Summary: Mechanical circulatory support has become an accepted treatment for patients with advanced heart failure ineligible for transplantation. It is anticipated that the growing heart failure population coupled with the shortage of suitable donor organs will result in further increases in the use of left ventricular assist devices (LVADs) as a means to enhance quality of life and survival. Critical evaluation of new and expanding technologies such as LVADs must include careful analysis of efficacy, safety, and cost-effectiveness. The most comprehensive study of LVAD cost-effectiveness was published 7 years ago based on very early clinical experience with mechanically assisted circulation and older generation devices. High device and implantation costs, as well as relatively modest survival benefits, resulted in an incremental cost-effectiveness ratio/quality-adjusted life year of more than $800 000. To place this in perspective, the per-patient cost of advanced heart failure in a Medicare population treated with standard medical and electric therapies has been reported to be $180 000, with short anticipated life expectancy and limited likelihood for improvements in quality of life. Thus, the “utility” of standard therapies in these patients is poor. The rapid improvements in LVAD technology, patient selection, center experience, and management strategies would reasonably be anticipated to improve the cost-effectiveness of this therapy by reducing perioperative and long-term mortality, decreasing complications, and enhancing functionality and quality of life over prolonged periods of time.

Conclusions: The cost-effectiveness associated with continuous-flow LVADs for destination therapy has improved significantly relative to the pulsatile flow devices. This change is explained by significant improvements in survival and functional status and reduction in implantation costs.1

Factors Related to Morbidity and Mortality in Patients With Chronic Heart Failure With Systolic Dysfunction: The HF-ACTION Predictive Risk Score Model

Summary: This study is an analysis from the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial of 2331 patients to understand the predictive variables of the primary end point of all-cause hospitalization and all-cause death and the secondary end point of all-cause death alone in a modern cohort of ambulatory patients with New York Heart Association class II to IV heart failure. The study revealed that despite a patient population with >90% use of angiotensin-converting enzyme inhibitors and β-blockers as background therapy and >40% background device therapy, peak oxygen consumption remained the most predictive determinant of the primary end point. This finding is remarkable because this test, which has been shown to be highly predictive in the advanced New York Heart Association class IV heart failure population, now emerges as the most significant determinant of clinically important outcomes in patients with milder forms of heart failure. These findings imply that the use of cardiopulmonary exercise testing in mild to moderate heart failure may be useful in risk stratification of patients. In addition, we found that a simple question on the Kansas City Cardiomyopathy Questionnaire regarding the stability of symptoms in the previous 2 weeks was highly predictive. Further, this finding could be easily incorporated into the patient history intake evaluation. More traditional risk factors were also found to be determinants of clinical outcome, such as renal function and sex. In summary, this modern predictive model with a risk score can be easily implemented to provide risk stratification for patients with heart failure and will help us to better understand how heightened surveillance can be used to monitor high-risk patients.

Conclusions: Risk models using simple, readily obtainable clinical characteristics can provide important prognostic information in ambulatory patients with chronic heart failure with systolic dysfunction.2

p53 Promotes Cardiac Dysfunction in Diabetic Mellitus Caused by Excessive Mitochondrial Respiration-Mediated Reactive Oxygen Species Generation and Lipid Accumulation

Summary: Diabetic cardiomyopathy is one of the leading causes of increased morbidity and mortality in the patients with diabetes mellitus. Although the pathogenesis of this cardiac contractile dysfunction is still not fully understood, much interest has been focused on the involvement of increased reactive oxygen species (ROS) production and altered mitochondrial function. Increased myocardial fatty acid utilization and cardiac triglyceride accumulation in diabetic patients were also demonstrated. Recently, activation of p53 and its target genes in the development of heart failure has received considerable attention. We found myocardial p53/SCO2 (synthesis of cytochrome c oxidase 2) signal is activated by diabetes-mediated ROS generation to increase mitochondrial oxygen consumption in both type I and type II diabetic (db/db) mice. The activation of p53/SCO2 results in excessive generation of mitochondria-derived ROS and lipid accumulation in association with cardiac dysfunction. Thus, p53 and SCO2 may be novel therapeutic targets to prevent the progression of diabetes-mediated cardiac dysfunction.
**Conclusions**: Myocardial p53/SCO2 signal is activated by diabetes-mediated ROS generation to increase mitochondrial oxygen consumption, resulting in excessive generation of mitochondria-derived ROS and lipid accumulation in association with cardiac dysfunction.3

**Testosterone Supplementation in Heart Failure: A Meta-Analysis**

**Summary**: Despite advances in evidence-based pharmacological therapies, patients with heart failure (HF) continue to exhibit significant morbidity and excess mortality at rates of up to 30% at 1 year. This high event rate, coupled with ongoing symptoms of fatigue, cardiac cachexia, and a metabolic shift toward catabolism, has led to an intense search for therapies to further improve HF symptoms. Low testosterone has been shown to be an independent predictor of reduced exercise capacity and poor clinical outcomes in patients with HF. Modestly sized randomized, placebo-controlled trials have explored the effects of testosterone therapy on exercise capacity in patients with HF; using a variety of exercise-based end points. In this meta-analysis of 4 published clinical trials involving 198 patients, testosterone therapy was associated with a significant improvement in exercise capacity compared with placebo. This improvement occurred without any improvement in myocardial structure or function. The mechanism for improvement in exercise capacity is complex and likely due to peripheral mechanisms. We also demonstrate the consistency of the effect of testosterone on the intermediate outcome of peak oxygen consumption, with a similar magnitude of effect to that of early development stages of angiotensin-converting enzyme inhibitors and cardiac resynchronization therapy. Although testosterone treatment has been linked to an increase in the number of cardiovascular events in asymptomatic patients without HF, there was no increase in clinical events across all 4 trials. Given the unmet clinical needs, the apparently favorable effects noted herein, and the limited number of patients reported to date in the literature, adequately powered randomized trials are needed to assess the benefits of testosterone on quality of life, clinical events, and safety in this high-risk population.

**Conclusions**: Given the unmet clinical needs, testosterone appears to be a promising therapy to improve functional capacity in patients with HF. Adequately powered RCTs are required to assess the benefits of testosterone in this high-risk population with regard to quality of life, clinical events, and safety.4

**Adipose Tissue Inflammation and Adiponectin Resistance in Patients With Advanced Heart Failure: Correction After Ventricular Assist Device Implantation**

**Summary**: Patients with advanced heart failure develop metabolic derangements that affect a multitude of organ systems including the lungs, kidneys, liver, and skeletal muscle. The current study investigated adipose tissue inflammation and the regulation of the adipose tissue-derived molecule adiponectin. Adipose tissue of patients with advanced heart failure showed increased infiltration of macrophages and reduced adipocyte cell size. Patients with advanced heart failure had increased circulating levels of adiponectin with reduced expression of myocardial adiponectin receptors AdipoR1 and AdipoR2 as well as reduced activation of AMP kinase, a known downstream signaling molecule. These findings are suggestive of a functional adiponectin resistance in advanced heart failure. Mechanical unloading of the failing myocardium with a concomitant increase in cardiac output after implantation of a left ventricular assist device resulted in reduced adipose tissue macrophage infiltration and reduction of circulating levels of adiponectin. Further, myocardial levels of AdipoR1 and AdipoR2 increased and activation of AMPK was enhanced after left ventricular assist device implantation. These novel findings suggest a potential role of adipose tissue inflammation and adiponectin resistance in the pathogenesis of advanced heart failure.

**Conclusions**: Adipose tissue inflammation and adiponectin resistance develop in advanced HF. Mechanical unloading of the failing myocardium reverses adipose tissue macrophage infiltration, inflammation, and adiponectin resistance in patients with advanced HF.5

**Plasticity of Surface Structures and β2-Adrenergic Receptor Localization in Failing Ventricular Cardiomyocytes During Recovery From Heart Failure**

**Summary**: Chronic heart failure is characterized by reduced myocardial contractile performance and blunted catecholamine-mediated inotropic responses. We have previously reported that abnormalities of the ventricular cardiomyocyte cell surface architecture, including loss of z-groove indentations and transverse tubules, and altered location of β2-adrenoceptors contribute to these functional abnormalities of the heart failure phenotype. In the present study, we demonstrate plasticity of the surface architecture, with recovery of both ventricular cardiomyocyte membrane microarchitecture and transverse tubule anatomy, as well as β2-adrenoceptor location, after rescue of a rat post-myocardial infarction chronic heart failure model using SERCA2a gene therapy. SERCA2a gene therapy is a novel strategy for advanced heart failure currently under assessment in clinical trials. These observed changes contribute to both the functional recovery and restoration of contractile responses and improved β2-adrenoceptor sensitivity and reflect molecular and structural changes that are required for beneficial reverse remodeling during recovery from chronic heart failure.

**Conclusions**: In summary, abnormalities of sarcolemmal structure in heart failure show plasticity with reappearance of z-grooves and T-tubules in reverse-remodeled hearts. Recovery of surface topology is necessary for normalization of β2AR location and signaling responses.6

**Habitual Coffee Consumption and Risk of Heart Failure: A Dose-Response Meta-Analysis**

**Summary**: The most recent statement on heart failure prevention from the American Heart Association states that coffee may increase heart failure risk, but the results from prior studies have yielded inconsistent results, and these studies did not have sufficient power to detect modest associations. Therefore, we conducted a systematic review and a dose-response meta-analysis of prospective studies that assessed the relationship between habitual coffee consumption and the risk of heart failure. The results of this meta-analysis indicate that there is a J-shaped relationship between coffee consumption and heart failure incidence, with a modest inverse association with moderate consumption. In light of these findings, the current heart failure prevention guidelines suggesting that coffee poses harmful effects may warrant revision to reflect the research showing that coffee may, in fact, provide moderate protection against heart failure incidence.

**Conclusions**: Moderate coffee consumption is inversely associated with risk of heart failure, with the largest inverse association observed for consumption of 4 servings per day.7

**Predictors of Objectively Measured Medication Nonadherence in Adults With Heart Failure**

**Summary**: As many as 60% of patients with heart failure are nonadherent in taking their medications. Hospitalizations, costs, and death
are higher in patients with heart failure who do not take their medications as prescribed. In this study we followed 202 adults with heart failure for 6 months, measuring their daily medication adherence electronically. Latent growth mixture modeling was used to identify patterns of adherence. The World Health Organization dimensions of adherence (socioeconomic, condition, therapy, patient, and healthcare system) were tested to identify contributors to nonadherence. We identified 2 distinct groups of patients: those (77.8%) who were persistently adherent in their medicines as prescribed and a subset (22.3%) who had a steep decline over time in adherence. Three contributors to the steep decline in adherence were identified: lapses in attention, excessive daytime sleepiness, and those taking a medication ≥2 times per day. Medications that need to be taken in multiple daily doses are known to be associated with poor adherence, but this study confirms the importance of prescribing once-a-day medicines whenever possible. Excessive daytime sleepiness and lapses in attention are likely correlated in that patients who do not sleep well are more sleepy during the day and may have trouble being sufficiently vigilant or attentive to remember to take their medicines. Thus, promoting sleep may be a modifiable factor that could improve medication adherence.

Conclusions: Two distinct patterns of adherence were identified. Three potentially modifiable contributors to nonadherence have been identified.8

Cardiovascular Remodeling in Response to Long-Term Exposure to Fine Particulate Matter Air Pollution

Summary: Air pollution is a widespread environmental health hazard occurring in many industrialized societies. Current evidence suggests that exposure to air pollution can cause significant cardiovascular risk even within a short time period, and that these effects increase with time. The present study used a mouse model of air pollution exposure to better understand increased cardiovascular risk after exposure to air pollution over a lifespan. Mice were exposed to air pollution or filtered air, 6 h/d, 5 d/wk for 9 months, which is a large portion of the lifespan of a mouse. The mice exposed to air pollution developed both systolic and diastolic dysfunction, as assessed using echocardiography. Interestingly, this dysfunction was evident at the cellular level, as cardiomyocytes isolated from mice exposed to air pollution had decreased function that is translatable to the dysfunction found at the whole heart level. Examination of heart tissue from mice exposed to air pollution also revealed molecular markers of hypertrophy leading to adverse ventricular remodeling. This study showed that long-term exposure to environmentally relevant concentrations of air pollution resulted in cardiovascular dysfunction evident at both the whole heart and cellular level.

Conclusions: Long-term exposure to environmentally relevant concentrations of PM<sub>2.5</sub> resulted in a cardiac phenotype consistent with incipient heart failure.9

Outcome and Complications After Implantable Cardioverter Defibrillator Therapy in Hypertrophic Cardiomyopathy: Systematic Review and Meta-Analysis

Summary: Patients with hypertrophic cardiomyopathy (HCM) are at increased risk for sudden cardiac death (SCD), most frequently caused by ventricular arrhythmias. Implantable cardioverter defibrillator (ICD) therapy may effectively terminate life-threatening ventricular arrhythmias and thereby prevent SCD. However, ICD therapy is not without risk, because inappropriate ICD interventions and device-related complications may occur. Although previous studies have reported on the use of ICD therapy for prevention of SCD in patients with HCM, a complete overview of outcomes and complications after ICD therapy in patients with HCM is not available. In this meta-analysis, we demonstrate a low cardiac and noncardiac mortality rate after ICD implantation in patients with HCM. Appropriate ICD intervention occurred at a rate of 3.3%/yr, thereby, most probably, preventing SCD. Inappropriate ICD intervention and complications occurred at a rate of 4.8%/yr and 3.4%/yr, respectively, in these patients. The most frequently observed complication was lead malfunction in 7%. Other complications were infection in 3% and lead displacement in 3%. Consideration of these outcome and complication data may help clinicians in decision making and counseling of patients with HCM at increased risk for SCD considered for ICD therapy. Additional research is warranted to further reduce inappropriate ICD intervention and complication rates.

Conclusions: This meta-analysis demonstrates a low cardiac and noncardiac mortality rate after ICD therapy in patients with hypertrophic cardiomyopathy. Appropriate ICD intervention occurred at a rate of 3.3%/yr, thereby, most probably, preventing SCD. Inappropriate ICD intervention and complications are not uncommon.10

Cardiac Resynchronization Therapy in Patients With Permanent Atrial Fibrillation: Results From the Resynchronization for Ambulatory Heart Failure Trial (RAFT)

Summary: Cardiac resynchronization (CRT) therapy improves symptoms and prolongs life in patients with systolic dysfunction, heart failure, and a broad QRS. However, CRT may not be effective in patients with chronic atrial fibrillation (AF), because they lack organized atrioventricular timing, and rapid conduction of AF may suppress the delivery of CRT. As patients with chronic AF have been excluded from all but 1 prior CRT trial in heart failure patients, guidelines do not give a class I recommendation for CRT in patients with chronic AF. The Resynchronization for Ambulatory Heart Failure Trial (RAFT) included 229 patients with chronic AF, making it the largest randomized evaluation of CRT in this population. It failed to demonstrate a reduction in its primary outcome of death or heart failure hospitalization with CRT. CRT also failed to improve surrogate measures, such as 6-minute hall walk distance or patients’ scores on the Minnesota Living with Heart Failure Questionnaire. There was a statistically borderline reduction in heart failure hospitalizations with CRT, while, conversely, there was a similar borderline (P=0.067) increase in all-cause hospitalizations. Overall, RAFT found no clear advantage to CRT in patients with chronic AF. However, during the first 6 months after randomization, only 34% of CRT patients had >95% biventricular pacing and only 47% had >90% biventricular pacing. Only a single patient had received an atrioventricular node ablation. Given the lack of benefit from CRT in RAFT, further trials are needed to evaluate the role of routine atrioventricular node ablation in this population.

Conclusions: Patients with permanent atrial fibrillation who are otherwise CRT candidates appear to gain minimal benefit from CRT-ICD compared with a standard ICD.11

National Survey of Hospital Strategies to Reduce Heart Failure Readmissions: Findings From the Get With the Guidelines-Heart Failure Registry

Summary: Reducing 30-day heart failure readmissions has become a national priority, yet which hospital-level processes of care might effectively accomplish this goal are unknown. To better understand those care processes currently being used by hospitals in the United States to lower 30-day readmission rates, the authors created a survey instrument administered to 100 randomly selected sites participating in the American Heart Association’s Get With the Guidelines-Heart
Evaluating Treatment Efficacy by Multiple End Points in Phase II Acute Heart Failure Clinical Trials: Analyzing Data Using a Global Method

Summary: Few new therapies for acute heart failure (AHF) have been approved since the introduction of furosemide in the late 1960s. This may be attributed at least in part to challenges in the design and selection of interventions and doses in phase II AHF studies. Because only a limited number of patients can be enrolled in phase II clinical studies, surrogate measures such as wedge pressure, remodeling or biomarkers have been used to identify potentially effective therapies. However, several new drugs with promising results on such surrogate measures in phase II failed to demonstrate positive effects on clinical outcomes in phase III, mostly because surrogate measures are not universally correlated with clinical benefit in AHF. Combining clinical outcomes into a composite in phase II allows simultaneous evaluation of an intervention’s effect on multiple aspects of the AHF disease process, and might allow identification of therapies that will demonstrate concordant effects on component outcomes in phase III. We have explored several methods of combining such end points. Because most clinical outcomes in AHF are only slightly correlated, such a combined end point approach increases the ability to identify interventions that potentially affect multiple clinical facets of AHF rather than surrogates. Among the composite approaches evaluated, transforming the end points to a common metric—the z score—and averaging seems to provide the highest power.

Conclusions: Assessing the effects of new therapies on multiple clinical end points using the average z score enables detection of therapeutic efficacy using sample sizes of 100 to 150 patients per group, approximately double the power achievable assessing the effects on dyspnea alone.

Irregular Rhythm Adversely Influences Calcium Handling in Ventricular Myocardium: Implications for the Interaction Between Heart Failure and Atrial Fibrillation

Summary: Atrial fibrillation is commonly associated with heart failure (HF) and their coexistence is associated with a poorer prognosis than that for HF with sinus rhythm. Various mechanistic explanations for this adverse combination have been proposed, including a more advanced degree of HF, loss of atrial mechanical function, associated mitral regurgitation, and poor rate control. Subgroup analyses of clinical studies suggest that the adverse influence of atrial fibrillation on HF may be explained by the presence of an irregular rhythm per se, and that irregular ventricular electromechanical activity may lead to cellular remodeling that contributes to a further decline in ventricular function. We examined the pattern of expression of genes and proteins related to intracellular Ca^{2+} handling in left ventricular tissue from patients with heart failure in sinus rhythm and atrial fibrillation, and in isolated ventricular cardiomyocytes electrically paced in a regular or irregular manner. We found that irregular rhythm in both human tissue and isolated cardiomyocytes was associated with reduced expression of the sarcoplasmic reticulum ATPase and the degree of phosphorylation of phospholamban. These observations demonstrate that ventricular rhythmicity significantly influences the expression of key Ca^{2+} handling proteins, providing a potential mechanistic explanation for the unfavorable clinical interaction between atrial fibrillation and HF.

Conclusions: Together, these data demonstrate that ventricular rhythmicity contributes significantly to excitation–contraction coupling by altering the expression and activity of key calcium-handling proteins. These data suggest that control of rhythm may be of benefit in patients with HF.

Care and Outcomes of Hispanic Patients Admitted With Heart Failure With Preserved or Reduced Ejection Fraction: Findings From Get With The Guidelines—Heart Failure

Summary: Hispanics comprise the largest ethnic group in the United States, data on differences between Hispanic patients with heart failure (HF) with preserved ejection fraction (PEF) and those with reduced EF (REF) are limited. Using the Get With The Guidelines database, the present study aimed to compare clinical characteristics, quality of care, and outcomes between Hispanic and non-Hispanic whites hospitalized for HF stratified by EF. We also evaluated temporal trends in adherence to process-of-care measures for both groups. From 247 participating hospitals from 2005 to 2009, 6117 Hispanics were compared with 71 859 non-Hispanic whites. Forty-six percent of Hispanics had PEF (EF ≥ 40%) and 54% had REF (EF < 40%); 55% and 45% of non-Hispanic whites had PEF and REF, respectively. Relative to non-Hispanic whites, Hispanics with PEF or REF were more likely to be younger and to have more cardiometabolic risk factors. Hispanics with PEF were more likely to have nonischemic cardiomyopathy, whereas those with REF were more likely to have an ischemic cause. In multivariate analysis, a lower mortality risk was observed among Hispanics with PEF but not in Hispanics with REF, compared with non-Hispanic whites. In all groups, composite performance improved within the 5-year study period. Our findings show that Hispanics with PEF but not those with REF had better in-hospital survival than non-Hispanic whites, even after adjusting for age differences. Quality of HF care was similar and improved progressively through time, underscoring the potential benefit of a process-of-care improvement program in advancing health care delivery, irrespective of race/ethnicity or EF.

Conclusions: Hispanic HF patients with PEF had better in-hospital survival than non-Hispanic whites with PEF. Inpatient mortality was similar between groups with REF. Quality of care was similar and improved over time irrespective of ethnicity, highlighting the potential benefit of performance improvement programs in promoting equitable care.
Should Women Receive Left Ventricular Assist Device Support?: Findings From INTERMACS

Summary: Several studies have suggested that women are more likely to have adverse events and worse outcomes than men after implantation of left ventricular assist devices. Most of these studies had insufficient power to properly address this concern, focused mostly on pulsatile-flow devices, and provided limited information regarding severity of illness before mechanical circulatory support. With 400 women participants and >1500 men in the Interagency Registry for Mechanically Assisted Circulatory Support, we have sufficient power to probe the question of sex differences with respect to outcomes and to further analyze differences related to pulsatile- versus continuous-flow devices. Our data provide evidence that both pulsatile- and continuous-flow left ventricular assist devices provide similar survival benefit in women and men, with no statistically significant sex difference in time to first infection, bleeding, or device malfunction. However, women were more likely to have neurological events, even after adjusting for type of device, body surface area, prior cerebrovascular accident/transient ischemic attack, and age.

Conclusions: There were no significant sex differences in mortality, time to first infection, bleeding, or device malfunction with either pulsatile- or continuous-flow LVADs. However, women had an increased risk of first neurological event. For urgent/emergent mechanical support, the benefit of LVAD support likely outweighs the risk, but it remains less clear for women undergoing elective LVAD implantation.

Decline in Heart Transplant Wait List Mortality in the United States Following Broader Regional Sharing of Donor Hearts

Summary: The sequence of donor heart allocation in the United States (US) was changed in July 2006 to promote a broader regional sharing of available donor hearts for sicker patients on the wait list before hearts are allocated to less sick, local candidates. Using the United Network for Organ Sharing database, the authors compared wait list outcomes in adults listed for heart transplant in the US before (2004–2006, Era 1) and after (2006–2009, Era 2) the change in allocation algorithm. There were 11,864 patients in the study, 4503 listed during Era 1 and 7361 during Era 2. Patients listed during Era 2 were sicker (more listed status 1A) and more likely to be supported on a continuous flow assist device (P<0.001 for distribution). Patients listed in Era 2 were at 17% lower risk of dying on the wait list or becoming too sick to transplant in multivariable analysis. The findings were similar when analysis was limited to patients who were not supported by a ventricular assist device at either listing or at transplant. Transplant recipients in Era 2 were more likely to be transplanted as status 1A (37% versus 48%), but this shift in hearts to sicker patients did not result in higher hospital mortality or worse 1-year survival among transplant recipients in Era 2. The authors conclude that although increased use of ventricular assist devices in patients waiting for a heart has contributed to improved outcomes after 2006, the change in allocation of hearts has been accompanied by a decreased risk of wait list death in the US.

Conclusions: The risk of death on the wait list or becoming too sick to transplant has decreased by 17% in the US since the allocation algorithm allowing broader regional sharing was implemented in 2006. The shift in hearts to sicker candidates has not resulted in higher in-hospital or first year post-transplant mortality.

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