HIGHLIGHTS FROM JACC

Highlights of the Year in JACC 2007

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As in past years, the Associate Editors have assembled this highlights article. We included those papers published in the Journal in the past 12 months that we perceived as having the greatest impact on cardiology. Space constraints resulted in omitting many excellent papers, for which we apologize in advance to the authors.

Interventional Cardiology

First Reports of New Randomized Clinical Trials

Unprotected left main coronary artery intervention. The role of percutaneous coronary intervention (PCI) in unprotected left main coronary artery stenosis in the current era is not well defined. Erglis et al. (1), in a relatively small study, randomized 103 patients to receive either bare-metal stents (BMS) or paclitaxel-eluting stents (PES) (n = 53). Lesions were pre-treated with cutting balloons, and stent placement was guided with intravascular ultrasound (IVUS). At 6 months, PES had less binary restenosis (6% vs. 22%, p = 0.02), less neointima volume (17% vs. 25%, p = 0.02), and greater major adverse cardiac event (MACE)-free survival (87 vs. 70, p = 0.03). These results need validation but suggest favorable outcomes in left main coronary artery interventions with drug-eluting stents (DES).

ST-segment elevation myocardial infarction (STEMI). The role of DES in STEMI is still evolving. The SESAMI (Sirolimus-Eluting Stent Versus Bare-Metal Stents in Acute Myocardial Infarction) trial (2) randomized 320 STEMI patients to sirolimus-eluting stents (SES) or BMS. At 1 year, the primary end point of binary restenosis occurred in 9% in SES versus 21% in BMS, p = 0.03. Target lesion revascularization (TLR) (4% vs. 11%, p = 0.02), target vessel revascularization (TVR) (5% vs. 13%, p = 0.01), MACE (6% vs. 16%, p = 0.005), and target vessel failure (8% vs. 18%, p = 0.007) were also lower with SES.

The RELAx-AMI (Randomized Early Versus Late Abciximab in Acute Myocardial Infarction Treated with Primary Coronary Intervention) trial (3) compared early (emergency room) versus late (catheterization laboratory) abciximab administration in 210 STEMI patients. Primary end points were Thrombolysis In Myocardial Infarction (TIMI) flow grade, corrected TIMI frame count (cTFC), myocardial blush grade (MBG), and echocardiographic left ventricular (LV) function recovery. The early group showed better parameters before as well as after PCI. Mean gain in left ventricular ejection fraction (LVEF) (8% vs. 6%, p = 0.02) was also better in the early group. Although this study was not powered for MACE, it strongly supports the concept that administration of abciximab in STEMI should be performed as soon as possible.

Proximal protection device. Distal protection devices reduce MACE in vein graft PCI, but proximal protection devices may have procedural advantages in select lesions. The PROXIMAL (Proximal Protection During Saphenous Vein Graft Interventions) trial (4) enrolled 594 patients undergoing stenting of 639 saphenous vein grafts using a noninferiority design. The primary composite end point of death, myocardial infarction (MI), or TVR at 30 days by intention-to-treat analysis occurred in 10.0% of the distal group and 9.2% of the proximal group (p for noninferiority = 0.006). Results were similar in device-specific analysis or in patients with lesions amenable to treatment with either proximal or distal devices. These findings indicate that proximal embolic protection produced outcomes similar to those with distal protection for saphenous vein grafts.

Renal protection during coronary angiography and PCI. Two randomized controlled trials (RCTs) described new methods for renal protection in high-risk coronary angiography or emergency PCI. Lee et al. (5) assigned 82 patients with baseline creatinine levels of 4.9 mg/dl to either saline or prophylactic hemodialysis immediately after catheterization. Hemodialysis blunted the decrease in creatinine...
clearance within 72 h and led to significantly lower peak (5.3 mg/dl vs. 6.7 mg/dl, \( p = 0.005 \)) and Day 4 (5.1 mg/dl vs. 6.3 mg/dl, \( p = 0.010 \)) creatinine. Thirteen percent of the control patients but none of the dialysis patients required long-term dialysis after discharge (\( p = 0.01 \)). This study suggests that one session of prophylactic hemodialysis is effective in improving renal outcome in chronic renal failure patients undergoing coronary angiography.

Recio-Mayoral et al. (6) randomized 56 patients to sodium bicarbonate plus 2,400 mg intravenous N-acetylcysteine just before contrast injection and for 12 h after PCI (group A) and 55 patients to saline (group B). In both groups, 2 doses of 600 mg oral N-acetylcysteine were administered the next day. A creatinine level >0.5 mg/dl from baseline after emergency PCI was observed in 1 patient in group A (1.8%) and in 12 patients in group B (21.8%, \( p < 0.001 \)). Acute anuric renal failure was observed in 1 patient (1.8%) in group A and in 7 patients (12.7%) in group B (\( p = 0.03 \)). This study provides a rapid method for minimizing renal injury in patients undergoing emergency PCI.

**PCI in high-risk groups: diabetic patients and complex lesions in the left anterior descending artery.** Specific RCTs to evaluate the safety and efficacy of DES are now being reported. Baumgart et al. (7) randomized 200 patients with diabetes and de novo coronary artery lesions to SES versus BMS, with angiographic parameters as the primary end point. In-segment late luminal loss, in-segment restenosis, and TLR were lower with SES (\( p < 0.0001 \)). The SES were effective in diabetic patients on oral agents and on insulin. At 12 months, the MACE rate was 14.7% in SES versus 35.8% in BMS. Petronio et al. (8) randomized 85 patients with complex lesions of the left anterior descending artery to SES or BMS implantation. The primary end point, percent neointimal hyperplasia area (NIHA%) by intravascular ultrasound at 9 month follow-up, was significantly lower with SES than PES (7.4 vs. 15.4, \( p < 0.001 \)), as was late loss.

**Registry Studies With DES**

Real-world registries reflect both on-label and off-label indications of approved devices, and may more closely represent actual safety and efficacy than randomized studies. Three important registries reported outcomes in patients receiving DES and suggested outcomes are at least equal if not better than with BMS. In the National Heart, Lung, and Blood Institute Dynamic Registry (9), patients receiving DES (\( n = 1,460 \)) had a lower rate of death/MI TVR and risk of any repeat revascularization compared with BMS. The 1-year incidence of stent thrombosis was 1.0% in DES patients.

The STENT (Strategic Transcatheter Evaluation of New Therapies) registry (10) collected data on all PCIs in 8 U.S. hospitals between 2003 and 2005. Patients who only received a PES (\( n = 4,671 \)) or SES (\( n = 4,555 \)) and completed 9-month follow-up (93.8% of eligible) were analyzed. The investigators observed that death, MI, and MACE were similar with PES and SES in real-world patients at 9 months. Similar data were noted in a smaller registry from Italy, which also analyzed late loss and angiographic restenosis (11).

**5-Year Outcomes of Landmark Trials**

Two landmark studies reported 5-year outcomes. The RAVEL (Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization) trial (12) was the first RCT of DES and included 238 patients with a single de novo native stenosis treated with either SES or BMS. The 1-, 3-, and 5-year rates of survival free from TLR were 99.2%, 93.8%, and 89.7%, respectively, in the SES group versus 75.9%, 75.0%, and 74.0% in the BMS group (\( p < 0.001 \), log-rank). Rates of all MACE at 5 years were 25.8% in patients treated with SES versus 35.2% with BMS (\( p = 0.03 \), log-rank). Rates of stent thrombosis were similar in both groups. Although relatively small, this study suggests a durable beneficial effect of DES up to 5 years.

The DEFER (Deferral Versus Performance of PTCA in Patients Without Documented Ischemia) trial (13) measured fractional flow reserve (FFR) in 325 patients scheduled for PCI of an intermediate stenosis. If FFR was <0.75, PCI was performed as planned (\( n = 144 \)), whereas if FFR was >0.75, patients were randomly assigned to deferral (DEFER, \( n = 91 \)) or performance (Perform, \( n = 90 \)) of PCI. The 5-year event-free survival was not different between the DEFER and Perform groups (80% and 73%), but was significantly worse in the Reference group (63%, \( p = 0.03 \)). The composite rate of cardiac death and acute MI in the DEFER, Perform, and Reference groups was 3.3%, 7.9%, and 15.7%, respectively (\( p = 0.003 \) for the Reference vs. both other groups). Freedom from chest pain was not similar for the Defer and Perform groups. The investigators concluded that 5-year outcome after deferral of PCI of an intermediate coronary stenosis based on FFR \( \geq 0.75 \) is excellent.

**DES Thrombosis and Restenosis**

Ellis et al. (14) performed a patient-based meta-analysis of the 4 principal Taxus (Boston Scientific, Natick, Massachusetts) randomized trials (3,445 patients) with a follow-up duration of \( \geq 1 \) year. Cumulative stent thrombosis occurred in 1.28% in the Taxus group and 0.76% in the BMS group at 3 years (hazard ratio 1.51, \( p = 0.26 \)). Hazard ratios (per 100 patients per 6 months) were similar in PES versus BMS during the prescribed clopidogrel period, with approximately 0.8% risk of stent thrombosis. From 6 months to 3 years there were more stent thromboses in the Taxus group (hazard ratio 0.19 vs. 0.02, \( p = 0.05 \)).

Dibra et al. (15) performed a meta-analysis of 4 randomized studies comparing SES and PES versus balloon angioplasty or vascular brachytherapy in 1,230 patients with BMS in-stent restenosis. No significant heterogeneity was found across trials. The risk of TLR (odds ratio 0.35) and
angiographic restenosis (odds ratio 0.36) (both p < 0.001), but not death or MI, were markedly lower with DES. It was concluded that DES should be considered as first-line treatment for patients with BMS in-stent restenosis.

The natural history of DES in-stent restenosis and stent thrombosis is not well known. Mishkel et al. (16) evaluated outcomes of 92 patients who developed restenosis (n = 84) or thrombosis (n = 8) inside DES. Patients were treated by the DES sandwich technique or by other methods. Over a mean follow-up of 15 months, the overall rates of death, MI, and TLR were 8.7%, 2.2%, and 30.6%, respectively. By actuarial analysis, the 12-month TLR and MACE rates were 28.2% and 42.9%, respectively. The investigators concluded that DES in-stent restenosis and stent thrombosis are associated with a significant long-term rate of MACE.

Two other studies documented that large thrombus burden is an independent predictor of MACE and stent thrombosis in patients treated with DES for STEMI (17), and that IVUS performed during PCI for DES stent thrombosis generally shows thrombotic occlusion within an underexpanded stent (18).

Clopidogrel Desensitization

Clopidogrel hypersensitivity can have devastating consequences in patients treated with DES. von Tiehl et al. (19) describe an apparently safe and effective outpatient method to desensitize patients. The technique, supervised by a dedicated drug desensitization nurse and an allergist, involves increasing oral doses of clopidogrel over 8 h, finally reaching a dose of 75 mg. Only 4 of 24 patients had reactions, mostly minor. The benefit persisted up to 6 months. The investigators warn that even a brief period of discontinuation of clopidogrel after desensitization may allow symptoms to recur once the drug is restarted.

Lesion Morphology With Advanced Imaging Techniques

Data are now accumulating showing that invasive techniques can determine plaque composition, which has been shown to determine risk of plaque rupture. Using IVUS radiofrequency data, Valgimigli et al. (20) determined that necrotic core content was quite minimal in left main coronary artery stenoses, but peaked in the first 6-mm left anterior descending (LAD) coronary segment and then progressively decreased distally. This is consistent with angiographic studies suggesting that most MIs occur in the proximal one-third of coronary arteries. Furthermore, Kawamoto et al. (21) showed that necrotic core content was associated with embolization of small embolic particles and reduced coronary flow reserve. Finally, Kubo et al. (22) compared culprit lesion morphology with IVUS, coronary angiography, and optical coherence tomography, and suggested that optical coherence tomography may identify plaque rupture fibrous cap erosion, intracoronary thrombus, and thin cap fibroatheromas more frequently compared with the other techniques. These invasive imaging techniques will ultimately need to show the ability to predict the benefit of therapeutic interventions and predict clinical events to have greater clinical utility.

Cardiac Imaging

Cardiac Computed Tomography (CT)

The Journal published the first studies looking at the prognostic power of computed tomographic angiography (CTA). In a study by Min et al. (23), the severity of atherosclerosis represented as number and location of segments involved with lesions as well as location and type of atherosclerotic plaque were correlated with all-cause mortality in 1,127 patients followed up for 15.3 months on average. Clinical scores measuring plaque burden and distribution predicted a higher absolute death rate (6.6% vs. 1.6% and 8.4% vs. 2.5%, p = 0.05 for both). Similar studies on the prognostic power of CTA showed a positive relationship between stenotic plaque and combined cardiac events (24) as well as between calcified plaque and all-cause mortality (25). These studies, although single-center and focused on symptomatic or referred patients, reveal the potential of CTA as a prognostic tool in patients with suspected coronary artery disease (CAD).

The limitations of cardiac CTA in advanced CAD were illustrated by a study looking at combined anatomical and perfusion information from hybrid multidetector CTA/ single-photon emission computed tomography (SPECT) in symptomatic individuals with suspected CAD (26). The hybrid approach increased the specificity and positive predictive value of detecting significant angiographic lesions that were associated with a corresponding perfusion defect. Given the possibility of coupling multidetector CTA with positron emission tomography (PET) or SPECT, or even in the future obtaining both sets of information from CT alone, this pioneering study is thought provoking. Finally, in an interesting study aimed at better defining which patients with CAD are most likely to benefit, Meijboon et al. (27) reported this year that multidetector CTA is most useful in patients with a low to intermediate estimated pre-test probability of having significant CAD.

Although CTA has been shown to be accurate in the identification of coronary stenoses, the clinical utility of the modality remains undefined. Goldstein et al. (28) conducted an important RCT to assess the value of CTA in patients with acute chest pain syndromes. The investigators randomized nearly 200 patients to either immediate CTA or the usual clinical evaluation for chest pain in the emergency room. No adverse events occurred in either patient group.

The CTA immediately identified coronary disease as the probable source of the chest pain in 75% of patients, whereas the remaining 25% required stress testing. Evaluation by CTA reduced diagnostic time from 15 to 3.4 h and lowered costs from $1,870 to $1,580. Although these data impressively showed the ability of CTA in the emergency room to reduce the time and cost required to evaluate chest
pain, the accuracy in identifying CAD was identical for CTA and traditional evaluation, and no adverse events were experienced. In addition, a subset of patients was exposed to radiographic procedures twice, and some on 3 occasions (immediate CTA, myocardial perfusion stress imaging, and cardiac catheterization).

Data regarding the ability of CTA to identify stenoses in stented coronary vessels has been lacking. Cademartiri et al. (29) took advantage of technological advances in CTA to study 182 patients with intracoronary stents. Only 7.3% of stented segments were excluded because of poor image quality. In comparison with invasive coronary angiography, CTA exhibited a sensitivity and specificity of 95% and 93% in diagnosing in-stent restenosis. Similarly, Konen et al. (30) studied the prevalence of intramuscular coronary arteries as visualized by CTA. They identified 47 muscular segments in 30.5% of patients evaluated, most located in the mid LAD. Prevalence of myocardial vessels observed was greater than reported with angiography and concordant with pathological findings.

The use of CTA to diagnose CAD in patients presenting with HF was examined by Andreini et al. (31) in 61 dilated cardiomyopathy patients who underwent both CTA and invasive coronary angiography. An excellent agreement between these 2 techniques for detection/exclusion of significant coronary artery stenoses was observed (sensitivity 99%, specificity 96%). Recent studies have extended the use of 64-slice CTA to evaluate patients with previous revascularization either by stenting or coronary artery bypass graft surgery. Ehara et al. (32) evaluated 81 patients with previous percutaneous coronary intervention and stent implantation with CTA and compared the results with invasive angiography. A sensitivity and specificity of 92% and 81% were reported to detect/exclude in-stent restenosis; when 15 uninterpretable segments were excluded from analysis, sensitivity remained unchanged, whereas specificity increased to 91%.

Meyer et al. (33) evaluated 138 patients with previous bypass surgery with CTA; 98% of grafts were adequately visualized on multislice CT. Direct comparison with invasive angiography yielded a sensitivity and specificity of 97% for both to detect/exclude graft stenosis/occlusion.

Weustink et al. (34) reported on the diagnostic accuracy of the newest-generation CT scanners, the dual-source CT. A total of 100 patients were evaluated in a head-to-head comparison with invasive angiography; 220 stenoses were detected in 1,489 evaluated segments on angiography. The sensitivity and specificity of dual-source CT were both 95%.

Cardiovascular Magnetic Resonance Imaging (MRI)

A meta-analysis in 3,707 symptomatic patients by Nandalur et al. (35) showed that both exercise and vasodilator stress MRI detects CAD (sensitivity and specificity of 0.83 and 0.86, and 0.91 and 0.81, respectively). Interestingly, although adenosine and dipyridamole are the most common modalities of stress-induced MRI testing today, dobutamine stress MRI was equally efficacious in the detection of occlusive CAD. In a different study, Bodi et al. (36) showed that vasodilator-based MRI tests also carry important prognostic information in patients being evaluated for suspected CAD, similar to nuclear-based stress tests. In combination, these studies support the use of vasodilator and dobutamine based stress MRI to assess CAD.

Contrast-enhanced MRI was used to define the prognosis of patients with myocardial disease. Valeti et al. (37) reported that myocardial damage quantified by delayed enhancement is less in hypertrophic cardiomyopathy patients treated with septal myectomy than with alcohol ablation, and this could underlie differences in prognosis.

The ability of cardiovascular MRI to characterize both myocardial and vascular disease processes was illustrated by two studies. The first, by Gilson et al. (38), used MRI in an experimental model of infarction showing that suppression of nitric oxide synthase enhanced border zone contractility and reduced post-infarct remodeling. These observations have important implications for understanding post-infarct remodeling at a time when stem cell-induced myocardial regeneration particularly targeted to the infarct border zone is being attempted. The second study, by Yeon et al. (39), combined vascular imaging by MRI and CT to identify coronary atherosclerotic plaque activity by delayed enhancement of vessel wall in patients with risk factors compared with normal control patients. The study provides a glimpse of the potential future of multimodal imaging to phenotype human cardiovascular disease.

Magnetic Resonance Perfusion Imaging

Although CMR myocardial perfusion imaging can diagnose coronary stenoses, its ability to discriminate the severity of obstruction remains uncertain. Costa et al. (40) compared the results of quantitative magnetic resonance perfusion imaging with FFR measurements from intracardiac pressure wires in 37 patients undergoing cardiac catheterization. Myocardial perfusion reserve (MPR), calculated from the ratio between stress and rest signal intensity curves using deconvolution analysis, was related to an FFR of greater or less than 0.75. An MPR cutoff of 2.04 showed a high sensitivity of approximately 90% with a moderate specificity of approximately 50% in predicting an FFR of above or below 0.75. Thus, these data indicate that magnetic resonance perfusion imaging provides a useful noninvasive tool for assessing the hemodynamic significance of coronary stenosis.

Nuclear Cardiology

An interesting study focused on the prevalence of CAD in asymptomatic patients with atrial fibrillation. Askew et al. (41) evaluated 374 patients with asymptomatic atrial fibrillation and 374 matched control patients with myocardial perfusion SPECT imaging. Abnormal SPECT studies were observed in 52% and 48%, respectively, suggesting a substantial relation between atrial fibrillation and CAD.
Another study evaluated the relative merits of calcium scoring and SPECT perfusion imaging for assessing long-term prognosis in 1,153 patients over a mean follow-up of 32 ± 16 months (42). The main finding was that patients without ischemia had an excellent prognosis, independent of the calcium score.

**Positron Emission Tomography (PET)**

Positron emission tomography remains one of the most important tools for probing human disease processes, and several publications in the *Journal* this year are good examples of such power. A study by Tahara et al. (43) showed that vascular inflammation is clearly associated with the metabolic syndrome by imaging carotid arteries with 18F-fluorodeoxyglucose (FDG). Vascular inflammation defined by PET was associated with waist circumference, hypertensive medication, carotid thickness, high-density lipoprotein cholesterol, insulin resistance, and C-reactive protein (CRP). This study is valuable for understanding how metabolic syndrome patients become vulnerable to events at the vascular level.

There is increasing interest in combined PET-CT scanners; Sampson et al. (44) used the CT component to perform attenuation correction of PET perfusion images obtained with rubidium-82. In a direct comparison with angiography, the sensitivity and specificity of this approach were 93% and 83%, respectively, to diagnose CAD.

Although PET identification of viable myocardium is often utilized in deciding to revascularize patients with severe LV dysfunction and CAD, evidence that such decisions alter clinical outcome is lacking. Therefore, Beanlands et al. (45) conducted the PARR-2 (PET and Recovery following Revascularization) study to assess the effectiveness of FDG-PET to assist in the management of these patients. Patients with severe LV dysfunction being considered for revascularization or transplantation were initially stratified according to recent angiography and then randomized to management assisted by FDG-PET (2,018 patients) or standard care (2,012 patients). The primary outcome was composed of cardiac death, MI, or recurrent hospitalization within 1 year. The percent of patients experiencing the primary end point was similar in the 2 arms: 30% in the PET arm and 36% in the standard arm. However, 25% of the patients with PET indications for revascularization did not have the procedure performed. The hazard ratio for the composite outcome in patients who adhered to PET recommendations was 0.62, p < 0.02. Thus, the study did not provide evidence that PET-assisted management altered outcomes in this clinical setting, although those patients treated according to PET recommendations did seem to have superior outcomes.

**Echocardiography**

**Exercise echocardiography.** It has been shown that echocardiography and radionuclide myocardial perfusion imaging (MPI) have equivalent accuracy in diagnosing CAD. However, the prognostic significance of the modalities remains uncertain. Metz et al. (46) compared the prognostic value of a normal exercise myocardial perfusion study to a normal exercise echocardiograph in a meta-analysis. They found that the negative predictive value for MI and cardiac death was 98.8% for MPI and 98.8% for echocardiography, and was similar for women and men. These data establish that both MPI and exercise echocardiography have a high negative predictive value for cardiac events.

Park et al. (47) reported on improved diagnostic accuracy of exercise echocardiography when imaging was included during as well as after exercise. The exercise echocardiography protocol in 104 patients consisted of baseline images, followed by image acquisition at 25 W, 50 W, and peak exercise. Inclusion of these intermediate stages improved the sensitivity for CAD (94% vs. 74%, p < 0.05); specificities were similar.

Vartdal et al. (48) used strain imaging in patients with acute infarction; global LV longitudinal strain was assessed immediately after reperfusion and was shown to relate well to infarct size assessed by contrast-enhanced MRI 9 months later (r = 0.77, p < 0.001).

**Dyssynchrony by echocardiography.** The role of dyssynchrony as detected by echocardiography in HF patients and in the decision for resynchronization therapy continued to be a topic of high interest. Left ventricular dyssynchrony was found to predict subsequent LV modeling after acute MI. In a study by Mollema et al. (49), 176 patients with acute MI underwent assessment of synchrony by tissue Doppler recordings within 48 h of intervention. Multivariate analysis showed that LV dyssynchrony was superior in predicting LV remodeling to other echocardiographic indexes such as wall motion score and E/E'. Therefore, LV dyssynchrony can be of value in predicting 6-month remodeling in patients with acute MI.

Yu et al. (50) studied the potential role of diastolic dyssynchrony in HF. They performed tissue Doppler recordings in 373 patients, 92 with diastolic HF, and assessed systolic and diastolic synchrony as the time to peak myocardial systolic and early diastolic velocities, respectively, using a 12-segment model. Time to peak systolic and diastolic velocity was prolonged in the HF patients. Patients with diastolic HF had comparable diastolic dyssynchrony (36%) but less systolic dyssynchrony (39%) than patients with systolic HF. Thus, the investigators concluded that both diastolic and systolic dyssynchrony were common in patients with diastolic HF despite the presence of a narrow QRS complex, but were not related to myocardial systolic or diastolic function. In the same issue, Wang (51) reported a similar prevalence of diastolic and systolic dyssynchrony in patients with diastolic and systolic HF. Interestingly, in this study one-third of patients with diastolic HF had systolic dyssynchrony. It is clear that dyssynchrony is increasingly being found wherever it is sought by echocardiography,
suggesting either an unrecognized mechanism of disease or overdiagnosis.

Although the significance of dyssynchrony remains uncertain, its response to medical therapy is even less defined. Takemoto et al. (52) performed standard and stain echocardiography in 25 patients with idiopathic dilated cardiomyopathy before and after treatment with carvedilol. They observed a marked improvement of both contractile function and dyssynchrony in HF patients with a normal QRS complex. Thus, it seems that mechanical dyssynchrony can be ameliorated by effective medical therapy of HF.

Echocardiographic detection of dyssynchrony has thus far been imperfect in identifying patients with a favorable response to cardiac resynchronization therapy (CRT). Therefore, Gorcsan et al. (53) tested the hypothesis that a combined evaluation of longitudinal dyssynchrony by tissue Doppler and radial desynchronization by speckle tracking could provide a more accurate assessment of the potential for a favorable response. In 166 patients they showed that when both longitudinal dyssynchrony and radial dyssynchrony were positive, 95% of patients had an increase in ejection fraction.

**Diastolic dysfunction.** Diastolic dysfunction is more properly termed heart failure with preserved (or normal) systolic function (HFNSF). Persson et al. (54) reported a substudy from the CHARM (Candesartan in Heart Failure) trial that tested the hypothesis that diastolic dysfunction was an important predictor of cardiovascular mortality in HFNSF patients. Diastolic dysfunction, identified on Doppler echocardiographic recordings or elevation determination of plasma NT-pro-brain natriuretic peptide, were assessed in 312 patients with an average ejection fraction of 50%. Echocardiographic evidence of diastolic dysfunction was present in 67% of patients, and moderate or severe diastolic dysfunction predicted a poor outcome (primary end point 18% vs. 5%, p < 0.01). This study was significant in showing that objective echocardiographic evidence of diastolic dysfunction carries a poor prognostic significance in patients with HFNSF. In another study, Melenovsky et al. (55) compared the cardiovascular features of patients with HFNSF with individuals with hypertensive LV hypertrophy and control patients. They observed that many cardiovascular characteristics were similar in the 2 patient groups. However, the HFNSF group had a greater concentric LV hypertrophy, higher estimated pulmonary artery wedge pressure, and greater degree of left atrial dilatation and dysfunction. The investigators concluded that the accentuated LV hypertrophy and left atrial dilatation/failure may help clarify the pathophysiology and help identify those at risk for HF in patients with LV hypertrophy.

**Hypertrophic cardiomyopathy (HCM).** Hypertrophic cardiomyopathy is classically associated with mildly impaired diastolic filling dynamics. However, Kubo et al. (56) described a group of patients in whom no or minimal (<15 mm) LV hypertrophy and severe restrictive diastolic filling abnormalities were observed in the setting of HCM. That these patients were part of the spectrum of HCM is evidenced by the facts that they had a family history of HCM, typical histology of the disorder at necropsy, and a mutation in the beta-myosin heavy chain or cardiac troponin I. The restrictive phenotype was observed in 1.5% of hypertrophic individuals from 2.3% of the families studied, and was associated with a poor 5-year rate of survival, cardiac transplantation, or use of implantable cardioverter-defibrillator (ICD).

Alcohol septal ablation provides an alternate therapy to surgical myectomy for patients with HCM, but it remains unknown whether surgical procedures can effectively be performed after a failed attempt at alcohol ablation. Nagueh et al. (57) reported the results of surgical myectomy in 20 patients who had failed alcohol septal ablation. There was no operative mortality, and a significant improvement was observed in New York Heart Association functional class with exercise duration increasing from 168 to 423 s and LV outflow track.

**IVUS.** Intravascular ultrasound has been used to answer many questions regarding the pathophysiology of coronary atherosclerosis. Nicholls et al. (58) applied IVUS to determine the ability of coronary atheromas to regress under aggressive lipid-lowering therapy with statins. The ability of lesions with a high calcium index to regress was markedly diminished. A lesser calcium index in a stenosis was associated with a higher rate of patients showing a change in atheroma burden of at least 5% compared with highly calcified lesions (70% vs. 53%, p < 0.001).

**Valvular Heart Disease**

**Statins and aortic stenosis.** Changes in the aortic valve in patients with aortic stenosis are similar to atherosclerosis and may therefore be responsive to treatment with statins. To test this hypothesis, Moura et al. (59) conducted the RAAVE (Rosuvastatin Affecting Aortic Valve Endothelium) study. They randomized 121 consecutive patients to treatment with rosvastatin (20 mg/day) or no treatment. Over the average course of 73 weeks of follow-up, the reduction in valve area in the rosvastatin group of 0.05 cm² per year was significantly less than the change in the control group at 0.10 cm² per year (p < 0.004). Thus, these data provide evidence that statin therapy may slow the progression of aortic stenosis. The beneficial effects in the RAAVE study, which were not observed in the SALTIRE (Scottish Aortic Stenosis and Lipid Lowering Trial, impact on Regression), were likely related the fact that patients in the SALTIRE study were excluded if they had an indication for statin therapy, whereas patients in the RAAVE trial were specifically put on rosuvastatin if they had elevated lipid levels. With regard to the treatment of aortic stenosis, Grube et al. (60) reported the results achieved with second-generation and third-generation self-expanding percutaneous aortic valve prostheses. Procedures were performed in 86 patients with severe high-risk aortic stenosis, with acute
device success of 88%, resulting in reduction of mean gradient from 43 to 9 mm Hg without a change in aortic regurgitant grade. Procedural mortality was 6%, and overall 30-day mortality was 12%. The combined rate of death, stroke, and MI was 22%. These data indicate that although percutaneous aortic valve prostheses are associated with a high complication rate, they provide a viable alternative for high-risk patients with aortic stenosis who are extremely high risk for surgery.

A paper from the Cardiovascular Healthy Study by Novaro et al. (61) examined the role of inflammation as represented by levels of CRP in the progression of aortic stenosis. They assessed the progression of aortic stenosis by echocardiography in 5,621 patients, and found a progression to aortic stenosis during 5 years in 9% of the 1,610 subjects with aortic sclerosis. C-reactive protein was associated with neither baseline nor progression to aortic stenosis. Thus, this study did not provide evidence that inflammation, at least as represented by CRP, played a major role in the progression of aortic sclerosis to aortic stenosis.

It remains unresolved whether mitral valve annuloplasty is of value in patients undergoing bypass graft surgery for CAD in whom at least moderate to severe functional mitral regurgitation is present. Milhaljevic et al. (62) performed a retrospective analysis of 390 such patients, in 290 of whom mitral annuloplasty was performed. Groups were propensity matched. No difference in 1-, 5-, or 10-year survival was observed despite the fact that patients undergoing bypass surgery alone were more likely to have a moderate to severe post-operative mitral regurgitation. Functional class improved in both groups. Although this study has all the limitations of a retrospective analysis, it did provide evidence that mitral valve annuloplasty in addition to bypass surgery does not enhance functional status or prolong survival in patients with moderate to severe mitral regurgitation.

**Biomarkers**

**Acute coronary syndromes (ACS).** Myeloperoxidase (MPO) is a neutrophil and monocyte enzyme that amplifies the reactivity of hydrogen peroxide through generation of hypochlorous acid, free radicals, and reactive nitrogen species. Mocatta et al. (63) provided possible new mechanistic and clinical data regarding MPO in ACS. They followed up 512 patients with MI for 5 years and observed a 1.8-fold greater adjusted risk of death in patients with plasma MPO >55 μg/ml.

Monocyte chemoattractant protein (MCP)-1 is a chemo- kine recruiting signal for monocytes that may function as both a mediator and a biomarker of ACS. de Lemos et al. (64) measured MCP-1 at baseline, 4 months, and 12 months after early stabilized ACS and correlated levels with clinical events in the Z phase of the A to Z (Aggrastat to Zocor) trial. They found that higher MCP-1 levels were associated with an increased risk for long-term death and major adverse cardiac outcomes, independent of low-density lipoprotein (LDL), CRP, and brain natriuretic peptide.

Heart-type fatty acid binding protein (H-FABP) is released into the circulation after myocardial ischemia and necrosis and thus may be of value in the setting of ACS. To this end, Kilcullen et al. (65) examined H-FABP within 12 to 24 h after symptoms of ACS. Heart-type fatty acid binding protein proved to be a powerful predictor of death, even when troponin levels were normal.

Liuzzo et al. (66) studied whether the expansion of unusual T lymphocytes, CD4+ CD28null cells, might represent a key pathogenetic mechanism of recurrent plaque instability. They examined T cells in patients with unstable angina grouped according to occurrence of prior and subsequent events. CD28null cells were independent predictors of future acute coronary events (odds ratio 3.1).

**Heart failure (HF).** Growth differentiation factor (GDF)-15 is a stress-responsive member of the transforming growth factor beta cytokine superfamily. Kempf et al. (67) measured circulating levels of GDF-15 in 455 patients with CHF and low ejection fraction. Growth differentiation factor-15 was closely correlated to New York Heart Association functional classification and showed that the risk of death at 48 months increased with increasing quartiles (56% mortality in highest quartile) independent of established biomarkers such as NT-pro-brain natriuretic peptide.

**Ultrafiltration.** Costanzo et al. (68) studied intravenous diuretics versus ultrafiltration for patients with decompensated HF in the UNLOAD (Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure) trial. Patients hospitalized for acute HF and hypervolemia were randomized to ultrafiltration or parenteral diuretics. Primary end points were weight loss and dyspnea assessment at 48 h. Ultrafiltration safely produced greater fluid and weight loss than diuretics, with no effect on dyspnea, and reduced resource use for HF at 90 days.

Cassar et al. (69) compared outcomes of patients treated for obstructive sleep apnea (OSA) versus patients with untreated OSA, all of whom had undergone PCI. The investigators concluded that treatment of OSA in patients who then underwent PCI resulted in a significant reduction in cardiac death but not in MACE or major adverse cardiovascular or cerebral events when compared with untreated OSA patients. They suggest that screening for and treating OSA in patients with CAD undergoing PCI may result in decreased cardiac death and overall mortality.

A problem in treating patients with advanced HF is that intravenous loop diuretics may produce worsening renal function or induce resistance. Therefore, Givertz et al. (70) tested a new adenosine A1-receptor antagonist in regard to its ability to produce diuresis and preserve renal function in patients with acute decompensated HF and renal impair-
ment or diuretic resistance. In 146 patients with acute decompensated HF, the new agent (KW-3902, rololofylline) increased urine output during 4 days and decreased the dose of furosemide administered. A single infusion of 10, 30, or 60 mg KW-3902 increased hourly urine output and estimated creatinine clearance with a peak effect at 24 h. Thus, adenosine A-1 receptor antagonism provides an effective means of inducing diuresis in patients in whom acute decompensated HF is complicated by renal impairment or diuretic resistance.

Considerable controversy has surrounded the use of recombinant human B-type natriuretic peptide (nesiritide) in the treatment of HF, particularly with regard to its ability to compromise renal dysfunction. Therefore, Mentzer et al. (71) conducted the NAPA (Nesiritide Administered Peri-Anesthesia in patients undergoing cardiac surgery) trial to examine the effects of this agent on post-operative renal function, clinical outcomes, and safety in patients undergoing coronary bypass. Compared with placebo, nesiritide was associated with an attenuation of the increase in serum creatinine (0.15 vs. 0.34, p < 0.001), a smaller decrease in glomerular filtration rate (10.8 vs. 17.2, p < 0.001), and a greater urine output during the initial 24 h after surgery. The study group was relatively small, and the use of other medications was not controlled, but the current study provides some reassurance regarding the use of the agent in this clinical setting.

Another study directed to assess the effect of nesiritide on renal function was performed by Witteles et al. (72) in patients with acute decompensated HF and pre-existing renal dysfunction. This randomized, double-blind, placebo-controlled clinical trial assigned 39 patients to nesiritide and 36 to placebo; serum creatine was 1.82 mg per dL/mg and 1.86 mg per dL/mg respectively. No significant differences were observed in the incidence of a 20% creatine increase, or in the change in serum creatine. Secondary end points also were similar. These findings mute, but do not resolve, concerns regarding the ability of natriuretic peptides to produce renal insufficiency in acute HF patients.

An important study reported improved survival in patients with end-stage HF who were currently listed for heart transplantation. Lietz et al. (73) examined records from the United Network for Organ Sharing for nearly 40,000 status 1 and status 2 and 3 patients awaiting transplantation. The investigators observed that the 1-year survival on the heart transplant waiting list improved from 49% to 69% for status 1 and from 81% to 89% for status 2 candidates between the years 1990 to 1994 and 2000 to 2005. The investigators observed that because the 1-year survival of status 2 candidates awaiting heart transplantation approaches that of transplantation itself, early listing of status 2 patients may be of little value. In an accompanying editorial, Young (74) questioned whether or not the time had come to perform a randomized clinical trial evaluating the benefit of cardiac transplantation in stable outpatients with chronic HF (United Network for Organ Sharing status 2).

It is clear that the majority of patients in whom an ICD is placed will never require its use, raising the question of whether we can predict which patients are most likely to benefit from ICD implantation. To address this, Goldenberg et al. (75) performed a post-hoc analysis of MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) to determine the relationship among blood pressure, risk of sudden cardiac death, and ICD benefit in patients with ischemic LV dysfunction. Multivariate analysis in the control arm showed that 10-mm Hg increments in systolic pressure were associated with 14% and 16% reductions in the risk of cardiac mortality and sudden death, respectively. Moreover, placement of an ICD provided the least survival benefit (e.g., hazard ratios [HRs] of 1.04 and 1.05, respectively) to the higher blood pressure quartile of the population (systolic pressure >130 mm Hg). These results raise the possibility that blood pressure measurement may be useful in identifying lower-risk patients in whom sudden death is unlikely to occur.

Low blood pressure has been noted to be an important risk factor for adverse outcomes in HF, and it often limits treatment options. A fixed-dose combination of isosorbide dinitrate/hydralazine (FDC I/H) improved survival in A-HeFT (African-American Heart Failure Trial). Anand et al. (76) examined whether blood pressure lowering is critical for FDC I/H efficacy and whether low blood pressure limits the efficacy by looking at treatment effects in A-HeFT patients whose systolic blood pressure was above or below the median of 126 mm Hg at study entry. Not surprisingly, patients with lower blood pressures had more severe HF and higher risk for death or HF hospitalization. Despite the fact that FDC I/H reduced blood pressures in patients above the median but not in those that were below the median, treatment had similar effects on mortality and hospitalization in patients above and below the blood pressure median. Moreover, FDC I/H did not further lower systolic blood pressure even in the lowest quintile group, whose baseline systolic blood pressure was ≤100 mm Hg. Thus, presence of low blood pressure should not be considered an absolute contraindication for the use of FDC I/H, particularly in asymptomatic patients.

Over the past year, several articles published in the journal have provided insights into fundamental mechanisms and new approaches to prevention and treatment of cardiac remodeling. Although statins possess properties beyond their ability to lower lipids and previous studies have shown favorable effects in HF patients, the mechanism(s) responsible have not been well defined. Zaca et al. (77) studied the effects of low-dose (LD; 0.5 mg/kg daily) and high-dose (HD; 3.0 mg/kg daily) rosvastatin on the progression of LV dysfunction and remodeling in dogs with HF induced by coronary microembolization. Although there was no significant effect of LD rosvastatin on LV volumes or function, treatment with HD significantly attenuated changes in LV volumes and ejection fraction compared to control. Moreover, HD but not LD rosvas-
tatin normalized levels of the pro-inflammatory cytokine tumor necrosis factor (TNF)-α and significantly increased the number of circulating bone marrow-derived stem cells. These results support the possibility that statins may improve outcomes in HF patients by mechanisms that transduce their ability to lower lipids.

Early post-MI activation of the sympathetic nervous system has been associated with the development of remodeling. Kasama et al. (78) compared the effects of 48-h infusion of isosorbide dinitrate (ISDN) or atrial natriuretic peptide (ANP) on cardiac sympathetic nerve activity (CSNA) and remodeling parameters in 50 patients with first anterior acute MI after primary angioplasty. Despite similar risk factors and extent of initial damage, patients treated with ANP showed reduced total defect score and 123I-meta-iodobenzylquanidine uptake (as an indicator of norepinephrine uptake) at 3 weeks post-MI and significantly lower EDV and higher EF. These findings raise the intriguing possibility that prophylactic treatment with ANP early in the post-MI period might be an effective way of inhibiting the sympathetic nervous system in the heart, which then translates into favorable effects on subsequent post-MI cardiac remodeling.

Although aldosterone receptor antagonists improve survival in patients with post-MI LV dysfunction and HF, their ability to favorably affect the remodeling process has not been fully established. Chan et al. (79) randomized 51 patients to either the angiotensin receptor blocker (ARB) candesartan or combination of an ARB and spironolactone. Reverse remodeling was assessed serially over 1 year by MRI and tissue Doppler imaging. Compared with the ARB alone, combination therapy reduced EDV, end-systolic volume, and LV mass index, and significantly increased peak basal systolic velocity and strain by tissue Doppler imaging.

Klotz et al. (80) hypothesized that angiotensin-converting enzyme inhibition (ACE-I) during LV assist device (LVAD) support in patients with end-stage HF could prevent potentially deleterious effects on the extracellular matrix. To study this, they obtained heart samples before and after LVAD implantation in 7 patients who received and 15 patients who did not receive ACE-I while being maintained on an LVAD. They found that Angiotensin II was reduced in the ACE-I group but increased in control subjects and that cross-linked collagen decreased during LVAD support in the ACE-I group. Moreover, LV mass and myocardial stiffness were lower in the ACE-I group, and LV and right ventricular (RV) matrix metalloproteinase-1/tissue inhibitor of metalloproteinase-1 ratio were normalized. Because increased fibrosis and LV stiffness have been demonstrated after LVAD placement, these results raise the possibility that ACE-I might prevent these changes and improve the likelihood of recovery of cardiac function.

There has been considerable controversy regarding the thiazolidinediones (TZDs) and their impact on cardiovascular disease. Dargie et al. (81) studied the effects of rosiglitazone (RSG) in patients with type 2 diabetes and mild New York Heart Association functional class I to II chronic HF. The 224 patients in the study were assigned to receive RSG in addition to other antidiabetic therapies. After 52 weeks, changes in LVEF were similar between the groups and patients receiving RSG had better glycemic control. Although new or worsening edema and increased HF medication was more common with RSG treatment, there were no differences in other adjudicated end points and withdrawal for adverse events was equal between groups. These findings were similar to those of a retrospective survey done by Aguilar et al. (82) of a national cohort of veterans with HF and diabetes. In this ambulatory population, the use of TZDs was not associated with an increased risk of HF hospitalization or total mortality.

**Coronary Disease and Atherosclerosis**

Controversies in cardiology. Two major issues generated considerable controversy during the past year and received in-depth analysis in the pages of the Journal. The first is the continued debate regarding the potential risk of stent thrombosis related to DES. Kaul et al. (83) reviewed the clinical data and emphasized that off-label use of DES may be responsible for late stent thrombosis events and advocated stricter adherence to evidence-based medicine and on-label use of therapies. Holmes et al. (84), in contrast, professed a more optimistic view of DES, emphasizing the lack of a mortality difference to BMS. All agreed to the need for further research.

Controversy regarding the role of interventional cardiology in clinical practice was heightened after the publication of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial (85), a study comparing intensive medical therapy plus PCI to intensive medical therapy alone in patients with stable coronary disease. The trial’s main conclusion was that there was no advantage to an initial strategy of PCI over intensive medical therapy alone. A critique of the COURAGE trial by Kereiakes et al. (86) emphasized the better angina-free status in the PCI group without additional mortality and further claimed that potential benefits of DES and more complete revascularization may further improve outcomes with the PCI approach. A spirited defense of the trial by Diamond and Kaul (87) emphasized the novel information in the trial and that indeed medical treatment is the preferred initial approach in stable CAD, with potential significant savings for the health care system.

**Angina pectoris.** One of the consequences of the COURAGE trial has been a renewed interest in new medical therapies for ischemic heart disease. Tolerance to nitroglycerine has been shown to be associated with free radical production and endothelial dysfunction; whether a similar phenomenon exists for isosorbide-5-mononitrate has hitherto been unknown. Thomas et al. (88) studied the effect of
120 mg isosorbide-5-mononitrate in 19 healthy subjects and showed that indeed the same phenomenon exists for this form of nitrate and that the endothelial dysfunction is reversed by co-infusion of vitamin C into the artery, alluding to an oxidative mechanism. These findings raise concerns regarding the impact of these medications on long-term vascular health (89). Novel antianginal drugs are therefore needed. The safety of one novel medication for angina, ranolazine, was evaluated in the ROLE (Ranolazine Open Label Experience) study (90). Over a mean follow-up of close to 3 years, there was no evidence of increased mortality and no episodes of torsades de pointes, despite a prolongation in mean QTc of 2.4 s.

**Platelets and antiplatelet therapy.** The central role of the platelet in acute coronary syndromes and in the complications of percutaneous interventions continued to be a focus of intense research in 2007. The *Journal* in 2007 published several key studies that addressed the role of platelet activation in high-risk groups such as diabetic patients (91), and the role of resistance to antiplatelet agents, particularly the thienopyridines. New data were also presented on emerging antiplatelet agents.

The role of persistent platelet aggregation despite dual antiplatelet therapy (aspirin and clopidogrel) in post-stenting ischemic events was studied by Blijden et al. (92) in a group of 100 patients undergoing elective PCI. The investigators found that increased platelet aggregation persisted, measured either by adenosine diphosphate (ADP)-induced platelet aggregation or by thromboelastography predicted ischemic complications. Assessment of residual platelet function may therefore be useful in targeting patients needing additional antiplatelet therapy, whether it is a higher dose of clopidogrel or a IIb/IIIa inhibitor. In the same study the investigators showed that addition of the IIb/IIIa inhibitor eptifibatide significantly further inhibited platelet aggregation in those patients with residual activity.

The importance of atorvastatin–clopidogrel interaction (which had previously attracted considerable attention given the wide use of atorvastatin in patients with coronary disease) was discounted in a retrospective analysis of the CHARISMA (Clopidogrel for High Atherothrombotic Risk, Ischemic Stabilization, Management, and Avoidance) trial (93). The lack of prospective data, however, particularly in subgroups with heightened platelet activation, emphasizes the need for further study of drug–drug interactions (123).

Various approaches have been taken to address the residual risk with dual antiplatelet therapy. Since clopidogrel is a pro-drug requiring activation by CYP3A4, a higher loading dose of 600 mg has been widely adopted. However, some patients still show nonresponsiveness. In an observational study with a total of 804 patients undergoing DES implantation, Buonamici et al. (94) demonstrated nonresponsiveness, even with the 600-mg loading dose, is associated with a 3-fold increased risk of stent thrombosis. Thus, clopidogrel nonresponsiveness is therefore not simply a laboratory curiosity, but an important clinical entity. Is nonresponsiveness a class effect or specific to one agent or another? In a crossover study, Campo et al. (95) showed that nonresponsiveness to either ticlopidine or clopidogrel was common, occurring in 1 of 5 patients, but that nonresponsiveness to both drugs occurred in only 3.5%, indicating that drug-specific mechanisms were more important. Newer agents may also lead to further therapeutic options. These include prasugrel as well as AZD6140, a reversible oral ADP antagonist, with encouraging results in the DISPERSE-2 (Dose Confirmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogRel in non-ST-segment Elevation myocardial infarction) study (96,97) published in the Journal this year.

**Advances in antithrombotic therapy.** Fondaparinux is a synthetic factor Xa inhibitor, which was compared with enoxaparin in the OASIS-5 (Fifth Organization to Assess Strategies in Ischemic Syndromes) study in patients undergoing PCI (98). The results confirmed the net clinical benefit of fondaparinux showing similar ischemic events but a lesser bleeding rate. Angiographic complications with fondaparinux (an increased risk of catheter thrombosis) were managed by an additional bolus of unfractionated heparin during the procedure.

**MI.** Despite recent advances, the mortality of patients with cardiogenic shock remains high. But what is the prognosis in those who survive the initial hospitalization? Data from the GUSTO-I (Global Utilization of Streptokinase and TPA for Oucled Arteries-I) (99) trial showed that in those who survived 30 days, annual mortality was 2% to 4%, similar to nonshock patients. Thus, there is a need to improve the immediate therapy of patients with cardiogenic shock to improve short-term mortality. One group of patients who are at increased risk of developing shock are those in whom fibrinolytic therapy has failed. A therapeutic option for these patients is rescue angioplasty versus repeat fibrinolysis. Which therapy is preferable was the subject of a meta-analysis published in the Journal (100). The analysis identified rescue PCI as having improved outcomes with no benefit for repeat fibrinolytic therapy and potentially increased harm.

**Obesity, the metabolic syndrome, and cardiovascular disease.** The obesity epidemic prompted multiple studies on the effect of obesity and the related metabolic syndrome on cardiovascular disease. Gami et al. (101) performed a systematic review and meta-analysis of longitudinal studies of obesity and showed an increased risk (risk ratio of 1.78) for cardiovascular events and death, with an even higher risk in women. Obesity was also linked with incident atrial fibrillation (102) in those age 65 or less in a retrospective study from Olmsted County, as was the related entity of obstructive sleep apnea.

The impact of the metabolic syndrome extends to interventions such as coronary artery bypass grafting (CABG). In a large retrospective study (103) of 5,304 consecutive patients undergoing CABG surgery, the relative risk of...
mortality was increased 3-fold in patients with the metabolic syndrome. The investigators hypothesized that the pro-inflammatory and pro-thrombotic milieu of the metabolic syndrome may be contributing to the increased mortality. Indeed the relationship between the metabolic syndrome and inflammation has now been confirmed not only in a Western population, but also in a large study from China (104), in which CRP was strongly associated with obesity and the metabolic syndrome.

What are the best measurements for overweight and obesity in predicting cardiovascular risk? Data from the Dallas Heart Study (105) assessed prevalent atherosclerosis with coronary artery calcium score. Waist–hip ratio rather than body mass index or waist circumference was found to be the better predictor.

The obesity epidemic is also affecting children and adolescents, but the criteria for metabolic syndrome have been developed in adults. An important step forward was published by Jolliffe and Janssen (106), who utilized growth curve modeling for each component of the metabolic syndrome. Using their derived age-specific definitions, the prevalence of metabolic syndrome in adolescents doubled over the last decade to about 1 in 10 adolescents.

What is the influence of specific dietary components on cardiovascular risk? Particular interest has been focused on the influence of refined carbohydrates and foods with high glycemic load and glycemic index. In a population-based study, Beulens et al. (107) showed an association between high dietary glycemic load and glycemic index with increased cardiovascular risk, particularly in obese women.

Cholesterol, statins, and pleiotropism. Over the past few years various studies have emphasized non-LDL factors for atherosclerosis, such as the independent influence of inflammation (most often reflected in high-sensitivity CRP levels) and the role of particle size (dense LDL vs. buoyant or fluffy LDL). A series of articles in the Journal during the past year allowed us to put these divergent emphases in perspective.

El Harchoui et al. (108) examined the relationship between atherosclerosis and LDL particle size and number in the EPIC (Evaluation of c7E3 for the Prevention of Ischemic Complications)-Norfolk Prospective Population Study. Although LDL particle number and size were predictive in univariate analysis, their additive value was lost after adjusting for triglycerides and high-density lipoprotein cholesterol. Similarly, a meta-analysis by Kinlay (109) showed that changes in CRP were primarily related to the magnitude of change in LDL, and that non-LDL effects of statins on inflammation are of much smaller magnitude.

These findings reinforce the National Cholesterol Education Program guidelines emphasizing LDL-C as the primary target of therapy, particularly in the stable outpatient setting. In the acute setting, statins may still have important pleiotropic effects as shown in the ARMYDA-ACS (Atorvastatin for Reduction of Myocardial Damage During Angioplasty–Acute Coronary Syndromes) trial (110). In 171 patients with non-ST-elevation acute coronary syndrome (NSTE-ACS), 80 mg atorvastatin before PCI and an additional 40 mg after PCI resulted in a marked reduction in procedure-related and 30-day MACE.

Traditionally risk assessment for coronary disease is carried out in middle age. However, cholesterol levels vary during life. Are levels measured earlier in life predictive of subsequent risk? The CARDIA (Coronary Artery Risk Development in Young Adults) study (111) examined the predictive value of early adult cholesterol level on coronary calcium measured 15 years later. Surprisingly levels measured in early adulthood predicted subsequent coronary calcium and were equally or more informative than levels measured later in life. These provocative findings argue for earlier risk assessment.

Given the large portion of the population that is eligible for cholesterol-lowering therapy, especially if started at a younger age, the safety of statin therapy is of great interest. In one of the most provocative articles of the year, data from large randomized statin trials were evaluated for the relationship between the magnitude of lipid lowering and the risk of liver function test abnormalities, rhabdomyolysis, and cancer (112). Surprisingly, the investigators found a correlation between lower achieved LDL levels and increased cancer risk. In an accompanying editorial (113), it was emphasized that these findings are hypothesis generating and do not change the overall risk–benefit ratio in patients who are at high risk for coronary disease.

Epidemiology. Ford and Capewell (114) investigated coronary artery disease (CAD) mortality rates from 1980 to 2002 using data from the U.S. Centers for Disease Control and Prevention and population counts from the U.S. Census. They concluded that although the overall CAD death rate has declined substantially during this period, among younger adults (ages 35 to 54 years) the decline in the CAD death rate has stabilized or even slightly increased in recent years. They also noted that these recent unfavorable trends in CAD mortality have coincided with substantial deterioration in several risk factors for CAD (obesity, diabetes, and hypertension) in this population of younger adults.

Congenital Heart Disease

Basic science insights. Hinton et al. (115) did a 3-generation family history and sequential sampling of 235 family members found after identifying 38 probands with hypoplastic left heart syndrome (HLHS). They concluded that HLHS was almost exclusively the result of a genetic cause. Fifty-five percent of the families had more than 1 affected member. Eleven percent of the probands who had aortic and mitral hypoplasia also had pulmonary and tricuspid valve abnormalities—most dysplasia. Among the 21 affected families, cardiovascular abnormalities were documented in 11 of the 51 siblings and 23 of 106 first-degree relatives, most commonly bicuspid aortic valve (10%), hypoplastic left heart, and aortic root dilation with aortic coarctation. There are factors that determine why left-sided gene defects in
genetically predisposed individuals end up with relatively mild abnormalities such as bicuspid aortic valve or the full form of HLHS. The implications for genetic counseling and the impetus for further family studies of left–sided heart defects are both among the most important aspects of this paper in the Journal.

Levy et al. (116) sought to evaluate the histologic basis of irreversible pulmonary hypertension in the clinical setting of congenital heart disease patients in whom Eisenmenger syndrome develops. This small but important study looked at antiapoptotic and pro-apoptotic markers in vascular and perivascular cells in lung biopsy samples from 18 patients, 7 with reversible and 11 with irreversible pulmonary hypertension, as well as 6 control patients. The antiapoptotic protein Bcl-2 was highly expressed by pulmonary endothelial cells in all cases of irreversible pulmonary hypertension, but in none of the reversible cases or control patients. Intimal proliferation was present in 10 of the 11 irreversible pulmonary hypertension patients, but never in the reversible cases. Similarly, perivascular inflammatory B cells expressed more antiapoptotic proteins in the irreversible cases than in the reversible. The reversible patients also had regulation of endothelial nitric oxide synthase and new small vessel formation at sites of occlusion. The data suggest that the remodeling process in the course of pulmonary hypertension caused by congenital heart disease involves an acquired apoptosis–resistant phenotype in endothelial cells, likely to result in impaired endothelial apoptosis so as to produce intimal proliferation and occlusion of distal vessels. Consistent with this hypothesis, CD34 was found in structures surrounding all vessels, and vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase are likely involved in neoangiogenesis. The investigators admit that this is only a cross-sectional study with histomorphologic data and some clinical hemodynamic correlations. However, this study highlights the role of impaired endocardial cell apoptosis and inflammatory cell apoptosis in the pathogenesis of irreversible pulmonary hypertension complicating congenital heart disease.

Cardiac mechanics in congenital heart disease. Pettersen et al. (117) studied 14 patients post-operatively after atrial switch for transposition of the great vessels and compared the contraction pattern of the systemic RV with findings in the RV and LV of 14 normal subjects using tissue Doppler imaging and MRI. They evaluated RV wall circumferential strain in the short axis and longitudinal strain, and performed MRI tissue tagging in both experimental and control patients. They examined circumferential strain at the midventricular area of the lateral wall as a reference method and measured global, basal, and apical rotation by MRI. Geometric RV diameter was larger than LV diameter, as expected, in the Senning patients. The RV free wall circumferential strain was greater than longitudinal strain—a finding that is opposite from the normal free wall and is similar to the contraction pattern of the normal RV. Strain rate also showed greater circumferential than longi-
tudinal strain; however, the values were significantly less in the systemic RV than the normal LV. In contrast to normal subjects, global rotation of the systemic RV was essentially absent at both apical and ventricular levels. The findings document a shift in the systemic RV free wall from longitudinal to circumferential contraction—a finding that brings it closer to the mechanics of the LV. Inherent torsion was absent. None of the patients had evidence of HF, so this dysfunction does not seem to be significant, but likely is an adaptive change to systemic load. As an adaptive response, the lack of torsion and the reduced strain rate may, however, imply abnormal function.

Congenital diseases of the aorta. Several articles dealt with the aortic valve and the aorta as a system, and the implications of altered flow and altered wall structure on the natural history of LV outflow tract obstruction. In the first (118), 310 patients with right and left coronary leaflet and right and noncoronary leaflet fusion bicuspid aortic valve were selected randomly from 1,192 patients followed up for 16 years. A right noncoronary morphology of fusion was predictive of valve intervention when compared with the right–left coronary fusion. In longitudinal evaluation of 799 echocardiograms, right nonfusion was also associated with a progressive degree of valve dysfunction. Right nonfusion patients were more likely to be male (73 vs. 45), less likely to have associated coarctation compared with right–left fusion (41 compared with 5), and more likely to have significant aortic stenosis or aortic regurgitation at first follow-up. The right nonfusion patients were much more likely to have progression in valve dysfunction and/or require intervention during childhood compared with other morphologic valves.

In the second study, Grotenhuis et al. (119) examined MRI and described reduced aortic elasticity and its association with aortic regurgitation and LV hypertrophy in patients with nonstenotic bicuspid aortic valve. Twenty control patients and 20 patients with nonstenotic aortic valve were studied. Distensibility and pulse wave propagation were evaluated—the latter in the descending aorta. Patients with bicuspid aortic valve had significantly increased pulse wave velocity and diminished distensibility at the level of the sinotubular junction. Aortic diameter was increased at all 4 levels—dilation was most prominent at the level of the sinus of Valsalva. The study showed frequently reduced aortic elasticity and aortic root dilation in the patients with nonstenotic valves. Reduced aortic wall velocity was associated with mild aortic regurgitation and LV hypertrophy even in the patients with relatively normal functioning bicuspid aortic valves.

Interventions in congenital heart disease. Butera et al. (120) reported a large single-center experience with the Amplatzer ventricular septal defect (VSD) occluder for muscular and perimembranous VSD (AGA Medical Corp., Plymouth, Minnesota). A total of 104 patients underwent transcatheter closure—with a median age of 14 years (66 were <10 years of age), and median weight was 26.5 kg,
with the smallest being 6.5 kg. The investigators performed their studies under transesophageal guidance and crossed the septum retrograde from the left ventricle. Device sizes were 14 to 17 mm. Multiple and surgical residual VSDs were called complex procedures. Although no deaths occurred, there were 13 significant complications in 11 patients including 2 device embolizations. No significant valve regurgitation occurred. Only trivial VSD prosthetic leak occurred. After 3 months, 4 developed complete AV block, symptomatic or asymptomatic, best predicted by young age. All of the patients in this study received a perimembranous VSD occluder, which is asymmetrical so as to not extend toward the aortic valve from the perimembranous implantation.

Jones et al. (121) reported a 2-year U.S. clinical trial involving 119 nontraining cases treated with the Helex septal occluder (Gore Medical, Flagstaff, Arizona) and 128 with surgical repair of a secundum ASD. Patients in each group were followed up at 24 h, 4 weeks, 6 months, and 12 months. Mean subject age was 12 years in the device group and 9 years in the surgical group. Estimated ASD size was 10 mm with the device and 15 mm in the surgical group. Major adverse events were reported in 5% of device patients and 7% to 10% of surgical patients. Removal of the device was required in 5 of the 7 patients with adverse events, and 2 patients had post-procedural device embolization. In the surgical arm, post-pericardiotomy syndrome occurred in 8 patients, with pericardial tamponade contributing to the death of 1. In conclusion, the study overall showed that the Helex septal occluder was a safe and effective alternative to surgery for secundum ASDs <22 mm balloon occlusion diameter.

**Congenital rhythm abnormalities.** A paper by Etheridge et al. (122) from 3 large centers reviewed the criteria for diagnosis and treatment strategies for children with long QT syndrome (LQTS).

A total of 128 patients were identified from 91 families, and these included 41% probands; 66% of the patients were female, and diagnosis was made at an age of 8 years. The QTc was a mean of 487 ± 39 ms. Genetic testing was done in 56%, family history having been the most frequent cause for referral. A KCNQ1 mutation was the most common defect identified; 98% of the study population was on beta-blockers, most commonly nadolol. A total of 27 patients had devices placed; 74% had dual-chamber devices. A total of 23 eventually underwent ICD implantation; 63% of patients had a prolonged pacing episode, with more than 30% of heartbeats paced. Five patients had had at least 1 appropriate and 4 patients had had at least 1 inappropriate discharge.

During a mean follow-up of 3.5 years, 13 patients (48%) required reinterventions. Device patients had a longer QT interval and were more likely to have symptoms than the group treated medically. There were 2 deaths. The investigators summarized that LQTS is being increasingly recognized in the absence of symptoms in conjunction with family history and genetic testing. Many of these patients are not highly symptomatic and generally do well. In the era of genetic testing and device implantation, overall mortality is low. Also, the patients in this group are relatively unlikely to need ICD implantation as long as there is compliance with necessary exercise restriction and adequate response to beta-blocker therapy.

**Adult congenital heart disease.** The ever-increasing population with adult congenital heart disease now presents a workforce issue. Guidelines for the treatment of adults with CHD are in the process of being developed by an American College of Cardiology/American Heart Association combined task force. Gurvity et al. (123) looked at the trends in hospitalization during the transition from adolescence to adulthood by analyzing data from the California Office of Statewide Health Planning and Development—a discharge dataset from 2000 to 2003. The upper age of the sample was 44 years. Admission for a cardiac-related principal procedure was an additional independent variable, as was admission from an Emergency Department versus a nonemergent source. There were 9,017 nonpregnancy-related hospitalizations in these patients in 368 hospitals in California. Only 9% were related to a CHD operation, and operations were performed in 70 hospitals. For the patients ages 21 to 44 years, there were 5,675 discharges from 346 hospitals; of these, only 25 hospitals averaged more than 12 discharges per year, and they accounted for 44.8% of the total number of discharges. For discharges associated with congenital heart operations, there were 484 discharges with 67 hospitals. Four of the hospitals alone accounted for 41.5% of the surgical discharges. With increasing age and transition to adult care, patients were more likely to be hospitalized by way of the emergency department into a hospital that did not specifically have expertise or a designated adult congenital heart center as part of its profile. Public insurance or uninsured status also increased the likelihood of admission through the emergency department. Although in the group under 21 years age, 70% of procedures were done in hospitals performing most of the surgeries, in the older age group, the most experienced facilities accounted for <45%. Thus, the pattern of hospitalization changes in and around the transition from adolescence to adulthood, with more use of hospitals that have fewer congenital heart disease hospitalizations and likely less congenital heart experience.

**Gene therapy.** Evidence that gene therapy is not dead was provided by Henry et al. (124), who assessed the effects of human adenovirus serotype 5 with human FGF-4 gene insert (Ad5FGF-4) to increase exertional capacity and myocardial perfusion in patients with CAD and refractory angina. In a pooled data analysis from 2 nearly identical trials the investigators reported a significant gender-specific (2 females) beneficial effect of Ad5FGF-4 on total exercise time, time to 1-mm ST-segment depression, time to angina, and Canadian Cardiovascular Society class in women. Thus, these data indicate that gene therapy for angiogenesis
may have a potential role in the treatment of patients with CAD.

**Stem cell therapy in acute myocardial ischemia—preclinical.** The mechanisms by which stem cell therapy has improved LV function and remodeling after acute MI would be important to delineate. Payne et al. (125) hypothesized that direct injection of muscle-derived stem cells (MDSCs) in the ischemic milieu has beneficial paracrine effects related to the release of VEGF. Injecting MDSCs into the ischemic zone of immunodeficient (NOD-SCID) mice induced neovascularization to reduce infarct size, improve infarct repair, and attenuate adverse remodeling with better preservation of LV function (fractional area changes by echocardiography) and less LV dilation over 2 weeks to 12 weeks compared with mice injected with phosphate-buffered saline. The cardioprotective effects of MDSCs were lost when MDSCs were engineered to express the soluble Flt1, a VEGF antagonist. There was greater VEGF secretion in MDSCs exposed to hypoxia or stretch in vitro. The accompanying editorial comment by Hammond (126) notes that although it is not novel to relate the benefits of stem cell transplantation to angiogenesis rather than cardiac myocyte regeneration, it has not previously been shown in such a convincing manner in a clinically relevant model. There are limitations that remain to be addressed, such as the duration of survival of engrafted MDSCs, the duration and sustained release of angiogenic proteins, the risk of engrafted MDSCs for inducing ventricular tachycardia, and the logistics of preparing autologous MDSCs that will delay the time of treatment after MI. Nevertheless, this is a significant advance for understanding a major (although not necessarily sole) contributing factor for the cardioprotective effects of stem cell therapy in acute MI and for improving post-MI ventricular remodeling.

**Lipopolysaccharide binding protein (LBP) as a novel marker of CAD—human biomarker study.** The role of chronic inflammation in the pathogenesis of atherosclerosis has been supported by evidence that activation of toll-like receptors (TLRs), the sensor of microbial infections in the innate immune response, is associated with the development of atherosclerotic lesions. Although the role of specific infectious agents is controversial, TLR4 recognizes lipopolysaccharide (LPS) from multiple organisms in the innate immune response. This requires initial binding of LPS by LBP, an acute phase reactant, and then the LPS/LBP complex is delivered to CD14, which binds to TLR4 on the cell surface. The roles of TLR4 and CD14 (to a lesser extent) in atherosclerosis have been studied, but the utility of LBP as a biomarker of CAD has not been evaluated.

Lepper et al. (127) found that higher serum LBP was in 172 patients with stable, angiographically proven CAD compared with 75 patients without CAD or 20 control patients with fibromyalgia, but lower than LBP levels in 20 patients with sepsis. On multivariable logistic regression models, LBP remained a significant and independent predictor of CAD even after adjusting for age, body mass index, other inflammatory markers (interleukin 6 and highsensitivity CRP), and known CAD risk factors including LDL, smoking, diabetes, and hypertension. Because LBP is a sensor of circulating LPS, it may be useful as a marker of activation of innate immunity that plays a role in the pathogenesis of atherosclerosis that differs from the risks associated with other biomarkers of inflammation.

**Doxorubicin-induced cardiomyopathy—preclinical study.** The clinical utility of doxorubicin is limited by cardiotoxic side effects with dose-dependent induction of an irreversible cardiomyopathy that causes HF. Mukhopadhyay et al. (128) evaluated a novel therapeutic approach of targeting the endocannabinoid system to protect against doxorubicin-induced cardiomyopathy in a mouse model. Endocannabinoids have cardiodepressant effects mediated by the cannabinoid-1 receptor (CB1), and effective CB1 antagonists are available. Mice develop a cardiomyopathy 5 days after a single intraperitoneal injection of doxorubicin, characterized by decreased systolic function and diastolic impairments. Pretreatment with 2 CB1 antagonists, rimonabant or AM281, immediately before and for 5 days after doxorubicin, attenuated the development of doxorubicin-induced cardiomyopathy and apoptosis in vivo. In vitro, doxorubicin induced apoptosis in a H9c2 myocardial cell line and increased one of the natural ligands of CB1 (anandamide, but not 2-arachidonoylglycerol), which were blocked by pretreatment with rimonabant or AM281. These results suggest that CB1 antagonists may be a novel therapeutic approach for treating doxorubicin-induced cardiomyopathy.

Fajardo and Bernstein (129) recognize the novelty of targeting the endocannabinoid system to reduce doxorubicin cardiotoxicity in an accompanying Editorial Comment, but note that further studies are needed to determine the mechanisms for the cardioprotective effects of CB1 inhibition.

**Rapid cooling of the heart for cardioprotective effects—preclinical study.** Myocardial hypothermia during myocardial ischemia has powerful cardioprotective effects to limit infarct size, but the maximal benefits have been difficult to achieve because of technical limitations in achieving hypothermia with sufficient rapidity. Tissier et al. (130) used a novel approach of total liquid ventilation (TLV) with cooled perfluorocarbon to decrease left atrial temperatures to 32°C within 5 min in intubated rabbits undergoing 30 min of ischemia and 3 h of reperfusion. Rapid cooling of the heart during ischemia reduced infarct size by 90%, whereas hypothermia during reperfusion was ineffective. This unique approach takes advantage of the large thermal mass for exchange with the central circulation. Perfluorocarbons are stable, inert compounds with low surface tension that permit effective gas exchange. Partial liquid ventilation (breathing an air–perfluorocarbon mixture) has been used safely compared with conventional mechanical ventilation in clinical trials with acute respiratory distress syndrome. The requirement for intubation and mechanical ventilation would delay definitive therapy and may make it unsuitable for primary PCI, but liquid ventilation could be applied...
readily in patients who are already intubated and mechanically ventilated. This could be used to induce therapeutic hypothermia in patients with post-operative MI or to induce rapid myocardial hypothermia in patients resuscitated after cardiac arrest to limit infarct size, which may have additive benefits to the neuroprotective effects of hypothermia.

Direct coronary blood flow measurements—preclinical and clinical study. Direct volumetric blood flow measurement in selective coronary arteries in humans has remained an elusive but important goal. Aarnoudse et al. (131) developed a thermodilution-based method for measuring coronary blood flow using a 2.8-F infusion catheter and a standard 0.014-inch sensor-tipped pressure/temperature guidewire. This method for measuring coronary blood flow was validated in dogs, and was reproducible and correlated well with absolute coronary blood flow measured by flow probe and despite varying degrees of coronary artery stenosis, infusion rates, and different positions of the temperature sensor. Preliminary studies were performed in 35 patients undergoing intracoronary catheter procedures. Because absolute coronary flow measurements are not possible, this method was indirectly validated by measuring coronary fractional flow reserve during adenosine-induced hyperemia or before and after stenting of coronary stenoses. This study provides a novel method for direct volumetric blood flow measurements that is accurate, feasible, and reproducible with potential application in humans.

Pleiotropic effects of lipid lowering agents—clinical study. The pleiotropic effects of lipid-lowering agents were examined by Piorkowski et al. (132) in 56 patients with stable CAD randomized to receive either 40 mg/day atorvastatin or 10 mg/day atorvastatin plus 10 mg/day ezetimibe for 4 weeks. Although both treatments produced a comparable decrease in LDL cholesterol, monotherapy with high-dose atorvastatin also decreased in vitro platelet activation and aggregation and lowered plasma chemokine levels (RANTES, a measure of in vivo platelet activation and inflammation). This suggests that higher statin doses may have platelet inhibitory pleiotropic effects that may be beneficial in patients with CAD.

Heart Rhythm Disorders

Amiodarone-induced thyrotoxicosis. An important paper by Conen et al. (133) draws attention to the potentially fatal sequelae of amiodarone-induced thyrotoxicosis. In a series of 84 cases, the investigators found a 50% incidence of serious events including death, heart transplantation, hospitalization for HF, MI, stroke, and other hospitalizations. Oral prednisone did not speed normalization of thyroid function and was associated with worse outcome, particularly after 1 year. These data raise awareness of the seriousness of amiodarone-induced thyroid abnormalities and the potential need for long-term clinical follow-up of these patients.

Congenital LQTS. Little information is available to help the cardiologist manage the risk for sudden death of individuals who survive adolescence to present with LQTS as adults. Sauer et al. (134) addressed this issue in 812 genotyped individuals in whom clinical data were available from ages 18 years to 40 years in the International Long QT Registry. Syncope, cardiac arrest, and sudden death during follow-up were predicted by female gender, longer QTc interval, LQT2 (vs. LQT1 or LQT3) and cardiac events before age 18 years. Surprisingly, genotype alone did not predict life-threatening arrhythmias. These factors differ from previous reports, suggesting that some clinical features confer age-dependent risk. Another notable finding was that beta-blocker use, modeled in time-dependent fashion (i.e., only for years of usage per patient) reduced fatal or near-fatal cardiac events by 60%.

Implantable defibrillators and safety of driving. A question asked of many physicians is whether it is safe for their ICD patients to return to driving. Albert et al. (135) used data from the multicenter prospective TOVA (Triggers of Ventricular Arrhythmias) cohort to study whether driving a car is associated with increased risk of appropriate ICD shocks. In 1,188 ICD recipients followed up for a median of 562 days, 80% of all participants and 75% of those within 6 months of implant self-reported driving a car at least once per week. Among those who received ICD shocks, shocks were twice as likely within 1 h of driving as during other activities. Risk was actually higher in the 30 min after driving than during driving, but remained low in absolute terms (1 episode per 25,116 person-hours of driving). Thus, the risk of ICD shocks causing a motor vehicle accident is low; indeed, only 1 of 7 shocks that did occur while driving resulted in an accident. Finally, there were trends toward higher risks of shocks among recent ICD recipients and those with prior ICD therapy, supporting guidelines for a period of driving abstinence for these individuals.

The risk for lethal ventricular arrhythmias. The search continues for strategies to improve risk stratification for lethal ventricular arrhythmias beyond the presence of reduced LVEF and symptomatic HF. This was the focus of several articles published in the Journal this year. Salerno-Uriarte et al. (136) published the primary results from the ALPHA (T-Wave Alternans in Patients With Heart Failure) study, a prospective study of the ability of T-wave alternans (TWA) to predict arrhythmic events in individuals with nonischemic cardiomyopathy. The investigators studied 446 individuals with LVEF of 40% or less in New York Heart Association functional classes II to III. Over 19 months of follow-up, patients who tested TWA negative had a significantly lower rate of ventricular arrhythmias (1.6%) than those with abnormal TWA (6.5%). Although these patients had a lower than expected event rate overall, this result is particularly important because TWA has had mixed success in patients with nonischemic cardiomyopathy.
Extending the link between repolarization variations and arrhythmic risk, Iacoviello et al. (137) studied ambulatory electrocardiogram (ECG) indexes in 179 nonischemic cardiomyopathy patients with LVEF 34 ± 10%. Nonsustained ventricular tachycardia and steeper QT/RR slope (QT dynamics) identified patients at particularly high risk for arrhythmic events over a mean follow-up of 39 months. The QT/RR slope is the noninvasive analogue of action potential duration restitution. Patients with higher QT/RR slope (>0.19) had higher arrhythmic risk than those with a shallower slope. Notably, this study suggests that abnormal QT dynamics can stratify arrhythmic risk beyond the traditional high-risk group because nearly half of the study population had LVEF >35%.

Risk stratifying patients with moderately reduced LVEF was also the focus of the REFINE (Risk Estimation Following Infarction, Noninvasive Evaluation) study by Exner et al. (138). In this study, 322 patients with mildly reduced LVEF (<50%, median 40%) were enrolled within 1 week of MI and received serial echocardiography and noninvasive risk assessments. No risk factor predicted events if measured within the first 4 weeks, yet many were predictive if measured after 10 to 14 weeks. Notably, the 20% of patients with impaired heart rate turbulence on ambulatory ECGs, abnormal T-wave alternans, and LVEF that remained below 50% had a risk for cardiac death or arrest 5.2 times higher than remaining patients. These data are among the first to combine risk factors, and the above constellation of risk factors identified 52% of at-risk individuals.

An interesting clinical study provided data to support a similar mechanism for outflow tract-related premature ventricular contractions, nonsustained VT, and sustained VT. Kim et al. (139) performed electrophysiologic study on 127 such patients, of whom 36 presented with sustained monomorphic VT, 46 with nonsustained VT, and 45 with single premature ventricular contractions. All groups showed similar anatomic preferences (RV outflow tract in 82%) and suppression by adenosine and, when sustained tachycardia was induced, similar response to catecholamines, vagal maneuvers, adenosine, and verapamil.

**Promise and pitfalls of CRT.** Cardiac resynchronization therapy is now mainstream therapy for patients with significant HF, reduced LVEF, and ventricular dyssynchrony. Several studies in the Journal extended our understanding of its benefits. Yannopoulos et al. (140) studied atrial tachyarrhythmias (AT) in 28 patients before and for 18 months to 24 months after CRT. Compared with 3 months pre-CRT, at 1 year post-CRT patients were more likely to be free of AT (90% vs. 14%, p < 0.001), and thus to have fewer episodes of AT of shorter duration. These patients also experienced improved LVEF and fewer hospitalizations. Although these data require confirmation in larger studies, they suggest that CRT-related improvements in ventricular performance may also lead to atrial reverse remodeling.

**Diagnosing intermittent arrhythmias.** A common and sometimes frustrating clinical problem is how best to evaluate patients with recurrent palpitations. Giada et al. (141) compared implantable loop recorders (ILR) versus an aggressive diagnostic protocol in 50 patients with recurrent palpitations. The ILRs were implanted for 1 year, whereas the aggressive protocol included 24-h ambulatory ECG monitoring, 4-week ambulatory ECG monitoring, and invasive electrophysiology study. The investigators made diagnoses in 21% of patients in the aggressive versus 73% in the ILR groups, translating into cost savings for the ILR approach.

**Mechanistic insights into focal atrial tachycardia.** Focal AT that terminates with adenosine likely reflects triggered or enhanced automatic mechanisms, yet it is unclear whether adenosine-insensitive AT reflects micro-re-entry or arises from distinct anatomic sites. Markowitz et al. (142) studied the mechanism of focal AT in 80 patients. Six cases (8%) that were adenosine-insensitive localized near pulmonary veins and in right atrium, distinct from adenosine-sensitive cases, which were distributed more widely. Consistent with micro-re-entry, adenosine-insensitive sites often showed fractionated electrograms, activity accounting for up to 69% of cycle length, and entrainment with post-pacing intervals equal to the tachycardia cycle length. These data provide direct evidence for de novo micro-re-entry in human atria, arising at different anatomical sites of triggered or automatic AT.

The use of oral anticoagulants in women has become a somewhat controversial issue in several recently published studies. A paper by Dagres et al. (143), from the Euro Heart Survey, raised significant concerns regarding the potential risk for stroke in women with atrial fibrillation. The investigators suggest that the recent CHF, hypertension, age >75 years, diabetes, stroke or transient ischemic attack stroke risk classification scheme (144) and the recently revised American College of Cardiology/American Heart Association/European Society of Cardiology guidelines classifying female gender into the “less validated or weaker risk factors” (145) may have inappropriately de-emphasized female gender as an independent stroke risk factor. Dagres et al. (143) analyzed data from 5,333 atrial fibrillation patients (42% female) enrolled in the study over a 10-month period. Symptomatic women and men received similar treatment with respect to rate versus rhythm control. Women underwent cardioversion less frequently than men (22% vs. 28%, p < 0.001), but oral coagulant use was identical (65%) in both genders. One-year overall outcome was similar, but women had a higher stroke rate (odds ratio 1.83, p = 0.019), a difference attributed to a higher stroke rate in women who did not receive oral anticoagulation, who had at least 1 stroke risk factor, and who were undergoing rhythm control (5% vs. 1.2%, p = 0.006). No difference was observed in women receiving rate control only. The investigators concluded that female gender should be an independent risk factor for stroke, warranting appropriate, consistent oral anticoagulation in women with atrial fibrillation.
The role of the autonomic system, particularly the parasympathetic system, in the initiation and maintenance of atrial fibrillation has recently become an area of significant research interest. Lellouche et al. (146) studied left atrial endocardial electrogram characteristics during sinus rhythm at 1,662 ablation sites in 30 patients undergoing ablation for paroxysmal atrial fibrillation, in an attempt to correlate these characteristics with parasympathetically mediated changes in sinus rate (≥20% decrease) or atrio-His interval (≥10 ms increase). Previous studies have suggested that complex fractionated atrial electrograms, observed in many patients undergoing ablation for atrial fibrillation, may physically co-locate with areas of local parasympathetic innervation, and that their ablation may eliminate recurrence of atrial fibrillation during long-term follow-up (147–150). The investigators also studied the effects of intravenous adenosine in patients with paroxysmal atrial fibrillation or accessory pathway mediated supraventricular tachycardia, intended to mimic the effects of acetylcholine signaling in myocytes. They also mathematically modeled the effects of adenosine and the effects of fibrosis on left atrial electrogram characteristics to determine whether abnormal left atrial electrograms similar to those observed spontaneously could be induced with such physiological manipulation. The investigators observed normal electrograms at 732 sites, low-amplitude fractionated electrograms at 667 sites, high-amplitude fractionated electrograms at 263 sites, and a parasympathetic response at 184 (11%) sites in 29 patients (97%). The observation of a parasympathetic response, slowing of sinus rate, and prolongation of HV interval was strongly associated with sites with high-amplitude fractionated electrograms (sensitivity 72%, specificity 91%), while the investigators characterized as having multiple deflections (≥4), high amplitude (≥0.7 mV), and prolonged duration (≥40 ms). They also noted that these sites were found predominately in the posterior left atrial wall. They also showed that adenosine administration could increase the number of electrogram deflections, mimicking those seen spontaneously in patients undergoing ablation for atrial fibrillation, although it did not affect electrogram amplitude or duration. Mathematical modeling of the effects of adenosine produced high-amplitude fractionated electrograms similar to those observed spontaneously in patients showing a sympathetic response at such sites during ablation, whereas modeling of fibrosis in a 2-dimensional patch of tissue produced low-amplitude fractionated electrograms similar to those observed in patients at sites where no sympathetic response was observed during ablation. The investigators concluded from the findings that normal electrograms must obviously arise from normal tissue, and that low-amplitude fractionated electrograms may arise from areas of fibrosis and may or may not be appropriate sites to ablate. However, high-amplitude fractionated electrograms, a larger percentage of which were associated with a parasympathetic response when ablated, may be attributable to local effects of acetylcholine in left atrial tissue, presumably resulting from a higher density of local parasympathetic innervation. The investigators did not report whether ablation at sites with high-amplitude fractionated electrograms influenced long-term efficacy of ablation in their atrial fibrillation patients, although previous reports have suggested a benefit of ablating sites associated with a parasympathetic response (151). Furthermore, whether parasympathetic stimulation plays a role in initiation or maintenance of atrial fibrillation cannot be determined from this study.

The indications for ICD implantation in patients with reduced LVEF ≤35% have expanded as a result of recent primary prevention trials of sudden cardiac death, including the MADIT II (Multicenter Automatic Defibrillator Implantation Trial), MUSTT (Multicenter UnSustained Tachycardia Trial), and SC-HeFT (Sudden Cardiac Death in Heart Failure Trial) studies (152–154). In these studies a large percentage of patients derived no benefit from ICD therapy. Chow et al. (155) evaluated the role of microvolt T-wave alternans testing to identify patients with ischemic cardiomyopathy and LVEF ≤35% who would be most likely to benefit from ICD therapy for prevention of sudden death. The investigators evaluated 768 patients with ischemic cardiomyopathy and LVEF ≤35% and no prior sustained ventricular arrhythmias, of whom 392 (51%) underwent ICD implantation. Patients were followed up for 27 ± 12 months. The investigators identified a total of 514 (67%) patients with non-negative microvolt T-wave alternans (MTWA) test results. After multivariable adjustment, ICDs were associated with a lower all-cause mortality in MTWA non-negative patients (hazard ratio [HR] 0.45, 95% confidence interval [CI] 0.27 to 0.76, p = 0.003), but not in MTWA-negative patients. The mortality benefit seemed to be predominately mediated through arrhythmic mortality reduction (HR 0.30, 95% CI 0.13 to 0.68, p = 0.004). The number of patients that needed to be treated with ICD therapy for 2 years to save 1 life was 9 among MTWA non-negative versus 76 among MTWA-negative patients. The investigators concluded that MTWA testing was a useful adjunctive risk stratification strategy to simple LVEF cutoffs for identification of patients with ischemic cardiomyopathy and LVEF ≤35% who would be most and least likely to benefit from ICD implantation, with potential national policy implications for ICD coverage.

Progress in cell therapy. Sufficient data using cell therapy in clinical trials has accrued to provide the basis for the first systematic reviews and meta-analyses of the results to date. Lipinski et al. (156) reviewed 698 patients in 10 studies that met criteria for outcomes after intracoronary cell therapy (bone-marrow-derived cells or peripheral mononuclear cells) for acute MI (recent MI, revascularized percutaneously, and follow-up >3 months) and concluded that intracoronary cell therapy after acute MI results in a modest improvement and LVEF with trends in reduced death and rehospitalization. Despite the potential benefits of cell
therapy, Penicka et al. (157) reported the premature termination of a prospective trial evaluating autologous bone marrow-derived mononuclear cells in anterior MI. At 4 months of follow-up there was no significant difference between the control and treatment groups in indexes of cardiac function, but in this small study of 24 patients (14 receiving cell therapy, 10 placebo control patients) there were 4 serious adverse events in the cell therapy group (1 VSD rupture/death, 1 stent thrombosis, 1 diagnosis of biliary carcinoma, and 1 reinfarction). Although inconclusive, these observations may temper enthusiasm for human cell therapy until further preclinical and clinical studies are completed that address a number of important clinical and methodological questions: What are the risks of cell harvest and the risks associated with infusion? What is the most appropriate setting for cell therapy? What are the optimal cells? Is there a rationale for cell choice or mode of delivery? Which outcome should be used to evaluate this new approach?

On a more positive note, progress has been reported in the strategy of cell therapy for a variety of cardiovascular disorders this year. In a particularly exciting preclinical study, Caspi et al. (158) showed that grafting of human embryonic stem cell (hESC)-derived myocytes improved cardiac function in a rat model of HF after MI. Although differentiated hESCs themselves form teratomas when injected in the myocardium of rats with HF, ex vivo differentiated hESC cardiomyocytes (CMs) survive, proliferate, mature, and form gap junctions in the transplanted myocardium. The animals receiving these cells have significant improvement in myocardial function that is dependent on the force generated by the hESC-CMs. Importantly these cells seem to be devoid of arrhythmogenic potential—a phenomenon that has plagued the use of skeletal myoblasts grafting for HF. Although there are significant hurdles to scaling up this technique for larger preclinical animal studies or later in humans (159), these observations and the potential advantages of this source of cells for an off-the-shelf cell therapy product for HF are exciting to contemplate.

Other noteworthy findings in the field of cell therapy include the observation in a rat model that recipient age determines cardiac improvement after skeletal myoblast implantation, likely because of reductions in the cardiac and systemic responses to the transplant in the older animals (160). In a human study, Kissel et al. (161) examined whether reduced levels of circulating endothelial progenitor cells in CHF are primary or secondary to exhaustion of hematopoietic stem cells in the bone marrow. Importantly, they found that ischemic cardiomyopathy is associated with selective impairment of progenitor cell function in the bone marrow and in the periphery.

One of the more stunning clinical findings was the report by Wang et al. (162) that transplantation of autologous endothelial progenitor cells (EPCs) may provide a clinical benefit to patients with pulmonary artery hypertension in an RCT. Sixteen patients with pulmonary artery hypertension received EPCs, and 15 received conventional therapy (which does not include epoprostenol) in China. In this small study exercise capacity, pulmonary artery pressure, cardiac output, and pulmonary vascular resistance were improved in the EPC-treated group. Presumably endothelial repair mechanisms are at work, and improved endothelial function is the mechanistic basis for this important observation. But plasma markers of endothelial function were not measured before and after therapy (163). In this uniformly fatal disease, the notion of EPC therapy in combination with other relevant modalities targeting the endothelial cell is a very exciting prospect.

Mechanisms of dilated cardiomyopathy (DCM). Two papers are notable for their insights into novel mechanisms underlying HF and the potential to point to novel therapeutic modalities. Staadt et al. (164) examined the ability of antibodies isolated from the plasma of 11 patients with DCM to affect the function of adult rat cardiomyocytes and the dependency of the effects on calcium transients and cell shortening on Fc receptors. In an elegant series of experiments, they report the novel finding that DCM-IgG-F(ab’)2 bind to cardiac antigens and that their Fc portion when bound to a novel Fc gamma receptor on cardiomyocytes results in a negative inotropic effect. Thus Fc gamma receptors may have a role in DCM and other immune-mediated cardiac diseases.

In another study, Hikoso et al. (165) investigated whether inhibition of apoptosis (specifically inhibiting apoptosis signal-regulating kinase 1 [ASK1]) would attenuate the progression of HF in the TO-2 hamster model of hereditary dilated cardiomyopathy. Using transcoronary gene transfer of a dominant-negative ASK1 deletion mutant, they showed that indeed reduced ASK1 activity results in suppressed progression of chamber dilatation, impairment of contractile and relaxation function, and fibrosis. These findings add additional evidence to the importance of targeting signaling pathways mediating apoptosis for the treatment of HF.

Cardiovascular genomics. In 2007, the Journal continued its series begun in 2006 on the prospects of genomics for personalized cardiovascular medicine. The field of genetics and genomics of cardiovascular disease continues to unfold rapidly, with many potential and several well established multimarker panels moving into daily practice of CVD disease management and prevention. Genetic findings in 2007 were remarkable, and the complexity of integration of these tools into patient care has also evolved. Genomics continues to be a key strategy in the diagnosis, prognosis, and management of patients with cardiovascular disease. With the U.S. Department of Health and Human Services commitment to personalized medicine (166) and the more widespread access of genomic technologies to clinical investigators, there will undoubtedly be more to report in 2008 and beyond in this exciting area of medicine—cardiovascular genomic medicine.
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