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J. Am. Coll. Cardiol. 2009;53;373-398
doi:10.1016/j.jacc.2008.12.005

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 53, No. 4, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2008.12.005

HIGHLIGHTS FROM *JACC*

Highlights of the Year in *JACC* 2008

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

Nuclear Cardiology

Because a high cardiac death rate is observed in hemodialysis patients, Nishimura et al. (1) evaluated 375 asymptomatic hemodialysis patients with single-photon emission computed tomography (SPECT) imaging and beta-methyl-p-[123I]-iodophenyl-pentadecanoic acid (BMIPP), reflecting myocardial fatty acid metabolism. Severely reduced BMIPP uptake might be related to repetitive ischemia and thus be predictive for cardiac death. Patients with severely abnormal BMIPP SPECT images had a significantly higher mortality rate at 3 years than those without (39% vs. 2%).

The volume of diagnostic imaging has increased exponentially over the recent years, and the appropriateness of these tests has been questioned (2). As a first step in evaluating the appropriateness, Gibbons et al. (3) applied recommended criteria to 284 patients who underwent SPECT myocardial perfusion imaging and found 64% of studies were classified appropriate, 11% were uncertain, 14% were inappropriate, and 11% were unclassifiable; similar numbers were reported for stress echocardiography. Application of these criteria will require refinement.

It remains uncertain whether cardiac medications need to be withdrawn before SPECT myocardial perfusion imaging. In a dedicated review, Zoghbi et al. (4) addressed this topic. They emphasized that, when detection of coronary artery disease (CAD) is the question, withdrawal of cardiac medication (e.g., beta-blockers) is appropriate to increase sensitivity of the technique. If the question is whether ischemia remains despite medical therapy, then medication should be continued.

The use of nuclear techniques in the field of molecular imaging is increasing. Terrovitis et al. (5) demonstrated in an elegant animal model that ectopic expression of the sodium-iodide symporter enables imaging of transplanted cardiac stem cells with either positron emission tomography or SPECT imaging. Thus far, these techniques are used in animal models but should eventually be suitable for patients (6).

Cardiac Computed Tomography (CT)

CT calcium scoring and angiography is being increasingly used. In 2008, the feasibility and excellent accuracy for detection of CAD of 256-row detector CT was first reported (7). However, Meijboom et al. (8) have demonstrated that 50% of the atherosclerotic lesions detected on CT angiography do not result in ischemia as demonstrated by normal intracoronary fractional flow reserve. More recently, the focus of CT angiography is shifting toward prognosis (9). Raggi et al. (10) assessed all-cause mortality in 35,388 patients after a mean follow-up of 5.8 ± 3 years. Increasing calcium scores were related to decreasing survival. Importantly, even in patients ≥70 years of age, calcium scoring contributed significantly to risk stratification. Ostrom et al. (11) evaluated 2,538 patients (suspected for CAD) with electron beam CT and demonstrated that CT angiography was an independent predictor of mortality.

Choi et al. (12) reported on the potential use of multislice CT for screening asymptomatic individuals for CAD. A total of 1,000 subjects underwent 64-slice CT angiography. Atherosclerotic plaques were identified in 215 patients (22%), whereas 40 individuals (4%) had only noncalcified plaques. Only 15 subjects had cardiac events, including 1 patient with unstable angina and 14 revascularizations; many of these procedures were driven by the CT results. The authors concluded that at present CT angiography should not be used to screen for CAD, particularly in view of the radiation burden. In this regard, a recent study showed that prospective electrocardiography (ECG) gating can reduce radiation by as much as 79% as compared with a helical scan (13).

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January 27, 2009:373–98

Echocardiography

The use of strain imaging by echocardiography was explored in several experimental studies. In 10 open-chest pigs with flow-limiting stenoses, myocardial deformation was evaluated at rest and during dobutamine infusion (14). Comparison with sonomicrometry revealed good agreement of longitudinal, radial, and circumferential strain. Reduction in the individual strains was demonstrated at rest and during dobutamine infusion in ischemic myocardium. Another experimental study reported a new echocardiographic method, velocity vector imaging, which can also be used to assess strain (15). In an occlusion–reperfusion model, a good agreement between circumferential and longitudinal strain by echocardiography versus sonomicrometry was shown, both in ischemic and nonischemic myocardium.

Myocardial deformation imaging was also used in patients undergoing revascularization. Becker et al. (16) evaluated 53 patients with ischemic left ventricular (LV) dysfunction and demonstrated that relatively preserved strain in dysfunctional myocardium correlated well with viability on contrast-enhanced magnetic resonance imaging (MRI). Moreover, dysfunctional myocardium with preserved strain showed improvement of function after revascularization.

Contrast echocardiography was the subject of a number of interesting studies. Contrast echocardiography was used in 110 patients with recent myocardial infarction (MI) to assess the status of the microvascular damage as reflected by perfusion defect by contrast echocardiography-predicted LV dilation at 6 months of follow-up (17). A new application for contrast echocardiography was evaluated in terms of its ability to image intraplaque neovascularization in the carotid arteries (18). In this study 32 patients with carotid plaques were examined by contrast-enhanced ultrasonic imaging, 17 of whom underwent endarterectomy. The data demonstrated that plaques with higher contrast intensity manifested greater neovascularization at histologic examination. Echolucent plaques showed a higher degree of contrast intensity. Thus, these studies laid the foundation for the application of contrast echocardiography to delineate the status of the vasa vasorumas an index of the presence and potential vulnerability of plaques, at least in the carotid circulation.

Concerns regarding the risk of contrast echocardiography were an important topic in 2008, during which time the Food and Drug Administration (FDA) actually issued a black box warning regarding the application of these agents. Kusnetzky et al. (19) performed a retrospective analysis of hospitalized patients undergoing clinically indicated echocardiography and compared those who received with those who did not receive a contrast agent. Of the 18,671 consecutive studies they reviewed, they found that major adverse events were quite uncommon (approximately 0.4%) and that there was no difference between the patients who received contrast and those who did not. Similarly, Doland et al. (20) retrospectively analyzed 42,400 patients at 3 different institutions who underwent echocardiography with or without contrast. Studies were both at rest and with exertion and included myocardial perfusion. Again, the major adverse events after echocardiography were very infrequent, and there were no significant differences in death rates or MI at 1 h or 30 days between those patients who received and those who did not receive contrast. Further analysis revealed that the contrast agent clearly contributed to the diagnostic enhancement of those echocardiograms with suboptimal images. On the basis of these studies and other considerations, the black box warning was modified by the FDA.

Real-time 3-dimensional transesophageal echocardiography became possible during 2008. An initial study published by Sugeng et al. (21) reviewed the initial experience of these agents with a fully-sampled matrix array probe. In a group of 211 patients they found excellent visualization of all scallops of the mitral valve in nearly 90% of patients and of the left atrial appendage in 86% of patients. Thus, real-time 3-dimensional matrix array transesophageal echocardiography is feasible in most patients and provides excellent images of the mitral valve that will certainly be of value in the planning and guidance of surgical and percutaneous interventions. Transesophageal echocardiography was also applied to a good advantage in studying the success of surgical procedures to close the left atrial appendage (22). These investigators observed that of a total of 137 patients only 40% of left atrial closure procedures were completely successful, those being primarily total excision of the left atrial appendage. These data should be of value in further therapeutic considerations regarding the left atrial appendage in patients undergoing cardiac surgery and in atrial fibrillation (AF). Finally, Lester et al. (23) updated a review on the use of cardiac ultrasound to assess diastolic function. Subtitled "Deciphering the Rosetta Stone 10 Years Later," the original study was among the most-cited articles in the *Journal* in the past decade, and the new review brings advances in the field up to date.

Valvular Heart Disease

The management of patients with aortic stenosis, low gradient, and LV dysfunction remains problematic. Levy et al. (24) evaluated a multicenter series of patients operated on for low-flow/low-gradient aortic stenosis. They reported on 217 consecutive patients with aortic valve areas of <1 cm^2, ejection fraction $<35\%$, and mean gradients <30 who underwent valve replacement. Although the perioperative mortality was 16% over a 15-year period, it was reduced in half from 20% to 10% in the last 5-year interval. A very low preoperative mitral valve gradient and a very low left ventricular ejection fraction (LVEF) and the absence of contractile reserve with dobutamine stress echocardiography were predictors of perioperative mortality. Nevertheless, given the high mortality associated with this condition, the authors concluded that aortic valve replacement is still the

treatment of choice in the majority of cases with low-flow, low-gradient aortic stenosis.

The role of mitral regurgitation in post-MI remodeling remains controversial. In an attempt to resolve this issue, Beeri et al. (25) instrumented 12 sheep with LV to left atrial shunt so that they could isolate the effects of mitral regurgitation from that of infarction. In this controlled model, mitral regurgitation clearly worsened after infarction remodeling with reduced contractility. These data clearly establish an important role for mitral regurgitation independent of infarct size and post-infarction remodeling.

An interesting study addressed the issue of whether surgical restrictive mitral annuloplasty in heart failure patients resulted in mitral stenosis. Magne et al. (26) demonstrated in 24 patients who underwent restrictive annuloplasty that a functional mitral stenosis was created, with elevated peak mitral valve gradients and elevated systolic pulmonary arterial pressures; these patients also had reduced 6-min walk distance as compared with control subjects.

The pathogenesis of calcific aortic stenosis includes striking similarities in risk factors and histopathology with atherosclerosis. Two clinical studies in the *Journal* advance the hypothesis that aortic valve stenosis is an active process but with differences from atherosclerosis. Toutouzas et al. (27) postulated that active inflammation should produce heat in the aortic valve leaflets. They used a thermographic catheter to measure local temperatures in vivo in each aortic leaflet and aortic wall in 18 nonrheumatic aortic stenosis and 7 aortic insufficiency patients. They observed a greater temperature difference between leaflets and aorta in aortic stenosis than aortic insufficiency (0.7 vs. 0.1). In an additional 10 explanted stenotic valves, temperatures gradients measured correlated with histology, greater inflammatory cell infiltration (T lymphocytes, monocytes, plasma cells), proinflammatory cytokines (tumor necrosis factor-alpha, interleukin-6), neoangiogenesis with vascular endothelial growth factor (VEGF) immunoreactivity, and calcium deposits. Carabello (28) noted in an editorial that coronary and carotid plaque temperatures are higher in the presence of inflammatory processes in acute coronary syndromes (ACS) compared with stable coronary disease. Despite these similarities, it remains uncertain how multiple factors including hemodynamic stress, genetics, and oxidative stress interact to cause inflammation with calcification in aortic valve stenosis.

Miller et al. (29) found increased oxidative stress in human valves with calcific aortic stenosis (removed surgically) compared with normal aortic valves (from hearts not suitable for transplantation) but by different mechanisms from atherosclerotic plaques. There were higher levels of superoxide and hydrogen peroxide in calcified than in noncalcified regions of stenotic valves or nonstenotic valves. This was associated with lower messenger ribonucleic acid (RNA) expression of antioxidant enzymes and the pro-oxidative enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase catalytic subunits Nox2 and Nox4. There was no difference in NADPH oxidase activity, but superoxide levels were reduced by a nitric oxide synthase inhibitor, suggesting uncoupling of nitric oxide synthase. In contrast, increased oxidative stress in atherosclerotic plaques has been attributed to increased NADPH oxidase activity with no change or an increase in antioxidant enzymes. Thus, treatments that effectively reduce oxidative stress in atherosclerosis will not necessarily slow down the progression of aortic valve stenosis. Towler (30) explores the implications of these differences in cell signaling in an accompanying editorial comment and notes this is the beginning of a new era of investigation to understand what enzymes are involved, how abnormalities develop, and what factors predispose to valve calcification, which might differ from the calcification that develops in the vasculature.

The first decade of this century is likely to be remembered for cardiovascular imaging. This year in the *Journal* would certainly confirm this trend because, despite the creation of a daughter journal (*JACC*: *Cardiovascular Imaging*) exclusively dedicated to noninvasive methods, the parent journal remained in the cutting edge by reporting some of the most important developments in this field.

Among the most important developments in vessel imaging by MRI are 2 landmark reports that the *Journal* published on plaque reduction induced by recombinant apolipoprotein (Apo) A-I_{milano} (31,32), discussed in detail by an editorial comment (33) highlighting the importance of these publications vis à vis prior clinical and basic developments in this field. Independent experiments using reliable quantification by imaging finally established the potential of these agents to induce atherosclerotic plaque regression. Moreover, in the field of vessel imaging, Saam et al. (34) demonstrated clearly the presence of complex carotid atherosclerotic plaques in vessels with <50% stenosis by Doppler. This observation opens the door to imaging-guided modulation of plaque composition in addition to plaque size, for patients with advanced atherosclerosis.

However, in the field of nuclear imaging research, the most important development this year was the documentation of cardiac lipid deposition and its manipulation by caloric restriction and weight loss. At a time when most industrialized societies face epidemics of obesity and diabetes, the development of noninvasive methods to quantify myocardial fat deposition represents a crucial step forward. The *Journal* has fostered such development this year by publishing an important contribution by Hammer et al. (35), reporting myocardial functional improvement in association with reduced myocardial fat deposition quantified by proton spectroscopy. The landmark efforts of this group are situated in context by an accompanying editorial (Virchow's metamorphosis revealed by Taegtmeyer and Harmancey [36]) that also discusses basic and applied efforts in the field of myocardial fat in vivo quantification by magnetic resonance methods.

Similar in magnitude and importance, the realization that the most important contributions of myocardial delayed

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enhancement to cardiovascular medicine might be yet to come was reinforced this year by the publication in the *Journal* of 2 articles relating myocardial scar to ventricular arrhythmias (37) in patients with hypertrophic disease and to prognosis (38) in patients with nonischemic dilated cardiomyopathies. Moreover, the publication this year of pioneering efforts to quantify myocardial fibrosis (39) by gadolinium enhanced MRI further advances the possibilities that these methods will be used to detect interstitial fibrosis in addition to formed myocardial scars secondary to the most diverse pathological processes. The *Journal* also published this year important articles establishing contrast enhanced MRI as indispensable phenotyping tools for the diagnosis of amyloidosis (40) and for the characterization of myocardial damage associated with transplant CAD (41).

Microvascular obstruction as "the final frontier for complete myocardial reperfusion" was the subject of an editorial by Rochitte (41) to a landmark report by Hirsch et al. (42) validating MRI methods against intra-coronary flow measurements in patients undergoing percutaneous coronary intervention (PCI). This elegant contribution heralds the potential use of these techniques to assess microvascular disease not only in the setting of infarction but also in chronic disease, as exemplified by the also important contribution of Lanza et al. (43) relating stress induced microvascular perfusion defects to coronary blood flow impairment measured directly by Doppler echocardiography in patients with chest pain, positive stress tests, and angiographically normal coronary arteries. Finally, the clinical and pathophysiologic implications of LV mass measurements in patients with hypertrophic cardiomyopathy were reported by Olivotto et al. (44) and discussed by Reichek and Gupta (45) in an accompanying editorial. The finding that LV mass measurements fall in the considered-normal range for 20% among 264 patients with documented hypertrophic cardiomyopathy was both important and unexpected. Similarly, the *Journal* published this year the unique observation that "left-to-right delay in peak shortening is related to right ventricular overload and LV underfilling" in patients with severe pulmonary hypertension. The importance of these findings as well as the possibility that such observation could eventually contribute to the development of novel strategies to treat pulmonary hypertension are framed in context by an editorial (46) published in the same issue.

Molecular imaging is receiving increasing attention and importance in clinical cardiology. In an important proof of principal, Korosoglou et al. (47) used positive contrast MRI to detect macrophage-rich atherosclerotic plaques that are presumably at high risk of rupture. They administered monocrystalline iron-oxide nanoparticles to rabbits who underwent positive contrast off-resonance imaging (inversion recovery with ON-resonant water suppression [IRON]). Signal enhancement of plaques was observed only in hyperlipidemic animals and correlated highly with the number of macrophages by histology. Thus, IRON-MRI with superparamagnetic nanoparticles might provide an approach by which to image macrophage-rich plaques noninvasively. In a comprehensive state-of-the-art review, Langer et al. (48) delineated the many active approaches currently being taken in the field of molecular imaging.

Wu et al. (49) examined whether evidence of fibrosis by delayed enhanced cardiac magnetic resonance could be of value in determining the prognosis in nonischemic cardiomyopathy. They prospectively followed 65 patients with MRI before the placement of implantable cardioverter-defibrillators (ICDs) and catalogued a composite end point of hospital stay for heart failure-appropriate ICD firing and cardiac death. Nearly one-half of the 27 patients with late gadolinium enhancement on MRI examination had events during a 17-month follow-up versus only 8% of those without such defects. Thus late gadolinium enhancement on cardiac magnetic resonance predicts adverse cardiac outcomes in patients with ischemic cardiomyopathy.

To evaluate the atherosclerotic plaque and morphology in the coronary vasculature in patients with ACS, Henneman et al. (50) performed a 64-slice CT angiography as well as evaluation of coronary calcium. In patients with CAD, 39% of the plaques were noncalcified, 7% mixed, and 14% calcified. Of significance, 33% of patients with CAD did not exhibit evidence of calcification but manifested plaques on CT angiography. The findings of this study indicate that the absence of coronary calcification cannot exclude the presence of significant atherosclerosis in patients with ACS.

Hypertension and Beta-Blockers

The role of beta-blockers in hypertension was the subject of several studies as well as viewpoints in the past year. A meta-analysis by Bangalore et al. (51) evaluated whether beta-blockers prevent heart failure in patients with hypertension. The meta-analysis included 12 trials in 112,177 patients with hypertension. Although there was a 23% reduction in heart failure compared with placebo, this reduction was of borderline statistical significance ($p = 0.055$) and no greater than with other antihypertensive agents; nor was there incremental benefit with regard to overall mortality, cardiovascular mortality, or MI. Stroke risk, however, was increased by 19% in the elderly, leading the authors to conclude that beta-blockers should not be first-line therapy for prevention of heart failure. In an accompanying editorial (52), Fowler points out that beta-blockers are heterogeneous, making it difficult to extrapolate from data obtained primarily with the selective beta-blocker atenolol and that beta-blockers are likely to be needed in combination with other agents.

ST-Segment Elevation Myocardial Infarction Care

The recent (2007) updated American College of Cardiology (ACC)/American Heart Association (AHA) ST-Segment Elevation Myocardial Infarction Guidelines and the Door-to-Balloon (D2B) Alliance generated controversy and de-

bate regarding the role of PCI, particularly in transfer patients. Terkelsen et al. (53), point out in an impassioned viewpoint that PCI, despite its superiority over lytic therapy, is being disadvantaged in the guidelines that mandate that PCI should be performed within 90 min "of first medical contact," whereas for lytics the clock starts ticking at arrival at the treating hospital. In an equally impassioned commentary, Antman (54) points out that the goal of the writing committee, particularly given the availability of pre-hospital activation, was to shorten ischemic time as much as possible (i.e., time is muscle). As pointed out by Antman, however, the situation is complex, and the choice of lytic versus PCI involves multiple variables.

Hyperlipidemia

Although the benefit of lipid lowering in general and statin therapy in particular has become widely accepted, lingering controversy remained regarding the benefit in specific subgroups such as the elderly. In a meta-analysis of 9 trials enrolling patients ages 65 to 82 years, Afilalo et al. (55) demonstrated a reduction of 22% in all cause mortality over 5 years, with even greater reductions in nonfatal MIs, strokes, and revascularizations. Most remarkably the meta-analysis revealed a 50% mortality reduction in those over the age of 80 years. Given the increased absolute risk with increasing age, this important finding translates into a marked absolute benefit. In a further analysis in an accompanying editorial, Diamond and Kaul (56) estimate this absolute mortality reduction at approximately 9%. They further argue for increased incentives, including financial ones, to further increase use of evidence-based treatments. Indeed, with 10-year Medicare data from pharmacy assistance programs in 2 states, Setoguchi et al. (57) identified 21,484 patients who survived for at least 1 month after a hospital stay for MI. They identified a 3% annual decrease in mortality, which was totally accounted for by the use of evidence-based medications (beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, statins, and antiplatelet drugs). Boden and Maron (58) in an editorial argue that these data, although circumstantial, are consistent with a large body of evidence supporting systemic anti-atherothrombotic therapy for secondary prevention and highlight the importance of these data for care of the elderly.

The issue of baseline risk and benefit from treatment was highlighted in a retrospective analysis from the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) study. Giraldez et al. (59) analyzed the relationship between baseline low-density lipoprotein cholesterol and benefit of intensive therapy with atorvastatin 80 mg versus moderate therapy with pravastatin 40 mg. The benefit of intensive therapy with atorvastatin declined at lower initial low-density lipoprotein cholesterol (LDL-C) levels and was no longer present below an LDL-C level of 66 mg/dl and was minimal and statistically nonsignificant for the lowest quartile of baseline LDL (mean LDL of 81 mg; hazard ratio [HR]: 0.98 with a p value of 0.89). These findings reinforce the importance of LDL-C as a risk factor and further support the belief that more intensive statin therapy is linked to better outcomes primarily through LDL-C reduction rather than pleotropic effects. It further suggests that, when baseline LDL-C levels are low, aggressive therapy might not be indicated (60).

Although the overall safety of statin therapy is widely accepted on the basis of multiple large-scale randomized studies, further study and critical assessment is of value. This rationale led the editors of the *Journal* (61,62) to accept a provocative and controversial series of studies from Alsheikh-Ali et al. (63,64) that analyzed statin trials in which cancer data were reported and pointed to a possible increase in cancer rates with lower achieved LDL-C levels. The first article (63) did not look at the relationship in the placebo arms of the trials. When this control population was examined, the same overall relationship appeared: in both statin and placebo arms there was an inverse relationship between LDL-C levels and cancer. For every 10-mg decrease in LDL-C in the statin-treated patients, there were 2.2 (95% confidence interval [CI]: 0.7 to 3.6) excess cancer cases/1,000 patient-years. Statins, in themselves, were not associated with increased cancer risk in meta-regression analysis. In an accompanying editorial, Steinberg (65) staunchly defended the safety of statins and lipid-lowering itself and attributed the higher cancer risk in the low LDL-C patients to pre-existing occult cancers or pre-existing comorbidities that are associated with lowered LDL-C values. Additionally, the overall risk seemed low and was far outweighed by the benefit of lower cardiovascular event rate.

Although LDL-C lowering remains the cornerstone of atherosclerosis management, interest continues in adjunctive therapies, particularly nutritional supplements, such as n-3 fatty acids and flavanoids. In a population-based cross-sectional study Sekikawa et al. (66) looked at 3 groups of subjects, each comprising from 281 to 306 men age 40 to 49 years: Japanese, Japanese-American, and white American. They compared intima-media thickness of the carotid artery, coronary artery calcification, and serum fatty acids. Japanese had the lowest levels of atherosclerosis as well as 2-fold higher levels of marine-derived n-3 fatty acids compared with the other groups. Significantly, the atherosclerosis level as well as the n-3 fatty acids levels were similar in the whites and Japanese-Americans, suggesting that the lower level of atherosclerosis in Japan is related to nutritional differences rather than genetic differences. In an accompanying editorial, Harris (67) points out that recent data show that Eskimos do not seem to be similar to the Japanese despite very high omega-3 consumption. Although high levels of omega-3 consumption, particularly when consumed over a lifetime, might be atheroprotective, Harris points out that this protection might not be enough to overcome an increase in saturated (and trans-fat)

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consumption, which has increased markedly in the Eskimo population.

Just as epidemiologic studies in the Eskimo and Japanese populations highlighted the potential effects of omega-3 fatty acids, the potential for flavanoid-rich cocoa stemmed from an observation that Kuna Indians living on an island off Panama had a low incidence of cardiovascular disease and high levels of flavanol-rich cocoa ingestion (68). The effect of flavanol-containing cocoa in diabetic subjects was reported by Balzer et al. (69). After an initial dose ranging study, they administered thrice-daily flavanol-enriched cocoa and compared its effect on endothelial function to a nutrient-matched control in 41 diabetic subjects. They found a sustained 30% increase in brachial-artery flow mediated dilation in the flavanol-enriched diabetic group over the 30 days of the study, highlighting the potential for such therapy to improve vascular health.

Whereas guidelines recognize LDL-C as the primary target for management of hyperlipidemia, high-density lipoprotein cholesterol (HDL-C) is an important secondary target. Epidemiologic studies demonstrate an inverse relationship of HDL-C levels and cardiovascular risk, but more recent data suggest that very high HDL-C levels might be deleterious. In an analysis from the IDEAL (Incremental Decrease in End Points through Aggressive Lipid Lowering) study and EPIC (European Prospective Investigation into Cancer and Nutrition)-Norfolk case control study, van der Steeg et al. (70) demonstrated that higher HDL-C in the IDEAL study and larger HDL particle size in the EPIC-Norfolk study were associated with increased risk after adjusting for Apo A-I and Apo-B levels (particularly at the high ends of the distribution). Higher Apo A-I levels remained associated with reduced risk. This study demonstrates the complexity of HDL particles and the need for better methods for assessing the quality of HDL-C rather than simply its quantity (71).

Just as Apo A-I might be more predictive than total HDL-C levels, Apo-B has been shown to be a better predictor than LDL-C on its own, because it reflects the presence of both LDL-C and other atherogenic particles. But measurement of Apo-B is not routinely performed in clinical practice and is not fully standardized. Ballantyne et al. (72), in an analysis from the MERCURY II (Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapY II) trial, demonstrated that while on statin therapy non–HDL-C measurement (total cholesterol − HDL-C) correlated closely ($R^2 = 0.92$) and might therefore serve as an acceptable surrogate for Apo-B. Therefore non–HDL-C might become a more important therapeutic goal (73).

Further simplification in clinical management was provided by data from the LUNAR (Limiting UNdertreatment of lipids in ACS with Rosuvastatin) study (74). The study protocol involved measuring lipid levels in ACS patients on day 1, 2, and 4. Surprisingly and contrary to current performance guidelines, the mean lipid levels did not vary to a clinically significant degree over the 4 days, thereby lengthening the window of opportunity to adequately measure and assess risk in acute coronary patients.

Stroke

The presence of plaques over 4 mm in thickness in the proximal aorta has long been associated with risk of stroke, but the relationship to hypercoagulability was unclear. In a case-control study (APRIS [Aortic Plaque and Risk of Ischemic Stroke]) Di Tullio et al. (75) performed transesophageal echocardiography in 255 stroke patients and 209 control subjects. They confirmed the finding of higher stroke risk with large plaques. Importantly, they not only found that superimposed thrombus and ulcerations tripled the stroke risk but also identified increased thrombin generation (as assessed by prothrombin fragment F 1.2) in stroke patients with large plaques. The study underscores the importance of both atherosclerosis and hypercoagulability in stroke and helps guide further trials of warfarin therapy. In an accompanying editorial Cohen (76) recommends oral anticoagulation when superimposed thrombi are present on transesophageal echocardiography, given the current lack of definitive randomized clinical data.

One of the difficult decisions facing cardiologists is whether to anticoagulate patients with AF. Fang et al. (77), with data from the ATRIA (AnTicoagulaion and Risk Factors In Atrial Fibrillation) study, a cohort of 13,559 Kaiser Permanente of Northern California patients with nonvalvular AF, assessed the predictive ability of 5 different risk stratification schemes (Atrial Fibrillation Investigators, Stroke Prevention in Atrial Fibrillation, $CHADS_2$ [Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Index], Framingham score, and the 7th American College of Chest Physicians Guidelines). Patients were followed over a median of 6 years, and the study focused on those patients not on warfarin, encompassing a total of 32,721 person-years. The major findings of the study included: 1) there was wide variability among the risk schemes in assigning patients to different risk categories, with the proportion considered high-risk ranging from 16.4% to 80.4%; and 2) the risk schemes' ability to discriminate stroke risk was only fair, with c-statistics ranging from 0.56 to 0.62. These sobering findings emphasize the need for better risk stratification models. In the interim, given the devastating nature of strokes, most patients and their physicians will continue to opt for warfarin treatment (78).

Antiplatelet Therapy

Resistance (nonresponsiveness) to aspirin and clopidogrel continued to generate interest. The exact incidence of resistance has been a matter of debate, especially when noncompliance is assessed. Gori et al. (79) prospectively followed 746 patients with successful drug-eluting stent (DES) implantation who had platelet function assayed after a loading dose of 600 mg clopidogrel and received aspirin and clopidogrel for 6 months. Dual nonresponsiveness to

both agents was relatively uncommon at 6%, but was associated with a higher incidence of stent thrombosis (11.1% vs. 2.1% in responders). Isolated nonresponsiveness to only 1 agent was not associated with increased stent thrombosis. As pointed out in an accompanying editorial (80), the findings highlight the potential importance of aspirin resistance.

Aspirin and clopidogrel nonresponsiveness are the end result of a complex interaction involving multiple factors including genetics, metabolism, drug–drug interactions, and dosing. A number of studies in the *Journal* provided new insights into this complex situation. Particular focus has been placed on the cytochrome P450 system and its effect on clopidogrel, which as a pro-drug requires conversion by cytochrome P450 to active metabolites. Trenk et al. (81) studied the effects of a loss of function polymorphism (CYP2C19 681G>A *2) on residual platelet aggregation and clinical outcomes in 797 consecutive PCI patients. Whereas the polymorphism did not affect baseline platelet reactivity, residual platelet aggregation was significantly higher in *2 carriers than in wild-type homozygotes and was associated with increased risk of stent thrombosis (3-fold increase in risk in 1-year death and MI).

Given the complex metabolism of clopidogrel, it is not surprising that drug–drug interactions as well as environmental factors might influence platelet reactivity while on the drug. Bliden et al. (82), in a study of 259 PCI patients undergoing stenting, identified smoking—a known inducer of CYP1A2, 1 of the p450 enzymes responsible for clopidogrel metabolism—as associated with greater platelet inhibition. Conversely, in the randomized OCLA (Omeprazole Clopidogrel Aspirin) study, Gilard et al. (83) found that omeprazole decreased the antiplatelet effects of clopidogrel on platelet P2Y12 as assessed by VASP phosphorylation test. Presumably omeprazole competes with clopidogrel for p450 metabolism. Whether these interactions are associated with clinical outcomes is the subject of controversy and will require further study.

One approach to overcome the metabolic and genetic interactions involving clopidogrel is to modify the dosing of the drug. In the PREPAIR randomized study, L'Allier et al. (84) randomized 148 PCI patients to 300 mg of clopidogrel the day before the procedure +75 mg in the morning of the procedure, 600 mg on the morning of the procedure, or 600 mg the day before and 600 mg on the morning of the procedure (double loading dose). They assessed multiple aggregation parameters and found a consistently greater platelet inhibition with the double bolus regimen. Further study is needed to assess the clinical impact of this approach.

Cardiac Risk of Common Conditions

Research in the past year drew attention to several conditions prevalent in society that might represent a risk marker of cardiovascular disease. Two publications associated the presence of erectile dysfunction (ED) with cardiovascular disease. Gazzaruso et al. (85) followed 291 type 2 diabetic patients with asymptomatic CAD for nearly 4 years and found that those with events were nearly twice as likely to have ED as those who did not develop events (61% vs. 36%). The incidence of events was reduced by the administration of statins and fell just short of statistical significance with phosphodiesterase inhibitors. In another study, Ma et al. (86) followed 2,306 diabetic men without evidence of CAD, 27% with ED also, for 4 years. Again, coronary disease appeared twice as commonly in the men with ED as in those without (19 of 1,000 patient-years vs. 9 of 1,000 patient-years). In an accompanying editorial, Kloner (87) observed that similar increased risk for events has also been observed in nondiabetic subjects but that both silent ischemia and ED are more prevalent in diabetic subjects. In addition, he speculated that the mechanism might be related to endothelial dysfunction or the earlier effects of atherosclerosis in smaller penile arteries.

It has been demonstrated that exposure to secondhand smoke increases the risk of cardiovascular disease. Heiss et al. (88) reported the effects of secondhand smoke on endothelial progenitor cell (EPC) activity and endothelial function in nonsmokers. They observed that exposure increased EPCs and plasma VEGF and decreased flow-mediated dilation and related this to blockade of VEGF-stimulated nitric oxide production. These results demonstrated that exposure to real-world levels of secondhand smoke affect not only the vascular endothelium but also EPC function.

Although atherosclerosis near the coronary artery bed attracts the most attention, atherosclerosis involving the peripheral arteries is being increasingly appreciated as an important medical problem. However, little is known about the prognostic significance of peripheral artery disease (PAD) in comparison with conventional coronary artery atherosclerosis. Therefore, Welten et al. (89) studied 2,730 PAD patients without overt coronary disease and compared them with a propensity-matched group of coronary patients undergoing angioplasty. They observed that the PAD patients had a worse long-term prognosis (HR: 2.40) and received less medications associated with reduced risks, such as statins, aspirin, beta-blockers, and the like, than did patients with coronary disease. The major cause of a long-term death in this group was cerebrocardiovascular complications. Thus, these data demonstrate that the long-term prognosis in PAD patients undergoing vascular surgery is significantly worse than that for patients with coronary disease undergoing angioplasty (90). There is a need for intensive risk reduction measures in these patients.

Recent data have demonstrated the importance of central blood pressure versus peripheral blood pressure. To determine whether central blood pressure is of particular value in untreated elderly hypotensive subjects, Pini et al. (90) followed patients >65 years of age for 8 years. They observed that central but not brachial blood pressure predicted cardiovascular events in this geriatric population.

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These data add to the body of evidence attesting to the importance of central blood pressure over brachial artery.

The treatment of AF continues to be a very important topic, as demonstrated by the large number of publications on this subject in 2008. Two such articles include that of Rostock et al. (91) and Nademanee et al. (92). The Rostock report expands on the now well-established concept that "atrial fibrillation begets atrial fibrillation." Rostock et al. (91) evaluated the conduction times and refractory periods in the right and left atrium and pulmonary veins (PVs) before and after 15 min of pacing-induced AF in 35 patients without a history of AF. They observed that the effective refractory period at baseline was longer in the PVs than in the atria. After 15 min of AF, the effective refractory period shortened more in the PVs than in the atria, and conduction was slowed in the PVs. In addition, AF was induced significantly more frequently during programmed stimulation after pacing-induced AF than at baseline. This study demonstrates that AF causes the most prominent changes in the PVs, where the triggers of paroxysmal AF are thought to arise and where ablation seems to be most effective. In addition, short durations of AF affect all PVs similarly, so one can argue that if a premature atrial contraction arises from 1 PV and triggers AF this might in turn lead to development of a substrate in all PVs that might lead to spontaneous electrical activity or re-entry, thus triggering or sustaining AF. The article by Nademanee et al. (92) addresses an alternative potential mechanism underlying AF, that of high-frequency drivers that maintain AF, manifesting as complex fractionated atrial electrograms (CFAE). Previously, Nademanee suggested that ablation of sites where CFAE are recorded might terminate AF and prevent its long-term recurrence (92). This paper addressed the clinical benefit of restoration of sinus rhythm and prevention of AF recurrence in patients at high risk for mortality or stroke. In this study CFAE ablation resulted in maintenance of sinus rhythm in 517 of 674 patients (81.4%) at 836 and resulted in a survival rate that was significantly higher than in those in whom AF persisted (94% vs. 64%, $p < 0.0001$). In addition, in those with an ejection fraction $\leq$40% before ablation, maintenance of sinus rhythm was associated with a significant improvement in ejection fraction from 31% to 41% after 6 months. Warfarin was discontinued after 3 months in sinus rhythm patients, and the stroke rate was only 3% compared with 23% in those continuing on warfarin as a result of persistent AF. Thus, this study demonstrated that CFAE ablation can prevent recurrence of AF, even in high-risk patients, with a reasonably high success rate, although a large percentage (13%) of patients remained on antiarrhythmic drugs, including amiodarone, during follow-up. In addition, this study suggests in a relatively large population of patients that maintenance of sinus rhythm results in a reduction in mortality and stroke rate and improves ejection fraction.

In their 2008 review of long QT syndrome (LQTS), Goldenberg and Moss (93) comprehensively reviewed the common clinical phenotypes; the genetic and molecular mechanisms; the methods for diagnosis including the role of genetic testing; the typical clinical course with emphasis on influences of sex, QT interval, time-dependent syncope, genotype, and biophysical function and location of the LQTS mutation; and the therapeutic options available for treatment of LQTS including beta-blocker therapy, defibrillator implantation, surgical left cervicothoracic sympathectomy, and even radiofrequency ablation of focal ventricular ectopy triggering ventricular fibrillation. Of particular interest is the author's description of the genetic mutations responsible for the common and uncommon LQTS syndromes, now numbered as LQTS 1 to 10. They also put into perspective the role and value of genetic testing in LQTS, particularly that the turnaround time is now significantly shortened to approximately 6 weeks, the yield is approximately 72% among those with a high clinical probability of having LQTS, and that a negative test does not rule out LQTS. The authors also note an important reversal in sex-related risk in LQTS after age 20 years, when women develop a greater risk than men of life-threatening cardiac arrhythmias and sudden cardiac death. Although previous studies have suggested that certain LQTS syndromes (e.g., LQT3) are associated with a higher lethality of cardiac events, more recent reports have not confirmed this. They note that patients with a dominant negative ion channel dysfunction and those with a transmembrane mutation had a significantly higher incidence of life-threatening cardiac events compared with those with mutations causing haploinsufficiency effects and those with C-terminus mutations. Although beta-blockers might be very effective for prevention of recurrent syncope and life-threatening ventricular arrhythmias in some patients, such therapy is still associated with a 10% to 30% incidence of cardiac events, in increasing order of frequency in LQT1, LQT2, and LQT3, respectively. Thus, in patients with recurrent events despite beta-blocker therapy and in those with a high-risk profile, ICD insertion seems to be a very effective, cost-effective alternative for prevention of sudden cardiac death. Finally, surgical left sympathectomy is relatively ineffective, and the role of radiofrequency catheter ablation of focal arrhythmia triggers requires further research.

The role of the ICD was reviewed in detail in 2 interesting articles, a state-of-the-art review by Tung et al. (94) and a commentary by Epstein (95). Tung et al. (94) contend that the benefit of ICDs has been overestimated and that this has been incorporated into the most recent guidelines for ICD insertion (94). Specifically, Tung et al. (94) note that only the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), CASH (Cardiac Arrest Study in Hamburg), and MUSTT (Multicenter Unsustained Tachycardia Trial) studies randomized patients to placebo in the control arm, whereas all other ICD trials randomized patients to antiarrhythmic drugs in the control arm, and most studies had a higher use of beta-blockers in the ICD arm, thus potentially causing a bias favoring the ICD arm in

overall benefit, including mortality reduction. However, Epstein notes that the data are clear that over a >10-year period ICDs have demonstrated a 20% to 30% reduction in total mortality in multiple clinical trial and a 5.6% reduction in absolute mortality in the MADIT II (Second Multicenter Automatic Defibrillator Implantation Trial). Epstein also comments that whether this apparent benefit is in part related to use of beta-blockers and comparison with antiarrhythmic drug therapy, which has a negative impact on mortality, is arguable, but even this small benefit should nonetheless be afforded to patients at risk in discussions with them regarding treatment alternatives. Tung et al. (94) also argue that this potential overestimate of ICD benefit was incorporated into current treatment guidelines for device therapy for prevention of sudden cardiac death (95), including a questionable cutoff for LVEF as an indication for device implantation. Epstein et al. (96) note that the guidelines for ICD therapy published in 2008 were compiled after extensive review by 2 independent panels of experts of all the same studies quoted by Tung et al. (94) and formal review by other experts and approved for publication after review by the governing boards of the Heart Rhythm Society, the ACC, and the AHA. Epstein et al. (96) also note that the current guidelines for ICD therapy were written on the basis of the specific inclusion criteria for ejection fractions used in the individual trials so that ICDs would be offered to patients with clinical profiles as similar to those included in the trials as possible. Tung et al. (94) also correctly note that the optimal timing for ICD insertion after MI has yet to be precisely determined from clinical trials, whereas the current guidelines recommend a 40-day blanking period on the basis of the DINAMIT trial (Defibrillator IN Acute Myocardial Infarction Trial). In addition, Tung et al. (94) note that there is a significant risk of complications acutely from ICD insertion and long-term risk of adverse effects including a reduced quality of life from inappropriate shocks, which might adversely impact survival, a finding also noted in a recent study from the MADIT II trial. Epstein et al. (96) argue, however, that many patients when given a choice might prefer the potential benefits of reduced mortality weighed against the potential risks of ICD insertion, most of which are manageable and acceptable to patients. In their review Tung et al. (94) also note that the cost-effectiveness of ICD insertion/life-year saved is still quite high when compared with other benchmark therapies such as renal dialysis, particularly because most ICD trials have not demonstrated as great a life-expectancy in patients at high risk of sudden death over which to average cost/life-year saved. In summary, Epstein (95) acknowledges that many of the issues raised by Tung et al. (94) in their review are valid, if perhaps overstated in his opinion in some cases, and that ongoing and future research to better identify patient groups who will benefit from ICD insertion as well as those who will not benefit should allow more precise guidelines for ICD therapy to be written, which should in turn improve overall outcomes and cost-effective application of this therapy.

Cardiac resynchronization therapy (CRT) is another important area of cardiac electrophysiology that has received significant attention in the published reports in the past year. Of particular interest is an article by Upadhyay et al. (97) reporting a meta-analysis of 5 studies, involving 1,164 patients, undergoing CRT for typical indications. One limitation of the meta-analysis was that the studies included were predominately prospective cohort studies rather than randomized clinical trials. The findings of importance were that the ejection fraction was noted to improve in both patients in sinus rhythm and AF, with a slightly greater improvement in the patients with AF (0.39%, $p < 0.0001$), whereas 1-year mortality was not different between groups. In patients in both sinus rhythm and AF there was significant improvement in New York Heart Association functional classification; however, there was a slightly greater improvement in New York Heart Association functional class, 6-min walk test distance, and quality-of-life score in sinus rhythm patients. The authors conclude that CRT provides similar or greater improvement in ejection fraction in patients with AF compared with those in sinus rhythm, whereas smaller benefits are seen in functional outcomes.

The reason that nearly one-third of patients who receive CRT do not benefit is not known with certainty. To evaluate the possibility that optimal LV lead positioning is of critical importance, Ypenburg et al. (98) compared the site of latest mechanical activation by speckle tracking echocardiography with the position of the LV lead on chest X-ray in 244 patients undergoing resynchronization. Patients in whom lead position was concordant with the area of latest activation showed a significant reduction in end-systolic volume and had fewer events during long-term follow-up than patients without concordant lead position. Thus, these studies demonstrated the importance of optimal LV lead positioning in obtaining benefits from CRT. In an accompanying editorial, Marwick and Starling (99) indicated that these results might help to explain why previous studies have failed to find a close correlation between evidence of mechanical dyssynchrony and benefit from subsequent CRT.

Management of AF

Despite continued growth and interest in ablation therapy for AF, it is a logistical reality that most patients with AF will be treated noninvasively with medical therapy for the foreseeable future. For this reason, the excellent review article by Ehrlich et al. (100), published in our Special Focus Issue on Atrial Fibrillation, is of considerable interest in highlighting current and near-future state-of-the-art approaches for the pharmacologic management of AF with atrial selective agents.

A common management problem is the management of anticoagulant and antithrombotic therapy in patients with

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AF in the context of ACS. It has been shown that aspirin plus thienopyridines (such as clopidogrel) are superior to other strategies for preventing stent restenosis but inferior to coumarins for stroke prevention in AF (101). This suggests that triple therapy might be warranted in patients with both conditions, although this raises natural concerns about bleeding complications. An interesting report in the *Journal* by Ruiz-Nodar et al. (102) described outcomes in 426 patients with AF undergoing percutaneous interventions with (predominantly) DES. In their observational series, 69% of patients had a $CHADS_2$ score ≥2. Aspirin plus clopidogrel was provided to 174 patients on discharge, whereas 213 patients received triple therapy with aspirin, clopidogrel, and warfarin. On median follow-up of 595 days, the authors report that absence of coumarin anticoagulation was associated with higher mortality (27.8% vs. 17.8%, HR: 3.43, 95% CI: 1.61 to 7.54, $p = 0.002$) and major adverse cardiac events (MACE) (HR: 4.9, $p < 0.01$). However, this study was not randomized so that analysis might have been confounded if coumarins were prescribed less often to sicker patients. Thus, these data cannot form the basis for clear guidelines, and so the use of antithrombotic and anticoagulant therapy must be individualized in patients with AF and co-existing ACS. Nevertheless, an independent and equally important finding was the very high rate of adverse events (36.6%) and all-cause mortality (22.6%) in this population. Although not representing the ideal condition of a randomized double-blinded trial, this study provides useful information to guide practice in this frequently encountered area (103).

Mechanisms of AF

Several excellent reports published in the *Journal* this past year studied tissue-level mechanisms for clinical AF. Kallergis et al. (104) tested the hypothesis that fibrosis might play an important role in the initiation and perpetuation of human AF and might be more pronounced in patients with more advanced AF substrates. To address this issue, the study compared serum indexes of collagen I turnover in 70 patients with persistent and paroxysmal AF and 20 control subjects without AF. The authors found that serum levels of C-terminal propeptide of collagen type-I (CICP), C-terminal telopeptide of collagen type-I (CITP), and tissue inhibitor of matrix metalloproteinases-1 were significantly higher in patients with AF than in control subjects. Moreover, there was a general tendency for higher levels of these indexes in patients with persistent rather than paroxysmal AF. These results add to growing evidence that atrial collagen content and/or turnover contribute both to the age-related incidence of AF as well as AF substrates. One of the functional correlates of fibrosis is conduction slowing. An important study published in the *Journal* by Roberts-Thomson et al. (105) used high-resolution intraoperative mapping of the posterior left atrium between PV ostia to study conduction velocity in several groups of patients. They found that individuals with structural heart disease, in whom AF is more prevalent, showed marked conduction slowing. As pointed out in the editorial by Gerstenfeld (106), this region is thought to be critically important in initiating and maintaining human AF, although conduction was studied at rates much slower than in AF. Another study published in the *Journal* by Narayan et al. (107) reported marked conduction slowing in the posterior left atrium for very early premature beats rather than during baseline pacing, particularly in patients with persistent rather than paroxysmal AF. This study also found evidence that the PV antra in patients with paroxysmal AF have repolarization characteristics ("steep restitution") that enable single premature beats to cause extreme repolarization oscillations and thus initiate AF.

A report by Takahashi et al. from the Bordeaux group (108) provides practical guidance for AF ablation that might reflect the pathophysiology of atrial conduction slowing. In this study, the authors studied a multitude of electrogram characteristics to determine those associated with slowing or termination of persistent AF at the time of ablation. Of numerous characteristics, the authors found that sites of continuous fractionation (>70% of the cycle), which might reflect slowed or anisotropic conduction (109), might be favorable for AF ablation.

The role of autonomics in the initiation and perpetuation of human AF remains controversial. An interesting report by Vaseghi et al. (110) evaluated the incidence of supraventricular tachycardia in 729 recipients of orthotopic heart transplant over a mean follow-up of 6.6 years. The authors report that 7% of patients developed supraventricular tachycardia over this period. However, AF did not occur in any patient in the absence of transplant vasculopathy or rejection. Thus, in these patients with cardiac dennervation, the authors suggest that the absence of AF provides indirect evidence for the role of autonomic innervation in the etiology of clinical AF.

Post-Operative AF

Atrial fibrillation is a very common problem after cardiac surgery and a significant cause of morbidity and mortality, yet its mechanisms and most effective therapy are largely unclear.

Echahidi et al. (111) provided a thorough review of the published data on the management of post-operative AF, including the role for pharmacologic agents such as beta blockade and amiodarone as well as the role of bi-atrial pacing. The article also examines some prevailing hypotheses for the mechanisms for post-operative AF, including the role of catecholamines and neurohumoral factors and the role of inflammation.

In this regard, the original research study published by Kim et al. (112) in the *Journal* is of particular importance. In this study, the authors tested the hypothesis that oxidative stress might be a causal mechanism for post-operative AF.

In 170 patients undergoing on-pump coronary artery bypass grafting (CABG) by the sternotomy approach, they prospectively measured levels of superoxide production in the right atrial appendage at baseline and after NADPH oxidase stimulation and plasma markers of lipid and protein oxidation. They found that tissue NADPH oxidase activity was significantly higher in the 42% of patients who developed post-operative AF than in those who remained in sinus rhythm and were the strongest independent predictor of post-operative AF (odds ratio: 2.41, 95% CI: 1.71 to 3.4, $p < 0.0001$). Notably, the percentage of patients developing post-operative AF rose steadily with quartile of atrial NADPH oxidase activity, from 12% in the first quartile to 67% in the fourth quartile, whereas tissue NADPH oxidase activity varied inversely with LVEF. Conversely, plasma markers of oxidative stress were elevated in both groups of patients by surgery compared with pre-surgical levels. Post-operative AF was also unrelated to the preoperative use of statins or renin-angiotensin-aldosterone axis inhibitors, the post-operative use of beta-blockers, age, or the presence of diabetes mellitus. Although further studies are required to prove a causative role for atrial NADPH oxidase activity in post-operative AF, these results suggest that therapy might be best-directed toward attenuation of cardiac-specific oxidases rather than systemic markers of oxidative stress.

Syndromes With Elevated Risk for Ventricular Arrhythmias

Studies of arrhythmogenic cardiomyopathy highlight both increasing numbers of patients with this potential fatal condition as well as increasing uncertainties in fundamental clinical characteristics. Notably, studies now suggest that, despite its previous name, arrhythmogenic right ventricular cardiomyopathy might indeed affect the LV. An important article in the *Journal* this year by Sen-Chowdhry et al. (113) addresses the dramatic question of whether a left-only or left-predominant form of condition might occur with minimal or no detectable right ventricular involvement. The authors carefully defined a population of 42 individuals who presented with ventricular arrhythmias of LV origin out-of-proportion to the degree of structural LV disease. Notably, even though some of these individuals had evidence for idiopathic myocardial fibrosis or myocarditis, the authors discovered desmosomal gene mutations at the same frequency as in studies of "classic" arrhythmogenic right ventricular cardiomyopathy. Thus, the authors suggest the new term "arrhythmogenic cardiomyopathy," in which an LV dominant form might exist where patients exhibit LV arrhythmias out-of-proportion to structural disease and delayed enhancement on cardiac magnetic resonance in the mid or epicardial regions and might demonstrate desmosomal mutations. An excellent editorial by Saffitz (114) places these findings in the context of the pathophysiology of arrhythmogenic cardiomyopathy.

A recent and welcome development in the study of congenital LQTS has been the study of genetic modifiers that might explain phenotypic variability in the risk for sudden death. An important study by Schwartz et al. (115) from the Italian cohort of the International Long QT Registry tested the hypothesis that differential autonomic responses might modify the clinical severity of LQTS1 in patients with KCNQ1 mutations, in whom sympathetic stimulation is an arrhythmic trigger. The authors addressed this hypothesis by comparing heart rate and baroreflex sensitivity in genotyped LQTS1 patients with and without arrhythmic symptoms. Compared with asymptomatic LQTS1 patients, symptomatic patients had higher resting heart rate and baroreflex sensitivity and were more likely to possess genetic polymorphisms associated with enhanced adrenergic responsiveness. The authors conclude that enhanced autonomic response in some patients might facilitate rapid oscillations and long-short heart rate sequences that initiate torsade de pointes in LQTS and thus explain a greater arrhythmic phenotype and vice versa. Thus, in contradistinction to post-MI patients, in whom depressed baroreflex sensitivity indicates higher risk for ventricular arrhythmias, depressed baroreflex sensitivity in LQTS patients might indicate a protective reduction in sympathetic responsiveness. This interesting concept is discussed in more detail in the accompanying editorial by Lazzara (116).

Autonomic Nervous System and Arrhythmias

Of the many noninvasive indexes of autonomic activity that might predict cardiovascular events, heart rate turbulence is one of the most promising (117). Heart rate turbulence measures fluctuations in sinus arrhythmia that follow a premature beat and might reflect the same pathophysiology as baroreceptor sensitivity. In the *Journal* this year, Bauer et al. (118) published standards for the measurement of heart rate turbulence on behalf of the International Society for Holter and Noninvasive Electrophysiology. This consensus document also provides an excellent overview of the state-of-the-art in the use of heart rate turbulence to predict cardiovascular mortality in various populations. An excellent general overview of the importance of the autonomic nervous system to human arrhythmias was provided in the state-of-the-art paper by Lahiri et al. (119).

Identifying Patients Who Are Most Likely to Benefit From the ICD

Despite well-developed guidelines for the insertion of ICDs, there remains an urgent need to improve the identification of individuals at high risk for arrhythmic death. A lively interchange of ideas on this topic was provided by paired point and counterpoint articles in the *Journal* by Tung et al. (120) and Epstein (121), respectively. Tung et al. (120) revisited data from the major multicenter trials comparing ICD with conventional medical therapy to suggest that the current guidelines might overstate the

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benefit of ICD therapy in some patient populations. Epstein (121) used data from the same trials to support the current guideline recommendations for ICD insertion. Both groups agreed that additional data would be helpful to clarify specific areas.

It is in this regard that several original research articles published in the *Journal* in 2008 are of particular interest. Goldenberg et al. (122) performed a retrospective analysis of the MADIT II trial to examine whether clinical risk factors could help identify individuals who were more or less likely to enjoy benefit from the ICD. The authors pre-specified 5 risk factors of New York Heart Association functional class >II, age >70 years, blood urea nitrogen >26 mg/dl, QRS duration >120 ms, and AF. The authors applied a best-subset proportional hazards regression analysis to study mortality in ICD-treated compared with medically treated patients with varying numbers of risk factors. The authors found a U-shaped relationship for ICD benefit depending upon the number of risk factors. The ICD therapy was associated with a 49% reduction in the risk for death in patients with 1 or more risk factors, but no ICD benefit was observed in patients with no risk factors or in a pre-specified subset at "very high risk" due to blood urea nitrogen ≥50 mg/dl and/or serum creatinine ≥2.5 mg/dl. This important study elegantly demonstrates an essential tenet of risk stratification for sudden cardiac arrest—the ICD is of greatest benefit in patients whose risk for arrhythmic mortality predominates but is less beneficial in patients with significant competing risks for mortality. This study also shows that variables obtained routinely during clinical evaluation might help to identify individuals who might or might not benefit from the ICD even if they qualify via current guidelines. Ideally, prospective randomized studies should be performed to test this hypothesis, although this might be difficult for logistic and ethical reasons as outlined in the accompanying editorial by Mittal (123).

Two important substudies of the SCD-HefT (Sudden Cardiac Death in Heart Failure trial) were presented in the *Journal* this year. Olshansky et al. (124) tested the hypothesis that syncope predicts adverse arrhythmic outcome in patients with heart failure, as suggested from early single center studies (125). The authors found that 6% of patients had syncope before randomization, 14% had syncope after enrollment and randomization in the trial, and 2% had syncope before and after enrollment. Syncope was significantly associated with appropriate device therapy in patients who received ICD therapy. Moreover, syncope after randomization predicted total mortality (HR: 1.41, 95% CI: 1.13 to 1.76, p = 0.002) and cardiovascular mortality (HR: 1.55, 95% CI: 1.19 to 2.02, p = 0.001) regardless of whether patients were treated with optimal medical therapy, optimal medical therapy plus amiodarone, or optimal medical therapy plus ICD. Post-enrollment syncope was significantly associated with QRS duration ≥120 ms and absence of beta-blocker use.

Another important substudy performed by Blatt et al. (126) represents the first prospective study of whether defibrillation threshold (DFT) testing at ICD implant confers any measurable benefit on outcome. This is particularly important because DFT testing remains the standard of care at many centers yet is associated with morbidity and even mortality. In 717 (88.4%) of the 811 patients randomized to the ICD limb of SCD-HeFT, Blatt et al. (126) found that the DFT in all patients was ≤30 J (i.e., within the maximum energy of contemporary ICDs), and ≤20 J in 97.8% of patients. When comparing patients with low DFT (≤10 J) and higher DFT (>10 J), there was no difference in outcome or in the ability of the first shock to terminate spontaneous ventricular arrhythmias on follow-up (83%). Of the 31 patients with an unsuccessful first shock, 28 survived after subsequent shocks or spontaneous arrhythmia termination, whereas 3 patients died after all 6 shocks failed to terminate the tachyarrhythmia. The authors conclude that DFT testing conferred no measurable benefit on outcome. This landmark study questions the current standard of care at many centers of performing routine DFT testing at ICD insert. The pros and cons of this perspective are discussed at length in the accompanying editorial by Curtis (127).

Whether CRT via biventricular pacing reduces the burden of ventricular arrhythmias remains a controversial topic, with studies suggesting that the arrhythmic burden might (128,129) or might not (130) be significantly reduced by this strategy. An interesting study in the *Journal* by Di Biase et al. (131) tested the hypothesis that reverse ventricular remodeling from CRT might cause a reduction in ventricular tachyarrhythmias. In 398 patients undergoing implantation of CRT with a defibrillator, the authors found that responders, defined as showing a reduction in end-systolic volume of >10%, showed significantly fewer ventricular arrhythmias over 12 months than nonresponders.

Pathophysiology of Ventricular Arrhythmias

Bogun et al. (132) present an innovative mechanistic study in which they demonstrated that ventricular tachycardias in the post-MI setting might arise from the papillary muscles. The authors describe a series of patients with sustained ventricular tachycardia in whom cardiac MRI demonstrated heterogeneous uptake of gadolinium in 1 or more papillary muscles. In these patients, ventricular tachycardia was subsequently mapped to these papillary muscles at electrophysiologic study, where ablation successfully terminated the arrhythmia without causing or worsening mitral regurgitation. Conversely, in patients with ventricular tachycardia arising elsewhere, no evidence for heterogeneous gadolinium uptake in the papillary muscles was found. All papillary muscle ventricular tachycardias had right bundle branch block morphology on the ECG with late R-to-S transition in the pre-cordial leads. Ventricular tachycardias arising from the posteromedial papillary muscle had a superior axis,

whereas those from the anterolateral papillary muscle had an inferior axis. This study has important implications for the mapping and ablation of ventricular tachycardia, a procedure that is becoming increasing frequent at many centers.

Although ventricular arrhythmias are frequently seen in patients with heart failure, the tissue-level mechanisms for this link are unclear. Animal studies suggest that cellular calcium overload in failing hearts might explain triggered or reentrant arrhythmias, yet this is difficult to establish in humans. A study published in the *Journal* this year tested this hypothesis in patients with heart failure (133). The authors found oscillations in ventricular action potential plateau voltage from beat-to-beat that predicted ventricular arrhythmias on long-term follow-up. Notably, computational analysis with a detailed model of human LV wedge showed that only reduced calcium uptake into the sarcoplasmic reticulum, which is well-recognized in heart failure (134), explained their results. This study provides indirect evidence of the role of calcium abnormalities in causing arrhythmias in patients with heart failure.

Although J point elevation of ECG has been considered a benign finding, recent data have suggested that it might be associated with an increased risk of idiopathic ventricular fibrillation. Rosse et al. (135) reported the results of a case control study of 45 patients with idiopathic ventricular fibrillation compared with normal subjects and athletes. J point elevation was found more frequently in idiopathic ventricular fibrillation patients than control subjects except for leads V_1 to V_4; athletes manifested intermediate prevalence. Thus, J point elevation might be a marker of idiopathic ventricular fibrillation and might represent an extremely low risk for this condition.

The therapeutic response to CRT has been variable, and not all patients benefit. Cleland et al. (136) analyzed data from the CARE-HF (Cardiac Resynchronization in Heart Failure) study to determine the effect of selected baseline variables and early response markers on long-term mortality. They found that plasma could predict CRT effects concentration of amino terminal pro-brain natriuretic peptide and the severity of mitral regurgitation at 3 months were the strongest predictors of mortality, regardless of therapy. An ischemic etiology of heart failure, New York Heart Association functional class IV symptoms, or the presence of less interventricular mechanical delay at baseline all predicted a worse outcome. Reduction in mortality with CRT, however, was not affected by adjustment for variables measured at baseline or at 3 months; thus the investigators could not predict which patients would be most likely to experience reduced mortality by assessing these parameters. Thus, defining heart failure patients that would be more or less likely to do well with CRT with standard clinical and laboratory variables remains elusive.

The treatment of decompensated heart failure and evidence of low cardiac output remains an issue in considerable flux. In an interesting single-center retrospective analysis of low cardiac output patients (i.e., ≤ 2 l/min/m^2). Mullens et al. (137) compared the response of patients who were or were not treated with sodium nitroprusside. Sodium nitroprusside was titrated to a target mean arterial pressure of 65 to 70 mm Hg. At baseline, patients receiving sodium nitroprusside had higher filling pressures but were otherwise similar to patients who did not. The group receiving sodium nitroprusside had greater improvement in hemodynamic variables during hospital stay, higher rates of oral vasodilator use at discharge and lower rates of all-cause mortality. Use of sodium nitroprusside was not associated with greater inotropic use or worsening renal function. These results suggest that sodium nitroprusside use in decompensated heart failure with low cardiac output might be associated with better long-term outcomes. A prospective trial using sodium nitroprusside in this population is warranted.

There is uncertainty about whether or not to discontinue or reduce the dose of beta-blocker in patients with decompensated heart failure. Fonarow et al. (138) analyzed continuation or withdrawal of beta-blocker therapy and clinical outcomes in nearly 6,000 patients from the OPIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) study hospitalized with systolic dysfunction. Continuation of beta-blockers was associated with lower risk when propensity-adjusted post-discharge death and death/re-hospitalization were compared with no beta-blocker. Withdrawal of beta-blocker was associated with a substantially higher adjusted risk for mortality than continuation. These results suggest that patients hospitalized with decompensated heart failure due to systolic dysfunction should not have beta-blocker dose adjusted unless there is a compelling indication.

Over the past decade multicenter clinical trials have used an increasingly large number of patients from different countries around the world. This practice assumes that there is homogeneity between populations from different countries and that regional differences would not alter the response to therapy. Blair et al. (139) looked at differences in clinical characteristics, management, and outcomes in the 4,133 patients hospitalized with worsening heart failure and LVEF ≤ 0.40 enrolled in the EVEREST study (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan). Mortality and outcomes were analyzed across North and South America and Western and Eastern Europe. Major differences between the groups were noted, with adjusted mortality being highest in South America, whereas Eastern Europe had the lowest cardiovascular death and heart failure hospital-stay rate compared with North America. These results demonstrate that there are major continental and regional differences in heart failure severity, etiology, and management that result in important differences in post-discharge outcomes that persist despite predefined selection criteria for clinical trials. As noted by Poole-Wilson in an accompanying editorial (140), these findings raise 3 important points: 1) differences in outcomes between continents might influence the power calculation and the definitions used for particular outcomes; 2) if results

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are to be applied globally, experience from centers in several continents is advisable; and 3) there is a need to study the social origins of heart failure and the impact of health delivery systems and to more carefully define end points other than mortality in large-scale clinical trials.

Despite the absence of disease in large conduit coronary arteries, patients with nonischemic dilated cardiomyopathy have been noted to have abnormalities in myocardial blood flow. Tsagalou et al. (141) examined the relationship between coronary flow reserve (CFR) and myocardial capillary density (MCD) in 18 patients with dilated cardiomyopathy and heart failure. Coronary flow was measured at baseline and during maximum hyperemia induced by IV adenosine; CFR was calculated for the ratio of mean transit times; and right ventricular endomyocardial biopsies were performed to determine MCD. The CFR correlated closely with MCD ($r = 0.75$). Patients with reduced CFR had lower MCD than patients with normal CFR or control subjects. Thus, in dilated cardiomyopathy a marked decrease in MCD was associated with depressed CFR. In an accompanying editorial Kaul and Jayaweera (142) speculate on the role that MCD-induced ischemia and resultant fibrosis might play in the etiology of idiopathic dilated cardiomyopathy. They further note, however, that haphazard increases in capillaries in which the new capillaries are not laid down would not positively effect CFR.

To better define the association of anemia and mortality in heart failure, Tang et al. (143) examined the presence of anemia at baseline and after 3 and 6 months' follow-up in over 6,000 patients with chronic stable heart failure. Anemia (hemoglobin <12 g/dl for men and <11 g/dl for women) was present in 17.2% and was associated with diabetes, B-natriuretic peptide (BNP) levels, LVEF, and estimated glomerular filtration rate. Anemia was evaluated in only 3% of patients. At 6 months, 16% of the patients developed new onset anemia, whereas 43% of patients who were anemic at baseline had resolution of their abnormal hemoglobin levels. Higher total mortality rates were seen with persistent anemia or with incident anemia at 6 months. The investigators concluded that anemia is under-recognized and -evaluated in heart failure patients; spontaneous resolution occurs commonly; and resolved anemia does not increase mortality risk whereas persistent anemia seems to have poorer survival than either incident, resolved, or no anemia. In an accompanying editorial, Levy (144) acknowledges the favorable outcome in patients whose anemia resolves spontaneously but adds that these findings do not provide information about whether resolution of the anemia with treatment will obviate the mortality risk.

The application of inotropic agents to heart failure has had mixed success. Gheorghiade et al. (145) reported the results of a randomized trial of IV istaroxime, a novel inotropic, lusitropic agent whose action is related to inhibition of Na/K ATPase and stimulation of sarcoplasmic reticulum ATPase. Three doses of istaroxime were given to 120 hospitalized patients with systolic dysfunction. Pulmonary capillary wedge pressure and heart rate decreased and systolic blood pressure increased at all doses; and cardiac index increased, systolic LV volume decreased, and deceleration time improved only at the highest dose. Adverse events were not life-threatening and were dose-related. These early data suggest that istaroxime might provide a novel inotropic/lusitropic agent to treat heart failure.

Congenital Heart Disease

Among the important studies published in the *Journal* related to pediatric and adult congenital heart disease are advances in fetal arrhythmia, interventional and natural history definition, and surgical therapy and outcomes.

An important article on arrhythmia detection—a multicenter study the senior author of which is Ronald T. Wakai of the Department of Medical Physics at the University of Wisconsin and 1 of the major developers of magnetocardiography—reported on 28 fetuses with atrioventricular block, 21 of whom were evaluated serially (146).

Second-degree and isolated third-degree block were often associated with structural disease, and those without structural disease (most commonly immune-related) had evolving and changing rhythm patterns. Acute onset of heart block was at times associated with detection of junctional, ectopic, or ventricular tachycardia.

Magnetocardiography, in fact, is the only definitive way of evaluating these rhythms in the unborn (147). Active treatment of second-degree atrioventricular block with maternal steroids and magnetocardiography monitoring was also documented. Ventricular reactivity and heart rate variability are key indicators of outcome and are present in most fetuses with isolated atrioventricular block.

In a paper from Germany, Kozlik-Feldmann et al. (148) presented a unique hybrid model for ventricular septal defect closure in pigs that underwent a left anterolateral thoracotomy and had muscular ventricular septal defects created by a punch. A closure therapy consisting of a patch with a nitinol frame was advanced retrograde through the carotid artery into the LV, and an instrument very much like a stapler was passed into the ventricle to fix the patch on the septum under echocardiographic and fluoroscopic guidance, after which the nitinol frame was removed. In 1 of the 6 animals, a residual defect remained. This is an exciting approach to hybrid therapy of a common congenital heart lesion, the major advantage of which is that no metallic foreign material remains.

Sachdev (149), of the National Heart, Lung, and Blood Institute published an interesting study of patients with Turner Syndrome: 253 individuals from 7 to 67 years of age, primarily screened with 2-dimensional echocardiography. Approximately 30% of these unselected Turner Syndrome subjects had bicuspid aortic valve, almost all resulting from fusion of the right and left coronary leaflets. The authors discuss a central theory of abnormal lymphatic development related not only to the aortic arch but to the aortic valve

leaflet development. More than 25% of the Turner's women with bicuspid aortic valve had aortic diameters >95th percentile and ascending aortic dilation at 40%—findings presenting a need for ongoing surveillance of both aortic valve function and aortic diameter.

One of the earliest multicenter studies of the follow-up of retrospective results after insertion of ICDs in pediatric and congenital heart disease was published by Berul et al. (150). Four hundred forty-three patients were included; 69% had structural heart disease, including tetralogy of Fallot and hypertrophic cardiomyopathy, over a 12-year period of study. Other common diagnoses were arrhythmogenic right ventricular dysplasia and dilated cardiomyopathy. The majority of patients with electrical diseases had LQTS. Acute complications occurred in 55 patients; lead placement and fracture issues, bleeding and vascular problems, insulation breaches, and changes in electrical characteristics were among the most common complications. Inappropriate shocks occurred in 87 of 409 patients. Although the patients were heterogeneous, the threshold of prescribing an ICD lowered over time. Prospective ICD registry and consensus development for definitions of pediatric and congenital ICD recipients is required—and, in fact, mandated—by the results of this study.

The Mayo Clinic experience provided an important report regarding the functional status after surgical repair of Ebstein anomaly, a rare and difficult condition (151).

This article reports on patients entered in a surgical registry from April 1972 through January 2006. They identified a total of 539 patients, of which follow-up was available in 448, and current information for 285. All patients were treated for symptomatic right heart failure or exercise intolerance not controlled by medication or catheter intervention.

Thirty-three patients (6.1%) died <30 days after operation. Fifty-six patients (11.5%) died during follow-up; 285 (64%) returned surveys. Survival and/or freedom from re-operation at 1-, 5-, 10-, 15-, and 20-year follow-up were found in 97%, 91%, 82%, 72%, and 56%, respectively. On the basis of exercise tolerance and lack of symptoms and functional status, 21% had an excellent result and 72% had a good outcome. Younger age at first operation, abnormal pulmonary artery architecture, a previous cardiopulmonary shunt, post-operative respiratory insufficiency, intra-aortic balloon pump, renal insufficiency or cardiac procedures, and a previous history of arrhythmia were major predictors of poor outcome As highlighted in an editorial by Van Arsdell (152), this experience shows that right ventricular performance remains the most important fundamental issue in this population and stresses the need for continued improvements in valve repair strategies and for right ventricular volume reduction therapy.

Four clinical studies related to risks and outcome measures for Fontan strategy, 3 of which were part of a mini-focus issue in July 2008. A multicenter study described Fontan results in patients who have been treated with Stage 1 palliation for hypoplastic left heart syndrome either with a modified Blalock-Taussig shunt or the procedure initially reported by Scheurer et al. in 2003 (153). During the study period 34 patients had right ventricular–pulmonary artery conduit palliation, and 46 had Blalock-Taussig palliation, most with hypoplastic left heart syndrome and severe mitral disease or mitral atresia.

Although results were generally comparable during the intermediate cavo-pulmonary connection stage, a trend toward improved cumulative survival up to 3 years was demonstrated with right ventricular-pulmonary artery conduit and suggests that there might be potential longitudinal survival benefit to this strategy.

A study from the Pediatric Heart Network reported on 546 children with long-term follow-up data after Fontan procedure, who underwent exercise echocardiography, serology for BNP, and exercise test and echocardiography—most of whom had LV morphology (154). Overall, patients had normal ejection fraction and normal range of score on a health status measure; however, depressed exercise performance, worse right ventricular morphology, and atrioventricular valve insufficiency continue to be problems.

A multicenter study also from Pediatric Heart Network investigators examined exercise performance during the first 2 decades of life after Fontan operation (155). They found that an increased oxygen uptake at peak exercise, probably due to higher stroke volume, was the most important determinant that distinguished a higher-functioning Fontan. Resting echocardiography abnormalities correlated with poor performance, as did higher body mass index and chronotropic incompetence.

A study by Meadows et al. (156) specifically examined the effect on exercise capacity in fenestration closure and showed that, although it did not significantly improve peak oxygen uptake, ventilatory abnormalities during exercise improved significantly. The population for this study was smaller and more diverse—20 patients ages 4 to 56 years who underwent pre- and post-fenestration closure exercise studies.

An important editorial comment provided by Backer (157) highlights these 3 focus articles. He reviews the evolution of the strategies from the initial Fontan through an era of fenestration to now lateral tunnels and extracardiac Fontans. Patients who underwent stage II applied directional cavopulmonary anastenosis generally do very well but do not keep up with their age-matched control subjects in exercise tolerance. Earlier age at Fontan improves the incidence of normal sinus rhythm and provides relative freedom from atrioventricular valve insufficiency. Fenestration—the Fontan operation—still remains a palliative procedure. The 3 papers tell of a dramatic improvement in this strategy for the patients with the most severe disorders.

Another multicenter study reported the long-term effects of inhaled Iloprost in patients with pulmonary artery hypertension (158). Ten patients with congenital heart disease and 12 with idiopathic hypertension underwent a duplicate of an adult study where patients were moved off IV therapy

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onto inhaled Iloprost while continuing their adjunct therapy. The initial inhaled dose of Iloprost was 2.5 μg, and over 24 to 96 h patients underwent serial reduction of their IV prostanoid medication.

Problems during this change of therapy involved vasoreactivity. One of the acute effects measured was a decrease in forced expiratory volume. Other side effects, including headache, cough, and dizziness, improved over several days. Two other patients had highly symptomatic lower airway obstruction several months after initiation of inhaled Iloprost. All in all, these patients who were on adjunctive therapy tolerated the weaning to ventilatory administration and the combination of therapy with the endothelianol phosphodiesterase medication.

Aging and MI: Pre-Clinical Studies

Aging is associated with adverse outcomes in the acute and chronic phase of MI. Age-dependent factors were investigated in 2 pre-clinical studies by comparing the cardiac response to ischemia and reperfusion in young (2- to 4-month-old) to senescent (2-year-old) mice. Przyklenk et al. (159) used stuttered reflow (3 to 6 cycles of reflow for 10 s) before complete reperfusion of ischemic isolated, buffer-perfused hearts to initiate a process termed post-conditioning. This was cardioprotective and reduced the infarct size in half in adult but not in senescent mice. Post-conditioning was related to upregulation of extracellular-signal regulated kinase 1/2 activity in young mice. This was offset in senescent mice by an increase in mitogen-activated protein-kinase-phosphatase-1, which inactivates extracellular-signal regulated kinase. A nonspecific mitogen-activated protein-kinase-phosphatase inhibitor partially restored post-conditioning in senescent mice. This raises the important concept that cardioprotective mechanisms, such as post-conditioning, are impaired with aging but can be restored with pharmacologic agents.

Bujak et al. (160) hypothesized that aging impairs the inflammatory and fibrotic responses of wound healing. They found adverse remodeling (LV dilation and dysfunction) in senescent mice 7 days after cardiac ischemia-reperfusion compared with young mice. This was associated with impaired inflammatory responses in the senescent mice with reduced infiltration of neutrophils and macrophages into the infarct zone, attenuated upregulation of chemokines, and inflammatory cytokines. Senescent mice had less effective clearance of dead cardiomyocytes, blunted response of cardiac fibroblasts to transforming growth factor-beta, and reduced collagen deposition in the healing infarct. This study demonstrates the adverse effects of age-dependent attenuation of inflammatory and reparative responses in acute MI, which should be considered when extrapolating data from studies performed in young adult animals to elderly patients.

In editorial comments, Jugdutt and Jelani (161) indicate that these 2 studies are clinically relevant. The elderly are a high-risk population, and the average age for the first MI is 66 years in men and 70 years in women. However, before extrapolating these pre-clinical results to humans, it is useful to consider that there are species differences in inflammatory responses with involvement of different cell types, chemokines, and cytokines.

Advances in Cell-Based Therapy for Heart Failure: Pre-Clinical Studies

Cell-based therapy for heart failure has generated considerable excitement but poses a number of technical challenges. Two studies in the *Journal* proposed methods to improve the efficacy of this novel therapy. Okada et al. (162) evaluated the effectiveness of different subpopulations of human skeletal muscle-derived stem cells transplanted into the myocardium after infarction in immune-deficient mice. Fluorescence activated cell sorting was used to separate cells on the basis of cell surface markers into myogenic (CD56 positive), endothelial (CD34 and CD144 positive), and myoendothelial (CD56, CD34, and CD144 positive) cells. Transplantation of all 3 cell types were beneficial, but myoendothelial cells were more effective than endothelial cells or myogenic cells in decreasing infarct size, improving contractility and decreasing heart size engrafting, promoting neoangiogenesis, activating endogenous cardiomyocyte proliferation, and secreting VEGF and hepatocyte growth factors at 2 and 6 weeks after infarction. Thus, cell sorting can be useful for selecting a subpopulation of skeletal muscle-derived stem cells to improve therapeutic efficacy. Menasche (163) in an editorial notes that despite disappointing results from early clinical trials with transplantation of unfractionated skeletal myoblasts, refined selection of more effective cells is a promising approach. However, myoendothelial cells comprise only 1.8% of muscular biopsies, so multiple passages will be required to scale-up the number of cells. Fortunately, myoendothelial cells retain their phenotype during expansion.

To improve survival and engraftment, Takehara et al. (164) combined cell-based therapy with an intramyocardial injection of basic fibroblast growth factor (bFGF) in pigs 4 weeks after anterior LV ischemia–reperfusion. The bFGF was incorporated into a gelatin hydrogel to provide sustained release. Pigs treated with bFGF had improved LV function (echocardiography), decreased infarct volume, improved myocardial perfusion (magnetic resonance), and increased arterial vessels in the border and necrotic areas at 4 weeks. The bFGF also augmented the beneficial effects of human cardiosphere-derived cell but not bone marrow-derived mesenchymal stem cell. In an editorial, Dimmeler and Tjwa (165) noted that the use of a biodegradable hydrogel provided sustained release of bFGF for several weeks to increase angiogenesis and create a "cardiogenic niche" that might indirectly improve engraftment and differentiation of transplanted cells. Further studies are needed to determine whether bFGF also has direct effects to

improve cell survival, engraftment, and differentiation of human cardiosphere-derived cell and to determine why bFGF did not produce similar enhancement of bone marrow-derived mesenchymal stem cell effects.

Stem Cell Mobilization With Granulocyte Colony-Stimulating Factor in Acute MI: A Meta-Analysis of Clinical Trials

Mobilizing endogenous stem cells by growth factors, such as granulocyte colony-stimulating factor (G-CSF), provides an attractive approach to increasing stem cells to the acutely injured myocardium that obviates several logistical and ethical issues associated with other forms of cell therapy. This motivated 10 clinical trials involving 445 patients, which were analyzed in a meta-analysis by Zohlnhofer et al. (166). These clinical studies documented that G-CSF can be used safely in acute MI. However, no benefits could be demonstrated in terms of reducing infarct size, improving LVEF, or altering restenosis or target vessel revascularization (TVR), such as the timing and dose of G-CSF and variable treatment group size, duration, and methods of follow-up, but these factors did not seem to contribute to the negative results. The authors note that there was significant heterogeneity amongst the different trials and that the mobilization of CD34+ bone marrow-derived stem cells that are pluripotent might not be fully reflected by CD34+ cell counts in the peripheral blood. Dudley and Simpson (167), in an editorial, comment that despite the negative results the hypothesis that mobilizing CD34+ cells is beneficial cannot be discarded without addressing several issues in future clinical trials, such as whether the dose-dependent increase in CD34+ cells is sufficient, whether cells with the appropriate ability for cell repair are mobilized, whether these cells home to the sites of injury, and whether G-CSF has counteracting effects that offset the potential benefits of CD34+ cells. They note the good news is that it is feasible and safe to use G-CSF immediately after MI.

Advances in the Pathogenesis of Atherosclerosis: Clinical Studies

A major source of noxious vascular reactive oxygen species is the Nox-based NADPH oxidase. Several homologs of the catalytic subunit of NADPH oxidase are present in CAD, including Nox2, Nox4, and to a lesser extent Nox1. Guzik et al. (168) reported that Nox5, a calcium-dependent homolog, is another major source of reactive oxygen species in human coronary atherosclerosis. In arteries from heart transplant patients with CAD (n = 14) versus without CAD (n = 11), there were higher levels of Nox5 messenger RNA and activity, 4-fold higher Nox5 protein, and a 7- to 8-fold higher calcium-dependent NADPH oxidase activity. Immunofluorescence staining localized Nox5 in endothelial cells in the absence of CAD, in the neointima with modest lesions, and in smooth muscle with complex lesions. Because Nox5 is calcium-dependent, calcium channel antagonists might be potentially useful for reducing Nox5 as a major contributor of reactive oxygen species in CAD. In an editorial, Schulz and Munzel (169) review the roles of the different NOX isoforms (Nox1, Nox2, Nox4), which now includes Nox5. They opine that this opens a new area of investigation and therapeutic targets. However, it is uncertain whether increased Nox5 contributes to atherosclerosis or is an epiphenomenon. Furthermore, endothelial cells lack voltage-dependent calcium channels, which might limit the effectiveness of calcium channel antagonists for inhibiting Nox5 activity.

Atherosclerotic lesions often contain calcium, so a link with bone metabolism has been postulated. Gossl et al. (170) hypothesized that this link involves bone marrow-derived endothelial progenitor cells (EPCs) and osteoprogenitor cells. Bone marrow-derived osteoprogenitor cells that express the anti-osteocalcin (OCN) antibody express osteoblastic markers and can form mineralized nodules and bone. Although endothelial cells and osteoprogenitor cells have been traditionally thought to derive from different progenitor cells, they found a significant population of EPCs costain for OCN. Costaining EPCs were 2- to 5-fold higher in 22 patients with early CAD or 29 patients with late CAD compared with 21 normal subjects. Peripheral blood mononuclear cells (CD34+) with a high percent OCN+ formed mineralized nodules when incubated in osteogenic media with calcium. The CD34+ cells expressed bone-related genes. Although this study does not prove a functional role of EPCs that costain for OCN, this novel biomarker might be useful for further studies to explore potential links between bone metabolism and the development of vascular calcification in CAD.

Biomarkers

Considerable research was published in the last year on the diagnostic, prognostic, and even therapeutic applications of a variety of biomarkers.

ACS

Giannitsis et al. (171) demonstrated that a single cardiac troponin T value, except 1 drawn on admission, correlated well with infarct mass determined by delayed enhancement cardiac magnetic resonance. The troponin level drawn on day 4 was particularly accurate to predict infarct size and might gain clinical acceptance due to its ease of acquisition and low cost.

In a study by Omland et al. (172), osteoprotegerin, a member of the tumor necrosis receptor family, was obtained within 24 h of admission in nearly 900 patients with ACS. After adjustment for conventional risk markers, including troponins, natriuretic peptides, and ejection fraction, there was a significant association of osteoprotegerin with mortality and heart failure hospital stay but not recurrent MI. Osteoprotegerin performed as well as BNP and ejection fraction and better than C-reactive protein and troponin I as

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a predictor of death, comparing receiver-operator characteristic curves.

Because thrombus formation is a critical step in the progression of ACS, a reliable measurement of activated coagulation could offer value for both diagnosis and risk assessment. To this end, Mega et al. (173) determined levels of thrombus precursor protein (TpP), a measure of soluble fibrin polymers involved in fibrin formation, in a large number of patients with ACS as well as healthy volunteers. They found that, after controlling for conventional risk factors, TpP was independently associated with an increased risk of death or ischemic complications. In an accompanying editorial, Goetze (174) cautioned that the physician is the ultimate translator of multiple biomarker risk profiles, and with HRs of 1.5, it is possible that some patients will be harmed by unreasonable clinical decisions on the basis of elevation of markers such as TpP.

Dai et al. (175) investigated the role of SCUBE 1 (signal peptide-CUB-EGF) as a biomarker of platelet activation in ACS and acute ischemic stroke. They found that plasma SCUBE 1 concentrations were undetectable in control subjects and stable CAD patients but were significantly higher in ACS and acute ischemic stroke patients. The increase was detectable as early as 6 h and remained in the plasma up to 84 h. The SCUBE1 was a predictor of stroke severity and correlated with sCD30L, providing support that SCUBE1 reflects platelet activation indicative of acute thrombosis. In an accompanying editorial, Peacock (176) cautioned that much work remains before SCUBE1 can be routinely used. There were limitations to the study including late enrollment, effect of confounders, and a prespecified population, but a sensitive marker of ischemia is clearly needed.

Biomarkers and Cardiovascular Events

Mohler III et al. (177) studied the effects of darapladib, a selective lipoprotein-associated phospholipase A (Lp-PLA2) inhibitor, on biomarkers of cardiovascular risk. Congenital heart disease and congenital heart disease equivalents being treated with atorvastatin were randomized to oral darapladib or placebo. Blood samples were analyzed for Lp-PLA2 activity. Darapladib produced sustained inhibition of plasma Lp-PLA2 activity in patients receiving atorvastatin therapy. Changes in interleukin-6 and high-sensitivity C-reactive protein after 12 weeks suggest a possible decrease in inflammatory burden. In an accompanying editorial, Koenig (178) pointed out that this promising study suggests that inhibition of Lp-PLA2 might have promise as a suitable strategy to combat residual cardiovascular risk and the appropriate patients.

Danik et al. (179) asked whether the association of lipoprotein (a) [LP(a)] to cardiac risk could be modified by concurrent hormone replacement therapy. As expected, they found that LP(a) was lower among women taking hormone replacement therapy. In women not taking hormone replacement therapy, the HR of future cardiovascular disease for highest LP(a) quartile compared with lowest quartile was 1.8. In contrast, among women taking hormone replacement therapy, there was little evidence of association with cardiovascular disease. In the editorial comment, Berglund and Anuurad (180) were encouraged by this study, because it provides evidence that detection of elevated LP(a) levels in a high-risk setting might be an appropriate sign to consider an intensified intervention.

However, they stress that further studies will be needed to firmly assess any possible therapeutic benefits of a reduction of LP(a) levels.

Findley et al. (181) sought to determine whether factors that regulate angiogenesis are altered in peripheral arterial disease (PAD) and whether those factors are associated with the severity of PAD. Levels of VEGF and soluble Tie2 were significantly increased in patients with critical limb ischemia, and sTie2 production was induced by VEGF. In an accompanying editorial, Cooke (182) points out that there are several genes that might be involved in the enhanced angiogenic response to ischemia and that the translational studies such as the one presented provide new clues to underlying impaired vascular regeneration in PAD. This could ultimately lead to new therapeutic approaches to promote angiogenesis.

Maisel et al. (183) examined the timing of measurement of BNP in patients with acute decompensated heart failure and its association with time to treatment as well as subsequent morbidity and mortality. Investigators studied patients in the ADHERE registry (Acute Decompensated Heart Failure National Registry) who were admitted to the emergency room with acute decompensated heart failure. They found that patients with the longest average time before BNP measurements were obtained also had the longest time to treatment and that, the later the treatment took place, the less likely that patients were asymptomatic at the time of hospital discharge. These data point to the importance of obtaining measurements of natriuretic peptide levels early in the management of acute decompensated heart failure.

Heart Failure

Lisy et al. (184) engineered a novel chimeric peptide CD-NP that represents the fusion of the 22-amino acid peptide C-type natriuretic peptide together with the 15-amino acid linera C-terminus of Dendroaspis natriuretic peptide. They demonstrated in vivo that CD-NP is both natriuretic and diuretic; it enhanced glomerular filtration and aided in cardiac unloading and renin inhibition. It was less hypotensive than BNP. Finally, CD-NP in vitro was able to activate cyclic guanosine monophosphate while inhibiting fibroblast activity. In an accompanying editorial, Francis (185) congratulated the team for "moving the field" through the powers of observation and reason. Further

studies should provide additional insight into this exciting new chimeric peptide.

Masson et al. (186) sought to evaluate the association between changes over time of N-terminal part of the pro-B-type natriuretic peptide (NT-proBNP) and outcome in patients followed in the Val-HeFT (Valsartan Heart Failure Trial). A Cox proportional hazards model demonstrated that stratification of patients into 4 categories according to NT-proBNP levels at 2 different time points 4 months apart provided prognostic information in patients with chronic heart failure better than a single determination. This suggests that natriuretic peptide monitoring in the outpatient setting might provide valuable information with regard to risk stratification.

A major question regarding the use of natriuretic peptide measurements in patients with heart failure is whether it can predict the potential for decompensation. Therefore, Nishii et al. (187) followed 83 patients with nonischemic cardiomyopathy who had previously been hospitalized but who were subsequently clinically stable class I to II for at least 6 months. Twenty-eight patients were readmitted for decompensation or died within 11 months, and among various predictors of decompensation only a 6-month post-discharge BNP value of >19 pg/ml was associated with combined events. Thus, BNP might be of value in predicting the long-term risk of compensation.

Outcomes of DES

Randomized clinical trials. DES IN ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION (STEMI). The role of DES in STEMI is not yet fully determined. In the MISSION! Intervention Study (188), a single-blind, single-center, randomized angiographic and intravascular ultrasound study, sirolimus-eluting stents (SES) were compared with bare-metal stents (BMS) in 310 STEMI patients. The SES were associated with lower in-segment late luminal loss (0.12 mm vs. 0.68 mm, $p < 0.001$). Late stent malapposition at 9 months was higher in SES (37.5% vs. 12.5%, $p < 0.001$); but despite this, event-free survival at 12 months was greater in SES (86.0% vs. 73.6%, $p = 0.01$), mainly driven by lower TVR in SES. The clinical impact of late stent malapposition with DES, particularly in the acute MI setting where vessel size might be underestimated, waits to be determined.

DES IN DIABETES MELLITUS. Lee et al. (189) evaluated the effectiveness of SES (n = 200) and paclitaxel-eluting stents (PES) (n = 200) in patients with diabetes mellitus in a prospective, multicenter, randomized study with the primary end point being in-segment stenosis at 6 months. The 6-month in-stent (3.4% vs. 18.2%, $p < 0.001$) and in-segment stenosis (4.0% vs. 20.8%, $p < 0.001$) and 9-month target lesion revascularization (TLR) (2.0% vs. 7.5%, $p = 0.01$) were significantly lower in the SES versus the PES group. The incidence of death or MI was similar, but major adverse cardiac events (MACE) were lower in the SES versus the PES group. The SES might have some advantage in diabetic patients.

DES IN IN-STENT RESTENOSIS. Until recently, long-term data on effectiveness of DES in BMS in-stent restenosis has been lacking. The RIBS-II (Restenosis Intra-stent: Balloon angioplasty versus elective sirolimus-eluting Stenting) Study (190) randomized 150 patients with in-stent restenosis (76 SES, 74 balloon angioplasty). At 1 year, death, MI, and TLR were better in the SES group (88% vs. 69%, $p < 0.005$). Definitive/probable/possible stent thrombosis was similar in both groups. At 4 years, the event-free survival was greater with SES (76% vs. 65%), and SES was an independent predictor of event-free survival.

DES IN COMPLEX LESIONS. The 3-year results of the SCANDSTENT (Stenting Coronary Arteries in Non-Stress/Benestent Disease) Trial (191)—which evaluated SES and BMS in patients with complex coronary artery lesions (total coronary occlusions or lesions located in bifurcations, ostial, or angulated segments) in 322 patients—demonstrated that both MACE (2% vs. 58%, $p < 0.001$) and TLR (4.9% versus 33.8%, $p < 0.001$) were lower in the SES compared with the BMS group. Stent thrombosis occurred in 5 patients (3.1%) in the SES group and in 7 patients (4.4%) in the BMS group (p = NS), and very late stent thrombosis was observed in 4 SES versus 1 BMS patient.

Registry studies. Three registry studies demonstrated either reduced MACE or an overall survival benefit with DES. In the largest registry (n = 76,525) to date encompassing an administrative elderly Medicare cohort matched to a similarly sized BMS cohort (192), treatment with a DES was associated with a significant survival benefit, with an adjusted mortality HR of 0.83 compared with contemporary control subjects, and an HR of 0.79 compared with historical control subjects (control group heterogeneity: $p < 0.001$). Patients with DES had significantly lower adjusted rates of revascularization procedures within the first 2 years after PCI and lower hospital stay rates for subsequent acute MI. A large (n = 8,032) registry from the Cleveland Clinic also showed an all-cause mortality benefit with DES compared with a propensity-matched group (adjusted HR: 0.54, $p < 0.001$) (193).

DES thrombosis, on-label and off-label. The long-term incidence of DES thrombosis is still being evaluated. In a combined registry of 8,146 patients undergoing PCI with SES (n = 3,823) or PES (n = 4,323), with 3 to 12 months of clopidogrel treatment and 4-year follow-up, Wenaweser et al. (194) reported a cumulative incidence of stent thrombosis of 3.3% at 4 years. The incidence of stent thrombosis continued at a steady rate of 0.53%/year between >30 days and 4 years. Diabetes, ACS, younger age, and use of PES were independent predictors of early stent thrombosis. In the ESTROFA (Estudio ESpanol sobre TROmbosis de stents FArmacoactivos) registry of 23,500 patients treated with DES in 20 centers in Spain (195), angiographically

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documented definite stent thrombosis developed in 301 patients: 24 acute, 125 subacute, and 152 late, including 62 occurring >1 year. The cumulative incidence was 2% at 3 years. Antiplatelet treatment had been discontinued in 95 cases (31.6%). No differences in incidences were found among stent types. Independent predictors for subacute stent thrombosis were diabetes, renal failure, ACS, STEMI, stent length, and left anterior descending artery stenting and, for late stent thrombosis, STEMI, stenting in left anterior descending artery, and stent length. Finally, in the Wake Forest registry, Applegate et al. (196) compared the 2-year outcomes in 1,164 consecutive patients who received BMS in the year before introduction of DES with 1,285 consecutive patients who received DES (>75% "off-label"). At 2 years, the HR for DES, compared with BMS for nonfatal MI or death, was 0.77 (95% CI: 0.62 to 0.95), for all-cause mortality 0.71 (95% CI: 0.54 to 0.92), and stent thrombosis 0.97 (95% CI: 0.49 to 1.91). "On-label" stent procedures were associated with lower risk of MI, death, and stent thrombosis than "off-label" stent procedures. These "real world" studies, in composite with other studies reported previously or elsewhere, suggest that DES can be associated with both a mortality and MACE benefit, and this likely is related to better patient selection and longer duration of antiplatelet therapy (197).

Antiplatelet and Antithrombotic Therapy

The role of antiplatelet and antithrombotic therapy in PCI is still evolving. Brar et al. (198) provided important data on long-term clopidogrel use among diabetic patients undergoing PCI. In 749 patients undergoing stent implantation with either BMS (n = 251) or DES (n = 498), they demonstrated that clopidogrel duration was associated with reduced incidence of death or MI (3.2% in the >9-month group, 9.4% in the 6- to 9-month group, and 16.5% in the <6-month group, $p < 0.001$) in both BMS and DES groups. Although the study was relatively small, uncontrolled, and observational, it does provide important scientific evidence of the empiric recommendation by the ACC/AHA for at least 1 year of clopidogrel duration in patients receiving DES.

The possibility of more efficacious thienopyridine inhibitors in the clinical armamentarium was demonstrated in the TRITON–TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel–Thrombolysis In Myocardial Infarction 38) trial, which showed that prasugrel, a $P2Y_{12}$ receptor inhibitor similar to but more potent than clopidogrel, was associated with a significantly lower rate of MI, stent thrombosis, and urgent TVR (199). However, major noncoronary artery bypass graft (CABG) bleeding was significantly greater with the use of prasugrel, although net clinical benefit significantly favored the agent. Future studies will need to address the overall balance between reducing ischemic events and bleeding complications, particularly with the ability to measure and tailor antiplatelet effect of these agents. In that vein, Patti et al. (200) evaluated the correlation of point-of-care measurement of platelet inhibition (VerifyNow $P2Y_{12}$ assay) with clinical outcome in 160 patients undergoing PCI receiving 600 mg clopidogrel 6 h before PCI. They demonstrated that 30-day MACE occurred more frequently (20% vs. 3%; $p = 0.03$) in patients in the highest quartile (lower effect of clopidogrel) of pre-procedural P2Y12 reaction units (PRU) compared with the lowest quartile, an effect that was entirely due to periprocedural infarction. Mean PRU absolute levels were higher in patients with periprocedural MI. On multivariable analysis pre-PCI PRU levels in the fourth quartile were associated with 6-fold increased risk of 30-day MACE. By receiver-operating characteristic curve analysis, the optimal cutoff for the primary end point was a pre-PCI PRU value ≥240 (area under the curve: 0.69). If validated in larger clinical studies, rapid point-of-care assays might not only provide prognostic information but also a valuable tool to optimize dosing of antiplatelet therapies.

Studies evaluating glycoprotein IIb/IIIa inhibitors in STEMI have focused mainly on abciximab, with a relative dearth of data on other IIb/IIIa inhibitors. In a retrospective analysis of a large (3,541 patients who underwent primary PCI for STEMI) regional database in Michigan, Gurm et al. (201) demonstrated that a large proportion of patients in the community are treated with eptifibatide, despite the fact that existing studies with abciximab have demonstrated a survival advantage in STEMI over placebo. However, after risk adjustment with propensity analysis of patients treated with abciximab (n = 729) or eptifibatide (n = 2,812), it was demonstrated that there was no difference in the incidence of in-hospital death, recurrent MI, or stroke/transient ischemic attack. There was no difference in the need for blood transfusion, whereas there was a greater incidence of gastrointestinal bleeding with abciximab (4.8% vs. 2.8%, $p = 0.01$). Although this level of evidence is not at the randomized controlled-trial level, this study does suggest that potent antiplatelet therapy with either agent is a reasonable approach in patients with STEMI undergoing PCI.

Finally, the 1-year results of the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) PCI substudy in moderate- and high-risk ACS patients (7,789 patients or 56.4% of entire cohort) were published. Two thousand five hundred sixty-one, 2,609, and 2,619 were randomized to unfractionated heparin or enoxaparin plus a glycoprotein IIb/IIIa inhibitor, bivalirudin plus a glycoprotein IIb/IIIa inhibitor, and bivalirudin monotherapy, respectively. There were no differences in composite ischemia or mortality among the 3 groups (202). In subgroup analysis, patients not treated with clopidogrel either before or after procedure seemed to be at particularly high risk of events.

Unprotected Left Main Interventions

Two important studies evaluated the clinical outcomes of unprotected left main interventions. In a small randomized trial, Buszman et al. (203) randomly assigned 105 patients with unprotected left main coronary artery stenosis to PCI (35% DES, 65% BMS) versus CABG, with the primary end point being a change in LVEF at 12 months and secondary end points being MACE. They demonstrated a significant increase in LVEF in the PCI group (3.3 after PCI vs. 0.5 after CABG; $p = 0.04$). Major adverse cardiac events at 1 year were similar but with a trend toward improved survival after PCI. In the DELFT (Drug Eluting stent for LeFT main) Registry (204), 358 consecutive patients who underwent PCI with DES implantation for de novo lesions on unprotected left main coronary artery were retrospectively selected and analyzed in 7 European and U.S. tertiary care centers, and all patients had a minimum follow-up of 3 years.

After 3 years, MACE-free survival in the whole population was 73.5%, with cardiac death occurring in 9.2% of patients, and reinfarction, TLR, and TVR occurring in 8.6%, 5.8%, and 14.2% of patients, respectively. Definite stent thrombosis occurred in 2 patients (specifically at 0 and 439 days). Elective cases were associated with lower MACE than emergent cases.

Carotid Stenting

The multicenter, single-arm BEACH (Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients) trial evaluated outcomes in high-surgical-risk patients with carotid artery stenosis treated with the Carotid WALLSTENT plus FilterWire EX/EZ Emboli Protection System (205). The trial enrolled 480 patients at high risk for carotid endarterectomy due to high-risk clinical (41.2%) and anatomical (58.8%) criteria; 76.7% were asymptomatic with flow-limiting carotid stenosis >80%. At 1 year, the composite primary end point—all stroke, death, or Q-wave MI through 30 days; non–Q-wave MI through 24 h; and ipsilateral stroke or neurologic death through 1 year—occurred in 8.9% (40 of 447), with a repeat revascularization rate of 4.7%. The BEACH trial results met the prespecified criteria for noninferiority relative to the calculated objective performance criterion plus noninferiority margin (16.6%) for historical surgical carotid endarterectomy outcomes in similar patients ($p < 0.0001$ for noninferiority).

End Points in Clinical Trials

The role of bleeding and blood transfusion as prognostic indicators is being increasingly recognized, leading to debate as to appropriate use as end points in clinical trials. In an analysis of 4 randomized controlled trials of 5,384 patients from the ISAR (Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment) database (206), bleeding was defined according to the Thrombolysis In Myocardial Infarction criteria and included all bleeding events within 30 days after enrollment with primary end point 1-year mortality. Within the first 30 days, there were 42 deaths, 314 MIs, 52 urgent revascularizations, and 215 bleeding complications. Mortality at 1 year was 3.6% ($n = 197$). A Cox proportional hazards model revealed that the 30-day occurrence of bleeding (HR: 2.96, $p < 0.001$), MI (HR: 2.29, 95% CI: 1.52 to 3.46; $p < 0.001$), and urgent revascularization (HR: 2.49, $p = 0.019$) independently predicted 1-year mortality. The authors suggest that these data support the inclusion of periprocedural bleeding in a 30-day quadruple end point for the assessment of outcome after PCI. In an insightful editorial, Dauerman (207) discusses the implications of this, including balancing the proper hypothesis testing of novel therapies versus determining net clinical benefit.

Due to the large cost and time required for clinical outcomes studies, surrogate end points are being evaluated for evaluating stent efficacy. Pocock et al. (208) evaluated 4 angiographic measures (late loss [LL] and percent diameter stenosis (%DS), both in-stent and in-segment) as potential surrogates for clinical restenosis (TLR) after stent implantation from 11 multicenter, prospective randomized stent trials with individual data on 5,381 patients with a single treated lesion and follow-up angiography at 6 to 9 months. The LL and %DS strongly predicted the risk of TLR, with in-segment %DS being the most highly predictive. Differences in TLR risk were fully explained statistically by their differences in LL or %DS, although LL as a surrogate was dependent on vessel size whereas %DS was not. However, because of the curvilinearity of the logistic model, trials comparing 2 effective DES can have significant differences in mean LL and %DS but small expected differences in TLR risk, especially at the lower ranges of LL and %DS, as has already been noted in several DES trials. Although the authors suggest that these angiographic measures are suitable primary end points in future DES trials to significantly reduce sample size, it remains to be seen how the interventional community and regulatory agencies accept surrogate end points versus clinical efficacy data in future stent trials.

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J. Am. Coll. Cardiol. 2009;53;373-398
doi:10.1016/j.jacc.2008.12.005