HIGHLIGHTS FROM JACC IN 2006

Highlights of the Year in JACC 2006

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The past year was an exciting one in cardiovascular medicine, with both advances as well as disappointments and controversy. Important technical advances in imaging occurred not only in computed tomography (CT) angiography and magnetic resonance imaging (MRI) but also in more established fields such as echocardiography. In the field of interventional cardiology the issue of stent thrombosis with drug-eluting stents took center stage, but should not eclipse other important developments in left main stenting as well as noncoronary interventions. The treatment of angina was advanced with the introduction of a new antinginal drug, ranolazine, while the hope for a new high-density lipoprotein (HDL) raising drug, torcetrapib, were dashed.

Many of these developments were reported in the pages of JACC. As in previous years, in the following paper the editors have summarized the key JACC articles in their respective areas: imaging, coronary disease, interventional cardiology, heart failure, electrophysiology, congenital and pediatric heart disease, and basic science. Undoubtedly not all excellent studies could be included in this review, but an attempt was made to highlight those articles that, in the opinion of the editors, were most noteworthy. As in past years this Highlights article will replace the Editor’s Page for January.

Echocardiography

Contrast echocardiography. Considerable research effort continues to be directed toward the development of contrast echocardiography. A major application of contrast would be in enhancing quantitation by echocardiography. In a study of 100 patients comparing unenhanced and contrast enhanced echocardiography, MRI, and cineangiography, Hoffman et al. (1) demonstrated that contrast administration not only dramatized the delineation of the intimal surface of the carotids, but also visualized the presence of luxuriant growth of the vasa vasorum and of inter-plaque vasculature of atherosclerotic lesions. These data raise the exciting potential that contrast echocardiography might have an important role in identifying vulnerable carotid plaques and in studying the blood flow to atheroma that might be analogous to that of tumors.

Assessment of aortic stenosis. Prior studies have demonstrated that measurement of effective orifice area (EOA) derived by Doppler techniques in the setting of aortic stenosis manifests flow-dependent changes, raising questions regarding the accuracy of the method. Kadem et al. (5) studied whether these flow-dependent changes in aortic valve EOA represent real findings or artifacts. With an in vitro model in which all variables could be closely controlled, they observed flow-dependent changes in EOA.
related to changes in flow volume. They concluded that these changes are not artifacts but represent real alterations that are explained by either the presence of unsteady effects at low flow rates or by an increase in valve leaflet opening. Therefore, effective orifice determinations made by Doppler in patients with aortic stenosis can be used for clinical decision making. In an accompanying editorial, Baumgartner (6) pointed out that in, certain subsets of patients with aortic stenosis, more sophisticated approaches might be necessary to provide measurements precise enough to guide appropriate clinical management, particularly in patients with aortic valve areas in the range of 0.8 to 1.0 cm².

**Tissue Doppler echocardiography.** Evidence continues to mount that tissue Doppler echocardiography and the extrapolated measurements of strain and torsion can be of great value in assessing regional myocardial performance. In a combined experimental and clinical study, Skulstad et al. (7) compared the ability of the tissue Doppler recording modalities of velocity, strain, and displacement to quantitatively assess regional myocardial systolic function. They measured these variables at baseline and during occlusion of the left anterior descending coronary artery in 10 canines with sonomicrometry as a standard. They demonstrated that systolic strain correlated very well with segmental shortening and work and differentiated both moderately and severely ischemic myocardium from normal. They also studied 10 patients with acute anterior infarction and 15 control subjects. In this clinical study they observed that systolic strain differentiated well between infarcted and normal myocardium, whereas displacement and ejection velocity showed overlap. They concluded that tissue Doppler echocardiography provides an excellent modality to assess the function of segmental ischemic myocardium and that strain measurements are clearly superior to other formulations in this regard. Another study from the same institution by Amundsen et al. (8) sought to validate the accuracy of myocardial strain measurements obtained by speckle tracking echocardiography. Strain measurements obtained by speckle tracking in the long and short axis views were compared with data derived by sonomicrometry in canine experiments. They observed a good correlation between strain measurements by ultrasound and sonomicrometry in both the long and short axis (r = 0.90 and 0.79, respectively, p < 0.001 for both). They also compared strain measurements by speckle tracking in a group of humans with values derived from tagged MRI examinations. They observed that 80% of segments were suitable for analysis, and that a good correlation existed between ultrasound and MRI (r = 0.87, p < 0.001). These studies provide strong evidence of the ability of this new speckle tracking approach to accurately measure myocardial strain in patients. The tracking approach is of particular value in enabling measurements of strain to be acquired in the short axis as well as in the longitudinal (apical) views.

**Assessment of left atrial (LA) volume.** It is now well appreciated that LA volume is a reflection of chronic intracardiac pressures and as such is a valuable marker of the presence and severity of heart disease. It is often said that LA volume is for heart disease as hemoglobin A1C is for diabetes. Further evidence of the importance of LA volume was provided by Tsang et al. (9) who compared the value of LA size measured as diameter, area, or volume in predicting cardiovascular risk manifested by the development of a first episode of atrial fibrillation (AF), heart failure, stroke, transient ischemic attack, myocardial infarction (MI), coronary revascularization, or death in 317 patients. Although LA size measured by any parameter was predictive of combined outcomes, LA volume yielded the best results in predicting cardiovascular events (area under receiver-operator characteristic curve = 0.71). In addition, they observed a graded association between LA enlargement and cardiovascular risk only for indexed LA volumes measured by bi-plane techniques, and that increased LA volume is clearly associated with the risk of subsequent cardiovascular events except for the population of patients who experience AF. In another study from the same institution, Osranek et al. (10) examined whether LA size could be used to predict the occurrence of AF during the postoperative period in patients undergoing cardiac surgery. They examined 205 patients undergoing cardiac surgery, and they observed AF postoperatively in 84 patients at a median of 1.8 days after the procedure. Only age and LA volume were independent predictors of postoperative AF, and patients with a LA volume >32 ml/m² had an almost 5-fold increased risk of this complication. In view of the fact that postoperative AF frequently results in increased morbidity and mortality and prolongs a hospital stay resulting in greater cost, the ability to predict patients at high risk of this complication by virtue of the presence of increased LA volume could be of significant clinical value. In an accompanying editorial, Manning et al. (11) point out that several pharmacologic agents have been shown to be of prophylactic value in preventing postoperative AF and that LA volume provides a potential guide to the application of these agents in individual patients.

**Intravascular ultrasound (IVUS).** Although IVUS has not found the role in interventional cardiology that was initially anticipated, it has made a major contribution to the understanding of the atherosclerotic process as well as providing a tool to observe the behavior of atheromas over time. A study by Sano et al. (12) analyzed the integrated backscatter of the IVUS images of 160 nonstenotic coronary lesions in 140 patients. The IVUS characteristics of 10 plaques that ultimately caused acute coronary syndrome (ACS) during follow-up were compared with those plaques that did not. Significant differences in plaque burden, eccentricity, remodeling index, and percent lipid area were observed in the vulnerable as opposed to these stable plaques. These data demonstrate that IVUS examination can distinguish characteristics of plaques that are high risk for developing a clinical ACS. In another IVUS study Nasu et al. (13) validated the accuracy of an in vivo technique for tissue
characterization with radiofrequency data analysis called Virtual Histology (Volcano Therapeutics, Inc., Rancho Cordova, California). The authors compared the radiofrequency IVUS data with histopathologic examination of specimens obtained by a single debulking directional coronary atherectomy cut in 15 patients with stable angina pectoris and 15 with ACS. They observed a range of predictive accuracy of IVUS virtual histology of 87% to 96% for fibrous, necrotic, and calcified regions. These data substantiate the fact that IVUS tissue characterization can be employed in identifying plaque characteristics in vivo.

Application of echocardiography to clinical issues. One of the major attributes of echocardiography is its ability to address pathophysiological issues in humans. One such issue is the continuing controversy of the role of a patent foramen ovale in cerebrovascular ischemia. Meissner et al. (14) from the Mayo Clinic performed transesophageal echocardiography in 585 randomly sampled subjects ages 45 years or older who were followed for a median of 5.1 years. A patent foramen ovale was identified in 24.3% of these patients but was not observed to be an independent risk factor for future cerebrovascular events. Actuarial event-free survival was less for patients with an atrial septal aneurysm than without (81% vs. 93%, p < 0.048). In an accompanying editorial, Meier (15) commented that, although these data did not completely resolve the issue, they pointed out that the prevalence of events with patent foramen ovales is sufficiently small so that very large numbers of patients will need to be randomized and followed to answer the question of the etiologic role and efficacy of interventional therapy for these lesions. Two studies published this year address pathophysiological issues in humans. One such issue is obesity, epidemiologic data indicate that increased body weight might actually be protective after the onset of cardiovascular abnormalities. Clearly the last word on obesity has not been written. In another report, Shivalkar et al. (19) used echocardiography to delineate abnormalities of the major attributes of echocardiography is its ability to identify plaque characteristics in vivo.
result was consistent across most subgroups tested after propensity analysis accounting for baseline differences in risk profile. The rates of death and MI were similar between groups. Wessely et al. (26) succinctly reviewed the mechanisms of action, therapeutic range, release kinetics, and clinical outcomes of SES versus PES.

As the debate over safety of DES increases, alternative and improved methods to prevent restenosis will be needed. The ORAR II (Oral Rapamycin After Coronary Bare-Metal Stent Implantation to Prevent Restenosis) trial (27) showed in 100 patients randomized to either oral rapamycin plus diltiazem or no therapy with BMS that the 1-year TVR (8.3% vs. 38%, respectively, p < 0.001) and MACE (20% vs. 44%, respectively, p = 0.018) were lower in the oral rapamycin group. Rapamycin was well tolerated (26% minor side effects) and was maintained in 96% of patients.

The role of DES in saphenous vein grafts (SVG) has not been extensively studied. Vermeersch et al. (28) randomized 75 patients with SVG lesions to SES versus BMS. In-stent late loss (0.38 mm vs. 0.79 mm, p = 0.001), restenosis (13.6% vs. 32.6%), neointimal volume, and TVR (5.3% vs. 27%, p = 0.012) were reduced in SES compared with BMS. The study was not powered to evaluate death and MI.

Safety. Several studies addressed the increasing concern of the long-term safety and effectiveness of DES. The long-awaited BASKET-LATE (Basel Stent Kosten Effektivitats Trial) (29) evaluated the incidence of late clinical events (from 6 to 18 months) and late stent thrombosis in DES (both SES and PES) versus BMS after clopidogrel discontinuation in 746 nonselected patients with 1,133 stented lesions surviving 6 months without MACE. Overall rates of cardiac death/MI from 0 to 18 months were not different between DES and BMS patients. However, after clopidogrel discontinuation (between months 7 and 18), death/MI occurred in 4.9% in the DES versus 1.3% in the BMS group. The TVR remained lower after DES, resulting in similar rates of all clinical events for this time period (DES 9.3%, BMS 7.9%). Documented late stent thrombosis and related death/target vessel MI were twice as frequent after DES versus BMS (2.6% vs. 1.3%). Thrombosis-related events occurred between 15 and 362 days after clopidogrel discontinuation presenting as MI or death in 88%. This study suggests that the early benefit of DES might be slowly eroded by increasing death/MI in the long term, particularly after clopidogrel discontinuation. It is not clear at this point whether continued clopidogrel prevents such events and whether late thrombotic events will continue to accrue after 18 months. This study emphasizes the importance of patient and lesion selection as well as adequacy of clopidogrel compliance in choosing DES compared with BMS.

Nebeker et al. (30), with clinical and autopsy data from the adverse-device-event database of the Food and Drug Administration (FDA) and the RADAR (Research on Adverse Drug/Device events And Reports) project, reported on 17 cases of systemic and intrastent hypersensitivity reactions that were probably or certainly caused by DES. Four autopsies confirmed eosinophilic inflammation, thrombosis, and lack of intimal healing within the stents. As a clinical correlate in living patients, Kotani et al. (31), with angiography, showed that most DES exhibited incomplete neointimal coverage 3 to 6 months after implantation, whereas all BMS showed complete coverage. Finally, in the ERACI III (Argentine Randomized Trial of Coronary Stents Versus Bypass Surgery) study (32), it was demonstrated that in patients receiving both DES or BMS in different arteries, both subacute and late stent thrombosis occurred predominantly in DES stents and mostly upon clopidogrel withdrawal. These studies confirm that DES display delayed healing compared with BMS, which is likely the major factor in late adverse events with DES.

Cost effectiveness. A cost-effectiveness analysis of the TAXUS-IV trial (33) showed that PES were cost effective relative to other accepted medical therapies, showing a 1-year cost difference of $572/patient with incremental cost-effectiveness ratios of $4,678/TVR avoided and $47,798/quality-adjusted life year gained. In a study comparing cost-effectiveness of SES versus PES in high-risk cohorts (diabetic patients or in-stent restenosis) in Germany, initial hospital costs were similar between SES and PES, whereas follow-up costs were higher for PES, mainly owing to need for repeat TVR (34). These findings were put into perspective by Vaitkus (35) noting that, relative to the American health care system, the cost savings benefit the overall health care system and the insurance companies, whereas hospitals bear both the upfront stent costs and the decreased revenue due to reduced repeat procedures.

Restenosis. The RIBS-II (Restenosis In Intrastent: Balloon Angioplasty Versus Selective Sirolimus-Eluting Stenting) study (36), a multicenter trial randomizing 150 patients with BMS in-stent restenosis (ISR) to SES versus balloon angioplasty, showed a reduced incidence of recurrent restenosis (11% vs. 39%; p < 0.001), TVR (11% vs. 30%; p < 0.003), and event-free survival (freedom from death, MI, and TVR) in the SES group. These results were corroborated in the TRUE (Tuscany Registry of Sirolimus for Unselected In-Stent Restenosis) Registry, derived from a real-world setting in which SES were implanted for BMS ISR showing an ischemia-driven TLR of only 4.9% (37). It is now clear that DES are effective for BMS in-stent restenosis, but the optimal treatment of DES ISR has not been defined yet.

Left main (LM) interventions. A series of publications presented new data on unprotected LM PCI with DES. In a single-center observational series of 110 patients from the combined RESEARCH and T-SEARCH registries comparing SES and PES for LM disease at a median follow-up of 660 days, the cumulative incidence of MACE (25% vs. 29%, p = 0.74), TVR (9% vs. 11%), and late loss were similar (38). In a follow-up study from the same group, Valgimigli et al. (39) showed that patients with distal LM disease had a higher cumulative incidence of MACE (30% vs. 11%, p = 0.007), primarily driven by higher rate of TVR.
(13% vs. 3%, p = 0.02) and correspondingly higher rates of late loss. In these studies, stent technique did not seem to influence the results, and there were no cases of early or late stent thromboses. Another small, single-center study of 50 patients, with serial angiography at 3 and 9 months' follow-up, also suggested worse outcomes for distal LM stenting compared with nondistal LM interventions (40). Late loss was significantly greater within the left circumflex (LCX) ostium compared with the LM body (0.83 ± 0.89 mm vs. 0.49 ± 0.72 mm, p = 0.04) with restenosis being primarily a focal process. Late loss continued to increase between 3- and 9-month follow-up. These studies suggest that LM stenting is associated with good outcomes in nondistal LM sites and that distal LM interventions will remain a challenging subset in the near future.

Until randomized clinical trials are performed comparing LM stenting versus coronary artery bypass graft surgery (CABG), observational studies might provide insights into what we can expect when such trials are completed. In a retrospective analysis, Lee et al. (41) compared the 6-month outcomes of 123 patients undergoing CABG with 50 patients undergoing PCI with DES for unprotected disease. The 30-day MACE was higher for CABG versus PCI (17% and 2%, p < 0.01). The estimated MACE and stroke-free survival at 6 months and 1 year was 83% and 75%, respectively, in the CABG group versus 89% and 83% in the PCI group (p = 0.20). In this short-term report with the obvious methodological limitations of a retrospective, nonrandomized study, the results for PCI were at least as good as those of CABG. Baim et al. (42) provided a historical perspective in an accompanying editorial suggesting that broad use of unprotected LM stenting, particularly in distal bifurcation stenoses, is not warranted at this point and should only be used in selected patients with high surgical risk and acceptable anatomical lesions.

In an additional study evaluating prognostic importance of nonsignificant LM stenosis (<50% diameter stenosis) in 1,385 patients, Gyenes et al. (43) showed similar 7-year crude mortality hazard ratio (HR) of PCI patients with <50% LM disease versus those with no LM CAD after risk adjustment for differences in baseline clinical profile. This suggests that patients with <50% LM diameter stenosis are not at increased long-term risk of cardiovascular events.

Noncoronary interventions—carotid, renal, and peripheral arterial disease. The CREATE (Carotid Revascularization with ev3 Arterial Technology Evolution trial) registry evaluated the safety and efficacy of a new distal embolic protection system in 419 patients with severe carotid stenosis and high-risk features for carotid endarterectomy (44). Technical success was achieved in 97.4% of patients. The primary end point was present in 6.2% of patients (death: 1.9%; nonfatal stroke: 3.3%; nonfatal MI: 1%). The overall fatal and nonfatal stoke incidence was 4.5%. These results of overall MACE were relatively similar to other published registries and trials (SAPPHIRE [Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy], ARCHER [Acculink for Revascularization of Carotids in High-Risk Patients], SECURITY [Stent in Patients at High Risk for Carotid Endarterectomy]).

A modest-sized study suggested that serial IVUS imaging provides insights into carotid in-stent restenosis and vessel remodeling. Clark et al. (45) performed postprocedural and 6-month follow-up quantitative carotid angiography and IVUS after self-expanding stent deployment in 50 internal carotid arteries (ICA). They demonstrated continued (49%) stent expansion over 6 months but a corresponding (37%) loss of luminal area due to neointimal proliferation. In addition, a correlation was noted between stent expansion and neointimal proliferation.

The long-term results after directional atherectomy of femoral-popliteal lesions was reported by Zeller et al. (46) in a prospective registry of 84 patients (100 legs and 131 lesions) with symptomatic peripheral arterial disease. The mean lesion length was 43 to 131 mm and the technical success rate was 86%. Primary patency, defined as freedom from >50% restenosis detected by duplex at 18 months ranged from 42% to 73%, and secondary patency ranged from 67% to 89%, with de novo lesions having the better outcomes. Randomized trials are awaited to assess whether atherectomy provides improved clinical outcomes compared with standard techniques.

De Bruyne et al. (47) advanced the field of renal artery physiology by defining both hyperemic renal flow as well as what constitutes significant renal artery stenosis with renal artery pressure gradients and flow velocity measurements. In 28 normotensive patients, quantitative angiographic measurements of the renal artery were obtained, and renal artery pressure and flow velocity were continuously recorded after various hyperemic agents. They determined that the normal renal flow reserve averages approximately 2 in humans with normal renal function and that a bolus injection of 50 μg/kg of dopamine intrarenally is the best means for eliciting maximal renal hyperemia. In a second study, trans-stenotic pressure measurements and plasma renin levels were obtained before and after graded stenoses were created in a stented segment by progressive inflation of a balloon catheter (48). Stenosis severity was expressed as the ratio of distal pressure (Pd) corrected for aortic pressure (Pa). It was shown that a Pa/Pd ratio of <0.90 determined the threshold value below which renin production is increased. Future studies will determine whether this level predicts the presence of renovascular hypertension and whether it predicts efficacy of stent placement.

Percutaneous heart valves. Cribier et al. (49) reported their mid-term results for a study of 36 inoperable patients with decompensated congestive heart failure and aortic valve area ≤0.7 cm² treated with an equine pericardium valve in a balloon-expandable, stainless-steel stent. Twenty-seven patients had successful implantation with improvement in valve area (0.60 to 1.70 cm², p < 0.0001) and transvalvular gradient (37 to 9 mm Hg, p < 0.0001) and improvement in LV function. Thirty-day major adverse events were 26%.

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Eleven patients are currently alive with a follow-up of 9 months. All patients experienced amelioration of symptoms. Percutaneous heart valve function remained unchanged during follow-up, and no deaths were device-related. This study shows the feasibility of this approach in inoperable patients but also highlights the poor prognosis of such patients in general.

**Contrast nephropathy.** The RECOVER (Renal Toxicity Evaluation and Comparison Between Visipaque [Iodixanol] and Hexabrix [Ioxaglate] in Patients With Renal Insufficiency Undergoing Coronary Angiography) (50) prospective, randomized trial in 300 patients compared iodixanol, a nonionic, dimeric, iso-osmolar contrast medium (IOCM) to ioxaglate, a low-osmolar contrast media (LOCM) in high-risk patients (creatinine clearance \( \text{CrCl} \) $\leq$ 60 ml/ min). The primary end point, the incidence of contrast-induced nephropathy (CIN), was significantly lower with iodixanol than with ioxaglate (7.9% vs. 17.0%; $p = 0.021$). This randomized controlled trial was corroborated by a meta-analysis of 2,727 subjects showing similar results (51).

**CAD**

This year, the first in a new class of agents, ranolazine, was approved by the FDA for the treatment of stable angina symptoms. Although the mechanism of action of ranolazine is not entirely clear, it might be related to reduction of the calcium overload that accompanies ischemia as well as heart failure and is related to the late sodium channel current. One of the pivotal trials that led to FDA approval was published as an expedited review in the Journal (52). The ERICA (Efficacy of Ranolazine in Chronic Angina) trial was a large ($n = 565$) study of patients with stable angina with 3 or more episodes/week despite therapy with amlo-dipine at 10 mg/day. Subjects were randomized to 1,000 mg ranolazine or placebo twice daily and followed for 6 weeks. The primary end point, angina frequency, was 5.63 episodes/week at baseline and was reduced in frequency by ranolazine compared with placebo (2.88 vs. 3.31, respectively). Patients with more frequent angina had a more pronounced treatment effect, and the drug was well tolerated without hemodynamic changes. In an accompanying editorial Cairns (53) highlighted the potential for dose-related QTc prolongation with the agent, although there have not thus far been any cases reported of torsades. Indeed, its effects on the late sodium channel current might actually decrease early afterdepolarizations (EADs), which have been associated with torsades.

Indeed, with the exception of high-risk groups such as patients with 3-vessel coronary disease and left ventricular dysfunction, revascularization has not been shown to be superior to medical management for stable angina in terms of survival, although surgical revascularization has been shown to be superior to medical treatment for eliminating anginal symptoms. With similar outcomes across treatment modalities, what is the role then for physician judgment? In an ingenious prospective substudy of the MASS II (Medicine, Angioplasty, or Surgery Study II) trial, Pereira et al. (54) analyzed the possible role of physician judgment, by comparing the outcomes of patients who were randomized to a treatment preferred by 2 experienced physicians (discordant patients) to those randomized to a different treatment (discordant patients). They found that discordant patients had a worse outcome, driven particularly by those randomized to PCI. Angiographic variables identified by the physicians were an important predictor of risk. As highlighted in an accompanying editorial (55), these findings support the role of physician judgment in clinical decision making, whether one labels this “the art of medicine” or simply “integration” of data elements that are not adequately included in our traditional risk stratification tools.

**Perioperative risk.** The highest-risk patients for perioperative ischemic complications are patients undergoing major vascular surgery. Poldermans et al. (56), in the second multicenter DECREASE-II (Dutch Echocardiographic Cardiac Risk Evaluation) study, randomized 1,476 patients receiving beta blockers with 1 to 2 risk factors (older than 70 years of age, angina, prior MI, heart failure, diabetes treated with medication, renal dysfunction, and prior stroke/transient ischemic attack [TIA]) to stress-testing versus only continued medical therapy before surgery. Although ischemia was documented in 26% of patients randomized to the stress-testing arm, the incidence of cardiac death or MI at 30 days after surgery was not improved in the stress-testing arm. Evidence of adequate beta blockade with a heart rate of $<65$ beats/min was associated with lower risk, irrespective of stress-testing. Obliating stress-testing reduced delay to surgery by almost 3 weeks. The authors could not exclude a benefit of revascularization in the 8.8% of patients who had extensive ischemia on noninvasive testing, but overall the no-stress-test approach seemed reasonable in the overall population.

**Antiplatelet therapy.** The treatment of coronary disease, particularly of unstable disease, employs aggressive antiplatelet and antithrombotic therapies. Recently, the adverse effect of bleeding has received increasing attention. In a retrospective analysis from the PROTECT–TIMI-30 (A Randomized Trial to Evaluate the Relative Protection Against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia Among Anti-Platelet and Anti-Thrombotic Agents) trial (57), the TIMI group analyzed predictors of bleeding in patients receiving the glycoprotein IIb/IIIa inhibitor eptifibatide. The authors found that reduced creatinine clearance and age were important predictors, with age being the independent variable. Age interacted with renal function in that elderly patients often had reduced clearance but did not have their dose of eptifibatide adjusted.

**Atherosclerosis and lipids. ADIPONECTIN.** The complexity of lipid metabolism, inflammation, and their interactions continued to be the focus of much new research in 2006.
Particular attention has been garnered by adiponectin, a cytokine secreted by adipocytes and purported to have antiatherosclerotic, anti-inflammatory, and insulin-sensitizing effects (58). Low levels of adiponectin are found in subjects with the metabolic syndrome in general and with abdominal obesity in particular. Two studies in 2006 in the Journal highlighted the potential importance of adiponectin. Otsuba et al. (59) from Japan showed in a study of 207 men with CAD that low plasma levels of adiponectin were associated with complexity of angiographic coronary lesions in both stable CAD and in ACS patients, with ACS patients having the lowest levels. Therefore, adiponectin might play an important role in plaque instability, which is associated with complexity of lesions. As diabetic patients are at increased risk of ACS, adiponectin might be an important link between diabetes and plaque rupture. Indeed, in an observational study from Germany, Koenig et al. (60) showed that subjects in the highest tertile of adiponectin levels had lower rates of incident type II diabetes and incident coronary heart disease. This relationship was no longer independently significant after adjustment for HDL cholesterol (HDL-C) levels. Importantly, subjects with both low adiponectin and low HDL-C levels had a significantly increased incidence of both diabetes and coronary disease compared with those with high HDL-C and high adiponectin.

HDL. High-density lipoprotein cholesterol itself continues to be the subject of intense interest, given the known epidemiologic association of low HDL-C levels and CAD. Two clinical trials (61,62) of torcetrapib, a novel cholesterol ester transfer protein (CETP) inhibitor, were published in the Journal (CETP as a target of therapy was also the subject of a State-of-the-Art paper [63]). Both trials were 8 weeks long and focused on patients with below-average HDL-C levels. The HDL-C levels increased in a dose-dependent manner in both trials in the presence of background atorvastatin therapy. Low-density lipoprotein cholesterol (LDL-C) levels decreased further beyond the levels seen with atorvastatin monotherapy. The HDL-C level increases were impressive: up to 54.5% in the monotherapy study and 40.2% with atorvastatin. As commented upon in an accompanying editorial (64), whether these HDL-C changes are associated with reduced atherosclerosis and clinical events such as MI can only be determined from longer-term randomized trials. Indeed, shortly after the publication of these 2 studies, the torcetrapib program was halted by its manufacturer, Pfizer Inc., due to a surprising increase in cardiovascular events in a long-term trial of the drug, highlighting yet again the importance of actual outcome studies as opposed to surrogate end points.

High-density lipoprotein cholesterol is a complex lipoprotein with both anti-inflammatory and pro-inflammatory properties. Dietary influences might affect HDL-C functionality, an issue that was highlighted in a study (65) of 14 subjects given either a saturated or polyunsaturated meal on 2 occasions. After the ingestion of a saturated fatty meal, HDL-C was less effective in inhibiting the expression of the inflammatory mediators ICAM-1 and VCAM-1 in isolated endothelial cells. Endothelial function as assessed by flow-mediated dilation was also adversely affected by the saturated fat meal. The HDL-C might also be made more pro-inflammatory and pro-atherogenic in the presence of elevated myeloperoxidase levels, a hemoprotein with antimicrobial properties. Indeed, in a large prospective study of carotid atherosclerosis (66), elevated myeloperoxidase levels were associated with progression of disease but only in patients with HDL levels below 49 mg/dl.

Studies in patients with heart failure and/or LV dysfunction. POLYUNSATURATED FATTY ACID AND BAROREFLEX CONTROL. Although data exist that polyunsaturated fatty acids (PUFA) have anti-arrhythmic effects in post-MI patients, the mechanism involved has remained uncertain. Radaelli et al. (67) carefully studied a group of patients with post-MI LV dysfunction to determine whether PUFA treatment enhances baroreflex control in patients with post-MI LV dysfunction. In the study, baroreflexes were assessed from responses to neck suction (NS) and by computation of the alpha spontaneous baroreflex sensitivity index at baseline and 4 months of treatment with 2 g/day PUFA or placebo. Both reflex depressor and bradycardic responses to NS increased after PUFA but not placebo, as did spontaneous baroreflex sensitivity, R-R interval variance, and low- and high-frequency spectral powers. These results indicate that, in post-MI patients with LV dysfunction, treatment with PUFA markedly potentiates baroreflex function and enhances heart variability, which might explain the favorable effects of PUFA treatment on ventricular arrhythmias.

AF in heart failure with/without systolic dysfunction. Although AF is the most common arrhythmia in heart failure, virtually all information regarding the prevalence, incidence, and effect of AF on prognosis comes from populations with systolic dysfunction. Consequently, Olson et al. (68) assessed these issues in patients included in the CHARM (Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity) program, which included populations with a broad range of ejection fractions (EFs), including a large number with an EF >40% that were followed in the CHARM-Preserved study. They found that baseline incidence was nearly the same in patients with heart failure and EF >40% as in patients with low EF (19% compared with 17%). Although AF was predictive of a high risk of cardiovascular mortality and morbidity in both groups, it was associated with greater relative increased risk of major cardiovascular outcomes in patients with preserved EF. During the study, new-onset AF occurred in 7.8% of the low EF group and in 4.9% of the population with an EF >40%. Although the absolute risk of an adverse cardiovascular outcome was highest in the low
EF new-onset AF patient group, the patients with EF >40% had a significantly greater relative increase in risk. The presence of AF did not alter candesartan effects in the CHARM study population. These results point out both the high prevalence of AF in heart failure patients with or without systolic dysfunction and suggest that relative risk for adverse cardiovascular outcomes might be greater in the population with an EF >40%, further debunking the concept that heart failure with preserved EF has a considerably better prognosis.

DO BENEFICIAL EFFECTS OF STATINS IN HEART FAILURE EXTEND BEYOND THEIR ABILITY TO LOWER LIPIDS? Controversy continues regarding whether statins might benefit heart failure through mechanisms other than reducing LDL-C and acute coronary events. Sola et al. (69) examined the effects of statin therapy on vascular markers of inflammation and echocardiographic parameters of LV structure and function in patients with nonischemic cardiomyopathy. They randomized 108 patients with LVEF <0.35 in a double-blinded fashion to receive either atorvastatin 20 mg/day or placebo in addition to standard heart failure therapy. Whereas LVEF tended to decrease and end-diastolic dimension (EDD) and end-systolic dimension (ESD) increased in the placebo group, EF increased 33% to 37% (p = 0.01), EDD decreased 57.1 to 53.4 mm (p = 0.02), and ESD decreased 42.4 to 39.1 mm (p = 0.007) with atorvastatin. The atorvastatin-induced increase in erythrocyte superoxide dismutase and decrease in C-reactive protein (CRP) and interleukin-6 suggested that statins improve cardiac function by reducing inflammation.

In contrast to these favorable results of statin therapy, Bleske et al. (70) found in a small group of nonischemic cardiomyopathy patients with average LDL-C levels that 12 weeks of 80 mg/day atorvastatin did not alter levels of biomarkers that reflected cardiac remodeling, endothelial cell function, and inflammation compared with placebo. In an editorial comment, Ramasubbu and Mann (71) theorized that the somewhat discrepant findings were due to the relatively small size and the differences in baseline characteristics of patients in the 2 studies. In particular, they noted that the population in the negative study by Bleske et al. (70) had minimal activation of neurohormonal and inflammatory systems, in which case “one might not have expected to have observed striking changes in the panel of biomarkers following statin treatment.” The editorial concluded that, although statins should be used in patients with heart failure who have elevated LDL levels and known coronary disease, the use of these agents in nonischemic patients remains unanswered.

INTERSTITIAL MATRIX REMODELING IN HEART FAILURE. Abnormalities in the extent and distribution of collagen within the remodeling heart have been recognized as playing an important role in the pathogenesis of heart failure. Lopez et al. (72) assessed the distribution of collagen deposits and collagen degradation in endomyocardial biopsy specimens from 39 hypertensive patients with either systolic heart failure (SHF) or diastolic heart failure (DHF). They found that myxial collagen that is related to muscle compartments was reduced in SHF patients but that perivascular and scar related collagen volumes were higher in both SHF and DHF hypertensive patients than in normotensive subjects and in SHF compared with DHF patients. Activity of matrix metalloproteinases (MMPs) (involved in collagen degradation), assessed as the ratio of MMP-1 to its tissue inhibitor (TIMP)-1, was increased in the SHF hypertensive group compared with control subjects and DHF patients. The MMP-1 expression was increased in the interstitium and in cardiomyocytes of SHF compared with both hypertensive and normotensive DHF patients. Moreover, the MMP-1/TIMP-1 ratio was significantly correlated with EF in an inverse manner, and it correlated directly with LV end-diastolic diameter. Thus, patterns of collagen deposition differ between SHF and DHF, suggesting that there is an association between the breakdown of myxial collagen and the development of SHF in hypertensive patients. The results also implicate alterations in the balance of the MMP/TIMP system in this process. As noted in an accompanying editorial by Shirwany and Weber (73), these findings raise the prospect that serum measurements of MMP and TIMP levels could be used to detect abnormalities in the interstitial matrix of the heart that could account for ventricular remodeling and dysfunction in hypertensive patients and that such markers might also serve to monitor interventions designed to alter the remodeling process.

On the basis of substantial evidence that MMPs are activated in the post–MI heart where they seem to play a role in interstitial matrix remodeling, Hudson et al. (74) studied the effects of the MMP inhibitor PG-116800 on post–MI cardiac remodeling. In the study, 253 patients with a first ST-segment elevation MI and reduced EF were enrolled within 48 h of the MI and randomized to either active drug or placebo treatment for 90 days. The results showed that MMP inhibition with PG-116800 did not significantly alter LV volumes, sphericity index, EF, or rates of death or recurrent MI. There was an increase in the incidence of arthralgia and joint stiffness. These results suggest that MMP inhibition after MI might not be an effective way to alter LV remodeling.

Fragasso et al. (75) published a randomized clinical trial of trimetazidine, a partial free fatty acid oxidation inhibitor, in patients with heart failure. In this study 55 patients with congestive heart failure were allocated to conventional therapy plus trimetazidine or conventional therapy alone. At study entry and follow up, patients underwent exercise testing and 2-dimensional echocardiography. The findings demonstrated that patients taking trimetazidine had improvement in New York Heart Association functional class, exercise tolerance, quality of life, and LV function. They also used fewer diuretic agents and digoxin and had lower B-type natriuretic peptide (BNP) levels. The authors concluded that the concept of shifting the energy substrate
preference away from fatty acid metabolism and toward glucose metabolism by trimetazidine is an effective adjunctive treatment in patients with heart failure. The accompanying editorial by Wilson Tang (76) notes that the study raises an important conceptual question about developing drugs for heart failure therapy. The prerequisite for drug approval in the U.S. mandates demonstration of hard end points such as mortality in large clinical trials, even for drugs like trimetazidine that have already been demonstrated to be well tolerated. The high barrier for approval makes it unlikely that trimetazidine will be approved for treating congestive heart failure in the near future.

**Heart rhythm disorders. Defibrillator therapy.** The role of implanted cardioverter-defibrillator (ICD) therapy in prevention of sudden death has been an important topic recently. Two papers in the *Journal* in 2006 addressed the issue of timing of ICD implantation in patients with ischemic and nonischemic cardiomyopathy. The first article, by Goldenberg et al. (77), evaluated 951 patients in whom a coronary revascularization (CR) procedure was performed before enrollment in the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial). This substudy of MADIT-II showed that in patients enrolled more than 6 months after coronary revascularization there was a significant survival benefit of ICD implantation versus conventional medical therapy (all cause mortality HR 0.64, p = 0.01). There was no benefit in those enrolled within 6 months of revascularization, probably owing to a low risk of sudden cardiac death and a higher risk of nonarrhythmic death in this group. In a similar article published in the *Journal*, Kadish et al. (78) evaluated the 458 enrolled in the DEFINITE (Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation) trial for an effect of timing of ICD implantation on survival. This substudy of DEFINITE analyzed the survival benefit of therapy on the basis of time from diagnosis. Patients receiving an ICD within 3 months of diagnosis had improved survival (p < 0.05) compared with conventional therapy, with borderline significant improvement (p = 0.058) in those receiving an ICD within 9 months of diagnosis. Thus, this study suggests that nonischemic cardiomyopathy patients should receive an ICD early after diagnosis, because the benefit conferred is not time dependent.

Some degree of controversy has surrounded the issue of cardiac resynchronization therapy (CRT) with respect to the necessity of additional defibrillator therapy in heart failure patients without prior ventricular arrhythmias. A study by Ypenburg et al. (79) addressed this issue in 191 patients with advanced heart failure, LVEF <35%, and QRS duration >120 ms. Seventy-one patients had a history of ventricular arrhythmias and were designated as the secondary prevention group, whereas 120 patients who had no history of ventricular arrhythmias were designated as the primary prevention group. During 18 months of follow-up the primary prevention patients experienced fewer appropriate ICD therapies than the secondary prevention group (21% vs. 35%, p < 0.05). However, no predictors of ICD therapy could be identified on multivariate analysis. Similar clinical improvement was observed in both groups, and the overall mortality rate was less in the primary versus secondary prevention group (3% vs. 18%, p < 0.05). The authors concluded that, because the appropriate ICD therapy rate was so high (i.e., 21%) in the primary prevention group, all patients with congestive heart failure and reduced LVEF undergoing CRT should have a CRT-ICD device implanted as opposed to a CRT-only device. The authors acknowledge that the small study size might have precluded identification of predictors of appropriate ICD therapy and that ICD therapy might not have been a definitive surrogate for mortality.

Risk stratification of patients to improve selection of candidates for ICD implantation has been an important area of research, both to reduce unnecessary implants and to manage spiraling costs. Two important articles were published in the *Journal* in 2006 providing evidence in favor of using microvolt T-wave alternans (MTWA) to risk stratify patients for potential lethal ventricular arrhythmias. The first study, by Bloomfield et al. (80), evaluated 549 patients, with LVEF ≤40% and no history of sustained ventricular arrhythmias (SVA). Ischemic heart disease was present in 49%, mean LVEF was 25%, and 66% had abnormal MTWA. During 20 months' follow-up, 40 deaths and 11 episodes of nonfatal SVA occurred (2.5% 2-year event rate in patients without abnormal MTWA and 15% in patients with abnormal MTWA). The MTWA tests resulted in an HR for the primary end point of 6.5 at 2 years. In a similar study, Chow et al. (81) showed, in 768 patients with ischemic cardiomyopathy and LVEF ≤35% and no history of SVA, that a non-negative MTWA test (observed in 514 patients, 67%) was associated with a higher all-cause (HR 2.24, p < 0.002) and arrhythmic mortality (HR 2.29, p = 0.049). An area of controversy has been the value of an indeterminate MTWA test (i.e., neither negative nor non-negative). Both this study by Chow et al. (81) and another by Kaufman et al. (82) demonstrated an increased risk of mortality and nonfatal SVA events in patients with indeterminate MTWA tests.

**Sudden death.** With respect to other possible predictors of sudden death in the general population, 2 studies published in the *Journal* in 2006 are of significance. Stecker et al. (83) reported 2-year findings from the Oregon Sudden Unexpected Death Study where all cases of sudden cardiac death (SCD) occurring in 1 county were analyzed clinically and demographically from available records. This study included 704 cases of SCD. The LVEF was severely reduced in 30% and mildly to moderately reduced in 22%. Patients with normal LVEF were younger, with a higher proportion of women, higher prevalence of seizure disorder, and lower prevalence of established CAD. The authors concluded that only one-third of SCD cases had severely
reduced LVEF and met criteria for ICD implantation, suggesting a need for development of alternative screening methods to enhance identification of patients at risk for SCD in the general population. One possible risk factor that could be screened in this manner was suggested by Strauss et al. (84) in a prospective, population-based cohort study comprising 3,105 men and 4,878 women ages 55 years and older as part of the Rotterdam Study. The authors evaluated the QTc interval on electrocardiography obtained in patients at baseline visit (1990 to 1993) and their first follow-up visit (1993 to 1995) and determined that over an average follow-up period of 6.7 years in the 125 patients that died suddenly, a prolonged QTc interval (>450 in men and >470 in women) was associated with a 3-fold increased risk of SCD (HR 2.5) overall and an 8-fold increased risk of SCD in those patients younger than the median age of 68 years.

No medical therapy has previously been shown to have a significant positive impact upon SCD. Recently, statin therapy has been shown to at least reduce the risk of SCD in 2 studies reported in the Journal. In the first study, published by Vyas et al. (85), statin use was evaluated in 654 patients receiving ICDs as part of the MADIT-II study. The patients were categorized by percentage days of statin use. The results showed that the cumulative rate of ICD therapy for ventricular tachycardia/ventricular fibrillation or cardiac death was significantly reduced in those with ≥90% statin use compared with those with lower statin use (p = 0.01). The time-dependent statin/no statin therapy HRs were 0.65. In a similar study, published by Goldberger et al. (86), they reported in 458 patients enrolled in the DEFINITE study that those on statin therapy had a reduced overall death rate (HR 0.22, p = 0.0001), reduced arrhythmic sudden death rate (HR 0.16, p = 0.08), and reduced rate of appropriate ICD shocks (HR 0.78). The authors of these studies suggest that statins have an antiarrhythmic effect, although the mechanism—either a direct or indirect effect—is unknown.

AF. Significant advances in the treatment of AF have also been made in recent years, particularly curative catheter ablation procedures. Catheter ablation has been suggested not only to be cost effective as a treatment compared with medical therapy but also to reduce morbidity and mortality, particularly in patients with congestive heart failure. The optimal approach to ablation of AF has not been proven, however. One study published in the Journal by Calo et al. (87) suggest that more extensive ablation, including both the right and left atria, might improve results with lower recurrence rates of AF. During 14 ± 5 months follow-up, AF recurred in 39% of patients in the LA ablation group but in only 15% of patients in the biatrial ablation group (p = 0.022), multivariable Cox regression analysis showed ablation technique to be an independent predictor of AF recurrence during follow-up.

With regard to the impact on outcomes of treatment, there is increasing evidence that maintenance of sinus rhythm has advantages over persistence of AF. Singh et al. (88) published a substudy, derived from the larger Veterans Affairs cooperative study (SAFE-T), in which AF patients were randomized to antiarrhythmic drugs amiodarone, sotalol, or placebo, and after 28 days they were cardioverted if not in sinus rhythm and followed for up to 1 year. In this substudy, patients’ quality-of-life scores and exercise capacity were analyzed by outcome at 8 weeks and 1 year. Patients remaining in sinus rhythm at 8 weeks had significantly better physical functioning (p = 0.03), physical role limitations (p = 0.03), general health (p = 0.002), vitality (p < 0.001), and at 1 year better general health (p = 0.007) and social functioning (p = 0.02) compared with AF. Patients remaining in sinus rhythm had better symptom checklist severity scores (p = 0.01), functional capacity, and AF severity scale symptom burden at 8 weeks and in symptom checklist severity scores (p < 0.01) and AF severity scale symptom burden at 1 year. Exercise performance was better in sinus rhythm versus AF at 8 weeks and at 1 year. Thus, restoration and maintenance of sinus rhythm compared with AF resulted in improvement in quality of life and exercise performance both short-term and long-term in this study.

Although rate control with antiarrhythmic drugs and atrioventricular (AV) node ablation have both been shown to increase LVEF in some patients with AF and depressed LV function, a recent study published by Gasparini et al. (89) in the Journal suggested that, in patients with congestive heart failure undergoing CRT, only those undergoing AV junction ablation derived benefit. Within the AF group, during a mean follow-up of 25.2 months, only patients undergoing AV junction ablation showed an increased LVEF (p < 0.001), reverse remodeling effect (p < 0.001), and improved exercise tolerance (p < 0.001), whereas no improvements were observed in AF patients who did not undergo ablation. These data are supported by another study published in the Journal by Hayes et al. (90), a sub-group analysis of the DAVID (Dual Chamber and VVI Implantable Defibrillator) trial, in which the effects of QRS duration on outcome was analyzed in patients undergoing ICD implantation with the device programmed to avoid (VVI-40) or produce more frequent ventricular pacing (DDDR-70). The DAVID trial showed that patients with substantial ventricular pacing (right ventricular) have an increased risk of a combined end point of death and new or worsening congestive heart failure. This substudy evaluated the effects of pre-existing QRS duration on outcomes. There was a significantly higher risk of developing the combined end point of death or congestive heart failure in the group with more ventricular pacing (DDDR-70) and an abnormal QRS duration, but the QRS duration had no effect on outcome in the minimal ventricular pacing group (VVI-40). This study, as noted by the authors, should not imply that right ventricular pacing is safe in patients with
normal QRS duration but rather suggests that right ventricular pacing should be avoided in patients with pre-existing abnormal QRS duration. A further interpretation, also suggested by other studies, is that if ventricular pacing is necessary because of AV conduction disturbance, then biventricular pacing should be considered in patients with pre-existing abnormal QRS duration.

Nuclear, cardiac magnetic resonance, and CT imaging. CARDIAC CT. A study by Leber et al. (91) reports on 20 patients in whom 64-slice CT was compared with IVUS to assess plaque morphology and composition. Although only moderate correlation was observed between plaque size by the 2 methods, the authors found significant agreement in classifying lesions as calcified, noncalcified, or mixed. They concluded that “64-slice CT reveals encouraging results to noninvasively detect different types of coronary plaques located in the proximal coronary system. The ability to determine plaque burden currently is hampered mainly by an insufficient reproducibility.”

Another article reported a meta-analysis of the published data comparing multi-director CT angiography (MDCTA) and invasive angiography, which included single and multi-center trials with 16-, 32-, and 64-slice MDCT. Hamon et al. (92) included 29 studies reporting on 2,024 patients’ syndromes referred for coronary angiography mostly with chest pain. The per-segment sensitivity and specificity were 81% (95% confidence interval [CI] 72% to 89%) and 93% (95% CI 90% to 97%), respectively, whereas the per-patient sensitivity and specificity were 96% (95% CI 94% to 98%) and 74% (95% CI 65% to 84%), respectively. Although at the segment level the difference between 16 to 64 MDCTA only showed a trend of borderline significance, on a per-patient analysis basis 64-MDCTA was superior (p = 0.026).

An article by Hausleiter et al. (93) examined the prevalence of noncalcified coronary plaques by 64-slice CT in patients with an intermediate risk for significant CAD. Noncalcified coronary plaques were detected in 48 (29.8%) of 161 patients examined by MDCTA. The prevalence of noncalcified plaques as the only manifestation of CAD was 6.2% (10 of 161 patients), whereas in 60 of the 161 (37.3%) only calcified plaques were present. The authors concluded that “with the use of 64-slice CT, clearly discernible noncalcified atherosclerotic coronary plaques can be detected in a large group of patients with an intermediate risk for having CAD.”

Several studies focused on the application of coronary MDCTA in specific patient groups. Limitations exist to the accurate identification of coronary stenoses in patients with left bundle branch block (LBBB). Ghostine et al. (94) performed MDCTA in 66 LBBBB patients undergoing standard angiography and observed a sensitivity and specificity of 97% and 95%. In an accompanying editorial, Iskandrian (95) comments that, despite the favorable data, it is premature to conclude that MDCTA will be the diagnostic procedure of choice for LBBB patients. Another obvious niche application for MDCTA is in the preoperative evaluation of coronary disease in valve disease patients. Gilard et al. (96) performed 16-slice MDCTA in 55 preoperative aortic stenosis patients. The positive and negative predictive value of MDCT compared with standard angiography was 55% and 100%, which would have enabled invasive angiography to be avoided in 805 patients with an Agaston score <1,000. In an editorial, Hoffman et al. (97) pointed out that the use of MDCTA for this application will depend greatly upon the prevalence of disease and coronary calcification and that more data will be required.

In combination with vessel imaging, MDCT has significant potential as a technology that could assess myocardial perfusion, function, and viability. In preclinical studies, Baks et al. (98) and George et al. (99) used MDCTA to measure infarct size and stress perfusion, respectively. In the first study, the authors documented the ability of MDCTA to accurately quantify MI relative to delayed enhanced MRI as the gold-standard technique. In the second, the authors demonstrate the ability to combine coronary angiography and stress perfusion induced by intravenous adenosine in animals with artificially induced left anterior descending stenoses. Myocardial blood flow and perfusion defects correlated well with microsphere blood flow and other histopathologic techniques, demonstrating the potential of combining coronary angiography with stress perfusion during a single MDCT data acquisition.

CARDIOVASCULAR MRI. The power of MRI to phenotype cardiovascular disease, particularly in large population studies, was exemplified by Barbier et al. (100), who examined the prevalence of “silent” myocardial scars in 259 randomly selected 70-year-old individuals in Sweden. Although scars consistent with MI were found in 60 study participants (24.2%), they reflected clinically silent episodes in 49 (19.8%) of them. However, the volumes of previously unidentified scars were significantly smaller than those reflecting clinically manifested infarction. In another thought-provoking population research study from the MESA (Multi-Ethnic Study on Atherosclerosis) trial, Wang et al. (101) examined the relationship between epicardial coronary atherosclerosis characterized by calcium scores and regional myocardial perfusion studied by contrast enhanced MRI at rest and during adenosine infusion. A total of 222 MESA participants, ages 45 to 84 years and free of past clinical cardiac disease, were enrolled in this study that demonstrated that “coronary vasodilatory response was associated inversely with the presence and severity of CAC in asymptomatic adults.” A third research study, using MRI to phenotype cardiovascular disease in the MESA population of asymptomatic adults, related carotid atherosclerosis to regional myocardial function measured by MR tissue tagging. In this report by Fernandes et al. (102) greater atherosclerosis was associated with reduced myocardial function measured as the magnitude of circumferential shortening in the lateral, posterior, and septal walls, whereas
diastolic function assessed as strain rate during early filling was decreased even after adjustment for age and other variables. The common theme of these studies was the documentation of cardiac involvement manifested as dysfunction, perfusion reserve, and fibrosis as detected by MRI earlier or to a greater extent than previously suspected.

Journal cardiovascular MRI highlights also included studies using delayed enhancement to predict response to cardiac resynchronization. Thus, White et al. (103) studied 23 patients with QRS duration >120 ms and dyssynchrony and found that a percent total scar of 15% yielded a sensitivity of 85% and specificity of 90% in predicting response to CRT. State-of-the-art coronary magnetic resonance angiography (MRA) with novel “whole heart” acquisition techniques was reported by Sakuma et al. (104). Free breathing whole heart coronary angiography was feasible in 86% of 113 patients and yielded a patient-based sensitivity of 82% and specificity of 90%.

Finally, the recently recognized potential of noninvasive MRI to provide unique prognostic information in terms of risk for sudden death and malignant ventricular remodeling is reflected in 2 studies focusing on patients with chronic myocarditis by De Cobelli et al. (105) and in patients with dilated cardiomyopathy by Assomull et al. (106). In the latter study, the pattern of midwall fibrosis as defined by contrast-enhanced MRI related to all-cause mortality and cardiovascular hospitalization independent of ventricular remodeling. As the authors remarked, “this suggests a potential role for CMR in the risk stratification of patients with dilated cardiomyopathy.”

**POSITRON EMISSION TOMOGRAPHY (PET)/CT.** Several studies using PET/CT to examine diverse aspects of cardiovascular pathophysiology appeared in the Journal this year. Among those, the study by Yoshinaga et al. (107) investigated the prognostic significance of alterations in myocardial perfusion quantified by Rubidium-82 PET in 367 patients who underwent dipyridamole 82Rb PET myocardial perfusion imaging (MPI). The annual hard events rates were 0.4%, 2.3%, and 7.0% in 3 groups of patients classified as normal, mild, and moderate-severe in terms of a summed stress score. Moreover, in adjusted survival models, 82Rb PET summed stress scores were the strongest predictors of total cardiac events and also a predictor of hard events, showing that 82Rb PET has significant prognostic power in patients with heart disease.

In another study focused on exploring the ability of "integrated PET/CT" to dissect cardiovascular biologic mechanisms from gene expression to physiologic function and morphology Wagner et al. (108) investigated regional angiogenesis in a model of local adenovirus transfer of the VEGF121 gene to myocardium of healthy pigs. They documented successful transgene expression 2 days after gene transfer by a reporter probe targeting co-expressed HSV1-\text{sr39tk} reporter gene. Increased local myocardial perfusion was identified in areas overexpressing VEGF, corroborating in vivo effects of microvascular tone and permeability. This elegant study documents the enormous potential of these molecular imaging techniques to probe the most basic mechanisms of myocyte and endothelial cell physiology and dysfunction secondary to diverse fundamental disease mechanisms.

**General Cardiology**

**Biomarkers.** It would be useful to find markers to identify atherosclerotic plaques that are prone to rupture. A novel candidate is pregnancy-associated plasma protein-A (PAPP-A), a zinc-binding matrix metalloproteinase used in prenatal screening. Elevated levels of PAPP-A occur in CAD and are associated with adverse cardiovascular events in ACS. Sangiorgi et al. (109) extended this observation from coronary to carotid atherosclerotic disease. Carotid endarterectomy specimens from 72 patients with stroke, transient ischemic attack, or no symptoms were characterized on the basis of histological examination. When compared with stable plaques, vulnerable and ruptured atherosclerotic plaques had thin caps with inflammatory infiltrates with PPAP-A expression that colocalized with monocytes and macrophages by immunostaining. Circulating plasma levels of PPAP-A were higher in patients with vulnerable and ruptured plaques, suggesting that PPAP-A might be a useful biomarker to identify unstable carotid atherosclerotic disease. Future studies are needed to determine whether PPAP-A can identify high-risk patients before the onset of symptoms and/or predict clinical outcomes.

Waxman et al. (110) studied the ability of the first troponin I measurement sent from the emergency department to be a predictor of all-cause mortality. They developed a model from data at a single center and then validated it in another. They demonstrated that in a heterogeneous population of acutely ill patients, the presence of troponin I, even at levels below the 99th percentile, is associated with an increased risk for mortality. Mortality risk varied in direct proportion to order-of-magnitude changes in troponin I, more than doubling with any 10-fold increase. The authors suggest that current recommendations for diagnostic cutoffs for the central role that any single cutoff assumes in the diagnosis of MI merit reconsideration. In an accompanying editorial, Jaffe (111) points out that structural heart disease can also be responsible for detectable values both below and above the putative 99th percentile. Data from a number of studies suggest that cardiac troponin, in addition to helping diagnose acute cardiovascular disease, might also be a more chronic risk marker. He therefore advocates more sensitive troponin assays, despite complaints from clinicians who are frustrated by the inability to find a reason for a high troponin in some patients. It is the clinicians who must educate themselves about the new assays and become comfortable in how to interpret them.

**Natriuretic peptides.** Tsutamoto et al. (112) measured the plasma BNP level in the aortic root (AO) and coronary
sinus (CS) in 366 consecutive patients with heart failure. They observed that hemodynamic parameters such as LV ejection fraction (LVEF) and LV end-diastolic pressure (LVEDP) but not estimated glomerular filtration rate (eGFR) were independent predictors of a transcatheter increase (CS-AO) in BNP; however, the BNP level in the AO was predicted by eGFR (p < 0.0001) in addition to LVEF and LVEDP. These findings suggested that BNP secretion is not affected by renal dysfunction, whereas BNP clearance is, and that decreased clearance from the kidney contributes to the elevated BNP in heart failure patients with renal dysfunction.

Schnabel et al. (113) evaluated the role of BNP in 1,085 stable angina patients, from AtheroGene study, in predicting cardiovascular events during a long-term follow-up of 2.5 years. The BNP concentrations were significantly elevated in patients with future cardiovascular events (median 119.2 pg/ml) compared with those who remained event-free (36.2 pg/ml; p < 0.001). These data demonstrated that BNP is a strong predictor of cardiovascular risk in stable angina independent of LV systolic performance and known risk factors.

Hypertension. Rossi et al. (114) prospectively investigated the prevalence of curable forms of primary aldosteronism (PA) in newly diagnosed hypertensive patients. Patients in 14 centers underwent a diagnostic protocol that consisted of 24-h urine and serum for sodium and potassium, seated plasma renin activity, and aldosterone at baseline and after 50 mg of captopril. Patients with an aldosterone/renin ratio >40 baseline and/or >30 after captopril underwent imaging tests and adrenal vein sampling or adrenocortical scintigraphy. An aldosterone-producing adenoma was diagnosed in patients who in addition to excess aldosterone secretion showed lateralized secretion of aldosterone, adenoma at surgery and pathology, and a blood pressure fall after adrenalectomy. Evidence of autonomous aldosterone secretion without such criteria led to a diagnosis of idiopathic hyperaldosteronism (IHA). The authors found that almost 5% of newly diagnosed hypertensive patients referred to specialized centers for hypertension have a surgically curable aldosterone-producing tumor. An additional 6.3% had idiopathic hyperaldosteronism, giving an overall prevalence of primary aldosteronism of 11.2%. This clearly warrants screening in newly diagnosed hypertensive patients. The biochemical identification of primary aldosterone represents a compelling indication for the search of a unilateral adrenal cause of aldosterone excess, which is feasible with adrenal vein sample and is felt to be mandatory by the authors before undertaking adrenalectomy.

**Congenital Heart Disease**

Among the most interesting areas related to pediatric and adult congenital heart disease and congenital heart surgery are those discussed in two articles related to new interventional methods—one that might revolutionize transcatheter atrial septal defect (ASD) and patent foramen ovale closure, and the other related to covered stents for aortic coarctation and recoarctation.

**Interventional methods.** A study by Jux et al. (115) reported the availability of a method to occlude the atrial septum while maintaining the normal shape and mechanics of the septum without cumbersome foreign bodies, an important development given the limitations of the popularly used devices. The BioSTAR device, by NMT Medical, Inc. (Boston, Massachusetts) in conjunction with Organogenesis (Canton, Massachusetts), provides a bioremodelable collagen matrix instead of a fabric scaffold. The device is coated with heparin. The experimental study reported placement of the BioSTAR or STARFlex devices in 36 sheep under fluoroscopy and guided by intracardiac echocardiography. Animals underwent intra-cardiac imaging to detect any residual shunting and were sacrificed at various time points. The ASD closure of these medium size defects was excellent. The BioSTAR showed less deposition of blood-derived materials than STARFlex. The BioSTAR occluder showed greater coverage with tissue and was completely reabsorbed by 2 years. This study represents an important chronic animal study as proof of concept.

Tzifa et al. (116) published an interesting multicenter study of a new platinum-covered stent for treatment of aortic coarctation. They reported 30 patients, 16 of whom had previous procedures, and 12 of whom had stent-related complications including fractures, aneurysms, and in-stent thrombosis. Thirty-three covered stents were implanted into 30 patients, with stent fracture occurring acutely in 6 patients, 1 of which was treated with implantation of a separate stent. One patient had a small subrenal aortic dissection that resolved; in 4 patients the stents were redilated. Follow-up imaging showed good position of the stents. Nine of 21 patients had some reduction of their hypertension medication. The study confirms early and intermediate results with the use of the platinum-covered stent as a rescue method.

**Congenital heart surgery.** A report by Li et al. (117) addresses the precarious hemodynamics and pharmacologic management that occurs in infants with hypoplastic left heart syndrome after first-stage Norwood, where resistances and pressures in the pulmonary and arterial circulation, cardiac work, and oxygenation need to be balanced. Thirteen sedated, paralyzed, and ventilated neonates were followed for 72 h after the Norwood procedure; systemic and pulmonary blood flows were calculated. Oxygen extraction, a rate/pressure product, and systemic oxygen consumption were also obtained. Dopamine was administered at 5 µg/kg in 12 patients and 7.5 µg/kg in the rest and terminated within the first 48 h in all patients. Dopamine was shown in this study to have adverse effects both on carbon dioxide and oxygen delivery. The adrenogenic receptor stimulation of the drug increased metabolic rate. Termination of the dopa-
mine did not specifically change pressures or $Q_{p}/Q_{s}$ but decreased heart rate and rate pressure product as well as decreasing oxygen extraction ratio. The study suggests that care must be taken regarding circulatory support of these neonates after cardiopulmonary bypass and the importance of understanding changes in oxygen use and delivery in critically ill neonates after the Norwood procedure.

An important study looked at long-range outcomes of pulmonary valve and proximal pulmonary artery imposed into the aortic position during arterial switch. This article from Losay et al. (118) reported follow-up data on 1,156 hospital survivors operated on between 1982 and 2000 with the follow-up data up to 7 years; 14.9% had significant aortic regurgitation at last follow-up, which was associated with complex transposition, prior pulmonary banding, aortic arch anomalies, older age at arterial switch, greater aortic/pulmonary size discrepancy, or the presence of aortic regurgitation or a residual ventricular septal defect at discharge. Nonetheless, even in this population, a secondary slow increase in heart rate occurs in older patients. Most aortic regurgitation remains trivial and without consequence, and repeat surgery has been performed in only 1.4% of survivors.

An editorial by del Nido and Schwartz (119) pointed out that the gradual increase in the presence of aortic regurgitation has been noted in patients after the Ross procedure where the pulmonary root is inserted into the LV outflow tract. Progressive aortic regurgitation is sometimes seen in 90% of these patients, and the long-term need for surveillance remains necessary.

Cheung et al. (120) reported a randomized trial of remote ischemic preconditioning to see whether it would provide protection against myocardial ischemic reperfusion injury and systemic inflammation in children undergoing cardiopulmonary bypass. The remote preconditioning protocol was induced by four 5-min cycles of lower limb ischemia and a 5-min reperfusion with a blood pressure cuff 5 to 10 min before bypass. Control subjects underwent sham placement (without inflation) of the blood pressure cuff. Patients included those with ventricular septal defects, AV septal defects, and tetralogy of Fallot. The control patients had a higher level of cardiac troponin I, even after excluding patients with extensive right ventricular muscle bundle resections. Inotrope use in the control group was also increased, and tumor necrosis factor alpha levels at 6 h were lower in the study than in the control group. This is a small clinical study involving ischemic preconditioning using lower-limb ischemia before pulmonary bypass—an interesting concept carried over from CAD valvular surgeries, which should be further explored in the congenital heart disease milieu.

Senzaki et al. (121) published an important hemodynamic study related to cardiac function in 17 Fontan patients (mean age 6.3 years) and 20 patients (mean age 6.6 years) with normal biventricular circulation as control subjects. Fontan patients were in New York Heart Association functional class I, and none had significant AV valve regurgitation. All had undergone a cavo pulmonary connection with a lateral tunnel. Ventricular pressure was measured with a high-fidelity manometer-tipped catheter, and ventricular cardiac area was measured by echocardiography. Stroke area and stroke volume were measured by a catheter-mounted electromagnetic probe. Maneuvers examined included increased heart rate induced by atrial pacing and adrenergic stimulation by dobutamine, and steady state beats and expiration were evaluated to look at end-diastolic and end-systolic pressure area relationships and dP/dt. Preload was also varied by inferior vena caval occlusion. The expected lower cardiac index and fractional shortening and higher central venous pressure were seen in the single-ventricle Fontan groups. Fontan patients had a baseline increase of afterload and a significantly delayed relaxation measured by tau. With increased heart rate the Fontan group had decreased systolic pressure and stroke area index. In response to dobutamine stimulation, the increase in cardiac index was significantly smaller in the Fontan group, associated with limited preload reserve. This study provides insight into the extent of abnormalities in young children with good Fontan results and an asymptomatic status. It suggests that efforts to overcome limitations of the Fontan circulation with medical interventions might be required to improve the long-term prognosis of these patients. The abnormalities also explain the known and expected decrease in exercise tolerance observed in patients after the Fontan procedure.

Preclinical research. NOVEL MECHANISMS AT WORK IN ATHEROSCLEROSIS. This year marked continued progress in our understanding of the underlying mechanisms of atherosclerosis and potential new targets for therapeutic modulation of this disease. The link between CRP and the disease process of atherosclerosis has become even clearer. Indeed, Monterol et al. (122) observed that CRP is a marker of plaque activity and can also participate in processes important in the development of ACS (123). They showed that CRP increased levels and activity of MMP-1 and -10 in human umbilical vein endothelial cells and aortic endothelial cells, which was abolished by inhibition of p38 and Jun N-terminal kinase pathways. They also observed elevated MMP activity in coronary patients with elevated CRP levels along with colocalization of CRP and MMPs in advanced human atherosclerotic lesions. In other investigations, Marfella et al. (124) used a very clever design to investigate the role of the ubiquitin proteosome pathway in destabilizing carotid plaques in patients undergoing carotid endarterectomy and given rosiglitazone. The excised plaques showed enhanced ubiquitin protease activity and inflammation that seemed to be inhibited by rosiglitazone. Thus, a key and “druggable” regulator of inflamma-
tion—the ubiquitin proteosome pathway—is active in plaque stabilization and can be modulated by a thiazolidinedione. Finally, Liu et al. (125) took an observation from neurology that naloxone inhibits microglial activation and applied it to the apolipoprotein E (apoE)−/− mouse and showed that this drug could reduce macrophage activation, inflammation, and neointimal formation. Thus a well-established compound emerges with a potentially new application to vascular disease.

NEW SIGNALING PATHWAYS IN HEART FAILURE. Cardiomyopathy is a well-known adverse effect of trastuzumab (Herceptin) therapy for breast cancer, and other receptor tyrosine kinases seem to depress myocardial function. Liu et al. (126) showed that the ligand of ErbB2/ErbB4 receptors given to murine and canine models of ischemic, dilated, and viral cardiomyopathy had salutary effects on cardiac performance, pathological processes, and prolonged survival in each of these models. This “bedside to bench” study highlights a new pathway and possible regulator of heart failure, because the ErbB2/4 signaling has been shown to be a key modulator of cardiomyocyte apoptosis and survival (127). This observation also now provides for the possibility of testing the hypothesis that neuregulin, the ligand for ErbB2/4, might offer a way to protect the heart in the setting of cardiotoxic therapeutics in the management of cancer.

PROGRESS AND ISSUES IN CARDIAC REGENERATION. Although progress continues in cellular approaches to cardiovascular disease, there remains controversy and uncertainty. Anversa et al. (128) and Murry et al. (129) have highlighted these in exquisite detail in their viewpoints and commentaries. Anversa et al. (128) argues that both bone marrow stem cells and multipotent cardiac stems show plasticity and ability to differentiate into cardiomyocytes and vessels, properties that have spirited their use in acute MI and heart failure. Murry et al. (129) argues that although cellular transplantation has been shown to improve cardiac function—both from skeletal myoblasts and bone marrow—the role of cardiac-specific progenitors is not clear and that although these cells home to the myocardium, it is not clear that they transdifferentiate. Moreover, important clinical questions are discussed: 1) Should stem cell trials be in the clinic today? Murry et al. (130) believe that stem cell trials are warranted on the basis of preclinical safety and efficacy data, although 1 report seems to suggest caution. 2) What is the most appropriate setting for cell therapy: acute infarction, heart failure, or both? The answer here is less clear, and studies in the acute infarct, chronic heart failure, and cardiomyopathy are ongoing. 3) What are the optimal cells? Right now there is no obvious rationale for cell choice or mode of delivery. Issues of cell potency, pluripotency, and potential for extracardiac effects (e.g., tumors) and timing are all important targets for clinical trials. 4) Which outcome should be used to evaluate this new approach? Early on myocardial function is a key outcome measure, and in the long term we can anticipate mortality-based trials. In the interim, novel imaging approaches (131) and biomarkers will undoubtedly be developed that will aid in the assessment of this very promising therapeutic modality.

CARDIOVASCULAR GENOMICS. This year brought a new section to the Journal in genomics of cardiovascular medicine. The Journal published State-of-the-Art reviews in genomics and personalized medicine (132) and for whole genome approaches to heart failure (133), arrhythmias (134), and evaluation of the perioperative patient (135) as well as the cardiovascular application of gene expression (136), molecular imaging (137), proteomics (138), endothelial cell progenitors (139), and cardiac regeneration (128,129). Genomics is now a key strategy in the diagnosis, prognosis, and management of patients with cardiovascular disease. With the National Heart, Lung, and Blood Institute’s commitment to genetics and personalized medicine and the more widespread access of genomics technologies to clinical investigators, there will undoubtedly be more to report in 2007 and beyond in this exciting area of medicine—cardiovascular genomic medicine.

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