

YEAR IN CARDIOLOGY SERIES

The Year in Heart Failure

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In this landmark year for the U.S. healthcare system, during which the Affordable Care Act was signed into law, there have been many notable advances in the area of heart failure (HF) and heart transplantation. In addition to scientific discoveries reviewed here and the publication of important clinical guidelines, scientific statements, and state-of-the-art reviews listed in [Tables 1 and 2 \(1–23\)](#), the cardiology secondary subspecialty of advanced heart failure and transplantation has been enhanced with the development of training competencies (8) and the first American Board of Internal Medicine Certification Examination in November 2010. In this review paper, we highlight the major published scientific and clinical advances in clinical HF and heart transplantation during the past academic year.

Epidemiology and Prevention

For many years, we have known that diabetes and obesity are associated with an increased risk of incident HF. Emerging epidemiologic studies focused on components of that risk, including glycemic status, metabolic syndrome, body mass index, and lipoproteins. The results of a large Finnish study following a cohort of almost 60,000 people demonstrated an increased risk of HF with increased body mass index and abdominal obesity and the protective effect of physical activity regardless of body mass index (24). In one of several follow-up publications from the Health, Aging and Body Composition Study, the authors observed that fasting glucose in elderly patients without diabetes is a predictor of incident HF (adjusted hazard ratio [HR] per 10 mg/dl: 1.10; 95% confidence interval [CI]: 1.02 to 1.18; $p = 0.009$), independent of other HF risk factors including age, body mass index, systolic blood pressure, history of coronary disease, and race. Additional measures of glycemic function, including insulin resistance, hemoglobin A_{1c}, and oral glucose tolerance testing, did not provide incremental predictive value (25).

Interestingly, in AMORIS (Apolipoprotein Mortality Risk Study), which observed a large cohort of Swedish

patients free of cardiovascular disease, all lipoprotein components measured were significantly associated with incident HF, with the apolipoprotein (apo)B/apoA-1 ratio most predictive in men and triglycerides most predictive in women. In this study, haptoglobin and uric acid were found to add predictive value to apoB/apoA-1, but glucose did not (26). An analysis from the Framingham Heart Study corroborated the independent predictive value of dyslipidemia for incident HF (27). Although epidemiologic studies continue to focus on these risk factors, it is still unclear what intervention will ameliorate the risk, given the disappointing outcomes of randomized trials evaluating the effect of statins such as CORONA (Controlled Rosuvastatin Multinational Study in Heart Failure) (28) and GISSI-HF (Effects of n-3 PUFA and Rosuvastatin on Mortality-Morbidity of Patients with Symptomatic CHF) (29) and the marginally beneficial outcome with n-3 polyunsaturated fatty acid therapy (30).

In a separate analysis of 534 patients from the Framingham Heart Study, Lee et al. (31) evaluated the differences in risk factors between patients in whom heart failure developed with reduced ejection fraction (HFREF) versus heart failure with normal ejection fraction (HFNEF). They found in multivariate analysis that left bundle branch block and history of myocardial infarction reduced the odds of HFNEF (odds ratios [ORs]: 0.21 and 0.32, respectively), whereas atrial fibrillation, female sex, and elevated systolic blood pressure (ORs: 4.2, 2.3, and 1.1 per 10 mm Hg, respectively) increased the odds of HFNEF. Despite these differences between HFNEF and HFREF, mortality was equally dismal, with median survival of 2.1 years (31). It will be important in the coming years to move away from studying HF in the context of risk factors for coronary artery disease and begin to focus on risk factors specifically associated with HF.

Risk Profiling

Global 2-dimensional strain (32) and myocardial iodine-123 meta-iodobenzylguanidine imaging (33) were demonstrated to prognosticate the risk of adverse events in HF patients, although the likelihood that these expensive diagnostic tools will be widely available is low, especially as regulatory constraints on cardiovascular imaging increase. However, for centers without access to advanced cardiovas-

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Table 1 Guidelines and Scientific Statements

Clinician's Guide to Cardiopulmonary Exercise Testing in Adults: A Scientific Statement From the American Heart Association (1)
The International Society of Heart and Lung Transplantation Guidelines for the Care of Heart Transplant Recipients (2)
Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension: The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology and the European Respiratory Society, Endorsed by the International Society of Heart and Lung Transplantation (3)
HFSA 2010 Comprehensive Heart Failure Practice Guideline (4)
Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: Proposed Modification of the Task Force Criteria (5)
International Society for Heart and Lung Transplantation Working Formulation of a Standardized Nomenclature for Cardiac Allograft Vasculopathy—2010 (6)
State of the Science: Promoting Self-Care in Persons With Heart Failure: A Scientific Statement From the American Heart Association (7)
ACCF/AHA/ACP/HFSA/ISHLT 2010 Clinical Competence Statement on Management of Patients With Advanced Heart Failure and Cardiac Transplant: A Report of the ACCF/AHA/ACP Task Force on Clinical Competence and Training (8)
ACCF/AHA 2010 Position Statement on Composite Measures for Healthcare Performance Assessment: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures (Writing Committee to Develop a Position Statement on Composite Measures) (9)
Current State of Knowledge on Aetiology, Diagnosis, Management, and Therapy of Peripartum Cardiomyopathy: A Position Statement From the Heart Failure Association of the European Society of Cardiology Working Group on Peripartum Cardiomyopathy (10)
2010 Focused Update of ESC Guidelines on Device Therapy in Heart Failure: An Update of the 2008 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure and the 2007 ESC Guidelines for Cardiac and Resynchronization Therapy. Developed With the Special Contribution of the Heart Failure Association and the European Heart Rhythm Association (11)

ACCF = American College of Cardiology Foundation; ACP = American College of Physicians; AHA = American Heart Association; HFSA = Heart Failure Society of America.

cular imaging or even cardiopulmonary exercise testing, a study by Hsich et al. (34) showed that treadmill time using the modified Naughton protocol prognosticated mortality risk in patients with HF reasonably well. For a 1-min change in exercise time, there was a 7% increased hazard of death. Use of this simple and relatively inexpensive tool in the community may facilitate evaluation by a specialized HF and transplantation center for consideration of advanced therapies in appropriate patients.

Biomarkers

As new biomarkers are rapidly being discovered, there are efforts to move from a single marker risk prediction strategy to a multimarker approach. It is evident that to be useful, new biomarkers need to show not only independent risk prediction but incremental value to the standard natriuretic peptides in robust statistical analyses. Table 3 (35–43)

Table 2 State-of-the-Art Reviews

Basic Science of Pulmonary Arterial Hypertension for Clinicians: New Concepts and Experimental Therapies (12)
Atrial Fibrillation and Heart Failure: Treatment Considerations for a Dual Epidemic (13)
Enhancing the Outcome of Cell Therapy for Cardiac Repair: Progress From Bench to Bedside and Back (14)
Cardiorenal Syndrome: New Perspectives (15)
Mitral Valve Surgery in Advanced Heart Failure (16)
Palliative Care in Congestive Heart Failure (17)
Assessment of Nonischemic Myocardial Fibrosis (18)
Use of Genetics in the Clinical Evaluation of Cardiomyopathy (19)
The Role of Cardiovascular Magnetic Resonance Imaging in Heart Failure (20)
Selection of Cardiac Transplantation Candidates in 2010 (21)
Appropriate Evaluation and Treatment of Heart Failure Patients After Implantable Cardioverter-Defibrillator Discharge: Time to Go Beyond the Initial Shock (22)
Clinical Management of Continuous-Flow Left Ventricular Assist Devices in Advanced Heart Failure (23)

outlines several markers that have emerged and may be included in future multimarker strategies. A recent analysis of more traditional biomarkers—troponin T, B-type natriuretic peptide (BNP), and C-reactive protein—showed that use of 2 biomarkers in combination was superior to a single biomarker for risk prediction (44). There is considerable research on how to optimally use multiple biomarkers in a practical manner. In addition, there is no consensus on how to use biomarkers to specifically direct therapy. Ultimately, if integration of a panel of biomarkers as part of an objective prognostic scoring system along with standard clinical variables is accomplished, there may be less reliance on relatively subjective endpoints such as symptoms and New York Heart Association (NYHA) functional class. Unfortunately, evidence supporting serial marker management strategies using natriuretic peptides is still lacking, as evidenced by the neutral results of the BATTLESCARRED (NT-proBNP Assisted Treatment to Lessen Serial Cardiac Readmissions and Death) trial and RED HOT II (Rapid Emergency Department Heart Failure Outpatients Trial) (45,46).

Pathophysiology

As outlined last year by Tang and Francis (47), the complex and important role of microribonucleic acid (miRNA)-mediated control of gene expression during cardiac muscle disease development continues to be the subject of reviews (48,49) and investigation. One example of the latter is from van Rooij et al. (50) who showed that 3 myosin genes, *Myb6*, *Myb7*, and *Myb7b*, encode related intronic miRNAs, which, in turn, control muscle myosin content, myofiber identity, and muscle performance. As reviewed by Williams et al. (49), the integration of miRNAs into the core muscle transcriptional program expands the precision and complexity of gene regulation in muscle cells because individual miRNAs are capable of regulating hundreds of mRNAs,

Table 3 Established and Emerging Biomarkers in HF

Biomarker (Ref. No.)	Postulated Pathophysiology	Study Population	Correlation With Outcome
Soluble ST2 (35)	A member of the interleukin-1 receptor family, identified as a potential mediator of myocardial fibrosis. The ligand for ST2 is interleukin-33.	LVEF \leq 45%, NYHA functional class II–III	OR: 1.39 (95% CI: 1.09–1.78, $p = 0.006$) for sudden cardiac death
Galectin-3 (36)	Affects the synthesis of new matrix components such as type I collagen and influences the degradation of extracellular matrix components through a set of tissue inhibitor metalloproteinases and matrix metalloproteinases	Mean LVEF 31%, NYHA functional class III–IV	HR: 1.24 (95% CI: 1.03–1.50, $p = 0.026$) for mortality in a full model with patient variables and NT-proBNP (37)
Neuregulin-1 (38)	Released from microvascular endothelial cells and acts as a paracrine factor via the ErbB family of tyrosine kinase receptors expressed in cardiac myocytes to regulate myocyte differentiation and stress response	Mean LVEF 32%, NYHA functional class I–IV	HR: 1.58 (95% CI: 1.04–2.39, $p = 0.03$) for death or transplantation
Copeptin (C-terminal pro-vasopressin) (39)	Essential in fluid retention and hyponatremia in patients with HF, causing vasoconstriction and left ventricular remodeling	Mean LVEF 33%, NYHA functional class II–IV	Not predictive for mortality in a robust model
Mid-region pro-adrenomedullin (40)	Vasodilatory peptide with potent hypotensive effects	Patients presenting with dyspnea to the emergency department	Superior to BNP and NT-proBNP for predicting 90-day mortality
Mid-region pro-atrial natriuretic peptide (40)	Vasodilatory peptide with potent hypotensive effects	Patients presenting with dyspnea to the emergency department	Equivalent to BNP or NT-proBNP in the diagnosis of HF in patients presenting with dyspnea
Red cell distribution width (41,42)	Measure of the variation in cell volume within the circulating erythrocyte population	LVEF $<$ 40%, NYHA functional class I–IV; NYHA functional class III–IV	HR: 1.12 (95% CI: 1.05–1.16, $p < 0.001$) for death; HR: 1.06 (95% CI: 1.01–1.11, $p = 0.022$) for death
Soluble TNF-like weak inducer of apoptosis (sTWEAK) (43)	A multifunctional cytokine and member of the TNF family, which regulates cell growth, migration, and survival	LVEF \leq 40%, NYHA functional class I–III	HR: 1.9 (95% CI: 1.3–2.6, $p < 0.0012$) for death

BNP = B-type natriuretic peptide; CI = confidence interval; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OR = odds ratio; TNF = tumor necrosis factor.

and individual mRNAs can be targeted by many miRNAs. Another example acknowledges that proper function of the heart depends on the expression of myosin heavy chain (MHC) proteins MYH6 (α -MHC) and MYH7 (β -MHC). Cardiac injury results in a decrease in the expression of the adult myosin gene *Myh6* and an increase in the expression of the embryonic myosin gene *Myh7*. Williams et al. (49) summarized that global profiling of miRNAs in different forms of human heart disease demonstrated that miRNA gene expression signatures are diagnostic for distinct but related forms of heart disease such as dilated cardiomyopathy, ischemic cardiomyopathy, and aortic stenosis. In this regard, miRNA-based diagnostics are likely to emerge as a useful means of molecularly defining specific forms of heart disease and disease progression.

Genetics and genomics of HF. In a prospective cohort study of $>2,000$ patients with HF, including both Caucasians and African Americans, Cresci et al. (51) found that genetic polymorphisms of the β_1 -adrenergic receptor and a kinase that terminates its signaling, GRK5, can significantly affect HF outcomes. They further reported that adjusting for these gene variants abrogates the apparent ethnic differences in beta-blocker treatment effect on HF survival. These findings support additional investigations into the determinants of response to a variety of HF therapies, moving away from only phenotypical characterizations. In a retrospective analysis of subjects enrolled in the Genetic Risk Assessment

in HF substudy of A-HeFT (African American Heart Failure Trial), the authors reported a pharmacogenetic interaction in African Americans with systolic HF carrying the dysfunctional corin allele I555(P568). This allele is almost exclusively present in people of African descent and is postulated to contribute to impaired processing of BNP. In this study, which has not yet been replicated, subjects who were heterozygous for the allele had an increased risk of death or HF hospitalization compared with noncarriers. Additionally, in the randomized subjects of the A-HeFT substudy who were already treated with neurohormonal blockade, this risk was mitigated by treatment with fixed-dose isosorbide dinitrate and hydralazine (52). In a related publication, Matkovich et al. (53) demonstrated the accuracy and utility of pooled sequencing to identify previously unknown rare gene variants to compare polymorphism expression among different populations and to identify novel associations between a cardiac signaling subgenome, *HSPB7* polymorphisms, and sporadic systolic HF. The power and potential applicability of this strategy may pave the way for additional insights into the variability of the syndrome of HF.

Evidence strongly supporting a genetic basis for many cardiomyopathies currently classified as idiopathic or secondary to myocarditis continues to grow as we discover new genetic mutations associated with dilated cardiomyopathy. The rapid expansion in our knowledge of mutations high-

lights the evolving importance of genetic screening and counseling (19,54). An extensive linkage study in 2 unrelated multigenerational families was reported by Lakdawala et al. (55) that established the pathogenicity of a novel missense mutation in the alpha-tropomyosin gene. Notably, in vitro functional analyses revealed opposite effects in calcium handling in the D230N alpha-tropomyosin mutation, which leads to dilated cardiomyopathy, and the D175N alpha-tropomyosin mutation, which leads to hypertrophic cardiomyopathy.

Three additional genetic studies published this year identified novel dilated cardiomyopathy genes. Brauch et al. (56) identified missense mutations in exon 9 of RNA binding motif protein 20 (RMB20), Moulik et al. (57) identified mutations in *ANKRD1*, the gene encoding cardiac ankyrin repeat protein, and Hassel et al. (58) identified mutations in *NEXN*, the gene encoding nexilin, a novel Z-disk protein. Interestingly, a fourth genetic study found an association between HF and a single nucleotide polymorphism in the gene *KCNE1*, which modulates potassium current and has previously been associated with atrial fibrillation. In this preliminary study, confirmed in a second population, both of which excluded patients with atrial fibrillation, the S38G polymorphism at the *KCNE1* locus modulated predisposition to HF (59).

Management of HF

Pharmacologic therapy. This year witnessed ongoing exploration of the role of aldosterone antagonists in the management of HF. In a clinically stable population of patients with mild to moderate HF symptoms and HFREF, 36 weeks of treatment with eplerenone added to optimal medical therapy had no detectable effect on parameters of LV remodeling (60). However, Bansal et al. (61) outlined a persuasive argument for the use of high-dose aldosterone antagonists in patients with resistance to commonly used loop diuretics. In patients with decompensated or advanced HF with volume overload, natriuretic doses of aldosterone antagonists (spironolactone >50 mg/day) may be an option. The competitive natriuretic response of aldosterone antagonists is related to activity of the renin-angiotensin-aldosterone system. The higher the renin-angiotensin-aldosterone system activity is, the higher the dose of aldosterone antagonist required to produce natriuresis. In addition, a post hoc analysis of EPHEsus (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) suggests that earlier eplerenone initiation, <7 days post-myocardial infarction complicated by systolic dysfunction and HF, was safe and associated with better outcomes that were not observed when the drug was administered after 1 week (62). Another study noted that less than one-third of eligible patients hospitalized for HF and participating in a quality improvement registry received HF guideline-recommended aldosterone antagonist therapy (63). We await the results of the EMPHASIS-HF (Effect of Epler-

enone Versus Placebo on Cardiovascular Mortality and Heart Failure Hospitalization in Subjects with NYHA Class II Chronic Systolic Heart Failure) to delineate the spectrum of HF patients who may benefit from aldosterone antagonism.

Several other HF management strategies were highlighted this year. The HEAAL (Effects of High-dose Versus Low-dose Losartan on Clinical Outcomes in Patients with Heart Failure) study demonstrated that losartan 150 mg daily reduced the rate of death or hospital admission for HF in patients with HF, left ventricular ejection fraction <40%, and intolerance of angiotensin-converting enzyme (ACE) inhibitors compared with losartan 50 mg daily. These findings show the value of up-titrating angiotensin receptor blocker doses to confer clinical benefit (64). The FAIR-HF (Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure) trial showed that treatment with intravenous ferric carboxymaltose in patients with chronic HF and iron deficiency, with or without anemia, improved symptoms, functional capacity, and quality of life with a reasonable side-effect profile (65). We also learned more about beta-blocker use in different populations. During acute HF, a study revealed that continuation of beta-blocker therapy was not associated with delayed or less improvement, but rather with a higher rate of long-term prescription of beta-blocker therapy after 3 months (66). In a second study, initiation of bisoprolol in patients with HF and concomitant moderate or severe obstructive pulmonary disease resulted in a reduction in forced expiratory volume in 1 s. However, symptoms and quality of life were not impaired (67). The summer ended with the intriguing SHIFT (Systolic Heart Failure Treatment with I_f Inhibitor Ivabradine Trial), showing improved outcomes with ivabradine added to standard HF therapy (68). The role of this drug that primarily slows heart rate will be debated for some time with respect to patients already on optimal doses of beta-blockers.

Nonpharmacologic therapy. Investigators continue to search for optimal methods and reasons to treat sleep apnea and HF. Gottlieb et al. (69) prospectively followed a total of 1,927 men and 2,495 women 40 years of age and older and free of coronary heart disease and HF at the time of baseline polysomnography. After adjustment for multiple risk factors, obstructive sleep apnea was a significant predictor of incident coronary heart disease only in men 70 years of age and younger but not in older men or in women of any age. Kasai et al. (70) suggest that patients with coexisting obstructive sleep apnea and Cheyne-Stokes respiration-central sleep apnea may receive greater benefit from treatment with flow-triggered adaptive servoventilation than with continuous positive airway pressure alone. Gottlieb et al. (71) found that in patients with stable HF, changes in BNP during the night were related to the severity of nocturnal hypoxemia rather than the frequency or type of sleep-disordered breathing episodes or associated arousals. Interestingly, Yumino et al. (72) argue the novel concept

that nocturnal rostral fluid shift contributes to the pathogenesis of both obstructive and central sleep apnea in patients with HF. The magnitude of overnight rostral fluid movement contributed not only to the severity of sleep apnea but also to its predominant type. This fluid shift was directly related to the degree of leg edema and sitting time and inversely related to the degree of physical activity, giving us possible clues to therapeutic interventions. It is our hope that advances in the pathophysiology and treatment of sleep disorders will lead to therapies that promote patient compliance as the compliance rate with continuous positive airway pressure remains suboptimal.

Remote Patient Monitoring

To combat the growing societal cost of repeated hospitalizations among chronic HF patients, American and European guideline committees have encouraged the use of remote patient monitoring, using a combination of structured telephone communication and electronic transmission of physiologic parameters through the use of external or implantable monitoring devices. The largest meta-analysis to date confirmed that this approach decreases mortality and hospitalizations (73). Importantly, a follow-up study from the DIAL (Randomized Trial of Telephonic Intervention in Chronic Heart Failure) concluded that a reduction in HF hospital admissions was sustained at 3 years, even after the telephone intervention ended (74). With regard to implantable devices, 2 studies evaluated patients with thoracic impedance monitoring and found that significant decreases in thoracic impedance are associated with a statistically significant risk of subsequent HF hospitalization (75,76).

With an abundance of data continuously available, it becomes critical to know how to monitor and react to daily changes in impedance and, furthermore, which member of the multidisciplinary team should be held responsible for interpretation of data. Whellan et al. (77) report that a monthly review of diagnostic data obtained from patients with pacing or defibrillator devices identified patients with significantly increased risk (HR: 4.8, 95% CI: 2.9 to 8.1; $p < 0.001$) for subsequent hospitalization with acute HF after adjusting for clinical variables. Finally, in a pilot study of an investigational left atrial pressure monitor in the HOMEOSTASIS (Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients) trial, the concept of physician-directed patient self-monitoring led to statistically significant improvements in NYHA functional class, left ventricular ejection fraction, up-titration of ACE inhibitors and beta-blockers, and a decrease in loop diuretic dose with twice-daily readings that dictated daily medication dose and dietary allowances (78).

Transplantation

As outcomes after cardiac transplantation continue to improve, an ongoing goal has been to develop a noninvasive, cost-effective, and accurate method of surveillance for rejection

to replace the current gold standard of endomyocardial biopsy. Two promising studies report results of using gene expression profiling of peripheral blood samples to diagnose and survey for acute rejection in transplant patients at low risk of rejection (79,80). In perhaps a complementary approach, cardiac magnetic resonance imaging showed potential for utility in noninvasive diagnosis (or confirmation) of acute allograft rejection (81). As noted previously, guidelines for the management of patients after transplantation were published this year (2).

Mechanical Assist Devices

Debate continues regarding appropriate patient selection for mechanical circulatory support and optimal timing of left ventricular assist device implantation. High on the priority list are risk scoring systems that can accurately predict which patients are likely to do well after implantation. In a recent paper comparing several risk scores with multivariate analysis, the Seattle HF Model (HR: 1.50, 95% CI: 1.02 to 2.21; $p = 0.04$) and APACHE II (HR: 1.10, 95% CI: 1.01 to 1.21; $p = 0.04$) best predicted 1-year mortality. The overall best predictor of mortality in a single institutional cohort of continuous-flow left ventricular assist device patients was the Seattle score (82). Meanwhile, the INTERMACS Coordinators' Council identified gaps in the clinical characterization of hospitalized patients on temporary mechanical circulatory support devices and of homebound patients with resting symptoms, which led to revised definitions of 2 profiles and the addition of new modifiers: 1 for temporary mechanical circulatory support devices in the hospital and 1 for frequent rehospitalization of patients at home (83). It is also gratifying to note that patient thresholds for left ventricular assist device insertion parallel objective survival and functional data, reported by Stewart et al. (84). From their interview of 105 patients with symptomatic HFREF, most would be receptive to referral for discussion of left ventricular assist device by the time expected mortality is within 6 to 12 months and activity is limited to <1 block.

A follow-up publication from the HeartMate II (Thoratec Corp., Pleasanton, California) left ventricular assist device as a bridge to transplantation study reported normalized hepatic and renal function within 1 month of continuous-flow left ventricular assist device implantation with normal function continuing up to 6 months (85). A randomized, controlled trial of a pulsatile-flow device (HeartMate XVE) versus a continuous-flow device (HeartMate II), in a population ineligible for transplantation, showed that the continuous-flow device is superior, with increased rate of survival, quality of life, exercise capacity, and device durability (86). With these promising results, the HeartMate II left ventricular assist device was approved by the U.S. Food and Drug Administration for destination therapy. However, as we accumulate longer follow-up time with destination therapy, there is growing evidence of

increased risk of bleeding (both gastrointestinal and cerebrovascular) with continuous flow, perhaps on the basis of arteriovenous malformations in conjunction with acquired von Willebrand syndrome (87). The complete pathophysiology of this clinically relevant adverse effect is not yet understood.

Novel Therapeutics

Several new therapeutic approaches targeted myocardial calcium handling this year, including gene therapy with AAV1/SERCA 2a in the CUPID (Efficacy and Safety Study of Genetically Targeted Enzyme Replacement Therapy for Advanced Heart Failure) trial (88), infusion of recombinant human neuregulin-1 (89), and the administration of apelin (90). These studies highlight the growing concept that inotropy can have salutary effects depending on the mechanism of increased contractility, in distinction to the deleterious long-term effects of inotropy via phosphodiesterase inhibitors.

The largest study to date investigating the role of intracoronary autologous transplantation of bone marrow-derived stem cells in chronic ischemic cardiomyopathy was published this year. The STAR (Acute and Long-term Effect of Intracoronary Stem Cell Transplantation in Chronic Heart Failure) heart study was a prospective, nonrandomized, open-label study comparing hemodynamics, left ventricular function, exercise capacity, arrhythmias, and mortality in 191 patients who received bone marrow-derived stem cells and 200 control patients who refused infusion of bone marrow-derived stem cells but consented to all other testing. There were statistically significant improvements in all parameters, including mortality, at approximately 5 years of follow-up, with an average mortality rate in the treated group of 0.75% per year versus 3.68% in the control group (91).

Because of the concordant results of countless trials showing the efficacy of ACE inhibition in HF, it is well-known that angiotensin I-converting enzyme, a membrane-bound zinc metallopeptidase, converts the pro-hormone angiotensin I to angiotensin II and inactivates bradykinin. The identification of an ACE-independent mast cell pathway for angiotensin II generation in the human heart raised the possibility that long-term ACE inhibitor therapy may not completely suppress angiotensin II, which may in turn cause adverse left ventricular remodeling by activating angiotensin II receptor subtypes 1 and 2. Chymase, an angiotensin II-forming serine protease found mainly in mast cells and the human heart, is also found in the cardiac interstitial space. Using mice and hamster models, Wei et al. (92) showed that chymase inhibition decreased left ventricular interstitial fluid space angiotensin II levels substantially, indicating the importance of mast cell chymase in regulating cardiac angiotensin II levels. These results suggest that chymase inhibitors could be a useful addition to ACE inhibitor therapy in the treatment of HF.

Cardiorenal Syndrome

Elucidating cardiorenal interactions more completely remains a major challenge in the field, both mechanistically and clinically. A timely review by Bock and Gottlieb (15) summarizes the scope of the problem and the complex mechanisms involved in the pathophysiology. Clinically, observations from 2 retrospective subgroup analyses were particularly thought provoking. The first, using data from COACH (Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure), concluded that worsening renal function at any time from admission for acute HF until 12 months of follow-up was associated with an increased risk of rehospitalization for HF or mortality: HR: 1.63 (95% CI: 1.10 to 2.40; $p = 0.014$) for in-hospital worsening renal function, HR: 2.06 (95% CI: 1.13 to 3.74; $p = 0.018$) for worsening renal function between 0 and 6 months, and HR: 5.03 (95% CI: 2.13 to 11.88; $p < 0.001$) for worsening renal function between 6 and 12 months after discharge (93). This study suggests that accurate risk profiling of this vulnerable population should take into account changes in renal function for much longer than the standard admission period and calls into question the mechanism by which worsening renal function is occurring in this subset of patients. A retrospective analysis of the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) dataset reported that subjects experiencing hemoconcentration during treatment for acute HF received significantly higher doses of loop diuretics, had higher odds of developing worsening renal function (OR: 5.3; $p < 0.001$), and had decreased adjusted mortality at 180 days (HR: 0.16; $p = 0.001$) (94). Clearly, we do not yet have a grasp of the intricate interplay between the heart and the kidney that leads to changes in renal function or how to predict which patients are at increased risk of mortality when their renal function changes. A final confounder in many of these studies is the inconsistent definition of worsening renal function. Large prospective clinical trials in this area are anticipated and sorely needed.

Arrhythmias and Device Therapy for HF

The excitement created by REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) (95) and MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) (96) is ongoing; echocardiographic observations from both studies have revealed that cardiac resynchronization therapy (CRT) in patients with NYHA functional class I and II resulted in major structural and functional reverse remodeling, which appeared to correlate with outcome (97,98). We expect that the RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial) will further elucidate the possible survival benefit afforded by CRT in addition to the implantable cardioverter-defibrillator (ICD) in NYHA functional

class II and III patients. Williams et al. (99) argued that CRT resulted in an improvement in short-term hemodynamic variables in patients with a QRS <120 ms related to both contractile improvement and relief of external constraint. Another team showed that in patients with HFREF and atrioventricular block requiring permanent ventricular pacing, CRT is superior to right ventricular pacing alone and should be considered the preferred pacing mode (100). In the midst of this enthusiasm came the sobering observation that endpoints in multiple CRT trials correlated poorly, which severely limits our ability to generalize results over multiple studies (101). Future trial designs will need to address this critical deficiency.

The role and implications of ICD therapy were further refined this year. Mishkin et al. (22) demonstrated that aggressive HF surveillance and management are required after an ICD shock because the risk of sudden cardiac death is transformed to an increased HF event risk. A clinical risk prediction model identified subsets of moderately symptomatic HF patients in the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) in whom single-lead ICD therapy was of no benefit and other subsets in which benefit was substantial (102). As extracellular matrix alterations affect the arrhythmogenic substrate in nonischemic dilated cardiomyopathy, Kanoupakis et al. (103) observed that serum markers of collagen turnover could predict arrhythmic events in ICD recipients. Finally, in a study of the clinical effectiveness of ICDs among older Medicare beneficiaries hospitalized with HF, ICDs were associated with a significantly lower relative risk of mortality over 3 years compared with no ICD use, after adjustment for the probability of treatment, other prognostic variables, and medical therapy at discharge (104).

HFNEF

The search to understand the pathophysiology leading to HFNEF continues. A small case-control study by Phan et al. (105) investigated the mechanism of HFNEF using echocardiographic techniques during rest and exercise. Significant differences between cases and controls in radial and longitudinal strain, delayed diastolic ventricular untwisting, reduced mitral annular velocities, and abnormal systolic rotation were observed. They hypothesized that symptoms during exercise in patients with HFNEF are more attributable to these abnormalities in function than to abnormal myocardial stiffness, which has been observed in other studies. In one such study, an observational investigation from the Rochester Epidemiology Project, Borlaug et al. (106) found that ventricular-arterial coupling is maintained in hypertensive patients with normal ejection fraction with and without HF. Further, they report that end-systolic stiffness and myocardial contractility are increased in hypertensive patients without HF. In contrast, in hypertensive patients with HFNEF, end-systolic stiffness is increased, but myocardial contractility is decreased. They postulate

that passive stiffening may contribute to the phenotype of HFNEF in the setting of decreased contractility. A follow-up cross-sectional study by the same group confirmed impairment of chronotropic, contractile, endothelial, and vascular reserve in subjects with HFNEF compared with hypertensive and normal controls (107).

In a small, open-label, randomized study evaluating the effect of eplerenone on measures of collagen turnover in HFNEF, the authors concluded that eplerenone at a 50-mg dose modestly attenuated the increase of pro-collagen type III aminoterminal peptide but unfortunately had no effect on clinical symptoms, BNP, or inflammatory markers (108). Another study investigated the mode of death in HFNEF. In contrast to a recent community-based study from the Mayo Clinic showing that 49% of patients died of noncardiovascular causes (109), analysis of the randomized I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction) data confirmed that the majority (60%) of subjects with HFNEF do succumb to cardiovascular death, with sudden death (26%) and HF (14%) proving most common and an annual mortality rate of 5.2% among trial participants, unaffected by treatment with irbesartan (110). Zile et al. (110) postulate that perhaps the older average age of patients with HFNEF and accompanying increased number of comorbidities compared with patients with HFREF account for the relative difference between cardiac and noncardiac cause of mortality between these 2 groups.

Comorbidities

Pulmonary hypertension. Pulmonary hypertension secondary to left heart disease continues to be an area in need of randomized clinical trials assessing the efficacy of available therapeutics including endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostanoids. Guidelines from the European Society of Cardiology (3) and from the 4th World Symposium on Pulmonary Hypertension (111) were published, but unfortunately the strength of evidence is lacking for many recommendations, especially with respect to the so-called nonpulmonary arterial hypertension pulmonary hypertension.

There were 2 clinical trials of treprostinil reported for the treatment of pulmonary arterial hypertension. The TRIUMPH I (Clinical Investigation into the Efficacy and Tolerability of Inhaled Treprostinil Sodium in Patients with Severe Pulmonary Arterial Hypertension) showed improved exercise capacity and quality of life with inhaled treprostinil in combination with sildenafil or bosentan (112), and a smaller placebo-controlled trial of 44 patients treated with intravenous treprostinil revealed safety and improvement in symptoms, exercise capacity, and functional class (113). A thorough review of the basic science of pulmonary arterial hypertension and novel therapeutic targets was published by Archer et al. (12).

Peripartum cardiomyopathy. Insightful advances into the pathogenesis and treatment of peripartum cardiomyopathy and pregnancy-associated cardiomyopathy were reported independently by several groups. Genetic testing of peripartum cardiomyopathy patients suggested that a subset have a genetic basis for their disease, including mutations that are known to segregate in familial dilated cardiomyopathy. Furthermore, a number of first-degree relatives of peripartum cardiomyopathy patients were found to have undiagnosed dilated cardiomyopathy when screened (114,115). These important findings may lead to changes in the guidelines to reflect the utility of screening first-degree relatives of patients with these pregnancy-related disorders. Meanwhile, in an open-label, randomized, pilot study of subjects with acute peripartum cardiomyopathy, bromocriptine in addition to standard HF therapy was found to significantly improve outcome at 6 months (defined as superior survival, ejection fraction, and NYHA functional class) compared with standard therapy alone, without adverse side effects (116). We expect larger clinical trials of this promising new therapy as well as mechanistic studies to emerge in the coming months.

Conclusions

This academic year has witnessed an absence of blockbuster therapies for HF, but important insights and discoveries have been made nonetheless. There is an emerging sense of the importance of the implementation of guidelines to individual vulnerable patients and increasing exploration of methods that may allow us to optimize care for all patients (117,118). Our basic science colleagues are uncovering novel targets for therapies that seem right around the corner. There is hope for the HF patient.

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