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HIGHLIGHTS FROM *JACC*

Highlights of the Year in *JACC* 2011

Anthony N. DeMaria, MD,* Jeroen J. Bax, MD, PhD,† Ori Ben-Yehuda, MD,* Gregory K. Feld, MD,* Barry H. Greenberg, MD,* Jennifer Hall, PhD,‡ Mark Hlatky, MD,§ Wilbur Y. W. Lew, MD,‖ Joao A. C. Lima, MD,¶ Alan S. Maisel, MD,¶ Sanjiv M. Narayan, MD, PhD,¶ Steven Nissen, MD,# David J. Sahn, MD,** Sotirios Tsimikas, MD*

San Diego and Stanford, California; Leiden, the Netherlands; Minneapolis, Minnesota; Baltimore, Maryland; Cleveland, Ohio; and Portland, Oregon

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

Antiplatelet and Antithrombin Therapy

Bonello et al. (1) investigated the relationship between thrombotic events and platelet reactivity (PR) using the vasodilator-stimulated phosphoprotein (VASP) index after a loading dose of prasugrel in a prospective multicenter study of 300 patients who underwent successful percutaneous coronary intervention (PCI) for acute coronary syndromes (ACS). High on-treatment PR was defined as a VASP index ≥50%. The mean VASP index after 60 mg of prasugrel was 34.3 and high on-treatment PR was observed in 76 patients. Patients experiencing thrombotic events after PCI had significantly higher VASP indexes of PR compared with those patients who were free of events (64% vs. 33%; $p < 0.001$). Receiver-operating characteristic curve analysis found a cutoff value of 53.5% of the VASP index to predict thrombotic events at 1 month ($r = 0.86$, $p < 0.001$). Thus, a significant number of patients undergoing PCI in the setting of ACS do not achieve optimal PR inhibition with prasugrel.

Brar et al. (2) systematically evaluated the significance of platelet reactivity during clopidogrel treatment on adverse cardiovascular (CV) events by a meta-analysis using patient-level data for the VerifyNow P2Y12 assay in 6 studies with 3,059 PCI patients. A peripheral resistance unit value >230 was associated with a higher rate of the primary endpoint (hazard ratio [HR]: 2.10), as well as the individual endpoints of death (HR: 1.66), myocardial infarction (MI) (HR: 2.04), and stent thrombosis (ST) (HR: 3.11).

In ARMYDA-6 MI (Antiplatelet Therapy of Reduction of Myocardial Damage During Angioplasty-6 Myocardial Infarction), Patti et al. (3) compared 600- and 300-mg clopidogrel loading doses in 201 patients with ST-segment elevation myocardial infarction (STEMI). Infarct size was significantly lower in the 600-mg regimen. In addition, TIMI (Thrombolysis In Myocardial Infarction) flow grade <3 after PCI was less frequent (5.8% vs. 16.3%, $p < 0.031$), left ventricular ejection fraction (LVEF) at discharge was improved (52% vs. 49%, $p = 0.026$), 30-day major adverse cardiovascular events (MACE) were fewer (5.8% vs. 15%, $p = 0.049$), and bleeding/entry site complications were not increased (secondary endpoints).

Cheema et al. (4) characterized clopidogrel hypersensitivity after PCI and described its successful management with oral prednisone without clopidogrel discontinuation. Clopidogrel hypersensitivity manifested as generalized exanthema in 79%, localized skin reaction in 16%, and angioedema or urticaria in 5% of patients and is caused by a lymphocyte-mediated delayed hypersensitivity in most patients. Allergenic cross-reactivity with ticlopidine, prasugrel, or both is present in a significant number of patients with clopidogrel hypersensitivity. Complete resolution of hypersensitivity reaction was observed in 98% of patients with a short course of oral prednisone.

Dangas et al. (5) investigated the outcomes of switching to bivalirudin after initial administration of heparin in STEMI patients undergoing primary PCI in the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. At 30 days, major bleeding occurred in 7.6% of the switch group versus 12.3% of the control group ($p < 0.0001$). Switch patients had lower 30-day cardiac mortality (1.6% vs. 2.9%, $p = 0.04$), major bleeding at 2 years (8.4% vs. 13.0%, $p < 0.0003$), cardiac mortality (2.3% vs. 3.8%, $p = 0.04$), and reinfarction (4.0% vs. 7.1%, $p < 0.0002$), but similar 2-year rates of definite/probable ST. The inves-

From the *University of California-San Diego, San Diego, California; †Leiden University Medical Center, Leiden, the Netherlands; ‡University of Minnesota, Minneapolis, Minnesota; §Stanford University, Stanford, California; ‖Cardiology Section, VA Medical Center, San Diego, California; ¶Division of Cardiology, Johns Hopkins University, Baltimore, Maryland; #Cleveland Clinic, Cleveland, Ohio; and **Pediatric Cardiology, Oregon Health Sciences University, Portland, Oregon.

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tigators concluded that with STEMI switching unfractionated heparin to bivalirudin before primary PCI in STEMI results reduced major bleeding and improved early and late cardiac survival.

Regarding second-generation DES, the SPIRIT IV (Clinical Evaluation of the Xience-V Everolimus-Eluting Coronary Stent System) and COMPARE (Comparison of the Everolimus Eluting Xience-V Stent With Paclitaxel Eluting Taxus Liberté Stent in All Comers) trials compared the 2-year results of EES to the paclitaxel-eluting stent (6,7). SPIRIT IV was a randomized multicenter trial, whereas COMPARE was a single-center study in real-life patients. Both studies showed a clear benefit of everolimus over paclitaxel that extended to 2 years. In an accompanying editorial, Alfonso and Fernandez (8) commented that both COMPARE and SPIRIT IV were large randomized clinical trials that demonstrated the clinical superiority of second-generation everolimus stents over existing paclitaxel first-generation stents for hard clinical endpoints with a long-term clinical follow-up.

Nakazawa et al. (9) studied the mechanism of late ST by analyzing the pathological specimens from 174 patients who died >30 days after receiving first-generation sirolimus and paclitaxel-eluting stents. They observed localized strut hypersensitivity in sirolimus stents, whereas malapposition secondary to excessive fibrin deposition was the underlying cause of thrombosis with paclitaxel. In another study, Nakazawa and colleagues examined both bare-metal stents and DES from autopsy cases for evidence of neointimal atherosclerotic disease in patients dying >30 days after stent implantation (10). Neoatherosclerosis was significantly greater (31% vs. 16%, $p < 0.001$) and appeared earlier in DES than bare-metal stents. The investigators concluded that neoatherosclerosis is a frequent finding in DES, occurs earlier than in bare-metal stents, and may be another contributing factor to late ST. In an accompanying editorial, Buja (11) pointed out that the characteristics in the patients receiving DES versus bare-metal stents differed, leading to caution in interpreting the vascular responses to these 2 difference stents.

The relationship between the metabolic syndrome and outcomes of PCI in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial was analyzed by Maron et al. (12). Of the 2,248 patients, 61% had metabolic syndrome and 34% diabetes. Death and MI were highest in the group with both disorders (25%, $p < 0.001$). However, after adjusting for individual components, metabolic syndrome was no longer significantly associated with outcome. The addition of PCI to optimal medical therapy did not significantly reduce the risk of death or MI regardless of the presence of metabolic syndrome or diabetes.

In another study directed toward improving outcomes after PCI, Suh et al. (13) reported the results of the CILON-T (Influence of Cilostazol-Base Triple Antiplatelet Therapy on Ischemic Complication After Drug-Eluting Stent Implantation) trial. At 6-month follow-up, there was no difference in the primary endpoint between dual aspirin/clopidogrel alone or those agents plus cilostazol. Thus, despite the greater reduction of platelet reactivity by cilostazol, the outcome was not improved. In an accompanying editorial, Antoniucci (14) pointed out that the results of this study were not consistent with those of 2 trials comparing triple antiplatelet therapy with dual antiplatelet therapy in patients at high risk of restenosis, such as those with diabetes. Thus, he opined that the benefit of triple antiplatelet therapy to enhance the results of percutaneous intervention remains uncertain.

Percutaneous Coronary Intervention

Tsai et al. (15) assessed the safety and efficacy of drug-eluting stents (DES) versus bare-metal stents in 283,593 patients >65 years of age related to renal function. In propensity-matched cohorts grouped by glomerular filtration rate, DES in patients with normal renal function was associated with significant reductions in 30-month MI and death (HR: 0.73), but no difference in bleeding (HR: 0.89). Lower MI and mortality rates were also observed after DES in all chronic kidney disease (CKD) subgroups except MI in the long-term dialysis group. Decreased rates of revascularization did not extend to any subgroup of patients with CKD. They concluded that DES is safe in all patients regardless of renal function and is associated with reduced rates of MI and death in some subsets of CKD patients.

The prospective, open-label, multicenter randomized trial EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) by Park et al. (16) compared the angiographic outcomes of everolimus-eluting stents (EES) and sirolimus-eluting stents in 1,428 patients. The primary endpoint of in-segment late loss at 9 months was noninferior. The incidence of clinical endpoints was also not statistically different between the 2 groups, including target lesion failure (3.75% vs. 3.05%) and ST (0.37% vs. 0.83%).

Baber et al. (17) evaluated the impact of the EES on the frequency of ST, target vessel revascularization, MI, and cardiac death in a meta-analysis of 13 randomized controlled trials comparing the EES to non–everolimus-eluting DES with a follow-up of 21.7 months. EES significantly reduced ST (relative risk [RR]: 0.55), target vessel revascularization (RR: 0.77), and MI (RR: 0.78). There was no difference in cardiac mortality. The treatment effect was consistent for different follow-up times and duration of clopidogrel use.

In the RESOLUTE All-Comers trial (A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention), Stefanini et al. (18) investigated the impact of patient and lesion complexity on outcomes with newer-generation zotarolimus-eluting stents (ZES) and EES.

Event rates were higher among complex patients, and results did not differ between ZES and EES, regardless of complexity. At 1 year, target lesion failure (TLR) was similar in ZES- and EES-treated complex patients. Rates of cardiac death, target-vessel MI, and clinically indicated TLR were similar for both stent types among complex patients. Definite or probable ST occurred in 20 (1.3%) complex patients with no difference between ZES and EES. Angiographic follow-up showed similar results for ZES and EES in terms of in-stent percentage diameter stenosis and in-segment binary restenosis in the complex group. This study concluded that newer-generation ZES and EES proved to be safe and effective, regardless of complexity.

In the PLATINUM trial (A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of Up to Two De Novo Coronary Artery Lesions), Stone et al. (19) evaluated the clinical outcomes with a novel platinum chromium EES compared with a predicate cobalt chromium EES in 1,530 patients undergoing PCI. The 12-month rate of target lesion failure was noninferior with cobalt chromium EES versus platinum chromium EES. By intention-to-treat, there were no significant differences in the 12-month rates of target lesion failure, cardiac death or MI, TLR or definite or probable ST.

Chen et al. (20) investigated the difference in MACE at 12 months in coronary bifurcation lesions after double kissing double crush or provisional stenting (PS) techniques in 370 unselected patients. At 8 months, angiographic restenosis rates in the main vessel and side branch were significantly different between the double kissing (3.8% and 4.9%) and the PS groups (9.7% and 22.2%, $p = 0.036$ and $p < 0.001$, respectively). Additional side branch stenting in the PS group was required in 28.6% of lesions. Target vessel revascularization of 6.5% in the double kissing group, occurred less often than in the PS group (14.6%, $p = 0.017$). There were nonsignificant differences in MACE and definite ST.

Park et al. (21) performed a 5-year follow-up in 3,042 patients with multivessel disease who underwent DES (n = 1,547) or coronary artery bypass graft (CABG) (n = 1,495) surgery for whom complete follow-up data were available for a median of 5.6 years. After adjustment for differences in baseline risk factors, 5-year risk of death (HR: 1.00, 95% confidence interval [CI]: 0.76 to 1.32, $p = 0.99$) and the combined risk of death, MI, or stroke (HR: 0.97; 95% CI: 0.76 to 1.24, $p = 0.81$) were similar between the DES group and the CABG group. However, the rates of revascularization were significantly higher in the DES group (HR: 2.93, 95% CI: 2.20 to 3.90, $p = 0.001$).

Nam et al. (22) investigated whether a fractional flow reserve (FFR)-guided SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial score (SS), termed "functional SYNTAX score" (FSS), would predict clinical outcome better than the classic SS in patients with multivessel coronary artery disease (CAD) undergoing PCI in 497 patients enrolled in the FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) study. FSS was determined by only counting ischemia-producing lesions (FFR ≤ 0.80). After determining the FSS for each patient, 32% moved to a lower-risk group. MACE occurred in 9.0%, 11.3%, and 26.7% of patients in the low-, medium-, and high-FSS groups, respectively ($p < 0.001$). Only FSS and procedure time were independent predictors of 1-year MACE. FSS demonstrated a better predictive accuracy for MACE than SS did. The investigators concluded that recalculating SS by only incorporating ischemia-producing lesions as determined by FFR decreases the number of higher-risk patients and better discriminates risk for adverse events in patients with multivessel CAD undergoing PCI.

Lee et al. (23) evaluated the incidence, predictors, and long-term outcomes of patients with in-stent restenosis (ISR) after PCI with DES for unprotected left main coronary artery (LMCA) disease in 509 consecutive patients, with 402 (80.1%) undergoing routine surveillance or clinically driven angiographic follow-up. The overall incidence of angiographic ISR in LMCA lesions was 17.6% (71 of 402 patients, 57 with focal-type and 14 with diffuse-type ISR). Forty patients (56.3%) underwent repeated PCI, 10 (14.1%) underwent CABG, and 21 (29.6%) were treated medically. During long-term follow-up (a median of 31.7 months), there were no deaths, 1 MI, and 6 repeated TLR. The incidence of MACE was 14.4% in the medical group, 13.6% in the repeated PCI group, and 10.0% in the CABG group ($p = 0.91$). Multivariate analysis showed that the occurrence of DES-ISR did not affect the risk of death or MI. The long-term clinical prognosis of patients with DES-ISR associated with LMCA stenting might be benign, given that these patients were optimally treated with the clinical judgment of the treating physician.

In the multicenter prospective LITRO study, de la Torre Hernandez et al. (24) evaluated 354 consecutive patients with intermediate lesions in unprotected LMCA with intravascular ultrasound using minimum lumen area (MLA) <6 mm^2 as criterion for revascularization. LMCA revascularization was performed in 90.5% (152 of 168) of patients with an MLA <6 mm^2 and was deferred in 96% (179 of 186) of patients with an MLA of ≥ 6 mm^2. At the 2-year follow-up, cardiac death-free survival was 97.7% in the deferred group versus 94.5% in the revascularized group ($p = 0.5$), and event-free survival was 87.3% versus 80.6%, respectively ($p = 0.3$). Only 8 (4.4%) deferred patients required subsequent LMCA revascularization, none with an infarction. The investigators concluded that angiographic measurements are not reliable in the assessment of intermediate LMCA lesions, and that an MLA of ≥ 6 mm^2 is a safe value for deferring revascularization of the LMCA.

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Structural Heart Disease

Paravalvular leaks. Two studies demonstrated the medium-term outcomes of percutaneous treatment of paravalvular leaks. Sorajja et al. (25) determined the long-term clinical efficacy of percutaneous repair of paravalvular prosthetic regurgitation in 126 symptomatic patients. The 3-year estimate for survival was 64.3%. Mortality occurred due to cardiac, noncardiac, and unknown causes in 9.5%, 7.1%, and 5.6% of patients, respectively. Among survivors, 72% of patients who had presented with heart failure (HF) were free of severe symptoms and the need for cardiac surgery. Severity of residual regurgitation was not related to overall survival but was an important determinant of other clinical events. For those with no, mild, or moderate or severe residual regurgitation, 3-year estimate of survival free of death or need for surgery was 63.3%, 58.3%, and 30.3% ($p < 0.01$), respectively. Ruiz et al. (26) reported results in 43 patients showing closure was successful in 86% of leaks with improvement in New York Heart Association (NYHA) functional class and overall clinical success in 89% of these patients. The survival rates for patients at 6, 12, and 18 months after paravalvular leak closures were 91.9%, 89.2%, and 86.5%, respectively. Freedom from cardiac-related death at 42 months following the procedure was 91.9%. These 2 studies demonstrate that percutaneous closure of symptomatic paravalvular leaks may result in high rates of acute and long-term success and is effective in managing symptoms of HF and hemolytic anemia.

Transcatheter aortic valve replacement. Rodés-Cabau et al. (27) studied 101 patients who underwent successful transcatheter aortic valve replacement (TAVR) and showed that TAVR was associated with some degree of myocardial injury in 99% of the patients as determined by a rise in cardiac troponin T and creatine kinase-myocardial band. A larger myocardial injury was associated with a smaller improvement of LVEF. The degree of rise in cardiac troponin T was an independent predictor of cardiac mortality at 9 to 10 months of follow-up (HR: 1.14 per each increase of 0.1 μg/l).

Rodés-Cabau et al. (28) also compared the incidence of cerebral embolism within 6 days of transapical versus transfemoral TAVR as evaluated by diffusion-weighted magnetic resonance imaging (MRI) in 60 patients. A total of 41 patients (68%) had 251 new cerebral ischemic lesions at the post-procedure diffusion-weighted MRI, 19 patients in the transfemoral group (66%) and 22 patients in the transapical group (71%; $p < 0.78$). Most patients with new ischemic lesions had multiple lesions (median lesions per patient: 3). There were no differences in lesion number and size between the transfemoral and transapical groups. No baseline or procedural factors were found to be predictors of new ischemic lesions. Cerebral embolism was not associated with a measurable impairment in cognitive function.

Wenaweser et al. (29) assessed the role of TAVR ($n = 257$) compared with medical treatment (MT) ($n = 78$) and surgical aortic valve replacement (SAVR) ($n = 107$) in patients with severe aortic stenosis (AS) (age: 81.7 years, mean logistic European System for Cardiac Operative Risk Evaluation: 22.3) as part of a prospective registry. Baseline clinical characteristics were similar among patients allocated to MT and transcatheter aortic valve implantation, whereas patients allocated to SAVR were younger and had a lower predicted perioperative risk. Adjusted HRs for death were 0.51 for TAVR compared with MT and 0.38 for TAVR compared with MT. Medical treatment, older age, peripheral vascular disease, and atrial fibrillation (AF) were significantly associated with all-cause mortality at 30 months in the multivariate analysis. At 1 year, more patients undergoing SAVR (92.3%) or transcatheter aortic valve implantation (93.2%) had NYHA functional class I/II as compared with patients with MT (70.8%, $p = 0.003$).

Rudolph et al. (30) assessed the median 1-year outcomes of 104 patients who were not surgical candidates undergoing MitraClip (Abbott Vascular, Abbott Park, Illinois) therapy for severe mitral regurgitation (MR). The MR grade $\geq 2+$ was present at follow-up in 82.5%, left ventricular (LV) end-diastolic and -systolic volumes were reduced, and forward stroke volumes were significantly increased. Improvements in NYHA functional class were observed in 80% of patients, with 69% in class I or II; the majority improved in the 6-min walk test and quality of life. Estimates of mortality and rehospitalization were 22% and 31%, respectively. Forward stroke volume at discharge predicted event-free survival.

Auricchio et al. (31) evaluated the safety, efficacy, and effect of MitraClip treatment on symptoms and LV remodeling in 51 nonresponders to cardiac resynchronization therapy (CRT). Functional class and reverse LV remodeling and LVEF improved over 12 to 14 months. Overall mortality at follow-up was 19.9 per 100 person-years.

Given the favorable findings regarding the use of the mitral clip (MitraClip), Siegel et al. (32) reported on the acute hemodynamic effects of this therapeutic intervention. They studied 107 patients with cardiac catheterization before and immediately following percutaneous mitral valve repair with the MitraClip device. They observed an increased cardiac output and forward stroke volume as well as a decrease in systemic vascular resistance ($p < 0.001$). Both LV end-diastolic pressure and volume were reduced. Thus, mitral valve repair with the MitraClip resulted in immediate improvement in cardiac hemodynamics.

Kenny et al. (33) evaluated the safety and effectiveness of the Edwards SAPIEN Transcatheter heart valve (Edwards Lifesciences, Irvine, California) in the pulmonary position in 36 patients with moderate-to-severe pulmonary regurgitation with or without stenosis. Successful deployment was achieved in 33 of 34 attempts. Conduit gradient decreased from 26.8 to 11.7 mm Hg ($p < 0.001$). At 6-month follow-up, all patients were alive and nearly all were func-

tional class I. Pulmonary regurgitation ≤2+ and freedom from reintervention was 97%.

TAVR represents a very promising strategy for management of patients with AS who are not optimal surgical candidates (34). Ewe et al. describe an important limitation of TAVR, specifically the mismatch of valve size in some patients undergoing this procedure. Patients with a mismatch in valve size have substantially less improvement in the hemodynamic and clinical response to valve replacement, findings that will require additional vigilance and further study as this procedure becomes more common in the United States.

Leon et al. (35) in a consensus report from the Valve Academic Research Consortium provided standardized endpoint definitions for transcatheter aortic valve implantation clinical trials. These standardized endpoint definitions should provide for consistency across the multiple studies currently being done in the evolving area of percutaneous valve implantation.

Peripheral Arterial Disease and Stroke

Schmidt et al. (36) evaluated paclitaxel-eluting balloons to treat long lesions in 104 patients with critical limb ischemia or severe claudication. At 378-day follow-up, clinical improvement was present in 91.2%. Complete wound healing occurred in 74.2%, and limb salvage was 95% for patients with critical limb ischemia. The investigators concluded that early restenosis of long-segment infrapopliteal disease is significantly less after treatment with paclitaxel-eluting balloons than historical data using uncoated balloons.

Bonvini et al. (37) evaluated the technical feasibility, safety, and 1-year efficacy of the endovascular treatment of atherosclerotic common femoral artery obstructions in 360 consecutive patients. Chronic total common femoral artery occlusions were recanalized in 60 cases (16.7%). Balloon angioplasty was performed as the primary intervention in virtually all cases (98.6%), whereas stenting was needed for suboptimal angioplasty results in 133 procedures (36.9%). Restenosis ≥50% and TLR were observed in 27.6% and 19.9% of procedures, respectively. This series suggests that the percutaneous approach may be a valid alternative to surgery for common femoral artery atherosclerotic obstructions.

Montorsi et al. (38) compared the rate of cerebral microembolization (MES) during carotid artery stenting in 53 consecutive patients with high-risk, lipid-rich plaque randomized to carotid artery stenting with proximal protection (MO.MA system, Invatec Inc., Brescia, Italy) (n = 26) or distal protection with a filter (FilterWire EZ, Boston Scientific, Natick, Massachusetts). Transcranial Doppler and diffusion-weighted MRI were performed. The MO.MA system significantly reduced mean MES counts ($p < 0.0001$) during lesion crossing, stent crossing, stent deployment, stent dilation, and total MES. By multivariate analysis, the type of brain protection was the only independent predictor of total MES number. No significant difference was found in the number of patients with new post–carotid artery stenting embolic lesions.

In an evolving area in the field, White et al. (39) provide a review on the potential for acute percutaneous stroke intervention. They note acute ischemic stroke, similar to acute MI, requires timely reperfusion. Improving outcomes for acute stroke will require patient education for early presentation, an aggressive expansion of qualified hospitals, and willing providers and early imaging strategies.

Platelet Function and Antiplatelet Therapy

Understanding of the factors influencing PR in response to the $P2Y_{12}$ inhibitor clopidogrel and its variation over time was enhanced by Campo et al. (40). In 300 patients undergoing PCI, they measured on-clopidogrel PR before PCI and at 1 and 6 months after (VerifyNow assay); tested for *CYP2C19**2, *17, *CYP3A5**3, and *ABCB1* polymorphisms; and did 1-year follow-up for both ischemic and bleeding outcomes. Surprisingly, PR varied over time, with 75 of 300 patients becoming full responders. Genotyping was able to account for only 18% of this trend. Platelet reactivity at 1 month was the best predictor of clinical events. This meticulously done study, as highlighted by an accompanying editorial by Angiolillo (41), provides a plausible explanation for the negative findings of the GRAVITAS (Gauging Responsiveness With a VerifyNow Assay–Impact on Thrombosis and Safety) study in that assessment of PR and adjustment of clopidogrel dose did not modify 6-month outcomes.

Clopidogrel requires a 2-step oxidative process mediated by hepatic *CYP* enzymes for activation that might be affected by calcium-channel blockers (CCB) that are metabolized by *CYP3A4*. Olesen et al. (42) examined such a possible interaction in 56,800 MI patients in Denmark followed for 1 year. They found that CCB use was associated with a higher event rate, most likely reflective of increased diabetes and renal function in those treated with CCB. This difference was similar to the increased risk associated with CCB in the absence of clopidogrel treatment. The investigators conclude that in this nationwide survey there was no evidence for a clinically significant decrease in the clinical efficacy of clopidogrel with CCB.

Clopidogrel-drug interactions were also the subject of an in-depth state-of-the-art paper by Bates et al. (43). The investigators reviewed the potential for treatment with proton-pump inhibitors (particularly omeprazole), as well as statins to impair the platelet response to clopidogrel. In keeping with the conclusions by Olesen et al. (42) regarding CCB, the investigators conclude that there is inconsistent evidence for the pharmacodynamic effect of any agent having an impact on clinical outcomes.

Acetylsalicylic acid has been shown to decrease saphenous vein graft thrombosis, the main mechanism for early bypass graft loss. Gluckman et al. (44) assessed acetylsalicylic acid

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responsiveness 3 days and 6 months after surgery in 229 patients undergoing CABG. Platelet function was assessed by platelet closure time, the VerifyNow Aspirin assay, and urine 11-dehydro-thromboxane B2 (UTXB2). The investigators found that whereas arachidonic acid–induced platelet aggregation was inhibited in 95% and 99% of patients at 3 and 6 months, 73% had evidence of elevated UTXB2 at 3 days, with 31% still having increased levels at 6 months. Persistent UTXB2 production as well as closure time (indicative of shear-dependent platelet reactivity) were predictive of early saphenous vein graft thrombosis. The elevated UTXB2 production is likely not the result of aspirin resistance given the almost complete inhibition of arachidonic acid–induced platelet aggregation. An accompanying editorial by Storey (45), underscores the need for further evaluation of non–acetylsalicylic acid therapies for patients undergoing CABG.

Sorensen et al. (46), using nationwide Danish registries, examined the use and efficacy of clopidogrel in 3,545 post-CABG patients. Clopidogrel was used in only 27% of patients, but was associated with a reduction in death or MI over a mean follow-up of 466 days: 4.1% vs. 7.8%.

Would novel antiplatelet therapies improve the outcome following CABG? Held et al. (47) analyzed the efficacy and safety of ticagrelor versus clopidogrel in patients undergoing CABG in the PLATO (Platelet Inhibition and Patient Outcomes) trial. A total of 1,899 patients underwent CABG, with 1,261 receiving drugs within 7 days of surgery. They found a reduction in total (9.7% to 4.7%, $p < 0.01$) and CV mortality (7.9% to 4.1%; $p < 0.01$) with ticagrelor versus clopidogrel in the CABG subgroup in PLATO without evidence for excess bleeding. In an accompanying editorial, Schneider (48) examined the potential mechanism for this reduction. Ticagrelor has greater antiplatelet effects as well as reversible binding. The increased antiplatelet efficacy of ticagrelor is unlikely to be the mechanism, as there was no correlation between antiplatelet effects and CV mortality, nor was there a difference in bleeding. The reversibility of ticagrelor, however, may allow its redistribution to new platelets as well as activated platelets accompanying blood transfusions. Ticagrelor also inhibits the uptake of adenosine into erythrocytes, and an additional mechanism for the reduced CV benefit may involve an increase in adenosine levels in the blood.

Ticagrelor has been associated with ventricular pauses. To evaluate this phenomenon, the PLATO trial included a substudy (49) in which subjects had 7-day continuous electrocardiogram (ECG) assessment at randomization and at 1 month. As reported by Scirica et al., ventricular pauses $\geq$3 s were more frequent in patients receiving ticagrelor versus clopidogrel (5.8% vs. 3.6%; $p = 0.006$) and the pauses decreased by the 1-month follow-up (2.1% vs. 1.7%). There was no difference in clinically reported bradycardic events, suggesting that this phenomenon was not clinically significant.

Risk Factors and Epidemiology

Cardiovascular disease has been increasing rapidly in the developing world (50). In a "From Around the World" report, Paradis and Chiolero (50) analyzed the incidence of CV risk factors in 1,100 urban Indians followed over 7 years from a mean age of 29 to 36 years. They found a significant increase in obesity as well as central obesity, hypertension, impaired glucose tolerance, and diabetes mellitus. These findings have important and alarming implications for the future of CV health.

One possible approach to improving CV health is to adopt a Mediterranean diet. Kastorini et al. (51) performed a meta-analysis of 50 studies (n = 534,906) that examined the link between the Mediterranean diet and the metabolic syndrome. The investigators report that adherence with the diet was associated with reduced risk of metabolic syndrome, reduced waist circumference, increased high-density lipoprotein-cholesterol (HDL-C), decreased triglycerides, and improved blood pressure and glucose levels, both in epidemiological studies and clinical trials.

The Mediterranean diet is a good source of potassium. To better determine whether potassium intake is associated with decreased CV risk, D'Elia et al. (52) performed a meta-analysis of 11 prospective epidemiologic studies of 247,510 subjects. A 42-mmol increase in potassium was associated with a 21% lower risk of stroke, with a possible reduction in coronary heart disease and total CV disease.

Berry et al. (53) examined whether a single exercise test in middle age predicted lifetime risk for CV mortality. They followed 11,049 men until death or age 90 years, with a median follow-up of 25.3 years. Cardiopulmonary fitness was significantly associated with decreased CV mortality. The presence of CV risk factors heightened these associations. This study, though limited to men, demonstrates the utility of a single fitness measurement at middle age to risk stratify for lifetime CV mortality.

Even though aerobic fitness has attracted the most attention, the influence of muscle strength as a prognostic indicator in hypertension was examined by Aretero et al. (54), who followed 1,506 hypertensive men for an average of 18.3 years. Both muscular strength and cardiorespiratory fitness were measured at baseline. After adjusting for CV fitness, hypertensive men in the upper third of muscular strength had a lower risk of death (HR: 0.66); men with both high muscular and aerobic strength had the lowest mortality risk (HR: 0.49). Thus, hypertensives may benefit from both strength training and aerobic training.

To assess whether hydrochlorothiazide, the most commonly prescribed antihypertensive, is efficacious, Messerli et al. (55) performed a meta-analysis of ambulatory blood pressure monitoring trials at both the lower (12.5 to 25 mg) and higher doses (50 mg). They report that whereas the 50-mg hydrochlorothiazide was similar in its effects to other agents, both the 12.5- and 25-mg doses were significantly less efficacious, with a reduction in systolic blood pressure of

6.5 mm Hg and in diastolic blood pressure of 4.5 mm Hg (approximately one-half of that seen with the other agents). This finding questions the appropriateness of lower-dose hydrochlorothiazide for first-line treatment of hypertension.

Many patients have resistant hypertension, which is persistent hypertension despite maximally tolerated treatment with 3 antihypertensive agents. The Rheos system uses electrical impulses to activate the carotid baroreflex. In a study directed toward resistant hypertension, Bisognano et al. (56) examined the effect of baroreflex activation therapy on systolic blood pressure in the Rheos Pivotal trial. In the trial, 256 resistant hypertension subjects received devices or served as controls (2:1) for endpoints of blood pressure response and procedural device safety. The trial did not meet the endpoints for acute responders or procedural safety. However, a protocol-specified ancillary analysis showed 42% of treated patients versus 24% of control subjects achieved systolic blood pressure of <140 mm Hg at 6 months. This study yielded intriguing results, suggesting that carotid sinus baroreflex activation could be of value in some patients with resistant hypertension. Further trials are likely to be undertaken.

Bisognano et al. (57) also reported on an echo substudy in 21 patients with paired data 3 and 12 months after device activation. The investigators report reduction in mitral A-wave velocity, left atrial (LA) dimension, and regression of LV hypertrophy, with 18% reduction in LV mass index. Although limited by lack of a control group, this initial study highlights the promise of new device-based therapies for a host of CV conditions.

Because percutaneous renal sympathetic denervation has been found to be of benefit to patients with resistant hypertension, Ukena et al. (58) studied whether this procedure influenced the cardiorespiratory response to exercise. In 37 patients who underwent bilateral renal denervation, compared with 9 untreated patients, blood pressure at rest and maximum exercise was significantly reduced by 31 and 21 mm Hg, respectively ($p < 0.0001$), after 3 months. Neither maximum heart rate nor heart rate after exercise was changed. Thus, renal denervation reduced blood pressure during exercise without affecting heart rate competence in patients with resistant hypertension.

The relationship between decreasing sleep-time blood pressure and CV risk reduction was studied by Hermida et al. (59). They studied 3,344 hypertensive subjects randomized into those ingesting medications upon awakening or at bedtime. The date revealed a 17% reduction in CV risk for each 5 mm Hg decrease in sleeping systolic blood pressure mean ($p < 0.001$) independent of other ambulatory blood pressure parameters. These data showed that a decrease in asleep blood pressure was the most significant predictor of event-free survival. In an accompanying editorial, Gradman (60) opined that a strong case could be made that the bedtime administration of at least some portion of antihypertensive regimen should become the default standard. He acknowledged that the ideal would be to achieve the benefits of reducing asleep blood pressure without the necessity to perform repeated ambulatory blood pressure monitoring in every patient.

The issue of arterial stiffness and its relationship to vitamin D was studied by Mheid et al. (61). They measured serum 25-hydroxyvitamin D and compared it to endothelial function assessed by brachial artery flow-mediated dilation and digital reactive hyperemia index (cardiac-femoral pulse wave velocity in radial tonometry-derived central augmentation index). Vitamin D insufficiency was associated with increased arterial stiffness and endothelial dysfunction in conductance and resistant blood vessels, irrespective of traditional risk burden. These data leave unanswered whether therapy with vitamin D would reverse these findings.

Statins and Endothelial Function

Most statin trials have compared different dosages of statins rather than comparing different low-density lipoprotein cholesterol (LDL-C) goals. Hsia et al. (62) examined a subgroup from the JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin), who attained an LDL-C level <50 mg/dl in the rosuvastatin treatment arm, compared with those in the placebo group and to those not achieving LDL <50 mg/dl, and assessed the efficacy on total mortality, CV events, and adverse events. Out of 8,154 subjects on rosuvastatin, approximately one-half achieved LDL-C cholesterol levels of <50 mg/dl. Those whose LDL-C levels were below 50 mg had a significantly lower HR of 0.35 for the primary endpoint compared with those in the placebo group. For those with HDL-C levels ≥50 mg/dl, the HR was 0.57. Similar findings were seen for all-cause mortality, and there was no signal of increased rates of myopathy, cancer, diabetes, or neuropsychiatric disorders in the group that achieved very low LDL-C levels.

Lee et al. (63) studied the interesting question of whether statin therapy would be beneficial in MI patients in whom baseline LDL-C levels were below 70 mg/dl. As compared to patients in whom statins were not prescribed, statin therapy reduced a composite primary endpoint including cardiac death with an adjusted HR of 0.56 ($p < 0.015$). Thus, statin therapy is of value following infarction even in patients with very low baseline levels of LDL. In an accompanying editorial, LaRosa (64) cautioned that this was not a randomized prospective trial, and that the level of LDL below which no further lowering reduces the risk of vascular disease remains undefined.

To more fully characterize the risk of diabetes with statins, Waters et al. (65) analyzed 3 large atorvastatin studies: TNT (Treating to New Targets), IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering), and SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels). They found that baseline fasting blood glucose, body mass index

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(BMI), hypertension, and fasting triglycerides were predictors of new onset diabetes. There was, however, no significant increase in CV events in those who developed new onset diabetes.

Statins may have various pleiotropic effects beyond LDL-C lowering. Liuni et al. (66) examined the effect of atorvastatin on endothelial function in the setting of nitrate use, which has been associated with endothelial dysfunction and generation of reactive oxygen species. Liuni et al. randomized 36 male volunteers to receive continuous transdermal nitroglycerin with either placebo or atorvastatin 80 mg daily. They measured endothelial function with a venous-occlusion strain gauge plethysmography in the setting of acetylcholine infusion with and without intravenous vitamin C. They found an improved acetylcholine response in the presence of atorvastatin. Vitamin C improved the endothelial response in the setting of nitroglycerin plus placebo but had no effect in the presence of atorvastatin. Blood pressure responses to sublingual nitroglycerin also improved with atorvastatin. Thus, atorvastatin improved endothelial function in the setting of nitrate treatment, and the mechanism is likely to be a reduction in oxidative stress.

Previous studies have demonstrated an antianginal effect with allopurinol. To explain the antianginal effect demonstrated for allopurinol, Rajendra et al. (67) conducted a placebo-controlled crossover study in 80 CAD patients with allopurinol 600 mg daily. They assessed endothelial dysfunction with forearm venous occlusion plethysmography, flow-mediated dilation, and pulse wave analysis. Infusion of acetylcholine and vitamin C were used to assess oxidative stress. They were able to demonstrate significantly improved vascular function, and allopurinol abolished vascular oxidative stress. Any long-term morbidity and mortality benefit remain to be determined.

Although epidemiologic data has consistently shown that diminished HDL-C is a potent risk factor for CV events even in the presence of low LDL-C levels, data on the utility of raising HDL, particularly during concomitant statin therapy, is inconclusive. One novel approach has been to increase levels of apolipoprotein A-I, the carrier protein of HDL. In 2010, Bailey et al. (68) reported positive results of an oral drug, RVX-208, that induces nuclear transport factors that increase hepatic and intestinal apolipoprotein A-I production in both monkeys and humans (for a short term). A follow-up study by Nicholls et al. (69), however, demonstrated only an 8.3% increase in HDL-C and 5.6% in apolipoprotein A-I and was accompanied by a 10% incidence of transaminase elevations. This trial demonstrates yet again the challenges of HDL-targeted therapies for atherosclerosis (70).

Acute Coronary Syndromes

Silvain et al. (71) examined thrombi obtained by thromboaspiration from 45 of 288 STEMI patients who underwent primary PCI. They tested for plasma biomarkers associated with thrombosis and analyzed the composition of the thrombi using high-definition scanning electron microscopy. They found that clots were composed, in descending order, of fibrin, platelets, erythrocytes, cholesterol crystals, and leukocytes. Longer ischemic time was associated with an increase in fibrin content and a decrease in platelet content. These findings have implications for fibrinolysis and provide an explanation for the greater efficacy of lytic therapy early in the time course of a STEMI.

Whereas plaque rupture and thrombosis have become the main focuses of research in CAD, alternative pathophysiologic processes may also play a role. Ong et al. (72) in the CASPAR (Coronary Artery Spasm as a Frequent Cause for Acute Coronary Syndrome) study (2008) showed that no culprit lesion was found in about one-third of ACS patients undergoing emergency angiography. This year, they reported on the 3-year follow-up of the 76 patients with only spasm as an explanation for their ACS (73). Persistent angina was reported by 36 of 76 of the spasm patients, but there were no cardiac deaths or nonfatal MIs during the follow-up. In comparison, 30 of 270 patients with culprit lesions died during the 3-year follow-up, with 11 nonfatal MIs. This highlights that the differing underlying pathophysiologic causes of ACS have differing prognostic and therapeutic implications.

Achieving rapid door-to-balloon times may be particularly challenging in a rural setting. Blankenship et al. (74) report on implementation of a rapid triage and transfer protocol in which the rural hospital directly contacted the accepting cardiology service with direct helicopter transfer to the catheterization lab, bypassing the accepting hospital's emergency room. They report that median door-to-balloon time decreased from 189 min to 88 min and was associated with a halving of the hospital mortality from a baseline of 6%.

The ability of nonlipid biomarkers to prognosticate CV events in patients with stable coronary disease was assessed by Arsenault et al. (75) for the TNT Study Investigators. They evaluated 18 nonlipid biomarkers 8 weeks after starting lipid-lowering therapy with atorvastatin. They observed that LDL-C and HDL-C in triglycerides were predictive of recurrent major CV events. However, many of the nonlipid biomarkers were not predictive of recurrent events at 8 weeks or 1 year.

From a therapeutic perspective, lowering the triglycerides–HDL-C ratio was associated with the beneficial impact of pioglitazone on the progression of coronary atherosclerosis in diabetic patients in the PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) study (76). In this study, multivariate analysis revealed that pioglitazone-induced effects on triglycerides to HDL-C were associated with changes in percentage of atheroma volume ($p < 0.03$). These findings emphasized the importance of atherogenic dyslipidemia in diabetic patients.

In terms of risk for CV disease, Dong et al. (77) conducted a meta-analysis to determine the effect of erectile dysfunction. Drawing from 12 prospective cohort studies involving over 36,000 patients, they observed a relative risk for CV disease of 1.48 in men with erectile dysfunction. Similar results were obtained when analyzing studies with control groups for conventional risk factors, suggesting that the increased risk associated with erectile dysfunction is probably independent of these factors.

Several niche issues were evaluated in patients with acute MI. The CONNECT (Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision) trial by Crossley et al. (78) evaluated the ability of wireless remote monitoring with automatic clinician alerts to decrease the time from the onset of a clinical event to the reaching of a clinical decision. The technology used the ability of implantable cardioverter-defibrillators to detect and wirelessly transmit diagnostics regarding individual patients. Just under 2,000 patients were monitored for 15 months for CV-related hospitalizations, emergency department visits, and clinic office visits. The median time from clinical event to clinical decision in patients who underwent monitoring was less than those treated in a conventional fashion, as was the hospital length of stay. Thus, these data suggest that beneficial clinical decision making can be markedly accelerated by remote notification.

Finally, Kar et al. (79) assessed the safety and effectiveness of a percutaneous ventricular assist device in patients with refractory cardiogenic shock despite intra-aortic balloon counterpulsation. They implanted the TandemHeart assist device (CardiacAssist, Pittsburgh, Pennsylvania) in 117 patients for an average of 5.8 days in both ischemic and nonischemic cardiomyopathy. The percutaneous assist device markedly improved systolic blood pressure, mixed venous oxygen saturation and urine output, and resulted in 30-day and 6-month mortalities of 40.2% and 45.3%, respectively. Thus, the percutaneous ventricular device appears to be of value in patients with refractory cardiogenic shock. In an accompanying editorial, Tallaj and Cadeiras (80) commented that the TandemHeart could be implanted relatively quickly, was associated with a low complication rate, and rapidly restored circulatory support. However, they cautioned that neither the patients who could benefit from this therapy nor the cost-effectiveness was certain.

Heart Failure

There is a need for information relating how health care is funded with regard to quality and outcomes. Kapoor et al. (81) analyzed the relationship between payment source and quality of care and outcomes in 99,508 HF admissions from 244 sites participating in the GWTG (Get With the Guidelines) program between January 2005 and September 2009. Patients were categorized according to payer status (private/health maintenance organization, no insurance, Medicare, or Medicaid) using private/health maintenance organization as the reference group. They found that the no-insurance group was less likely to receive evidence-based beta-blockers, implantable cardioverter-defibrillators, or anticoagulation for AF, and the Medicaid group was less likely to receive evidence-based beta-blockers or implantable cardioverter-defibrillators. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and beta-blockers were prescribed less frequently in the Medicare group. Overall, Medicare, Medicaid, and no-insurance groups had longer hospital stays, and there were higher in-hospital mortality rates in Medicaid and in uninsured patients with reduced systolic function. These results suggest that quality of care and outcomes of patients admitted for HF is influenced by payer source. In an accompanying editorial, Konstam (82) commented that this analysis offered potentially important information about the impact of future models of funding. He suggests that consideration be given to bundling payments for patient populations and allowing providers to manage their overall costs by improving efficiency and eliminating unnecessary utilization, and to offering patients financial incentives, allowing them to share in the global payment in return for keeping appointments and adhering to dietary and medication prescriptions.

Although diuretics are the main treatment for congestion in HF patients, there are concerns about their effects on kidney function. Damman et al. (83) studied the pharmacodynamic effect of withdrawal and reinstitution of diuretics on markers of renal and tubular function. In 30 euvolemic patients with systolic dysfunction receiving standard furosemide therapy, withdrawal of the diuretic for 72 h resulted in increases in atrial and B-type natriuretic peptides. Whereas serum creatinine was unaffected, both urinary kidney injury molecule-1 and urinary N-acetyl-beta-D-glucosaminidase concentrations, but not serum or urinary neutrophil gelatinase-associated lipocalin, rose significantly after diuretic withdrawal. After reinitiation of furosemide, both urinary injury molecule-1 and N-acetyl-beta-D-glucosaminidase concentrations returned to baseline. These findings support the concept that diuretic withdrawal and reinstitution can increase and decrease markers of tubular dysfunction in stable HF, suggesting that diuretic therapy may favorably affect renal and tubular function by decreasing congestion. As noted by Gottlieb (84) in the accompanying editorial, there is still much to be learned about diuretics and our current views of diuretic actions may need to be modified in the future.

There is evidence that dependent edema and overnight rostral fluid shift from the legs correlates with the severity of sleep apnea in HF patients. Recognizing that excessive sodium intake can cause fluid retention, Kasai et al. (85) assessed whether the severity of sleep apnea is related to sodium intake in HF patients. They determined the amount of sodium intake in 54 HF patients who underwent overnight polysomnography. They found mean sodium intake

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was higher in those with than in those without sleep apnea and correlated with the apnea-hypopnea index. These findings suggest the possibility that sodium intake plays a role in the pathogenesis of sleep apnea.

The HeartMate (HM) II (Thoratec, Pleasanton, California), approved by the Food and Drug Administration, is a continuous flow device for bridge to transplant or destination therapy that was required to demonstrate comparable results to available devices. Starling et al. (86) reported results from the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) in which 169 consecutive patients treated with the HM II LV assist device were compared for outcomes with patients treated with other devices. The adverse event rate was similar or lower for HM II. Operative 30-day mortality for HM II was 4% versus 11% for the comparison group. The percentage of patients reaching transplant, cardiac recovery, or ongoing LV assist device support by 6 months was 91% for HM II and 80% for other devices, and the Kaplan-Meier survival for patients remaining on support at 1 year was 85% for HM II versus 70% for the other devices. These findings confirm that use of the HM II outside of clinical trial settings is associated with highly beneficial clinical results.

The HeartWare Ventricular Assist Device (HeartWare International, Framingham, Massachusetts) is a new mechanical circulatory support system that is smaller and more durable than previous LV assist device systems and can be placed within the pericardial space, thereby avoiding the need for abdominal surgery. Strueber et al. (87) reported the initial clinical evaluation of the HeartWare Ventricular Assist Device in a multicenter, prospective, nonrandomized single-arm clinical trial in which 50 heart transplant candidates with NYHA functional class IV symptoms were supported until heart transplant, myocardial recovery and device explant, or death. Of the 50 patients, 20 received transplants, 4 had the pump explanted after myocardial recovery, and 17 continued support at 2 years. Nine patients died during support from sepsis (n = 3), multiple organ failure (n = 3), or hemorrhagic stroke (n = 3). The actual survival at 6, 12, and 24 months was 90%, 84%, and 79%, respectively. In the survivors, measures of quality of life showed a significant improvement over baseline values, and there were significant improvements for recognition memory at 3 months after implant. These results demonstrate that patients with end-stage HF can be safely and effectively supported by the HeartWare Ventricular Assist Device system with improved quality of life and neurocognitive function. In an accompanying editorial, Pamboukian (88) noted the progress that has been made as ventricular assist devices have evolved over the past several years. He defined 6 major hurdles that have limited the widespread application of the technology: 1) device size; 2) device durability; 3) survival; 4) driveline infections; 5) thrombotic and bleeding complications; and 6) awareness of the benefits of this technology in the greater cardiology community.

Heart failure with preserved ejection fraction (HFpEF) is present in approximately one-half the cases of HF. Haykowsky et al. (89) investigated the mechanisms responsible for reduced aerobic capacity (peak Vo_2) in HFpEF patients. They found that reduced peak Vo_2 in HFpEF patients was associated with a reduced peak cardiac output and arterial-venous O_2 (A-Vo_2) difference. The strongest independent predictor of peak Vo_2 was the change in A-Vo_2 difference from rest to peak exercise (A-Vo_2 difference reserve) for both HFpEF patients and controls. Because A-Vo_2 difference reserve is an independent predictor of peak Vo_2, these findings also support the concept that peripheral, noncardiac factors are important contributors to exercise intolerance in these patients. In an accompanying editorial, Maurer and Hummel (90) comment that this report emphasizes the role of peripheral mechanisms rather than the more traditional view of abnormalities in diastolic function.

Although HFpEF patients have impaired exercise capacity, the effects of exercise training are uncertain. Edelmann et al. (91) sought to determine whether structured exercise training improves maximal exercise capacity, LV diastolic function, and quality of life in HFpEF patients. In this first multicenter trial of exercise in HFpEF patients, they randomized 64 patients to supervised endurance/resistance training in addition to usual care or to usual care alone. Peak Vo_2, the primary endpoint, significantly increased with exercise training but not with usual care, with a mean benefit of 3.3 ml/min/kg. E/e' and LA volume index decreased with exercise training and remained unchanged with usual care. These results demonstrate a beneficial effect of exercise training in HFpEF patients. In an accompanying editorial, Kitzman (92) noted that the changes demonstrated in HFpEF patients were of similar magnitude to those reported with systolic dysfunction, and that they clearly exceeded the threshold for a clinical meaningful change in exercise capacity.

Treatment of HFpEF remains problematic because the results of large-scale clinical trials have been negative. Holland et al. (93) performed a meta-analysis of trials in HFpEF patients and found that pharmacotherapy demonstrated a quantifiable improvement in exercise tolerance but not in measures of diastolic function or in mortality. Given the advanced age of HFpEF patients compared with systolic dysfunction patients, improvement in outcomes such as exercise tolerance might be more achievable and pragmatic.

There is increasing appreciation that multiple factors can contribute to the HFpEF phenotype. Kasner et al. (94) investigated the relationship of changes in myocardial collagen using echo-Doppler assessment of diastolic function in a cohort of HFpEF patients. Overall, 26 (of 41) HFpEF patients showed a significant increase in total collagen and collagen I expression accompanied by enhanced collagen

cross-linking and lysyl oxidase overexpression compared with that of 15 control subjects. Among all Doppler flow variables, only E deceleration time was associated with the collagen volume fraction from heart biopsy specimens, whereas Doppler tissue parameters correlated with collagen volume fraction, collagen I at the protein and messenger ribonucleic acid levels, and LV filling index. Collagen overexpression correlated with reduced exercise capacity. The findings support a causal association between changes in myocardial collagen and abnormal diastolic function in HFpEF patients and raise the possibility that altering collagen production could benefit patients with this condition.

Two papers published this year dealt with the effect of obesity on cardiac function. Owan et al. (95) evaluated the effect of gastric bypass surgery on cardiac remodeling and function. Compared with a reference group, gastric bypass in 423 severely obese patients resulted in a substantial decrease in BMI (15.4 kg/m^2). The bypass group had decreased LV mass index, right ventricular cavity area, increased mid-wall fractional shortening, and right ventricular fractional area change. These data provide support for the application of gastric bypass surgery in patients with morbid obesity.

Russo et al. (96) evaluated the effect of excess weight and obesity on LV diastolic function. They divided 950 subjects into normal weight, overweight, and obese (BMI >30 kg/m^2) categories. In multivariable analysis, BMI was independently associated with an increased E/E′ radio. Overweight and obese had lower E′ velocities and higher E/E′ ratios (both $p < 0.01$). Compared to normal weight subjects, the risk of diastolic dysfunction in overweight subjects was 1.52 and in obese subjects 1.60. The abnormalities of diastolic dysfunction observed in overweight and obese individuals in this study may partially explain the increased risk of HF in these individuals.

Electrophysiology

In the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) study (97), Smit et al. reported data from a randomized comparison of strict (<80 beats/min) versus lenient (80 to 110 beats/min) ventricular rate control in patients with permanent AF. No independent effect of rate on LA size or volume or LV end-diastolic diameter was observed in 256 patients randomized to strict versus 261 to lenient rate control, but female sex adversely affected LA size and LV end-diastolic diameter. The findings support a more liberal effort to control ventricular rate, as compared with the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) and original RACE studies. Wyse, in an editorial comment on this paper (98), points out several issues with this study that may limit its clinical applicability. First, the difference in average heart rate achieved over the 3-year duration in the strict arm was small (approximately 85 beats/min vs. 75 beats/min), but the mean heart rate was <100 beats/min in both groups. The AFFIRM and original RACE study showed adverse effects of heart rates >100 beats/min. Second, Wyse notes that to overcome the modest study size the composite endpoint included at least 8 components, including bleeding risk, which is not likely to be affected by rate control. Wyse also notes a trend for decreases in LA and LV size in the strict rate control group that may not have been statistically significant due to the relatively small size of the study. In addition, the time course of remodeling of the human LA is unknown, and it is not clear what effect this may have had on the study outcomes. Lastly, there were only a modest number of baseline variables included in the statistical model in this study and other unknown variables could have potentially negated the finding with respect to gender effect in this study. For these reasons, it may be best to consider RACE II a stimulus for further research on this subject, rather than proof that more lenient rate control is without risk in patients with persistent AF.

In the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) study, Goldenberg et al. (99) reported data on 1,820 patients, randomized in a 3:2 ratio to cardiac resynchronization therapy with defibrillator (CRT-D) versus defibrillator therapy only, who were followed for 4.5 years. Inclusion required ischemic cardiomyopathy with NYHA class I or II, or nonischemic cardiomyopathy with class II only, sinus rhythm, LVEF ≤30%, and QRS duration ≥130 ms. CRT-D significantly reduced risk of first (HR: 0.54, $p < 0001$) and subsequent HF events (HR: 0.62, $p = 0.003$) compared with implantable cardioverter-defibrillator (ICD) therapy alone, most prominently in patients with left bundle branch block at enrollment (HR: 0.38, $p < 0.001$) with no effect without left bundle branch block. The occurrences of the first and second HF events were associated with 7- and nearly 19-fold increased risk of subsequent mortality. There was some crossover between study arms, but this was nearly equal between groups, and most of the crossover from CRT-D to ICD only was before a first HF event. This study showed for the first time that CRT was associated with a reduction in the risk of recurrent HF episodes and confirms that recurrence of HF events is associated with a marked worsening of prognosis.

In a MADIT-CRT substudy, Barsheshet et al. (100) compared the risk of first ICD therapy for ventricular tachyarrhythmia (VTA) between high- and low-echo responders to CRT-D therapy (defined as ≥25% and <25% reduction in LV end-systolic volume at 1 year) and ICD-only patients. The risk of VTA at 2 years after assessing echocardiographic response was highest among low responders to CRT-D (28%), intermediate among ICD-only patients (21%), and lowest among high responders to CRT-D (12%), with $p < 0.001$ among the groups during follow-up. There was a 55% reduction in VTA in high responders to CRT-D, with no significant difference in risk in other patients. For every 10% reduction in LV end-

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systolic volume, there was a corresponding reduction in risk of subsequent VTA. These findings suggest that reverse remodeling during CRT-D is associated with a significant risk reduction of life-threatening VTA, and that early resynchronization with CRT-D in ischemic and nonischemic cardiomyopathy patients with reduced ventricular function may benefit those who respond to therapy. In an editorial, Curtis (101) comments that there appears to be a slightly increased risk of VTA (a possible proarrhythmic effect) in patients who do not respond to CRT-D with reverse remodeling, and it may be important to avoid such therapy in those patients. Perhaps one should consider turning off CRT and rely only on the ICD function in those without ventricular remodeling after initial implantation.

Eckart et al. (102), in a study of sudden death in young adults, evaluated demographic and autopsy data from the Department of Defense Cardiovascular Death Registry over a 10-year period, comprising 15.2 million person-years of active surveillance. The investigators identified 902 subjects, mean age 38 ± 11 years, in whom the cause of death was adjudicated as potentially cardiac in etiology. The mortality rate for sudden cardiac death (SCD) was 6.7 per 100,000 in men and 1.4 per 100,000 in women ($p < 0.001$) and was attributable to a cardiac condition in 715 (79.3%). The incidence of unexplained sudden death was 1.2 per 100,000 in those <35 years of age, and 2.0 per 100,000 in those ≥35 years of age, with the incidence of atherosclerotic coronary artery disease 0.7 per 100,000 in those <35 years of age, and 13.7 per 100,000 in those ≥35 years of age ($p < 0.001$). The investigators concluded that prevention of sudden death should focus on evaluation for primary arrhythmia in those <35 years of age, with an emphasis on evaluation for CAD in those ≥35 years of age.

Greenspon et al. (103) reported on a trend in infection burden in cardiac implantable electrophysiological devices (CIED) in the United States from 1993 to 2008. The Nationwide Inpatient Sample discharge records were queried, with CIED infection defined as either an ICD-9 (International Classification of Diseases-9th Revision) code for device infection (996.61) and any CIED procedure or removal code, or a CIED procedure code along with systemic infection. In addition, patient comorbidity codes for renal, heart, or respiratory failure or diabetes were evaluated. The investigators found a 4.7% annual increase in CIED implantation during the study period, primarily due to ICD implantation (504% increase in ICD versus 45% in pacemaker implantation). The average incidence of CIED infection was 1.61%, which remained constant until 2004 when there was a marked increase coinciding with an increase in major comorbidities. This was associated with a marked increase in mortality (1% per decade) and in-hospital financial charges (an increase of 47% per decade). Thus, the absolute number of CIED implantations (particularly ICDs) significantly increased over the past 2 decades, and this is associated with a significantly greater risk of infectious complications and dramatic cost increases.

Gollob et al. (104) proposed diagnostic criteria for the short QT syndrome (SQTS), a relatively newly described cardiac channelopathy associated with AF and SCD. In some cases, the cause of the SQTS has been identified as a mutation in the *KCNH2* gene resulting in up-regulation of the *IKr* or *HERG* potassium channel, which accelerates action potential repolarization. Mutations in the *KCNQ1* gene, resulting in functional up-regulation of the *IKs* channel have been identified in other cases, as have those in the *KCNJ2* gene resulting in functional up-regulation of the *IK1* gene. The wide overlapping range of QT intervals between cases and healthy subjects, with no arrhythmias occurring in populations with QT intervals equally short or shorter than some cases with sudden death due to ventricular arrhythmias, has made the definition of the syndrome difficult. The investigators identified 61 reported SQTS cases in the English language MEDLINE database, and presentation, sex, ECG criteria including QT interval, genetic analysis when available, and family history. From this data, the investigators proposed diagnostic criteria for SQTS, with major emphasis on QT interval and J-point to T-peak interval, also including history of cardiac arrest, polymorphic ventricular tachycardia or ventricular fibrillation, unexplained syncope, AF, family history in first- or second-degree relatives of SQTS or unexplained sudden death, or sudden infant death syndrome, and genotype. They then assigned a point score to each of the diagnostic criteria. The proposed criteria may not be agreed on by all, but this paper represents a first step toward identifying patients with this rare but lethal genetic syndrome.

Giustetto et al. (105) described the long-term outcome of patients with SQTS, a rare channelopathy that has also recently been associated with sudden cardiac arrest (SCA). The investigators identified 53 patients from the European Short QT Registry (75% men; median age: 26 years) who were followed for 64 ± 27 months. Eighty-nine percent of individuals had a familial or personal history of SCA, with 32% presenting with SCA. The average QT interval corrected for heart rate (QTc) in the population was 314 ± 23 ms. A defined mutation was found in 23% of probands, most having a gain of function mutation in *HERG* (SQTS1). Twenty-four patients received an ICD, and 12 patients received hydroquinidine. During follow-up, the event rate was 4.9% per year in the patients without antiarrhythmic therapy. No arrhythmic events occurred in patients receiving hydroquinidine. The investigators concluded that SQTS carries a high risk of SCA in all age groups, that symptomatic patients had a high risk of recurrent arrhythmic events, and that hydroquinidine was effective in preventing arrhythmic events follow-up.

Treatment for Atrial Fibrillation

There is growing awareness of the epidemic of AF (106–108). In a Viewpoint, Mittal et al. (107) discuss how rigorous ECG monitoring, facilitated by new and emerging technol-

ogies, is increasingly linking AF with conditions such as cryptogenic stroke and will likely intensify our monitoring and therapy goals for AF patients in the future. Several studies this year focused on the therapy, management, and underlying mechanisms of AF.

Saksena et al. (109) reported an important substudy from AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management trial) that examined CV outcomes based on specific antiarrhythmic medication in 1,603 patients initially receiving amiodarone (45%), sotalol (38%), and flecainide or propafenone (17%). Using propensity scores to match antiarrhythmic groups, the investigators showed that the composite endpoint of mortality or cardiovascular hospital stay (CVH) was worse for amiodarone or sotalol ($p = 0.02$ or $p < 0.001$, respectively) than rate control was. Amiodarone also conferred a higher risk of non-CV death (HR: 1.11, $p = 0.04$), higher CVH event rates at 3 years, and shorter time to CVH with intensive care unit stay or death (HR: 1.22, $p = 0.03$). There were no significant differences in overall survival between antiarrhythmic medication groups and matched rate control subjects. The investigators concluded that CVH event rates during follow-up were high for all cohorts, but were higher for all groups receiving antiarrhythmic medications. The editorial commentary by Markowitz (110) points out that clinical differences may still contribute to these data (for instance, some coronary disease patients received class I agents) and emphasizes that antiarrhythmic medications have been shown to improve outcomes in some trials.

Disappointment with antiarrhythmic medications for AF continues to fuel interest in nonpharmacological therapy to restore sinus rhythm. Several studies in the *Journal* in 2011 examined outcomes from percutaneous AF ablation. Gertz et al. (111) examined the impact of successful ablation of AF on MR. Out of 828 patients undergoing first AF ablation, they retrospectively compared 53 with at least moderate MR to 53 with mild or undetectable MR. The investigators found that patients in sinus rhythm on follow-up had less MR and greater reduction in LA size on echocardiograms, than those not in sinus rhythm. They conclude that these data support the concept of atrial functional MR, in contradistinction to functional MR from ventricular dilation. In an accompanying editorial, Hoit (112) writes that these provocative data may be the first to show a cause-effect relationship between LA enlargement and functional MR.

Although clinical stroke or transient ischemic attack is an uncommon complication of AF ablation (<1%) (113), Herrera Siklódy et al. (114) compared silent cerebral emboli using 3 competing ablation catheters: a conventional irrigated catheter; a cryoballoon; and a new multielectrode phased pulmonary vein ablation catheter (PVAC). The investigators performed cerebral MRI in 74 patients 1 day before and within 2 days after pulmonary vein isolation, ensuring strict periprocedural anticoagulation. The investigators report that post-procedure MRI detected a single new embolic lesion in 2 of 27 patients of the irrigated catheter group (7.4%), 1 of 23 patients of the cryoballoon group (4.3%), and 9 of 24 of the PVAC group (37.5%), demonstrating 2.7 ± 1.3 new lesions (range 1 to 5; median: 3; $p = 0.003$). Clinical examination (not performed by neurologists) was normal in all patients after ablation. The investigators conclude that the PVAC catheter is associated with a higher incidence of subclinical intracranial embolic events. Similar data were also recently reported elsewhere in a parallel study (115). An accompanying editorial (116) discusses these issues in detail. Of note, the U.S. Food and Drug Administration recently decided against approval of the novel PVAC catheter (117) citing safety concerns including these data. On this topic, a separate report from the Taipei group in 2011 suggests that the CHADS2-VASc score may identify risk of thromboembolism after catheter ablation for AF better than the CHADS2 score (118).

As catheter ablation for AF continues to grow in utilization, it is increasingly important to fully understand the long-term results following this procedure. Weerasooriya et al. (119) systematically followed 100 patients for 5 years after a single initial catheter ablation procedure. They document steady erosion in the arrhythmia-free survival with only 29% of patients free of recurrence at 5 years. This realistic assessment of long-term success rates provides the CV community with useful insights into the natural history of AF following ablation.

The field of surgical, nonpercutaneous ablation for AF also continues to grow. An interesting study by Onorati et al. (120) evaluated the impact of different surgical lesions for AF ablation in 141 patients followed prospectively after mitral valve and maze surgery. Patients received either a "limited" LA radiofrequency lesion set in 32 patients or an "extensive" set in 109 patients that combined left and right atrial lesions with ganglionic plexus isolation in some cases. The investigators found the post-procedural prevalence of AF to be lower in patients receiving extensive versus limited ablation (adjusted RR: 0.10; $p < 0.001$) at discharge, 3 months after, and 18 months after. This was associated with fewer patients in NYHA class II/III, lower rates of hospitalization and of the combined endpoint of death/hospitalization over time, and lower usage of antiarrhythmic drugs in the extensive ablation arm. The investigators concluded that adding right-sided lesions improved results from the surgical maze procedure. These data support the report by Hocini et al. (121), who reported that percutaneous ablation in the right atrium was required for optimal results in some patients.

Several studies dealt with issues related to AF. Melduni et al. (122) examined the relationship between new-onset post-operative AF within 30 days of surgery and evidence of LV diastolic dysfunction. Post-operative AF was observed in 38.5% of 351 patients. Left ventricular diastolic dysfunction was an independent predictor with an odds ratio (OR) of 5.12 ($p < 0.006$). Thus, LV diastolic dysfunction appears to be a pre-disposing substrate for post-operative AF and a finding that has mechanistic implications.

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The issue of warfarin-associated hemorrhage in AF patients was studied in the ATRIA (Anticoagulation of Risk Factors in Atrial Fibrillation) study. Fang et al. (123) examined the follow-up of 9,186 AF patients to derive a risk score for the likelihood of hemorrhage. Five independent variables were included in the final model: anemia (3 points); severe renal disease (3 points); age greater than 75 years (2 points); prior bleeding (1 point); and hypertension (1 point). Major hemorrhage rates ranged from 0.4% with 0 points to 17.3% per year with 10 points. Thus, this risk score applying easily obtainable parameters affectively quantified the risk of warfarin-associated hemorrhage in patients with AF.

Mechanisms of Human Atrial Fibrillation

Several studies in the *Journal* this year shed light on the sustaining mechanisms for human AF. The 2 prevailing hypotheses are, first, that AF is caused by spatially meandering electrical waves (the multiwavelet hypothesis (124)) and, second, that AF is caused by electrical spiral waves (rotors) or focal beat sources from which activity disorganizes to the surrounding atrium (the localized source hypothesis (125)). Chou et al. (126) provided data to support the localized source hypothesis, in Langendorff-perfused LA-pulmonary vein preparations from 13 dogs. Sustained AF was induced by rapid pacing and acetylcholine infusion and was characterized by rotors in all animals with additional focal beat sources in just over one-half. Epicardial ablation of rotor sites suppressed subsequent AF initiation and shortened the duration of induced AF. Notably, AF was suppressed even in animals in which the pulmonary veins continued to exhibit triggering ectopy. Preliminary human data recently showed that percutaneous ablation of AF rotors and focal beat sources can provide acute termination and long-term elimination of AF (127).

The mechanisms for re-entrant circuits in AF are often attributed to electrical and structural remodeling (128) that in turn is often attributed to atrial fibrosis and age. Platonov et al. (129) reported unique histologic analyses of autopsies from 30 consecutive patients without a documented history of AF, or with paroxysmal AF or permanent AF. Remarkably, the investigators found no correlation between age and fibrosis at any atrial location. Conversely, the extent of fibrosis and fatty infiltration were 2- to 3-fold higher in patients with AF, particularly permanent AF. The editorial commentary by Asirvatham and Gard (130) questions whether these data are sufficient to overturn conventional wisdom linking atrial fibrosis with aging.

In a separate report examining electrical remodeling, Tsai et al. (131) studied cultured atrial myocyte monolayers exposed to stretch, a known precipitant of AF. The investigators found that stretch caused oscillations in cellular calcium and repolarization, which are known to predispose to AF. These data also agree with a recent human report in which repolarization oscillations were most likely in patients with remodeled atria and indicated imminent AF onset (132). Tsai et al. (131) found that overexpression of sarcoplasmic reticular adenosine triphosphatase reversed cellular abnormalities in their preparation, suggesting a novel therapeutic avenue for AF.

Clinical Syndromes That Elevate Sudden Death Risk

It remains extremely difficult to identify individuals at risk for SCA from VTA (133). Despite the emphasis of risk stratification schemes on LV dysfunction, most cases of SCA occur in individuals with preserved ejection fraction. Several studies in the *Journal* in 2011 focused on early repolarization syndrome (ERS), a recently reported cause of SCA in individuals with structurally normal hearts. Derval et al. (134) examined the prevalence of ERS in the CASPER (Cardiac Arrest Survivors with Preserved Ejection Fraction Registry), of whom 100 patients (40 women, age 43 ± 14 years) underwent extensive clinical and genetic testing and blinded independent ECG analysis. Early repolarization was defined as ≥0.1 mV J-point elevation in 2 or more contiguous inferior and/or lateral leads. Forty-four patients had an established cause for cardiac arrest, with early repolarization in 19 patients, including 6 with a primary diagnosis that explained their cardiac arrest (14%), compared with 23% of the 56 patients with idiopathic ventricular fibrillation ($p = 0.23$). J-point elevation in IVF patients had higher amplitude (0.25 ± 0.11 mV vs. 0.13 ± 0.05 mV; $p = 0.02$) and wider distribution (4.3 ± 1.3 leads vs. 2.8 ± 0.8 leads; $p = 0.01$) than in patients with established causes for cardiac arrest. Notably, J-wave amplitude was labile on serial ECGs. The investigators concluded that early repolarization is present in both etiology-identified as well as idiopathic ventricular fibrillation.

In a separate report, Nunn et al. (135) hypothesized that ERS is inherited and may be responsible for some cases of sudden arrhythmic death syndrome. In 363 first-degree relatives from 144 families of sudden arrhythmic death syndrome probands, the investigators found that J-point elevation (0.1 mV from baseline in 2 or more inferior or lateral leads) was higher than in 359 matched controls (23% vs. 11%; OR: 2.54; $p < 0.001$). The investigators concluded that ERS is a potentially inheritable marker of proarrhythmia in sudden arrhythmic death syndrome. In a separate report examining 3,955 participants in the Framingham Heart Study and 5,489 participants in the Health 2000 Survey, Noseworthy et al. (136) found ECG evidence of early repolarization in 6.1% and 3.3% of their cohorts, respectively. In the Framingham cohort, siblings of individuals with early repolarization had this pattern in 11.6% of cases, for an elevated unadjusted OR of 2.22 ($p = 0.047$). The investigators concluded that the ECG pattern of early repolarization is inherited, but they did not examine clinical features and thus could not assign the diagnosis of ERS.

As discussed, many of the various ECG markers for SCA are labile. Goldenberg et al. (137) examined the natural history of patients with "genotype-confirmed LQTS" yet normal QTc intervals. The investigators studied 3,386 genotyped subjects from the United States, Western Europe, and Japan in whom they examined clinical and genetic risk factors for aborted cardiac arrest (ACA) or SCA from birth through age 40 years. The investigators found that although the probability of ACA or SCD in patients with long QT syndrome (LQTS) with normal-range QTc (4%) was lower than in those patients with prolonged QTc (15%) ($p < 0.001$), it was higher than in unaffected family members (0.4%) ($p < 0.001$). Risk factors for ACA or SCD in patients with normal-range QTc included the specific mutation and LQTS genotype, but clinical factors were associated with increased risk only in patients with prolonged QTc. The investigators concluded that genotype-confirmed patients with concealed LQTS constitute 25% of the at-risk LQTS population, and that genetic data identify increased risk for ACA or SCD in this overall lower-risk subgroup. This provocative report opens up the potentially enormous field of investigating and treating patients with genetic abnormalities yet no clinical abnormality, as discussed in an accompanying editorial by Roden (138).

Several approaches are being taken with novel pharmacological therapies for arrhythmic syndromes. Den Ruijter (139) studied rabbit cardiomyocytes in vitro and found that superfusion with reconstituted HDL (to simulated elevated HDL-C) shortened ventricular action potential duration. In a pilot clinical study by the investigators, reconstituted HDL infusion in dyslipidemic and control subjects caused a shortening in QTc on the ECG in all subjects. The investigators concluded that shortening of repolarization by reconstituted HDL might explain the salutary effects of HDL, lipid management, and statins on reducing sudden death. Clearly, these data need validation in a larger cohort. In a separate report, Fabritz et al. (140) tested whether a reduction of vascular volume prevented the arrhythmogenic phenotype in a murine model of arrhythmogenic cardiomyopathy (ARVC). In heterozygous plakoglobin-deficient mice, in which the ARVC phenotype was induced by endurance training (daily swimming) (141), administration of furosemide and nitrates prevented right ventricular dilation and, in Langendorff preparations, prevented conduction slowing and reduced the incidence of inducible ventricular arrhythmias. In an accompanying editorial, Calkins (142) opines that these data may have implications for treating patients with ARVC. Separately, van der Werf et al. (143) studied whether flecainide may prevent clinical arrhythmias in catecholaminergic polymorphic ventricular tachycardia (CPVT), building on the investigators' recent report that flecainide may directly inhibit premature Ca(2+) release and triggered beats in CPVT models in vitro (144). The investigators collected data from 33 consecutive genotype-positive CPVT patients treated by flecainide at 8 centers for the endpoint of reduction of ventricular arrhythmias during exercise testing. Twenty-two patients had partial or complete suppression of exercise-induced ventricular arrhythmias with flecainide ($p < 0.001$), and none had worsening ventricular arrhythmias. Over a median follow-up of 20 months, 1 patient experienced appropriate ICD shocks for polymorphic ventricular arrhythmias. The investigators concluded that flecainide reduced exercise-induced ventricular arrhythmias in patients with CPVT that is not controlled by conventional drug therapy.

The search for risk stratifiers for SCA continues, and this year the *Journal* published the consensus guideline document regarding the use of T-wave alternans from the International Society for Holter and Noninvasive Electrocardiology (145).

Ablation of Ventricular Arrhythmias

The ablation of ventricular arrhythmias is largely dependent on the completeness and quality of either endocardial or increasingly epicardial (146) mapping. It has been demonstrated that high-quality surface ECG imaging, using mathematical algorithms to infer the sources of signals on the heart, can identify important components of the circuit for ventricular arrhythmias noninvasively (147,148). Cuculich et al. (149) used this approach to noninvasively identify regions of ventricular scar that were critical for the initiation and maintenance of ventricular tachycardia and targeted for ablation. These data continue dramatic recent advances in imaging complex arrhythmias that are significantly improving the efficacy of ablation for these disorders.

Device Therapy

Several studies have questioned the need for more complex devices when more simple devices may suffice. Dewland et al. (150) used data from 104,049 patients in the NCDR (National Cardiovascular Data Registry) to report that the periprocedural adverse event rate (3.17% vs. 2.11%; $p < 0.001$) and in-hospital mortality rates (0.4% vs. 0.23%; $p < 0.001$) were higher in 64,489 patients receiving dual-chamber devices than in those receiving single-chamber devices. These differences were maintained after multivariate adjustment for comorbid conditions. The editorial commentary by Al-Ahmad and Freeman (151) places these data into perspective, discussing the differences in comorbidities between populations that may not be fully adjusted by multivariate analyses and reminding us of the proven benefits of dual-chamber devices in selected populations.

There is also an increasing focus on the potential hazards of cardiac implanted device therapy. Morrison et al. (152) compared outcomes in 1,030 patients with Medtronic Sprint Fidelis ICD leads (Memphis, Tennessee) identified as having a higher-than-expected failure rate compared with outcomes in 1,641 patients with Medtronic Quattro ICD leads without this issue, in 3 tertiary care centers. Managed conservatively, patients with Sprint Fidelis leads had a similar outcome adjusted for clinical comorbidities as those

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with Quattro leads did. No patient deaths were associated with lead fracture. In the accompanying editorial, Faddis (153) discusses these data, in the context of the needs for rigorous monitoring as part of conservative management, weighed against the potential drawbacks of the aggressive alternative of replacing Fidelis leads. In a complimentary study, Swerdlow et al. (154) used novel ICD diagnostics to discriminate ICD lead fractures (in which electrical impedance rises) from normally functioning leads with a high impedance or connection problems between the lead and header. The investigators used a development set of 91 leads to construct a stepwise algorithm based on ICD diagnostics, and then they applied this algorithm to an independent test sample of 100 leads. The algorithm included changes in impedance, changes in the interval from surgery to impedance rise, and other changes. In the test set, the algorithm correctly classified 100% of fractures and 87% of connection problems that had been misdiagnosed as fractures. The investigators concluded that these methods might have clinical applicability in separating lead fractures from normally functioning leads with high but stable impedance.

The problem of inappropriate defibrillator shocks represents a major source of patient discomfort that can sometimes be psychologically disabling. Van Rees et al. (155) carefully classified the incidence and predictors of inappropriate shocks in more than 1,500 patients. Surprisingly, they found that inappropriate shocks are both a source of morbidity, and can predict an increase in mortality, independent of whether the patient also received appropriate shocks.

The ability of resynchronization therapy to reduce the risk of atrial tachyarrhythmias was studied in MADIT-CRT. Brenyo et al. (156) classified patients as having small (<20%) or high (>20%) decreases in LA volume in response to CRT. As compared to high responders, the probability of atrial tachyarrhythmias was increased in low-responder and ICD-only patients (3%, 9%, and 7%, respectively; $p < 0.03$). Patients who developed atrial tachyarrhythmias manifested a greater risk for both HF and death. Thus, this study demonstrated that CRT could reduce LA volume and result in a subsequent decrease in atrial tachyarrhythmias enhancing the ultimate outcome.

The controversial topic of mandatory electrocardiographic screening of athletes to reduce the risk of sudden death was studied by Steinvil et al. (157). During a 14-year period of mandatory electrocardiographic screening, they documented 24 sudden deaths or cardiac arrests in competitive athletes by screening 2 main newspapers in Israel. The rate of events during these years was not different from the incidence during adjacent decades in which mandatory electrocardiographic screening was not required. The investigators concluded that the electrocardiographic screening did not have a significant effect on sudden death in athletes. In an accompanying editorial, Bove (158) reviews the data for and against mandatory electrocardiographic, and even echocardiographic, screening. He points out that the issue is confounded by the very low incidence of sudden death in athletes and the frequent prevalence of electrocardiographic and echocardiographic false-positive abnormalities. Given the emotional response to the death of an athlete, it is likely that this controversy will continue.

Advances in CT Imaging

Several studies addressed the expanding role of computed tomography (CT) imaging in coronary artery disease. Two studies provided further information on the prognostic value of coronary calcium scanning. In 5,660 patients in the MESA (Multi-Ethnic Study of Atherosclerosis), calcium scores were related to Framingham risk scores (159). The prevalence of a significant calcium score was low in patients with very low-risk Framingham score (≤5%), but became significantly higher in patients with low-intermediate risk Framingham scores (>5% to 20%). Thus, calcium scoring in very low-risk Framingham score patients may not yield reclassification value. Another study analyzed Framingham risk variables high-sensitivity C-reactive protein and coronary calcium score in 3,966 individuals without known CAD or acute inflammation (160) to predict hard events (death, infarction) at 5-year follow-up. Improvement in risk prediction was provided primarily by coronary calcium score, but high-sensitivity C-reactive protein was of significant value in the patients with very low calcium scores. An accompanying editorial acknowledged the potential use of calcium score and high-sensitivity C-reactive protein, but also stated that future studies need to address how these data can be used to guide therapy in these individuals (161).

Rozanski et al. (162) reported the results of the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) prospective randomized trial examining the impact of coronary artery calcium scanning on coronary risk factors and downstream testing. They randomized 2,137 volunteers to either coronary calcium scanning or no scanning, but not before risk factor counseling. The endpoint was a 4-year change in coronary risk factors. They observed a mean rise in Framingham risk score in the no scan group, whereas risk remained unchanged in those undergoing scanning. In those patients scanned, increasing calcium score was associated with a dose-response improvement in multiple risk factors and the Framingham risk score ($p < 0.003$), whereas costs were similar in both groups. Thus, coronary calcium scanning resulted in improved CAD risk factor control without increasing downstream testing or expenses.

Several studies reported the utility of computed tomography angiography (CTA). Using low-dose CT with prospective ECG gating, the mean effective radiation dose was 1.8 ± 0.6 mSv in 612 patients undergoing 64-slice CTA, with good diagnostic image quality in 96.2% of segments (163). Meta-analysis of 11 studies with 7,335 patients undergoing CTA (electron beam in 2 studies, 16-slice in 2 studies, and 64-slice in 7 studies) confirmed that the extent

and severity of coronary lesions were predictive of future CV events, independent of coronary calcification and risk factors (164). Nonobstructive plaques are also relevant for outcome; in 2,583 patients from 2 centers, the presence and extent of nonobstructive lesions better predicted mortality over 3.1 years than the Framingham risk score did (165). An accompanying editorial (166) stressed that it would be very important to better define plaque composition to further improve risk stratification. In another important paper on the value of CV CTA, Kristensen et al. (167) demonstrated the prognostic implications of having nonobstructive CAD in patients with non-STEMI. They followed 312 patients for a median period of 16 months, documenting the relationship of nonobstructive lesions with cardiac events (HR: 1.18 per 100-mm^3 plaque volume increase; $p = 0.01$). Neither Agatston score nor the amount of calcium in atherosclerotic plaques was associated with an increased risk of cardiac events. The latter findings further support previous and recent studies published in the *Journal* and other journals documenting the absence of absolute protection in symptomatic patients with 0 calcium score.

The prognostic value of CTA was derived from an international multicenter registry of 24,775 patients undergoing ≥64-slice CT, with follow-up of 2.3 years (168). Absence of coronary disease on CTA was associated with excellent outcome (annualized death rate: 0.28%); the mortality increased in parallel with severity and extent of stenoses. In an accompanying editorial, De Bruyne and Van Mieghem (169) emphasize that, in addition to assessing luminal obstruction, it will be important to evaluate the hemodynamic significance of these stenoses for proper patient management. The power of cardiac CT to define prognosis was reported in a meta-analysis by Hulten et al. (170). In that comprehensive study, the investigators compiled data from 18 reports that evaluated 9,592 patients with a median follow-up of 20 months. Very importantly, the pooled negative likelihood ratio for MACE after a normal CT angiographic exam was 0.008 (95% CI: 0.0004 to 0.17; $p < 0.001$), whereas the pooled annualized event rate for patients with at least 1 >50% coronary stenosis versus normal CTA was 8.8% versus 0.17% per year for MACE ($p < 0.05$) and 3.2% versus 0.15% for dearth or nonfatal infarction ($p < 0.05$). The investigators concluded that adverse CV events in patients with normal CTA are rare and that incremental rates of MACE are associated with increasing CAD by CTA. Finally, Chow et al. (171) demonstrate the potential use of coronary opacification in CT angiography to estimate the presence of coronary flow obstruction. In this proof-of-concept study involving 52 patients, normal coronaries were compared for coronary opacification with vessels containing >50% obstructions or with abnormal TIMI flow grade (<3). The investigators found that coronary opacifications across stenoses were related to abnormal TIMI flow grade. The findings from this innovative pilot investigation were discussed in an accompanying editorial by Rybicki (172), who was among the first to propose the concept of coronary opacification analysis for the detection of CAD.

FFR can assess the hemodynamic significance of a stenosis, but has thus far required invasive angiography. Recently, the feasibility of assessing FFR noninvasively has been reported (173). In a multicenter study including 103 patients (and 159 vessels), FFR derived from CTA was compared to invasively assessed flow reserve. The agreement between the 2 approaches was good ($r = 0.717$; $p < 0.001$), with minimal underestimation by CTA. The accuracy of CTA to detect hemodynamically significant obstruction compared with invasive FFR improved from 58.5% when the stenosis severity was used to 84.3% when the CTA-derived FFR was used. Further studies are needed, but this CTA approach may allow integrated assessment of anatomy and functional consequences (174).

A 16-center study evaluated the use of CTA for acute chest pain evaluation in the emergency room; 361 patients were randomized to CTA and 338 to myocardial perfusion imaging (175). The CTA approach reduced time to diagnosis (primary endpoint) by 54% compared with myocardial perfusion imaging and reduced cost by 38% compared with standard care. The rate of major adverse events at 6 months was similar (0.8% and 0.4%, respectively) in patients in whom CTA and perfusion imaging was normal. In an accompanying editorial, Salerno et al. (176) emphasized that some patients may benefit more from functional imaging for ischemia and others by direct visualization of the coronary arteries; the choice should be individualized.

Advances in Cardiac Imaging

With the increasing use of rubidium Rb 82 positron emission tomography (PET), it becomes feasible to both assess perfusion defects and evaluate regional myocardial flow reserve (MFR) in a quantitative manner. In 51 patients with atherosclerosis on CTA, rubidium Rb 82 PET-measured MFR varied significantly among individual coronary stenoses (177). Importantly 38% of nonobstructive stenoses also had abnormal flow reserve. On a patient basis, predictors of reduced MFR were the modified Duke coronary artery disease index and the number of segments with mixed plaque. Importantly, CTA variables had only modest value in predicting MFR, and further studies are needed to determine the relation between coronary plaque characteristics and MFR (178).

The prognostic value of impaired MFR was evaluated in 704 patients undergoing rubidium Rb 82 PET with a median follow-up of 387 days. Quantitative MFR provided incremental prognostic value over visual assessment of perfusion defects (summed stress score) (179). These findings stress the potential advantage of quantitative perfusion assessment over visual interpretation (180). Another quantitative PET perfusion study employed ^{13}N ammonia and demonstrated that a reduced coronary flow reserve (defined as <2.5) was related to plasma biomarkers of inflammation

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in asymptomatic subjects (181). Importantly, when perfusion was visually evaluated (by summed stress score), a relation was found for only 1 plasma biomarker, supporting the superiority of absolute quantification of coronary flow.

Fluorodeoxyglucose F-18 (FDG) with PET permits assessment of regional inflammation. In patients with increased periodontal uptake, there was also an increased FDG uptake in carotid arteries and the aorta, suggesting vascular inflammation, which was confirmed histologically in patients undergoing carotid endarterectomy (182). These findings suggest a global process of inflammation, rather than a regional phenomenon. Another study used FDG PET imaging to evaluate valvular inflammation in patients with AS (183). Interestingly, patients with mild and moderate AS had increased FDG uptake, whereas patients with heavily calcified, severely stenotic aortic valves did not. These observations suggest active valvular inflammation occurs early in the development of AS and is reduced in end-stage disease.

This year, the cutting edge development in CV imaging clinical investigation was set by magnetic resonance methods to assess myocardial fibrosis, Dweck et al. (184) reported that mid-wall pattern of myocardial fibrosis defined by MRI delayed enhancement (n = 54) was the strongest independent predictor of all-cause mortality by multivariate analysis (HR: 5.35; p = 0.03) among 143 nonischemic cardiomyopathy patients followed for 2.0 years. An editorial by Nazarian (185) opines that these results raise important questions about mechanisms of mid-wall fibrosis in patients with LV overload and nonischemic cardiomyopathy, as well as its potential relationship with sudden death and ultimate mechanical failure. Myocardial fibrosis was also related to the risk of sudden death in patients with severe LV dysfunction. Iles et al. (186) followed 103 patients for primary prevention of sudden death for 573 days and demonstrated a 29% discharge rate among nonischemic cardiomyopathy patients with fibrosis by MRI versus 14% with ischemic cardiomyopathy. By contrast, there were no discharges with nonischemic cardiomyopathy without delayed enhancement. In a different study, Daccarett et al. (187) related the presence of LA fibrosis to a history of stroke in 387 patients with AF referred for ablation. Patients with previous strokes had a greater percentage of LA fibrosis (24.4% vs. 16.2%; $p < 0.01$) than those without history of stroke. Barbier et al. (188) published an extension of these observations to populations by documenting in a community-based study that the presence of MI by clinical, ECG, and MRI criteria was related to presence of cerebral infarction defined by contrast-enhanced MRI.

The cardiac-cerebral connection received increasing attention this year. Rodriguez et al. (189) documented the relationship between mitral and aortic annular calcification and aortic sclerosis by echo and cerebral infarction by MRI among 2,680 participants of the Cardiovascular Health Study without clinical history of stroke or transient ischemic attacks. The degree of annular or valvular calcification was directly related to the presence of covert cerebral alterations by MRI. In another study, Lee et al. (190) performed magnetic resonance angiography to assess the presence and severity of intracranial and extracranial atherosclerosis in 1,367 patients before CABG. Strokes within 14 days from operation (n = 33) were independently associated with the atherosclerotic score (OR: 1.35). The study suggests that the pre-operative evaluation of cerebral arteries by MR angiography may be useful to predict the likelihood of post-CABG stroke. Noguchi et al. (191) documented the relationship between coronary events and high-intensity signals observed in carotid plaques by inversion recovery 3-dimensional T_1-weighted imaging. Noguchi et al. (191) demonstrated a potential link between carotid and coronary plaque vulnerability because high-intensity inversion recovery 3-dimensional T_1-weighted imaging signals were the strongest independent predictor of cardiac events among 217 stable CAD patients followed up to 72 months (HR: 3.15; $p < 0.0001$) compared with carotid intima-media thickness and coronary risk factors in multivariate analysis.

State-of-the-art MRI techniques to further the noninvasive evaluation of myocardial perfusion evolved in 2011. Lockie et al. (192) employed 3.0-T MRI perfusion imaging to study the relationship between myocardial perfusion reserve estimated by Fermi deconvolution and invasive fractional flow reserve. Using receiver-operator characteristic analysis, the investigators found that the method had an area under the curve of 0.89 to identify lesions that had FFR <0.75. In a related study, Manka et al. (193) used 3-dimensional dynamic stress MRI at 3-T to quantify the "volume" of perfusion defects before and after coronary intervention in 48 patients. Percentage of LV volume subtended by the hypoenhanced defect during adenosine stress was reduced from 14.2 to 3.2 by coronary stenting. Additionally, state-of-the-art strain imaging by strain-encoded MRI was used to detect regional myocardial dysfunction during dobutamine stress before the onset of visually obvious wall motion abnormalities. In 320 patients with suspected CAD followed for 28 months, 67 events occurred. Stress-induced wall motion abnormalities increased the ability to predict cardiac outcomes relative to clinical variables (chi-square: 39.3 vs. 13.0). Adding quantitative strain analysis by strain-encoded MRI further increased predictive power (chi square: 52.5; $p < 0.01$). Finally, McGann et al. (194) documented the power of microvascular obstruction defined by contrast-enhanced MRI to predict atrial scar formation in patients undergoing ablation for AF. In 37 patients imaged immediately after ablation, equal numbers of atrial wall segments were classified as hypo-enhanced (34 due to profound microvascular injury and obstruction), hyperenhanced (38 ± 13% due to myocyte injury without profound microvascular damage), and normally enhanced (28 ± 11% minus preserved myocyte wall integrity and microvasculature). However, 3 months after ablation, the presence of 59% of tissue classified as scar corresponded to hypo-enhanced segments im-

mediately after ablation as opposed to 31% to hyperenhanced segments and 10 ± 5% to normally enhanced regions. Because scar formation correlates with procedure outcomes, the study highlighted the use of magnetic resonance techniques to aid in the prediction of success from AF ablation procedures.

Echocardiography studies also make the list of the best in the *Journal* this year. In a study using established strain imaging by echocardiography, Fallah-Rad et al. (195) demonstrate that lateral S′ by tissue Doppler as well as peak global longitudinal and radial strain measures signaled the presence of myocardial dysfunction before ejection fraction became abnormal in patients being treated for breast cancer with trastuzumab. Ten of 42 patients under therapy developed tissue Doppler and strain abnormalities 3 months before reduced ejection fraction could be detected. The importance and implications of these findings are discussed by accompanying editorial by Edvardsen (196) emphasizing the ability of strain measurements to detect myocardial abnormalities prior to conventional wall motion and ejection fraction.

In another study, established MRI LV mass quantification was employed to quantify the impact of impaired pulmonary flow on LV underloading and atrophy. Hardziyenka et al. (197) studied LV mass measured by MRI in 36 patients with chronic thromboembolic pulmonary hypertension and showed that these patients had lower LV mass than normal volunteers did. Moreover, LV mass increased after pulmonary endarterectomy (from 38 to 44 g/m^2) as right ventricular ejection fraction improved from 31% to 56% ($p < 0.001$ for both). The implications of these findings to the field of pulmonary hypertension are placed in perspective by accompanying editorial by Dell'Italia (198).

Patients with large hiatal hernias often complain of CV in addition to gastrointestinal symptoms. Naoum et al. (199) reported exertional dyspnea was present in 25 of 30 hiatus hernia patients despite normal baseline respiratory function. Significant LA compression was present in 23 of 30 patients on CT, whereas pulmonary vein and coronary sinus compression was present in 11 and 26 of the 30 patients. After surgical treatment, resolution of cardiac compression was documented and exercise capacity improved significantly. In fact, LA diameter change by echo was the only independent predictor of exercise capacity improvement after hiatal hernia surgery. An accompanying editorial by Marwick (200) points out that this is a common clinical issue.

Biomarkers

Natriuretic peptides. In a significant report, The PROTECT trial by Januzzi et al. (201) was a prospective single-center study that drove N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels <1,000 pg/ml in patients with systolic dysfunction (201). With a mean follow-up of 10 months, there was both a significant decrease in NT-proBNP levels and events and an impact on quality of life. In an accompanying editorial, Maisel (202) pointed out that the definition of an ideal biomarker should include those that are clinically actionable, can be used for "biomarker-guided therapy," and could also be "biomonitored" during treatment as an effective surrogate of improvement.

DeFelippi et al. (203) found that the addition of an abnormal LVEF to a low baseline NT-proBNP level did not improve estimation risk for HF in older adults. An initially elevated or rising NT-proBNP level was associated with an increased risk of developing an abnormal LVEF. In an accompanying editorial, Richards (204) opined that, given the accumulating evidence, we should consider controlled therapeutic trials in patients with combinations of pre-defined NP and echocardiographic abnormalities.

Lam et al. (205) studied the relationship between sex hormones and natriuretic peptide levels in community-based adults. They found that the higher circulating NT-proBNP concentration in women was related to the lower levels of circulating androgens and the potentiating effect of exogenous female hormone therapy. In an accompanying editorial, Clerico (206) points out that although the effects of androgens (inhibitory) and estrogens (excitatory) clearly influence cardiac endocrine function, we still lack information on how this balance exerts its influence in either sex throughout the human lifespan.

Even though natriuretic peptides are independent predictors of CV events in noncardiac and vascular surgery, Rodseth et al. (207) performed a meta-analysis to examine whether their addition to clinical risk indexes might improve pre-operative risk stratification. Their findings were positive, especially in the intermediate-risk group with a net reclassification improvement of 84%. This adds to the growing data promoting the use of natriuretic peptides on top of clinical criteria for pre-operative evaluation.

ACS. To assess whether very small increases in troponin T measured by high-sensitivity assay could reflect ischemia without necrosis, Turer et al. (208) took serial coronary sinus samples from 19 patients during rapid atrial pacing. Brief periods of ischemia, without frank infarction, caused low-level troponin T increases, even in those with no demonstrable coronary disease. In an editorial, White (209) suggested that there are 5 potential pathobiological mechanisms other than coronary necrosis for troponin release: apoptosis; normal myocyte cell turnover; cellular release of proteolytic troponin degradation products; increased cellular wall permeability; and formation and release of membranous blebs.

Body et al. (210) evaluated chest pain patients with both a standard and a high-sensitivity troponin T assay (see also Maisel [202]) and found that all MI patients had detectable high-sensitivity troponin T measurements on the first blood draw. A 99% negative predictive value was seen in an additional clinical practice cohort. In an accompanying editorial, Peacock (211) points out that a specific test is of great value because it indicates who will need an intervention, and a poorly sensitive test is of little value to an

emergency department doctor because patients cannot really be sent home based on a negative result. He points out that further troponin testing if the first is negative is of little value with the assay in this study. Thus, as we characterize high-sensitivity assays, we may be able to more accurately rule out patients at the time of presentation.

Damman et al. (212) investigated whether multiple biomarkers improved prognostication in 1,034 STEMI patients undergoing primary intervention. In a Cox regression analysis, glucose, glomerular filtration rate, and NT-proBNP best predicted mortality and were the basis of a score that identified a high-risk STEMI group undergoing acute intervention. In an accompanying editorial, Biasucci et al. (213) noted that this study provides important pathophysiological information confirming the common roots of ACS (STEMI vs. non-STEMI vs. unstable angina) and promising clinical improvements in STEMI treatment.

Cardiac troponin has become the biomarker of choice for myocardial injury due to its specificity to myocardium. However, Jaffe et al. (214) detected elevated troponin T but normal troponin I in 16 patients with skeletal myopathies. All antibodies used for troponin T assay were immunoreactive with a protein obtained from 4 skeletal muscle biopsies. Thus, certain skeletal muscle diseases can cause an increase in circulating levels of troponin T and lead to the false-positive diagnosis of cardiac injury.

Arrhythmias. Plasma von Willebrand factor has been related to stroke and vascular events in AF. Roldan et al. (215) demonstrated that von Willebrand factor levels were an independent risk factor for bleeding and stroke in 829 anticoagulated AF patients, who were followed for 2 years. In an accompanying editorial, Serebruany (216) points out that we should measure von Willebrand factor serially in AF patients to better validate this promising biomarker, especially in groups that are using direct thrombin inhibitors.

Renal. Early markers of renal injury are on the front burner of biomarker research. Hasse et al. (217) performed a multicenter-pooled analysis of prospective studies on the role of neutrophil gelatinase-associated lipocalin in subclinical kidney injury. Examining pooled data from 2,322 critically ill patients, they detected likely subclinical kidney injury in the absence of diagnostic increases in serum creatinine. These patients also had increased risk of adverse outcomes. In an accompanying editorial, McCullough et al. (218) suggest that neutrophil gelatinase-associated lipocalin, and perhaps other early injury biomarkers alone or in a multimarker panel, might be valuable in patients in whom creatinine has not yet changed. This could lead to new therapies, allowing us to better prevent further renal damage.

Renal injury is a serious problem in patients admitted with acute HF. Manzano-Fernandez et al. (219) prospectively studied 200 hospitalized patients with acute HF and reported that, whereas neither beta trace protein nor cystatin C was associated with worsening renal function, during hospitalization, both were superior to standard measures of renal function for prediction of death and rehospitalization. Chen (220), in an editorial, recommends further studies to assess the prognostic value of beta trace protein in various CV diseases such as CAD, hypertension, and diabetes.

Treatment. In an effort to demonstrate efficacy of natriuretic peptide infusion, 303 patients with CKD undergoing CABG were randomized to carperitide or placebo (221). In the post-operative acute stage, Carperitide showed cardiorenal protective effects that prevented post-operative cardiac events and initiation of dialysis. In an accompanying editorial, Boerrigter and Burnett (222) pointed out that although many questions remain as to the usefulness of guanylyl cyclase agonists as therapeutic agents, it remains a therapeutic target worthy of further study.

Vigorous physical activity is known to reduce the risk of CV disease. Although it might seem intuitive that being sedentary should increase the risk of CV disease, this question has not been carefully examined. Stamatakis et al. (223) examined whether "screen time"—the number of hours in front of the television or computer—was associated with future CV events in 4,512 individuals. They found a dose-response relationship between screen time and the risk of CV events, even after adjusting for known risk factors and time spent in moderate and vigorous physical activity. Individuals with ≥2 h of screen time a day had a 2.2-fold increase in CV events.

Outcomes

The American Heart Association recently identified 7 characteristics of "ideal" CV health: not smoking; BMI <25 kg/m^2; regular physical activity, either moderate (≥150 min/week) or vigorous (≥75 min/week); a healthy diet (≥4 components); total serum cholesterol <200 without medication; blood pressure <120/80 mm Hg without medication; and fasting blood glucose <100 without medication. Whereas anyone who met all 7 of these criteria would clearly be classified in ideal CV health, can many Americans actually make the grade? The ARIC (Atherosclerosis Risk in Communities) investigators (224) addressed this question in 12,744 individuals free of CV disease, mean age 54 years. The results were disheartening: only 17 participants in the study (0.1%) were in ideal CV health, and only 2.8% met 6 of the 7 criteria. Conversely, 82.5% of the ARIC population were judged to be in "poor" CV health.

Public reporting of the outcomes of CV procedures has been mandated in several states. This well-intentioned practice could, however, have unintended adverse consequences if doctors avoided treating the sickest patients. The Massachusetts Angioplasty Registry addressed this concern by adding data elements to its reporting form that captured objective information on critically ill patients about to undergo PCI: coma on presentation; active hemodynamic support; and ongoing cardiopulmonary resuscitation (225). Patients who met 1 or more of these compassionate use criteria were 27 times as likely to die in the hospital and

including these data in risk adjustment models improved the accuracy of the hospital outcomes reports.

The use of invasive coronary angiography varies considerably across the United States. Douglas et al. (226) used the NCDR to examine the results of elective coronary angiography at the hospital level, omitting patients with known coronary disease (prior ACS, MI, PCI, or CABG). There were 691 hospitals with at least 50 such cases per year, with an average rate of obstructive disease of 45%. There was far more variation in the rate of positive angiograms than expected by random chance: 91 hospitals (13%) had fewer than 35% patients with obstructive CAD, whereas 82 hospitals (12%) had at least 75% with obstructive CAD. Much of this variation was explained by patient characteristics, with the pre-test likelihood of CAD of 0.39 in the lowest quartile of hospitals, compared with 0.55 in the highest. Although it is unclear whether there is an optimal rate of CAD at the time of angiography, the substantial interhospital variation in this rate should be examined further.

A fascinating communication regarding national spending on CV disease was received by the *Journal*. Miller et al. (227) developed time series estimates of the portion of the National Health Expenditure Accounts devoted to CV *ICD* codes in the International Classification of Diseases-Tenth Edition. They found that overall spending on CV disease grew at a compound annual growth rate of 5.7% since 1996, which is somewhat less than the overall rate of growth of all expenditures during the same period. Spending on prevention was higher for CV disease than for other categories and grew to more than 20% of total CV expenditures. Conversely, spending on CV research amounted to roughly 1% of CV expenditures in recent years. Obviously, these data cannot indicate whether the money has been well spent. However, the data do indicate that expenditures for CV disease have not increased inordinately over this 12-year span, have increasingly been devoted to prevention, and have supported research to only a small extent.

A study by Kim et al. (228) reported the degree of international participation in CV randomized control trials sponsored by the National Heart, Lung, and Blood Institute. Of 24 studies examined, 19 included international participation with a median of 9.5% of patients contributed from outside the United States. CAD trials had nearly 50% international enrollment. Many of the trials that had greatest influence on clinical practice had a majority enrollment from outside the United States. Given the many genetic, environmental, and cultural differences between populations, these findings raise questions regarding the applicability of trial data to patients in the United States, and the ability of institutions within the country to enter patients into trials. In an accompanying editorial, Califf and Harrington (229) discuss the "offshoring" of clinical research from the United States and question whether the American clinical research enterprise can be competitive. While recognizing that globalization of clinical research is a powerful social good, they recognize that the results obtained may not reflect those that will be achieved in a different population. They provide 5 recommendations to transform the clinical research system in the United States.

With the increasing emphasis on quality of clinical care, Yang et al. (230) examined the correlation of hospital performance for acute MI with that of HF from the GWTG program. They compared core measures for these 2 disorders in 283 hospitals. Only a modest correlation between hospital performance for these 2 entities was observed ($r = 0.50$). However, hospitals that had consistently superior performance for both infarction and HF care had significantly lower risk-adjusted mortality than those with superior performance for either alone. Thus, excellent hospital quality for 1 cardiac disorder does not necessarily apply to others; however, high-quality performance for multiple disorders translates into superior outcomes.

A challenge for clinicians is to prescribe an effective warfarin dose that avoids both hemorrhage and thrombosis (231). Does genetic testing improve dosing? The 2 genes shown to have the greatest impact on predicting warfarin dose are *CYP2C9* and *VKORC1*. The study from Finkelman et al. (232) from 1,378 patients at 3 anticoagulation centers showed that clinical data and genetic information combined in an algorithm provided the best predictor for warfarin dose. These findings combined with the MM-WSE (Medco-Mayo Warfarin Effectiveness Study), comparing 6-month incidence of hospitalization of patients receiving warfarin genotyping versus an historical control group, would argue in favor of clinical effectiveness of genetic screening for individuals on warfarin (231).

Genetics/Genomics

Our textbook understanding of atrial natriuretic peptide as a neurohormone is rapidly evolving. Cannone et al. (233) provide new data showing an association between individuals harboring the minor allele of single nucleotide polymorphism (SNP) rs5068 in atrial natriuretic peptide and a favorable cardiometabolic profile. Approximately 10% of the population harbored 1 copy of the minor allele, which was associated with lower blood pressure and BMI and higher levels of pro-atrial natriuretic peptide. The genotype frequencies for this SNP were similar to those reported in previous studies (Framingham Heart Study, Malmo Diet, and Finrisk97) (234).

The hunt is still on for SNPs in the chromosomal region 9p21.3 that increase risk of CAD. Ardissino et al. (235) showed that individuals harboring the SNP rs1333040 in the gene desert on chromosome 9p21.3 have an increased likelihood of undergoing a subsequent revascularization procedure following MI. An association was also found between this SNP and the progression of atherosclerosis as measured by the Duke Coronary Artery Disease Index. No association was found between this SNP and death or recurrence of MI (235). An editorial from Muhlestein and

Anderson (236) provided a framework highlighting the strengths of this study in better understanding the phenotype. Harismendy et al. (237) identified 33 enhancers in the 9p21 gene desert, demonstrating that this interval is the second densest rich region with enhancers in the entire genome and providing a potential mechanism for how the SNPs may be associated with progression of atherosclerosis and risk of revascularization.

The controversy over whether individuals with the *KIF6* Trp719Arg genotype showed greater response to statin therapy may have ended. A study by Hopewell et al. (238) in 18,348 individuals showed that the effect of simvastatin therapy was similar (i.e., reduced the incidence of coronary and other major vascular events) irrespective of the *KIF6* Trp719Arg genotype. Thus, this large study supports an effective role for statins in decreasing CV events regardless of one's *KIF6* genotype. Similarly, Kapplinger et al. (239) showed the background noise in genetic testing results focusing on mutations in the genes associated with ARVC. These investigators screened 93 probands with ARVC/dysplasia and 427 presumably healthy control subjects for deoxyribonucleic acid variants in the coding exons/splice junctions of *PKP2, DSP, DSG2, DSC2,* and *TMEM43*. Compared with 58% of individuals with ARVC, the background noise, or percent of "healthy" control subjects that manifested mutations in these genes was 16%, a high value compared to the percentage of "healthy" control subjects with mutations in long-QT genes (240). These findings stress the importance of genetic counseling and careful interpretation of the genetic tests. Kapplinger et al. (239) did provide the pathogenic likelihood of different deoxyribonucleic acid variants from a positive ARVC genetic test result, grouping mutations that included insertions/deletions, splice junctions, and nonsense mutations as "radical mutations" and the most likely pathogenic. Missense mutations were binned as variants of undetermined significance and then subdivided into more or less likely to influence pathogenicity. When split into these subgroups, radical mutations were only found in 0.5% of control individuals versus 43% of ARVC cases, whereas missense mutations were found in 16% of control subjects and 21% of ARVC cases. This study was accompanied by an editorial from Mestroni and Taylor (241) that focuses on the importance of expertise to help separate pathogenic mutations from background noise, as well as family history to aid in the interpretation.

Mounting evidence suggests that disruptions/mutations in ion channels lead to dilated cardiomyopathy (DCM) and arrhythmias. McNair et al. (242) showed that both previously established and novel mutations in the ion channel gene, *SCN5A,* are associated with DCM. How mutations in sodium channels are associated with DCM is not entirely clear. Towbin and Lorts (243) speculate that mutations in *SCN5A* leading to DCM may be caused by disruption of cytoskeletal binding partners to *SCN5A,* electrical dysfunction caused by the channel leading to mechanical instability, myocardial dysfunction and ventricular dilation, or primary disruption of a channel leads to DCM. Two-thirds of the mutations were localized in the highly conserved S3 and S4 transmembrane segments, which has previously been shown to regulate voltage-sensing of the channel (242). This current study from McNair et al. is important in that it raises new questions including: Do variants in *SCN5A* lead to DCM in the absence of arrhythmias?

Barc et al. (244) provided the first evidence of copy number variants (deletions) in the genes *KCNQ1* and *KCNH2* in 3 unrelated families segregating with the LQTS phenotype. Over 90% of the genotyped cases of LQTS are due to mutations in *KCNQ1, KCNH2,* and *SCN5A.* However, these mutations are base change mutations, not copy number variants in which stretches of deoxyribonucleic acid are either inserted or deleted. Barc et al. (244) identified deletions in *KCNQ1* and *KCNH2*. The deletion in *KCNH2* included the entire gene, likely leading to haploinsufficiency. This deletion in *KCNH2* perfectly cosegregated between the phenotype and the copy number variant inheritance in the family, strongly suggesting this deletion was responsible for the effect. The other 2 deletions in *KCNQ1* were not fully penetrant, leaving unanswered questions. This study opens up new directions for the field of LQTS (245).

The mechanisms explaining why diabetic patients present with high platelet PR are not clear. A study by Angiolillo et al. (246) provides evidence that diabetic patients that carry the C allele of the rs956115 marker of the *IRS-1* gene (approximately 20% of patients) have a hyper-reactive platelet phenotype and increased risk of major adverse CV events. This association did not hold true for patients without diabetes and the mechanism is unknown. The clinical implications of this study are that diabetic patients may benefit from antithrombotic treatments that are personalized to their disease status and genotype. The rs956115C allele was also an independent predictor of major adverse CV events—independent of the hyper-reactive platelet phenotype— suggesting that mutations in the *IRS-1* gene may be important predictors for diabetic patients of CV disease.

The *Journal* published a state-of-the-art paper from O'Sullivan et al. (247) that reviews and explores the potential role of microribonucleic acid–guided therapy for the prevention of plaque rupture and in-stent restenosis. The paper focuses mainly on miR-143 and -145. In addition to an elegant review of clinically relevant biology, these investigators address delivery of microribonucleic acid–based therapeutics with an eye on the past and the future.

The quest continues for optimizing stem cell repair of the heart after a myocardial infarction. A pre-clinical study with a combined gene therapy approach (sonic hedgehog gene transfer to improve angiogenesis) and AMD3100 administration (to induce mobilization of progenitor cells) improved cardiac functional recovery (248). Combination therapy significantly increased (nearly doubled) the number of bone marrow–derived progenitor cells in the myocardial endo-

thelium 28 days following surgically induced myocardial MI. Whether this is the reason why LVEF improved significantly in the group of mice receiving the combination therapy is not clear. Combination therapy also resulted in a significant reduction in fibrosis. Identification of efficacious combination therapies for a class of patients that promotes the mobilization of endogenous progenitor cells to the heart to improve the coronary circulation and improve myocardial function will continue to be an area of growing research.

The Best in *JACC* also provides an Update for 2011 on the clinical and genetic issues in familial DCM by Hershberger and Siegfried (249). A section in this state-of-the-art paper that is particularly helpful for clinical care is the flow diagram in Figure 1 providing guidance in straightforward steps for determining new idiopathic or familial DCM diagnoses. Information is provided on genetic counseling, as well as what has changed and what has not changed in the past 5 years.

Pediatric Cardiology

A study from the Boston Children's Hospital describes a large experience with primary cardiac tumors in children and characterizes associated rhythm disorders. A single-center review studied 173 patients from 1968 to 2010 (250): 106 had rhabdomyoma; 25 fibroma; 14 myxoma; 6 other vascular; 4 teratoma; 3 lipoma; and 15 other tumors. The age of diagnosis was pre-natal to 21 years with a mean age of 7 months. Ventricular tachycardia was the single most common type of arrhythmia that announced a cardiac tumor. Surgical excision for rhabdomyomas and fibromas was an effective management in eliminating ventricular arrhythmias.

Another study from Toronto used MRI to characterize cardiac tumors from a multicenter experience (251). They collected 78 cases from 15 centers in 4 countries: 30 fibromas; 14 rhabdomyomas; 12 malignant tumors; 9 hemangiomas; 4 myxomas; 3 teratomas; 2 other tumors. Reviewers blinded to histologic diagnosis identified the correct type of tumor in 97 cases, but also included a differential diagnosis in 42% of the cases. The conclusion was that MRI could predict the tumor type in the majority of children, especially with a comprehensive imaging protocol that included steady-state free precession, T_1- and T_2-weighted contrast imaging, and myocardial gadolinium contrast imaging as well. An editorial comment by Bardo (252) points out that, to some extent, there was a selection bias against rhabdomyomas, which, though the most common form, might not be referred. She points out that MRI potentially joins molecular imaging, to include PET and/or some hybrid MR/PET combination and/or specific molecularly targeted agents that might be attached to gadolinium or iron oxide.

Another study examined the issue of recurrent obstruction and the need for reintervention in patients who have already undergone balloon aortic dilation for arch obstruction after the Norwood procedure for hypoplastic left heart (253). The investigators studied 116 patients who underwent balloon dilation from 1983 to 2009. A significant proportion of these patients required a reintervention for residual arch obstruction, especially those who had obstruction proximal to the left subclavian artery. The investigators emphasized that there really are diffuse aortic abnormalities in the reconstructed aortic arch after Norwood procedure, and that this represents ongoing risk. A helpful editorial by, Lamberti (254) contrasts this information with a smaller series that did not come to the same conclusion. The Bautista-Hernandez group suggested that coarctectomy at the time of Norwood was protective of late coarctation. The publication in the *Journal* concludes that coarctation at the time of Norwood procedure is not persistent and the problem of late coarctation after the Norwood procedure has not been solved.

In a paper addressing the optimal antithrombotic regimen after the Fontan procedure from Australia and Toronto, Canada, 111 patients were randomized: 57 to aspirin and 54 to heparin/warfarin (255). Transthoracic and transesophageal echoes were performed for surveillance, and major bleeding and death were the primary adverse outcomes. In the heparin/warfarin group, there were 13 thromboses with 3 determined clinically and 10 by routine echo. Similarly, 12 thromboses occurred in the aspirin group, 4 were found clinically and 8 by routine echo. Overall freedom from thrombosis 2 years after Fontan surgery was only 19%. Thus, alternative antithrombotic approaches will need to be considered. In an editorial comment, Canter (256) acknowledges the results of the study and points out that it confirmed another study by Jacobs and Geary in 2002 (257) and then states that it is likely that newer anticoagulants undergoing evaluation in adults with AF will need to be tested in Fontan patients. Canter (256) then references a paper by Schirmer et al. (258), enabling the beginning of phase 2 and 3 clinical trials on factor Xa and inhibitors rivaroxaban, apixaban, betrixaban, and edoxaban.

A multicenter study from Australia, Europe, and the United States described the first percutaneous tricuspid valve replacement using the Melody pulmonary valve (Medtronic) in patients with congenital or acquired tricuspid disease in 15 patients (259). The indications for tricuspid intervention included severe hemodynamic compromise and high perceived surgical risk. All had had previous tricuspid surgery and had significant stenosis and/or regurgitation of the bioprosthetic valve for right atrial to right ventricular conduit. Technical success was achieved in 12 patients; the only procedural complication was third-degree heart block. One patient developed tricuspid valve endocarditis 2 months after implant and 1 had multiorgan failure and did not improve. The majority of valves were placed via femoral or internal-jugular approach. The advent of a newer Melody valve beyond 22 mm, or other suitable bioprosthetic implantable valves, will open a new window for therapy. As Moore (260) points out in his editorial comment, reporting

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procedural success does not give any data about long-term outcomes. It does open the door for use of larger-diameter valves, such as the Sapien valve, to extend the range of applicable valve annuli or patients who may be eligible for percutaneous valve therapy.

A large study from Germany, China, and the United States reviews 92 patients (mean age: 7 years 12 days to 18 years) who received single- or biventricular assist device support (261). The devices included the Berlin Heart EXCOR ventricular assist device (VAD), the Berlin Heart Incor VAD, the World Heart Novacor VAD (Salt Lake City, Utah), and the HeartWare VAD. Thirty-day and 6-month survival was 82.9 ± 5.3% and 67.8 ± 7.5% for LV assist devices and 63.5 ± 8.9% and 37.9 ± 10.5% for biventricular support. The report provides a comprehensive overview of implantation of VADs in younger patients. VAD mortality was increased in children who had congenital heart disease and those who had a pre-operative requirement for norepinephrine.

A paper from the Mayo Clinic (262) reviews the outcomes of 46 patients with congenitally corrected transposition of the great arteries undergoing systemic atrioventricular (AV) valve replacement, 27 of whom had pre-operative systemic ventricular ejection fraction (SVEF) of ≥ 40% and 19 with <40%. All had good-sized ventricles. Pre-operative SVEF was the only independent predictor of 1-year survival. SVEF >40 was preserved in 63% of the patients who underwent surgery with >40%, whereas only in 10% of patients who underwent surgery with SVEF <40%. Other variables for late mortality included subpulmonary ventricular systolic pressure, a concomitant of increased pulmonary vascular resistance, and atrial flutter at functional class III to IV. This paper points out the special expertise necessary not only to manage these patients but also to perform adequate surgical valve replacement as well. An accompanying editorial by Bacha (263), a surgeon, points out that this is the largest modern surgical series published to date in these patients and emphasizes the demonstrated mandate for an early move to surgery at a time when SVEF is preserved.

In a related issue, Goossens et al. (264) report on the issue of transfer of adolescents with congenital heart disease (CHD) from pediatric cardiology to adult health care. They describe 794 patients, 58 of which were lost to follow-up. The investigators' SWITCH (Self-Management and Well-Being Improvements by Transitioning Adolescents with Chronic Disorders in Hospital and at Home) research program in Belgium studied patients at a tertiary care center that cares for 27% of Belgian patients with CHD. Of the 794 patients studied, 79% with significant CHD received follow-up at a tertiary care center and 97.8% of those patients were successfully transferred to adult CHD programs. The likelihood of no cardiac follow-up after leaving pediatric cardiology were male sex and no prior heart surgery—probably defining the milder spectrum of disease. Only 2 of 74 patients with complex heart disease (2.7%) and 31 of 448 with moderate heart disease (6.9%) were not in the follow-up group. This record is far better than most regions and represents the results of an organized transitioning policy–not without its problems.

A paper from a Pediatric Heart Network investigation group follows 536 Fontan patients post-operatively (mean age: 11.9 years), 361 of whom had a fenestration performed (265). At the time of cross-sectional testing (8 ± 3 years after Fontan), fenestration remained open in 19%; had been closed by catheter intervention in 59% and by surgical intervention in 1%; and 40% closed spontaneously. Patients with Fontan were taking more medication and had lower resting saturation. Early post-operative benefits occurred in the fenestrated group: length of stay was 2.5 days shorter than without fenestration. The percentage of procedures including fenestration increased rapidly over the period of the study. Performance of fenestration, however, was not associated with changes in exercise performance, functional health status, or echocardiographic function, although the patients with persisting Fontan conditions continued to receive more medications after hospital discharge. The strategy of leaving the fenestration open has been more widely adopted.

A population study from the Netherlands analyzed out-of-hospital cardiac arrest in victims younger than 21 years (266). With a total of 923 pediatric deaths, there were 233 out-of-hospital cardiac arrest cases, 221 of whom died and 12 of whom survived. The out-of-hospital cardiac deaths totaled 24% of pediatric mortality. Natural causes (49% of cases) were the most prevalent, with cardiac causes accounting for 39%. Of the 51 victims resuscitated, 12 (24%) survived; 10 of them had a neurologically intact outcome. A helpful editorial comment by Chugh (267), a sudden death specialist, emphasized the overall rate of hospital discharge being 24% and neurological recovery occurring in 83% of those cases. He states that renewed emphasis needs to be placed on community healthcare providers to obtain detailed family histories with appropriate referrals for genetic screening and counseling. For unexplained sudden death, a molecular autopsy should become part of the community forensic investigation to establish familial incidence of diseases.

A large Canadian population-based study, with 23 years of follow-up from 1983 to 2005, examines the impact of pulmonary hypertension combined with CHD on outcomes and healthcare utilization (268). Of 38,430 adult CHD patients in the database, 2,212 have pulmonary hypertension. The greatest impact was in those patients <39 years compared with those older than 40 years. Morbidity risk was increased 3-fold, as were hospitalizations or intensive care rates. There was a doubling of all-cause mortality and a tripling of morbid complications. As in previous studies, women had a higher risk of pulmonary hypertension, but the same risk for death. This study calls for more investigation of pulmonary hypertension-targeted therapy in CHD.

A study from Toronto examined 165 fetuses of 142 anti-Ro/LA antibody positive women referred for serial echocardiographic evaluation of fetal AV conduction (269). They found that 150 fetuses had persistently normal AV conduction; 15 had AV prolongation, but none developed progressive heart block. Two of the 15 had neonatal first-degree block that spontaneously resolved, and 1 has not progressed on follow-up. In this study, fetal AV prolongation was not predictive of complete AV block. Close monitoring of these fetuses can be suggested without treatment.

A multicenter study (270) reports a 1,648-patient LQTS registry. The patients included had a QTc of >250 ms, and the endpoints were a first syncope and subsequent second- through fourth-syncope episodes between birth and 20 years. Patients with a QT interval >500 ms had a significantly higher cumulative probability of experiencing their first syncope (75% vs. 48%). The rate of subsequent events also was increased both in those who had QTc <500 ms and >500 ms (74% and 76%). In childhood, male patients who had LQT_1 had the highest cumulative probability of a fourth cardiac event (36%), though after the first event, the probability of a subsequent event in the next 2 years was increased in all sex and genotype groups (35% to 46%). After the onset of adolescence, there was an age–sex risk reversal in female patients, with female patients having LQT_2 manifesting the highest rate of a first cardiac event (38% over 5 years of follow-up) and subsequent events (58% during 2 years of follow-up). The risk of a first nonfatal syncope episode was clearly defined in both groups, but other than the female patients with LQT_2, the risk associated with this electrocardiographic marker was attenuated after the first event.

An international multicenter coarctation of the aorta registry reported comparison of surgical approaches to stenting and balloon angioplasty in children >10 kg (271). They enrolled 350 patients: 217 underwent stent implantation; 61 had balloon angioplasty; and 72 underwent surgery. All showed significant reduction in systolic blood pressure and upper to lower extremity systolic blood pressure gradients. Stenting was superior to balloon angioplasty in lowering gradient; surgery was also superior to balloon angioplasty in reducing gradient. Surgery was, for the most part, anastomotic (63%); 17% of patients underwent tube graft interposition, 14% patch angioplasty, and 6% subclavian flap repair. Stent procedures (271) were performed in 217 patients, and 19 required a second stent, either to cover the entire coarctation segment or because of stent migration. Patients undergoing stent implantation were significantly older and weighed more than balloon angioplasty or surgical patients, and stent patients had significantly smaller coarctation measurements as a function of body surface area than balloon angioplasty patients did. In the surgery group, there was 1 spinal injury; in the stent group, 1 patient developed large femoral hematomas, and in 3 patients, stent migration occurred during the procedure. Fifty-four patients had reinterventions; some anticipated as a function of staged approach and some for somatic growth. Among the unanticipated reinterventions, all except for 1 stent aneurysm were because of reobstruction. Wall injury was more often encountered in the balloon angioplasty group than in the surgery or stent groups. Stent patients had lower acute complications than surgery patients did, and stent patients achieved superior short-term hemodynamics. Stent patients were also likely to have a planned reintervention for further dilation or additional stent placement. Stents appear to be gaining in popularity as a primary approach method, especially because they can be redilated and can avoid some of the complications that occur with surgery.

A report described a less invasive approach to relieve severe hypertrophic obstructive cardiomyopathy in children (272). Thirty-two children with a mean age of 11 years and mean weight of 31 kg had ablation of the septum performed using a cool-tip catheter via a femoral artery approach. The procedure was guided by transesophageal echo and temporary pacing electrodes were placed in the right atrium and the right ventricle to later check whether dual-chamber pacing also decreased gradient. There was 1 procedure-related death. Two patients had complete AV block and required dual-chamber pacemakers; in 1 of them, the block resolved within a month. The median pre-procedure pull-back gradient of 80 mm Hg decreased to 34 mm Hg. Also, during the post-procedure period, there was a reduction in MR in 12 patients, who had varying degrees of systolic anterior motion. The investigators view the method as promising and potentially more controlled for tissue destruction than alcohol septal ablation is.

Obesity and Adipose Tissue: Cardiotoxic Effects

Obesity and cardiac aging. Neimann et al. (273) examined if obesity causes premature aging of the heart. Right atrial tissue samples were taken from 60 patients undergoing cardiac surgery, who were subdivided into 4 groups based on age (young: <55 years vs. old: >70 years) and BMI (nonobese: 18.5 to 25 kg/m^2 vs. obese: 30 to 35 kg/m^2). Young obese patients had phenotypes similar to old obese and nonobese patients, with higher fasting plasma glucose, insulin, and leptin levels and increased NT-proBNP, compared with young nonobese patients. Right atrial cardiomyocytes from young obese patients also had impaired mitochondrial function with increased oxidative stress, decreased complex I, and increased markers of apoptosis. These results suggest that obesity may induce premature aging of the heart. In an editorial comment, Abel (274) discussed potential mechanisms for these intriguing results. Although patients with diabetes had been excluded, obese patients may be at increased risk for developing diabetes so that mild impairments in glucose tolerance and insulin resistance may be sufficient to impair mitochondrial function and increase oxidative stress. Although LV function was preserved, elevated NT-proBNP with obesity may suggest subtle

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degrees of LV dysfunction. Finally, decreased adiponectin and insulin resistance may impair mitochondrial function.

Adipose tissue: location and phenotype. The CV effects of obesity may vary with inflammatory changes in adipose tissue, which may have local effects on vascular function and the atherosclerosis. Local changes in adipose tissue were directly examined in a series of 3 studies.

Farb et al. (275) obtained abdominal subcutaneous adipose tissue from 109 overweight (BMI >25 kg/m^2) and 17 lean subjects. The adipose tissue showed inflammatory changes with macrophage crownlike structures in 78% of overweight subjects, whereas 22% had noninflamed fat. Overweight subjects with inflamed subcutaneous adipose fat had higher insulin levels, homeostasis model assessment, impaired brachial artery flow-mediated dilation, and elevated expression of inflammatory markers in adipose tissue (clusters of differentiation CD68, leptin, and MMP9) compared with overweight subjects without inflammation or lean control subjects. Overweight subjects without inflamed fat had intermediate risk factor profiles, indicating that subjects of similar weight have additional risks with inflammation in their adipose tissue. Reducing inflammation in adipose tissue may be a potential therapeutic target.

Virdis et al. (276) compared arteriole function in visceral fat biopsies (obtained during laparoscopic surgery) from 14 severely obese (BMI 48 kg/m^2) with 14 nonobese control subjects. Obese subjects had higher plasma and vascular tumor necrosis factor-alpha levels with impaired endothelial-dependent relaxation in arterioles that was associated with increased superoxide production and reduced nitric oxide availability. This is a mechanism for visceral fat to impair endothelial function in small resistance vessels, which may contribute to impaired endothelial function in obesity.

Hirata (277) compared epicardial adipose tissue and subcutaneous adipose tissue from the same individual in 38 patients with CAD undergoing coronary artery bypass, and 40 patients without CAD undergoing cardiac valve surgery. In patients with CAD, epicardial adipose tissue showed evidence of infiltration by inflammatory macrophages with an increased ratio of inflammatory to noninflammatory macrophages and increased expression of pro-inflammatory cytokines; both correlated with the severity of CAD. These changes were not observed in subcutaneous adipose tissue. Patients without CAD did not have evidence of inflammation in either epicardial or subcutaneous adipose tissue. Thus, local inflammatory changes in adipose tissue are associated with coronary atherosclerosis.

In an editorial comment, Dandona et al. (278) place these 3 studies in context. Adipose tissue produces inflammatory cytokines including tumor necrosis factor alpha that contribute to insulin resistance and vascular abnormalities. These 3 studies support the concept that adipose tissue has proinflammatory effects in obesity, with regional effects that may contribute to hepatic insulin resistance, systemic inflammation, and arterial atherosclerotic inflammation.

Chemokines in Myocardial Injury and Repair: Pre-Clinical Studies

Chemokines are chemotactic cytokines that regulate a complex series of events after MI from acute inflammatory changes to reparative processes. Liehn et al. (279) examined the role of the CXCL12/CxCr4 signaling pathway in MI in mice. The CxCr4 receptor and its ligand CXCL12 play a beneficial role in MI by recruiting progenitor cells, inducing angiogenesis, and activating cardioprotective pathways. CxCr4-heterozygous (CxCr4$^{+/-}$) and bone marrow chimeric mice had decreased infarct sizes compared with wild-type mice. This was associated with decreased inflammatory cell recruitment, delayed monocyte infiltration, as well as decreased angiogenesis. In an editorial comment, Frangogiannis (280) discusses the challenges in studying the role of the stromal cell-derived factor 1/CXCR4 axis, and sorting out the complex roles that may be cell type– and context-dependent. There is interest in this field because agents such as AMD3100 that target this axis are clinically approved for use in other fields, such as for the mobilization of stem cells.

A state-of-the-art paper reviews major advances over the past decade in understanding the role of chemokines in MI and identifying potential therapeutic targets (281). Chemokines play an important role in the first few days after MI, where the inflammatory phase is characterized by neutrophil infiltration and the removal of debris. This is followed by a proliferative phase over the ensuing 3 to 4 weeks, where chemokines attract reparative monocytes, induce angiogenesis, and recruit stem cells. Finally, during the healing phase, chemokines regulate factors to improve scar formation and remodeling. An increased understanding of the time-, cell-, and context-dependent role of chemokines will provide the potential to identify novel targets to improve outcomes.

Targeting the Mitochondria in Cardiomyopathy: Pre-Clinical Studies

The abnormal generation of reactive oxygen species (ROS) causes cardiac damage in cardiomyopathies. However, clinical trials with antioxidant therapies have produced variable or disappointing results. Mitochondria are the major source of ROS in the heart. Novel mitochondrial targets and therapies have been identified that may be more effective in improving outcomes.

Dai et al. (282) used the Szeto-Schiller (SS)-31 peptide, which selectively targets the inner mitochondrial membrane to scavenge superoxide, hydrogen peroxide, peroxynitrite, and hydroxyl radicals. Mice infused with angiotensin II for 4 weeks developed a cardiomyopathy with increased LV mass and preserved systolic function, but with abnormal diastolic function and fibrosis. Mitochondrial protein oxidative damage occurs with increased expression of reduced nicotinamide adenine dinucleotide phosphate oxidase-4, a

major source of mitochondrial ROS. All of these abnormalities were attenuated by SS-21, but not by the nontargeted antioxidant N-acetyl cysteine. In a second cardiomyopathy model induced by overexpression of Gαq, SS-31 attenuated cardiac enlargement, preserved systolic function, and reduced mitochondrial protein oxidation. These results suggest that mitochondrial-targeted antioxidants may be a useful approach to treat cardiomyopathies.

Maack and Böhm (283) place these results in the broader context of mitochondrial impairments that increase mitochondrial ROS in HF, including increased formation of superoxide by impairments in electron transport chain complexes, and decreased removal of superoxide and peroxide in the mitochondrial matrix (e.g., by decreased manganese-superoxide dismutase). Generation of ROS may have maladaptive effects on remodeling, or protective effects such as enhancing angiogenesis. This duality may underlie variable or modest results with nontargeted therapy, whereas antioxidants that target mitochondrial microdomains may be more effective. It is intriguing to speculate that this approach may be useful for treating HF with preserved ejection fraction, such as is produced in the angiotensin II infusion model.

Zhu et al. (284) used the novel approach of dietary nitrate supplementation to attenuate mitochondrial impairments in doxorubicin-induced cardiomyopathy. Mice injected with doxorubicin developed cardiomyopathy after 5 days with decreased LV contractility and increased cell death and tissue lipid peroxidation. These abnormalities were attenuated in mice fed dietary nitrate supplementation in their drinking water (started 7 days before doxorubicin). However, subcutaneous delivery of nitrate was not effective. Dietary nitrate may be bioconverted and reduced by bacteria in the gut to increase nitric oxide availability with protective effects. Daiber et al. (285), in an editorial comment, note that doxorubicin-induced cardiomyopathy is characterized by mitochondrial impairments that produce oxidative stress. Bioconversion of the inert nitrate to nitrite by bacteria in the gut may facilitate conversion to bioactive nitric oxide. The effectiveness of oral, but not subcutaneous, nitrate supports this concept. The use of dietary inorganic nitrate to prevent mitochondrial dysfunction and reduce oxidative stress may be a promising area for future clinical investigations.

Identifying a Novel Mechanism for Aspirin Resistance

Resistance to aspirin may mitigate the cardioprotective effects of this mainstay therapy. Aspirin reduces platelet activity by inhibiting the cyclooxygenase-1 enzyme in platelets. Mattiello et al. (286) examined aspirin resistance that occurs after CABG and identified a new mechanism that involves multidrug resistance protein (MRP)-4. MRP-4 belongs to a family of transporters that remove organic anions from cells. MRP-4 is localized in dense granules, which are released after platelet activation. Mattiello et al. (286) identified aspirin as a substrate for MRP-4, which extrudes aspirin from platelets. Platelets from patients 5 and/or 10 days after CABG, compared with healthy control subjects, had up-regulation of MRP-4 with reduced effects of aspirin. Inhibiting MRP-4 pharmacologically (dipyridamole or MK-571) or with simian ribonucleic acid led to aspirin accumulation in platelets with greater cyclooxygenase-1 inhibition. Eikelboom and Hankey (287) indicate that it is a novel observation that aspirin is a substrate for MRP-4, which can remove aspirin from platelets to decrease its effectiveness. The mechanism by which CABG up-regulates MRP-4 is unknown, but this may be a mechanism for increased aspirin resistance.

Chronotherapy—Optimizing the Timing of Angiotensin-Converting Enzyme Inhibition to Improve Cardiac Remodeling: Pre-Clinical Study

Molecular clocks exist in nearly all cells and produce circadian variations in biological functions. Martino et al. (288) investigated how the timing of therapy with captopril influences its effect on ventricular remodeling in mice with pressure overload hypertrophy (transthoracic aortic banding). Captopril given before sleep was more effective than giving treatment during awake hours, in terms of decreasing LV dilation and myocyte hypertrophy and increasing angiotensin-converting enzyme messenger ribonucleic acid expression. These benefits were unrelated to diurnal changes in blood pressure or alterations in circadian genes. In an editorial comment, Jugdutt (289) reviews the concepts in chronobiological therapy that have emerged over the past decades. Circadian rhythms have been identified for several variables relevant for cardiac remodeling, including increases in atrial natriuretic peptide, growth hormone, and cortisol, renin, angiotensin, aldosterone, and catecholamines. Prior studies have shown the benefits of chronotherapy in managing essential hypertension. The current study adds that the peak effectiveness of a short-acting angiotensin-converting enzyme inhibitor to benefit remodeling occurs when given during sleep.

Although leukocytes appear to play an important role in the genesis of atherosclerosis, immunosuppression has generally not shown clear benefits in retarding lesion formation in animal models of atherosclerosis. Von Vietinghoff et al. (290) studied a novel strategy, using mycophenolate mofetil to inhibit T-lymphocyte–mediated immunity, resulting in a decrease in aortic lesion size in an atherosclerosis-prone genetic model in mice. These findings suggest the potential for novel strategies to prevent of treat atherosclerosis targeting interleukin-17.

Genetic causes of dilated cardiomyopathy have received considerable attention in recent years. Diegoli et al. (291) describe the prevalence and natural history of X-linked DCM associated with dystrophin defects. The paper alerts the HF community to the importance of this disorder and suggests that

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there may be a distinct pattern of disease dominated by end-stage HF, but not life-threatening arrhythmias.

Elevated levels of apolipoprotein A represent a vexing problem in CV medicine with no truly effective treatments. Merki et al. (292) developed and tested in mice a novel approach for reducing lipoprotein A levels using an antisense oligonucleotide. Although the effect size was modest, this approach offers the opportunity to develop a new pharmacological strategy for treatment of a previously untreatable disorder.

Reprint requests and correspondence: Dr. Anthony N. DeMaria, Cardiology Division, University of California, San Diego Medical Center, 3655 Nobel Drive, Suite 630, San Diego, California 92122. E-mail: ademaria@ucsd.edu.

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