coronary angiography, highlighting the fact that the absence of coronary calcification does not exclude obstructive stenosis. The article steered an ongoing debate about the use of calcium score assessment in symptomatic persons with suspected CAD. Also in the field of coronary imaging by CT, Chow et al. (246) demonstrated that 64-slice multidetector CT coronary angiography provides important prognostic information not only in patients presenting to the emergency room with chest pain, and typically lower of prevalence of CAD (Hoffman et al. [247]), but also among patients with established CAD or at high risk for CAD. They studied 2,076 patients who had CTA and were followed up prospectively for a mean of 16 months. The researchers found that using CTA, CAD severity, LVEF, and total plaque score had incremental prognostic value over routine clinical predictors, supporting the concept that CTA indeed has prognostic value over and above diagnostic power.

Magnetic resonance imaging. Rijzewijk et al. (248) report, in patients with type II diabetes mellitus, the relationship between hepatic triglyceride content, measured by MRI, and insulin sensitivity, myocardial function, and high-energy phosphate metabolism. Patients with high levels of hepatic triglycerides had decreased insulin sensitivity, reduced myocardial perfusion and glucose uptake, and lower high-energy phosphate stores, compared with patients with low hepatic triglyceride content. These findings demonstrate that hepatic steatosis has a strong relationship with cardiac metabolism and function in patients with type II diabetes.

Valvular Heart Disease

Efforts in the field of percutaneous prosthetic valve implantation have progressed very rapidly in the last year, particularly with regard to aortic stenosis. Rodes-Cabau et al. (249) reported acute and late outcomes of a Canadian multicenter experience with transcatheter aortic valve implantation (TAVI) for aortic stenosis patients at very high surgical risk. In all, 339 patients underwent procedures, with a success rate of 93.3% and a 30-day mortality of 10.4%. At a median follow-up of 8 months, the mortality rate was 22.1%. Significantly, patients with either porcine aorta or frailty exhibited similar outcomes. Thus, utilizing both transfemoral and transapical approaches, these investigators showed a comparable mortality with TAVI compared with surgical risk calculators. In an accompanying editorial, Iung et al. (250) pointed out that this study was performed in 6 centers rather than 1 expert center and utilized standard evaluation protocols including both transapical and transfemoral approaches. These factors in addition to the evaluation of the porcine at aorta and frailty were felt to provide growing evidence of the ability of TAVI to be a useful alternative in aortic stenosis patients with very high or prohibitive surgical risk.

In many patients, the transfemoral approach to TAVI is not possible owing to vascular limitations. Therefore, Pasic et al. (251) reported the use of transapical aortic valve implantation in 175 consecutive cases. Technical success was achieved in 100% of patients; the 30-day mortality was 5.1%, and survival at 12 months was 82.6%. Procedures were done in a hybrid catheterization laboratory, and the potential for cardiopulmonary bypass or combined elective coronary artery stenting was available. The authors concluded that, although the transapical approach to TAVI is still evolving, this appears to be an extremely attractive approach and one that requires the integration of a team of both surgeons and cardiologists.

An interesting application of TAVI has been in the setting of a bioprosthetic aortic valve with significant stenosis or regurgitation (so called valve-in-valve). Khawaja et al. (252) presented the first series of patients with degenerative bioprosthetic valves treated with TAVI. These investigators achieved excellent results in patients with degenerative changes resulting in a valve malfunction. They conclude that this is a very viable approach in patients with bioprosthetic valves for whom the risk for direct surgical intervention is high.

The prevalence of metabolic syndrome is increasing dramatically, but it remains uncertain whether this condition has an adverse effect upon LV geometry and function in patients with aortic stenosis. Therefore, Page et al. (253) analyzed data from the ASTRONOMER (Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin) study and found that patients with metabolic syndrome and aortic stenosis had a higher LV mass index, relative wall thickness ratio, and prevalence of hypertrophy. They also

manifested lower diastolic and systolic tissue velocities. Thus, metabolic syndrome is independently associated with more pronounced LV hypertrophy and worse myocardial function in patients with aortic stenosis.

Assessing the severity and prognosis of mitral regurgitation continues to be a challenging problem. Le Tourneau et al. (254) assessed the impact of left atrial (LA) volume upon ultimate outcome in 492 patients in sinus rhythm with mitral regurgitation. Adjusting for established prognosticators of outcome, the LA index was independently associated with survival after diagnosis (HR: 1.3, $p < 0.001$). Patients with LA index of >60 ml/m^2 have an increased mortality over patients with LA index <40 ml/m^2 (HR: 2.8, $p = 0.016$). In an accompanying editorial, Levine and Nattel (255) point out that LA size is elevated in a variety of conditions and has been considered by many to be the equivalent of the "body temperature" of the heart. They emphasize that the current study has demonstrated that LA size is a marker of prognosis independent of the severity of regurgitation and is not an irreversible marker of adverse prognosis after surgical repair. In a related article, Magne et al. (256) examined the relationship between symptom-free survival and exercise-induced changes in regurgitation and pulmonary artery pressure in patients with mitral regurgitation. They performed resting and bicycle exercise Doppler echocardiography with 61 asymptomatic patients who had moderate or severe mitral regurgitation. During exercise, the effective regurgitant orifice and regurgitant volume markedly increased in 32% of patients, which correlated with changes in systolic pulmonary artery pressure and were accompanied by a lesser symptom-free survival. In an accompanying editorial, Flachskampf (257) comments that these findings extend the previous observations of the investigators regarding the increase of mitral regurgitation with exercise in patients with functional mitral regurgitation to patients with degenerative regurgitation. However, he cautions that although these data are very robust, it is still too early to translate them into clinical practice.

The search for improved prosthetic heart valves continues. In this regard, Schmidt et al. (258) describe work in progress on minimally invasive implantation of a living tissue engineered heart valve. The trileaflet heart valves were fabricated from biodegradable synthetic scaffolds and self-expanding stents and seeded with autologous vascular or stem cells. Transapical implantation of these valves was performed in sheep. The study demonstrated the feasibility of merging tissue engineering and minimally invasive valve replacement technologies, and may well be a harbinger of the future of prosthetic heart valves to be used in the clinical setting.

Lipid Disorders

Secretory phospholipase A_2 is a family of proatherogenic enzymes that hydrolyze lipoprotein phospholipids, contribute to cholesterol loading of macrophages, and activate inflammatory pathways. Rosenson et al. (259) conducted a randomized prospective trial to assess the effects of inhibition of secretory phospholipase A_2 with varespladib versus placebo as an adjunct to atorvastatin 80 mg daily. After 8 weeks varespladib/atorvastatin reduced LDL and secretory phospholipase A_2 levels but not major adverse CV events compared with placebo at 6 months after randomization. Thus, varespladib did reduce LDL cholesterol and inflammatory biomarkers in ACS patients, but did not result in a reduction of events.

Considerable attention has focused upon the ability to increase HDL in humans. Waksman et al. (260) evaluated the safety and feasibility of an autologous delipidated HDL infusions in patients with ACS. Patients received either 7 weekly HDL-selected delipidated infusions or control plasma apheresis. The levels of delipidated pre-HDL in the plasma, the most effective form of HDL for lipid remover from arteries, increased from 5.6% to 79%. A trend toward regression of total atheroma plaque volume by IVUS was also identified. Thus, delipidated HDL may provide an alternate approach to attack the residual risk in patients in whom LDL reduction has been maximized.

A study that attracted much attention was ARBITER 6–HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6–HDL and LDL Treatment Strategies in Atherosclerosis) trial (261). This trial studied the effects of adding niacin or ezetimibe to conventional statin treatment, using carotid intermedial thickness as the endpoint. Although the initial study was terminated early, this final report included the 14-month follow-up of 208 patients. The addition of niacin therapy continued to show regression of carotid intermedial thickness that was superior to ezetimibe. As this study addressed the surrogate endpoint, the effect of these agents upon CV events and heart endpoints remains uncertain and awaits the result of future trials.

Finally, an interesting series of viewpoints and commentaries address the question of how soon and how intensively lipid-lowering therapy should be applied in primary prevention. Steinberg (262) argued that atherosclerosis is a progressive life-long disease that results in events only later in life. It follows, he opined, that treatment earlier in life would result in substantial reduction of "life-long" events. Following the same theme, Forrester (263) contends that current guidelines for reduction of LDL cholesterol are too high. He points out that "normal" values for lipid levels derived from population studies are misleading, and that neither other animals nor hunter-gatherer people would have such high LDL levels. In addition, LDL levels are low in childhood and increase progressively during life. Both authors point out that virtually all studies of lipid reduction are of 5 years' duration, which may underestimate the overall effect of this therapy. In a commentary on this article, Fletcher and Hulley (264) point out that data are not available to substantiate the contention that earlier or more intense lipid-lowering therapy would actually result in

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benefits. In addition, the potential for side effects such as myopathies or rhabdomyolysis could be increased, and the cost to society would not be inconsiderable. While uncertainty remains and debate continues, it does appear that the trend is for earlier and more aggressive lipid-lowering therapy in industrialized societies.

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