Heart failure (HF) has been the subject of a number of important published clinical and translational investigations over the past year. We also anticipate that updates of the American professional societies’ major clinical guidelines will be published later this year. In this article, we summarize the year’s publications that we believe have the greatest clinical relevance to the understanding and management of the HF syndrome.

**Pathophysiology and Diagnostic Testing**

**Genetics of cardiomyopathies.** With the increasing availability of commercially available testing for common genetic mutations found in patients with inherited cardiomyopathy, there is now a serious dialogue as to how these tests should best be used (1). It is becoming increasingly clear that the 8 commonly tested genes for hypertrophic cardiomyopathy are especially prevalent in childhood cases (2). Proband with these gene mutations (found in about 60% of cases) appear to have poorer long-term prognosis as a group compared with those having no identifiable mutations (3). Interestingly, the use of genetic counseling and testing of relatives has remained relatively uncommon despite the availability of preventive measures, in part because the risk-benefit of genetic testing is still uncertain and because incomplete penetrance is common (4). A similar molecular genetic diagnostic approach in patients with dilated cardiomyopathy has been less productive, with only about 10% of cases identified by a 6-gene mutation panel (5) and another 6% of cases identified by lamin A/C mutation analysis (6). There is hope that genetic findings may ultimately provide additional insight for patients and their family members with these otherwise unexplained cardiomyopathies.

A “genetic beta-blockade” phenomenon has been reported in patients of African-American descent (7). In several patient cohorts, a polymorphism in GRK5 (glutamine→leucine) was found in approximately 10-fold higher prevalence in allele frequencies in African Americans than in Caucasians. The presence of GRK5-Leu41 was associated with diminished isoproterenol-stimulated β-adrenergic receptor signaling effects on the basis of desensitization of ligand-occupied receptors (7). This genetic profile may be protective against disease progression (rather than disease onset) in a manner similar to treatment with beta-blockers. The investigators provided proof of concept by demonstrating remarkably lower event rates for patients with GRK5-Leu41 polymorphism in 2 separate cohorts, although the actual number of events was small. Nevertheless, one of the greatest challenges of pharmacogenetic analyses related to gene polymorphisms of neurohormonal pathways is the associative nature of the analysis. Such analyses are sometimes plagued by biases and lack of reproducibility (8). An example of this confounding influence can be seen in a study (9) that attempted to compare the effects of 2 distinct beta-adrenergic blocking agents on the basis of 5 different polymorphisms in the adrenergic signaling pathway. The investigators found no impact of these polymorphisms on the variable responses to different beta-blockers, in contrast with the remarkable differences previously seen with bucindol in those with the Arg389Arg ADBR1 allele (10). Clearly, the impact of genetic profiling on treatment responses needs further validation and careful scrutiny. Nevertheless, the field is moving forward, and both investigator and commercial interests are growing stronger.

The incomplete penetrance of monogenetic mutations has allowed for emergence of an alternative strategy using a transcriptomic approach, although the need for both tissue samples and an overwhelming amount of data remain important obstacles. Recent demonstration (11) of the ability of a targeted transcriptomic array from endomyocardial biopsy samples in patients with new-onset HF to distinguish between favorable and unfavorable prognosis is promising. Clearly, current recommendations (12) do not favor routine endomyocardial biopsy as part of standard clinical evaluation, but this may change with improvement in diagnostic techniques, and endomyocardial biopsy is indicated for specific diagnostic purposes.

**Biomarkers in HF.** The field of HF biomarkers continues to grow exponentially, although the gap between published evidence and clinical practice remains (13). Published reports are becoming bloated with descriptive studies that match a specific biomarker with a specific diagnostic feature.
or match a cutoff value to predict a specific risk profile. For example, more data regarding the potential prognostic role of ST2 were reported this year. Baseline (14) as well as follow-up (15) measurements of ST2 levels in patients admitted to the hospital with HF or with ST-elevation myocardial infarction (16) have been reported. Other novel markers with incremental prognostic value recently described include osteopontin (17), copeptin (18), advanced glycation end products (19), and methylated arginine metabolites (20), to name a few (all yet to be clinically available).

Using biomarkers as surrogates of therapeutic responses has been the subject of several clinical studies this year. Interestingly, the lack of improvement in neurohormonal levels in the BEST (Beta-blocker Evaluation of Survival Study) is consistent with the lack of efficacy of bucindolol (21). In the ALOFT (Alikiren Observation of Heart Failure Treatment) study, where alikiren (150 mg daily) was compared to placebo as an add-on therapy for 12 weeks in 302 patients with HF (New York Heart Association [NYHA] functional class II to VI, B-type natriuretic peptide [BNP] >100 pg/ml, creatinine ≤2 mg/dl), significant reductions in neurohormonal activity were observed without increasing adverse drug effects (22). Still, not all favorable changes in biomarker levels are associated with favorable long-term outcomes, as in the case of CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure), where a substantial reduction in high-sensitivity C-reactive protein did not match the primarily neutral results of the study (23). However, very few therapeutic studies have provided insight into how these biomarkers can help in the clinical management of patients with HF. The OPT-CHF (Oxypurinol Therapy for Congestive Heart Failure) study published this year (24) outlined the potential benefits of xanthine oxidase inhibition by oxypurinol in patients with HF who demonstrate elevated uric acid levels.

The logistics of applying biomarkers to clinical practice are elegantly illustrated in a study conducted in a large British general practice population of older patients with diabetes mellitus or ischemic heart disease (i.e., Stage A). Following initial BNP testing, approximately 19% of these minimally symptomatic patients were found to have elevated plasma BNP levels, and subsequently 10% had persistently elevated plasma BNP levels on repeated testing. Initiation or up-titration of evidence-based HF treatment facilitated normalized BNP levels in 28% of patients (25). Diabetic retinopathy has been identified as another risk factor for HF (26). Indeed, early identification of at-risk patients and aggressive risk factor modification and therapeutic interdiction are the core promise of prevention, as outlined in a recent consensus statement (27). Because simple clinical characteristics can identify individuals at risk of developing HF (28), we believe that biomarker-guided strategies should be pursued not simply for the sake of detecting the presence of structural heart diseases, but also to signal appropriate interventions in at-risk individuals. Preventing disease, rather than predicting events, should remain the primary focus.

Cardiorenal interactions. The concept of renal preservation in patients with acute heart failure syndrome (AHFS) has become more widely recognized, but determining the precise mechanism whereby an individual patient’s cardiorenal function becomes impaired in this syndrome is challenging. Traditionally, inadequate renal perfusion has been the prevailing hypothesis and has been attributed to a reduced cardiac output and low renal blood flow. A rise in serum creatinine still provides a crude estimate of renal compromise and worsening prognosis (29,30). Persistent hyponatremia is also a clear marker for poor survival (29,31,32). There is now interest in examining the utility of blood urea nitrogen, both as a single time point and by increase over time, as a strong prognostic marker in both stable patients (33) and those with decompressed HF (34). Newer markers have yet to be widely examined in this population. Cystatin C can identify a subset of patients with normal serum creatinine levels and a poor outcome (35). Underlying conditions (e.g., diastolic dysfunction, right HF) that contribute to worsening venous congestion can also be associated with higher cystatin C levels (36,37) and a greater likelihood of worsening renal function (30). In the setting of chronic HF, shorter leukocyte telomere length has been associated with renal insufficiency (38), but the mechanisms have remained unexplained.

The traditional simple model of cardiorenal syndrome assumes that impaired cardiac output contributes to diminished renal perfusion, leading to reduced filtration and/or renal ischemia. Clearly, the degree of antecedent intrinsic renal disease is very important, and hemodynamic alterations contribute only in part to the development of acute worsening renal function (39). Several groups (30,40) have recently rediscovered the importance of venous congestion as a contributing factor to the progression of worsening renal function independent of forward cardiac output. However, routine hemodynamically guided therapy does not appear to provide any substantial advantage in managing these patients (39). An extrarenal component of abdominal congestion leading to raised intra-abdominal pressure may worsen on central venous pressures (41) and may contribute to renal function impairment (42). Persistently raised intra-abdominal pressures despite aggressive medical therapy may warrant further investigation and treatment (43). The challenge is to find safe and effective ways to relieve salt and water retention.

Defining diastolic HF. The struggle to best define the diastolic HF (or HF with preserved ejection fraction [HFpEF]) population is persistent. Observations from the PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure) and the I-PRESERVE (Irbesartan in Heart Failure with Preserved Systolic Function) trials indicate that existing inclusion criteria for diastolic HF are heterogeneous, and long-term clinical outcomes are highly dependent on markers of severity such as natriuretic peptide levels and previous hospitalizations for HF exacerbations (44,45).
The updated consensus statement published by the European Society of Cardiology this year (46) has proposed 3 obligatory conditions for the diagnosis of HFrEF: the presence of signs and symptoms of congestive HF, the presence of a normal or mildly abnormal left ventricular (LV) systolic function (left ventricular ejection fraction [LVEF] >40%), and evidence of diastolic LV dysfunction (including abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness). Besides standard invasive and echocardiographic measurements, there is a heavy emphasis on the role of tissue Doppler indexes. However, there is controversy as to whether diastolic abnormalities are always present in such patients. Notably, LV hypertrophy and clear laboratory evidence of diastolic impairment appear to be absent in some patients with clinical HF and HFrEF even in the setting of hypertrophic cardiomyopathy (47), suggesting that we still do not understand this syndrome very well.

**Pharmacologic Treatment**

**Standard pharmacologic therapy.** Contemporary outpatient management of HF has been examined in the IMPROVE-HF (Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting). Although use of standard neurohormonal blocking agents was high in the 80% to 86% range, aldosterone receptor antagonists were prescribed in only 36% of eligible patients, and rates of device therapies were also lower, both decreasing with increase in age (48). Both registry and post-hoc trial data analysis also suggest (49,50) that unless withdrawal is deemed clearly necessary, beta-adrenergic blockers should be maintained during an episode of decompensated HF.

An elegant prospective study of a practical nature (51) described the fallacy of logical deduction regarding diuretic use and dosing as a “cause” of morbidity and mortality, a perspective that has been repeatedly found in many post-hoc analyses. In 183 patients with advanced HF, the prognostic value of high-dose (>80 mg/day furosemide equivalent) diuretic therapy was negated when adjusted for clinical stability (which is not readily available in most databases), suggesting that diuretic dosing is simply a marker, rather than a cause, of poor prognosis (52). This highlights the enduring value of careful clinical investigations to clarify the issues raised by interrogating large databases (53).

**Statins in HF.** The CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial was the focus of debate regarding the potential role of statin therapy in chronic HF. CORONA was a multicenter, randomized-controlled, placebo-controlled trial of 5,011 older patients (age ≥60 years, mean age 73 years) with ischemic cardiomyopathy (LVEF ≤40% for NYHA functional class III to IV or LVEF ≤35% for NYHA functional class II). Patients were randomized to either rosuvastatin at 10 mg daily or placebo and received a median of 2.7 years follow-up (23). The study did not reach the primary combined end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (hazard ratio [HR]: 0.92; 95% confidence interval [CI]: 0.83 to 1.02; p = 0.12) or any coronary event end point (HR: 0.92; 95% CI: 0.82 to 1.04; p = 0.18) (Fig. 1). However in post-hoc analysis, there was a trend for fewer cardiovascular hospitalizations and HF hospitalization in the rosuvastatin group. These relatively tepid results are in stark contrast with the many positive findings of statin therapy in a broad range of patient populations and challenge the large volume of research implicating broad benefits of statin therapy in patients with HF (54). In the recently reported GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico–Insufficienza Cardiaca) trial, rosuvastatin also did not demonstrate a reduction in mortality (adjusted HR: 1.00; 95% CI: 0.90 to 1.12; p = 0.943) or cardiovascular hospitalizations (adjusted HR: 1.01; 95% CI: 0.91 to 1.11; p = 0.903), independent of underlying etiology (55). Therefore, the current level of evidence has yet to support routine statin use in patients with HF.

**Vasoactive therapy.** Nesiritide was the subject of a large randomized trial in ambulatory patients with severe HF, and intermittent administration was found to be safe but not effective in achieving its end points (56). Two prospective randomized studies in patients admitted with decompensated HF and underlying renal insufficiency also demonstrated a neutral impact of nesiritide administration on renal function (57,58). High-dose boluses of intravenous nitroglycerin given in the emergency department setting were associated with fewer in-hospital cardiac or respiratory complications in an open-label study, even though length of stay and readmissions were similar (59). In contrast, an observational study of patients with advanced low-output HF (60) found that the use of intravenous sodium nitroprusside was beneficial in improving hemodynamic derangements, and it allowed for the implementation of oral vasodilator therapy at discharge. These studies highlight the importance (and potential benefits) of careful patient selection and titration of vasodilators when used in the AHFS setting, which is the primary focus of an ongoing, very large multinational clinical trial of nesiritide.

There are exciting new compounds on the horizon that are also worth mentioning. First, a unique lusitropic and inotropic agent called istaroxime was tested in HORIZON-HF (A Phase II Trial to Assess Hemodynamic Effects of Istaroxime in Patients with Worsening Heart Failure and Reduced Left Ventricular Systolic Function). Istaroxime demonstrated significant hemodynamic and diastolic volume improvement over placebo without a noticeable increase in arrhythmias, ischemia, or myocardial oxygen consumption (61). Another compound has recently made its debut: a synthetic chimeric hybrid natriuretic peptide based on the recognized properties of 2 different members of the natriuretic peptide family. It was specifically designed to better enhance renal function without causing hypotension (62). Early-phase human studies are currently underway.

Regarding the role of vasodilator therapy in chronic HF, there is accruing interest in the use of sildenafil in patients.
with chronic HF because of its vasoactive effects incremental to standard medical therapy. In a small mechanistic study, patients treated with 6 months of sildenafil demonstrated greater improvements in brachial artery flow-mediated dilatation, cardiopulmonary exercise testing indexes, and ergoreflex testing data when compared with those receiving placebo (63). This was also evident in patients with secondary pulmonary hypertension treated with sildenafil (64).

Managing diastolic HF. Amidst the debate regarding the definition and therapeutic regimen to best manage diastolic HF, the Hong Kong Diastolic Heart Failure Study provided some interesting insight (65). This prospective, multicenter, open-label study (with a blinded end point) randomized 150 patients with preserved LV function (LVEF >45%) and recent HF admission to diuretics only, diuretics with ramipril, or diuretics with irbesartan. Despite improved quality-of-life scoring, outcomes were not different among the groups, except for a very slight improvement in 6-min walk distances in the ramipril and irbesartan groups (65). Readmission rates were similar, although both ramipril and irbesartan demonstrated improved tissue Doppler indexes and lower plasma natriuretic peptide levels at follow-up when compared with those receiving only diuretic therapy, despite a similar reduction in blood pressure. These results, though promising, were underpowered to provide reassurance that improvement in echocardiographic and biochemical surrogates corresponded to improved clinical outcomes.

The incremental role of aldosterone receptor antagonism in reversing cardiac remodeling has been challenged in a small, prospective mechanistic study (66) in asymptomatic patients with moderate-to-severe aortic stenosis but preserved LV systolic function. Patients randomized to eplerenone failed to demonstrate any beneficial effect on myocardial structure, severity of aortic valve stenosis, or LV systolic and diastolic performance when compared with placebo.

Managing anemia in HF. Anemia is associated with poor long-term outcomes in patients with HF, but much of the hemoglobin data have focused on levels derived at a single time point with a single cutoff value. A large, single-center experience observing sequential measurements over time indicated that almost one-half of the anemia resolved without any specific therapy, and the outcomes for those with resolution were comparable to those without anemia (67). Two recent studies comparing intravenous iron administration with placebo clearly demonstrated reduction in plasma natriuretic peptide levels (68), systemic cytokines (69), and exercise capacity (70). Reports of 2 early-phase studies have highlighted the potential benefit of replacement therapy with darbepoetin-alpha in anemic patients with HF (71,72), which was associated with improvement in echocardiographic indexes when compared with placebo (73). This concept is being tested in a multicenter study.

Renal preservation in AHFS. Even though there is broader acceptance for the use of ultrafiltration for salt and fluid removal, a small but carefully performed randomized
study (74) comparing intravenous diuretic therapy with ultrafiltration did not find significant differential impact on renal hemodynamics. Another trial using continuous aortic flow augmentation aimed at preserving renal function (75) also failed to demonstrate noticeable clinical benefits and was associated with increased bleeding. In contrast, clinical investigations regarding the role of adenosine A_1 receptor antagonism seem to be going in the right direction. The results of the pilot phase of the large Phase III trial evaluating add-on intravenous rololufilline in AHFS were highlighted in the American College of Cardiology 2008 Scientific Sessions. Among the 301 patients with AHFS and impaired renal function (creatinine clearance 20 to 80 ml/min) and volume overload, increasing success/decreasing treatment failures (defined as death, rehospitalization, or worsening HF or renal function), as well as improving serum creatinine were associated with increasing rololufilline dosing (up to 30 mg/day) (75).

**Nonpharmacologic Treatment**

**Rate and rhythm management in HF.** This year saw the presentation of several landmark clinical studies that provide useful information regarding the management of atrial fibrillation in patients with HF. The AF-CHF (Atrial Fibrillation in Congestive Heart Failure) trial enrolled 1,376 patients with systolic HF (LVEF <35%, NYHA functional class II to III) and found no significant differences between routine rate and rhythm-control strategies in reducing long-term clinical outcomes (including death, stroke, or worsening HF) (76). These findings were not surprising, considering the fact that the long-term predictors of adverse clinical outcomes following cardioversion for atrial fibrillation were not the rhythm, but predominantly inadequate HF treatment regimens and comorbidities (77,78).

The challenge of ventricular tachyarrhythmia (so-called electrical storm) is becoming increasingly common in the era of widespread defibrillator implantation, and the potential benefits of contemporary catheter ablation have been demonstrated in an Italian series published this year (79). Several groups (80–82) also have reported their experience with catheter ablation of premature ventricular contractions as a potential strategy in the reversal of LV dysfunction, highlighting an overlooked but potentially treatable cause of cardiomyopathy.

**Cardiac resynchronization therapy (CRT) in HF.** The field of CRT continues to catalyze interdisciplinary investigations, especially regarding the role of echocardiography in the prediction and assessment of treatment responses. The first was the RethinQ (Resynchronization Therapy in Normal QRS) study (83), which tested the hypothesis that correction of an echocardiographically defined mechanical dyssynchrony independent of conduction delay may produce clinical benefits in the form of improving functional capacity and cardiac performance. However, the 172-patient study showed similar outcomes with or without CRT, although the study was limited by the relatively short follow-up duration and low event rates (83). The second trial was the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) study, presented at the American College of Cardiology meeting (79), that showed benefit of early CRT in preventing or even reversing progression of LV impairment as well as reducing time to first HF hospitalization in 610 patients with wide QRS but mild symptoms. Critics may argue that the trial missed its intended primary end point of improving symptoms and quality-of-life measures, but in the CARE-HF (Cardiac Resynchronization in Heart Failure) subanalysis, symptom severity appeared to provide less important prognostic information than other criteria (84). These results are consistent with subgroup analyses from prior studies that included NYHA functional class II patients and highlight the importance of adhering to established criteria of QRS and echocardiographic criteria for LVEF for CRT indications (85). The current challenge is to justify the risks and validate the benefits, which demands further clinical investigation in larger populations.

Identification of before-implantation predictors of response to CRT has been controversial. In the CARE-HF study population, greater interventricular mechanical delay, more severe cardiac dyssynchrony, and lower systolic blood pressure appeared to obtain greater benefits from CRT (86). Clearly, “responders” to CRT often demonstrate reversal of cardiac remodeling and morphologic as well as molecular improvement (87–89). The results of the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) study (90) demonstrated that in the 69% of the 426 patients who improved following CRT, no single echocardiographic measure of dyssynchrony was reliable in predicting responders, which can be attributable in part to interobserver variability when making these measurements.

**Mechanical support for advanced HF.** Treatment for end-stage HF remains challenging. This year, we witnessed the approval of the HeartMate II (Thoratec Corporation, Pleasanton, California), the first nonpulsatile left ventricular assist device (LVAD), as a bridge to cardiac transplantation. These nonpulsatile LVADs provide improvement equivalent to traditional pulsatile LVADs in exercise capacity and symptom relief, even though the traditional LVADs achieved greater unloading (91). Ventricular restoration surgery with the CorCap (Acorn Cardiovascular, St. Paul, Minnesota) device also led to favorable long-term results in preventing cardiac remodeling, justifying additional studies (92,93). Implantable electrophysiological device therapy has reached beyond simple pacing or defibrillation functions. Nonexcitatory, cardiac contractile modulation devices have further demonstrated proof-of-concept clinical effects in Phase II studies and associated mechanistic illustration of up-regulation of myocardial contractile genes (94,95).

**Outcome measures.** There are new data (96) to suggest that different factors may have varying implications for long-term outcomes. High blood pressure and arrhythmias,
for example, can be easily identified and treated, whereas pneumonia and worsening renal function (occurring in almost one-quarter of patients) were primarily comorbid markers of poorer prognosis.

Quality and content of the patient-provider interaction has been critically evaluated in several studies this year. Patient recall of adherence advice at the time of hospital discharge from a HF admission was still dismal (97). Also, patients with advanced HF may have a wide range of preferences when it comes to choosing between quality or quantity of life, and there may be a discrepancy between prognostic expectations of patients and their providers (98,99).

A very provocative report (100) on the cause of death in patients with a diagnosis of HF from the Olmsted County database highlights the core issue facing clinical investigators in HF. A heavy reliance on all-cause mortality as the most definitive end point has been called into question, as careful evaluation of noncardiac causes of death ranged from 36% in those with systolic HF to almost one-half (49%) in diastolic HF. Clearly, any therapeutic intervention that acts on specific pathways to mediate cardiovascular benefits will likely be effective in a subset of individuals. We should, to some extent, be wary of all-cause mortality as an end point, particularly in older patients with HFpEF, many of whom can die from noncardiac causes.

Conclusions

The reliance on mega-trials to formulate clinical evidence for the treatment of HF over the past decades is beginning to wane. Clearly, the role of genetic, biochemical, and echocardiographic profiling is increasingly important. The outcome measures themselves have been challenged. We should embrace these challenges as opportunities rather than frustrations and should always remind ourselves that the road to beta-blocker as HF therapy took more than 2 decades and many detours to reach broad adoption. We must continue to learn to better interpret our existing data and to explore how to predict responsiveness to therapies using emerging molecular and genetic techniques.

Rapid technological advances have broadened HF care into a highly skilled expertise that requires specialist training, and this year we witnessed updates of cardiology training requirements for HF and cardiac transplantation (101), as well as an ongoing move toward specialist accreditation by the American Board of Internal Medicine. This is clearly an exciting new era, one that legitimizes training in the complex field of HF. It is hoped that this era will inspire a generation of new ideas and more innovations.

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