Comprehensive Treatment of Heart Failure: State-of-the-Art Medical Therapy

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Despite advances in therapy and better outcomes for heart failure, this disease remains burdensome in terms of hospitalization costs, quality of life, and mortality. Many treatment strategies are available for heart failure, including medical therapy with agents such as angiotensin-converting enzyme inhibitors, and β-blockers, and device therapy including implantable cardioverter-defibrillators and cardiac resynchronization. However, data now demonstrate that compliance with these evidence-based strategies is well below acceptable thresholds, negatively affecting quality of care. The implementation of guidelines such as those of the American College of Cardiology/American Heart Association and the application of dedicated disease management programs are two mechanisms aimed toward helping physicians construct and adhere to effective treatment regimens for their patients with heart failure.

[Rev Cardiovasc Med. *2005;6(suppl 2):S43-S57*]

Key words: Angiotensin-converting enzyme inhibitors • β-Blockers • Cardiac resynchronization therapy • Heart failure • Implantable cardioverter-defibrillator

Heart failure has emerged as one of the most pressing cardiovascular disease entities in contemporary medicine. Arguably, heart failure is now a treatable illness; however, despite noteworthy advances in therapy and improved outcomes, significant challenges remain. The costs of hospitalization resources amount to more than $10 billion annually, quality of life is often worse than that of patients with cancer, and hundreds of thousands of lives are lost on an annual basis.[1] It is therefore important to give careful thought to the

comprehensive treatment of heart failure in order to reduce the ever-increasing burden of this disease.

Recently, effective medical treatment strategies have emerged focusing on modulating an activated neurohormonal system responsible for the observed pathobiologic changes in the heart that predispose to ventricular dysfunction, symptomatic heart failure, disease progression, and death. These discoveries in medical therapy for heart failure have yielded a robust cohort of therapeutic options, resulting in the potential to significantly improve outcomes. Available medical treatment strategies now include renin-angiotensin-aldosterone system inhibitors, sympathetic nervous system antagonists, diuretics, digoxin, natriuretic peptides, and electrolyte replacement.[2] New device options include implantable cardioverter-defibrillators (ICDs),[3] pacemakers for cardiac resynchronization therapy (CRT),[4-6] and combined ICD/CRT.[5] Adjunctive therapeutic options include correction of sleep-disordered breathing and cardiac rehabilitation. Emerging surgical approaches include high-risk coronary artery bypass grafting for significant coronary artery disease with severe left ventricular dysfunction, surgical reverse remodeling, mitral valve repair, surgical restraint devices, and left ventricular assist devices (LVADs). The new dynamic is one of "disease management," the full potential of which has not yet been realized in heart failure. This surfeit of treatment choices must be carefully navigated and implemented on a patient-by-patient basis.

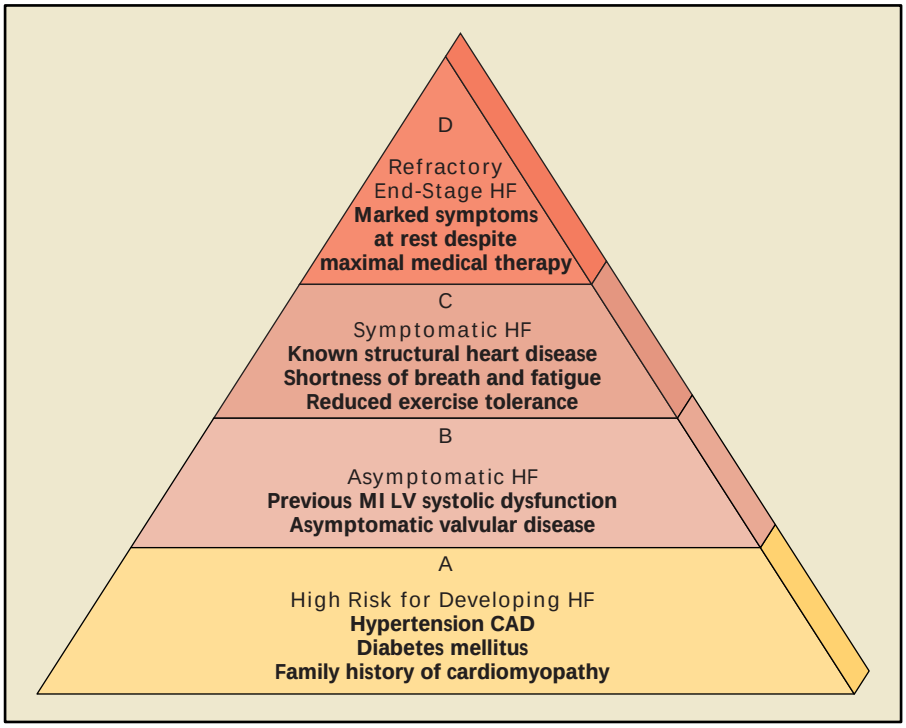

Figure 1. *American College of Cardiology/American Heart Association practice guidelines: pyramid approach to heart failure (HF) stages. CAD, coronary artery disease; LV, left ventricular; MI, myocardial infarction. Adapted with permission from Brozena SC and Jessup M.* Geriatrics. *2003;58(6):31-36.*

The best template available to facilitate the most effective medical therapy for heart failure is the 2001 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of chronic heart failure in the adult.[2] These guidelines, which provide a rigorous review of available peer-reviewed data followed by appropriate recommendations for therapy based both on the strength of the recommendation and the quality of the data supporting the recommendation, represent the best available approach. In concert with the new guidelines, a new staging scheme was proposed to more adequately address disease severity (Figure 1). The new staging nomenclature does not replace the more traditional New York Heart Association (NYHA) classification scheme. The ACC/AHA nomenclature represents disease progression, whereas the NYHA class implies symptom status, which is much more dynamic and is modifiable with medical therapy. The anticipated update of the ACC/AHA 2001 guidelines is not likely to digress from this staging scheme; therefore, it is valid to structure treatment concepts for heart failure that parallel this staging system.

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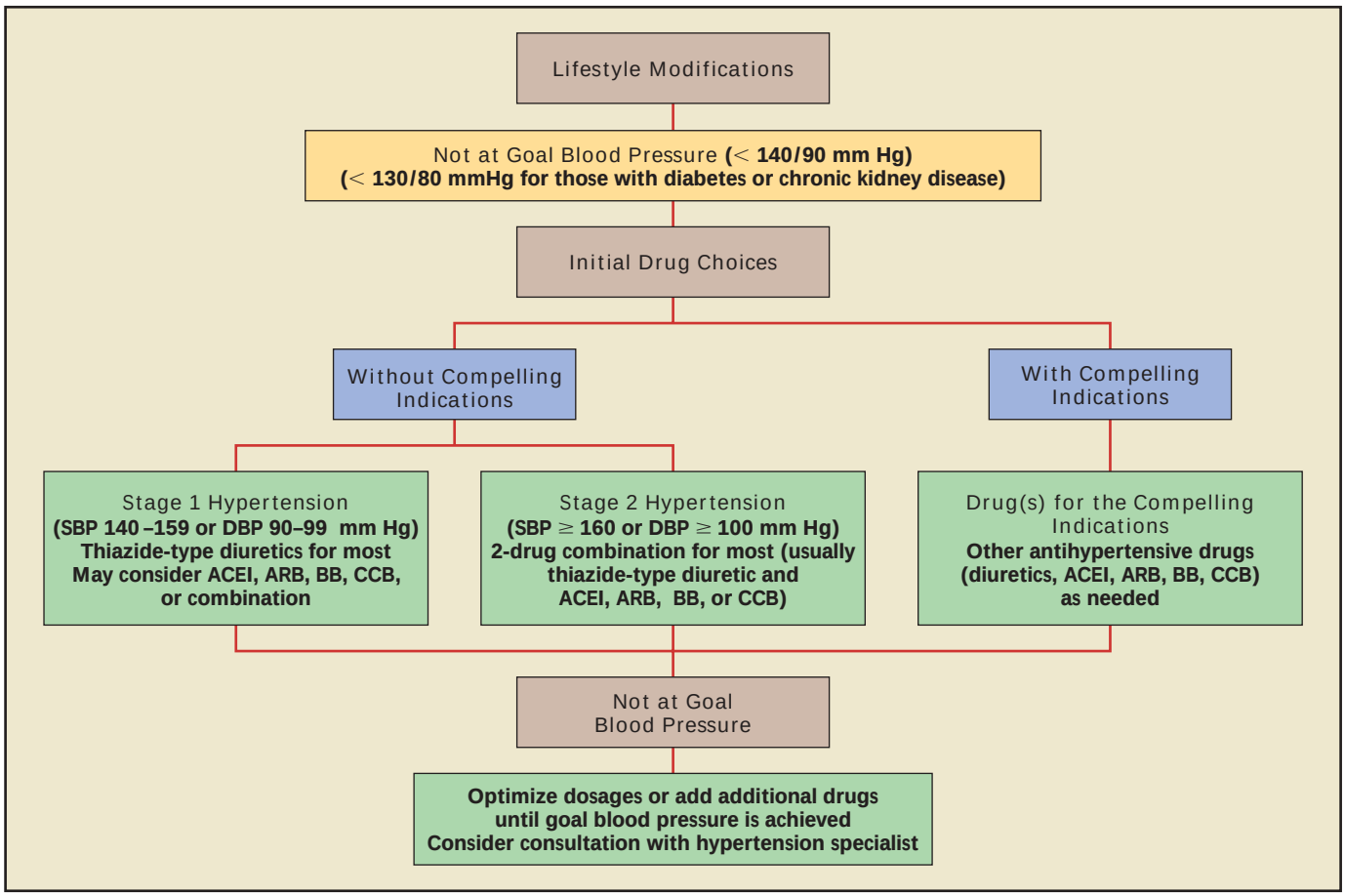
The new heart failure diagnosis and management guidelines provide an opportunity to bridge the treatment gap for patients with heart failure. This new classification scheme is intended to complement, rather than replace, the New York Heart Association (NYHA) classification system, which is based on symptom severity. The NYHA classification

system relies on a subjective assessment of symptoms that can be difficult to place into a particular class and that change frequently. Changes in NYHA symptom class do not necessarily lead to changes in therapeutic approach, whereas the progression of disease defined by the ACC/AHA classification system leads to a better-defined evolution of heart failure therapies. The new system allows for improved matching of therapies, including lifestyle management, drugs, and devices for patients ranging from those in pre-heart failure Stage A to those with Stage D end-stage heart failure. It is clear that mechanical therapies, including ICD and biventricular pacing, along with optimal medical therapy, play a significant role in patients with stages B, C, and D heart failure.

ACC/AHA Stage A Heart Failure

For patients with stage A heart failure or "pre–heart failure," aggressive prevention and treatment strategies are strongly advised. The treatment of heart failure must begin with prevention, including appropriate therapy for hypertension and aggressive modification of known risk factors for cardiovascular disease, especially dyslipidemia and diabetes. The current recommendations from the Seventh Joint National Committee on the treatment of hypertension suggest that as much as a 50% reduction in heart failure episodes may be realized with effective therapy of hypertension.[7] For the patient with uncomplicated stage I hypertension and no other compelling indications, the use of thiazide diuretics is associated with reduction in cardiovascular events, provided that blood pressure is controlled and potassium homeostasis is maintained. Hypertension at stage II or greater mandates combination therapy at the outset. For the patient with diabetes or established renal disease (ie, proteinuria) combination therapy should include inhibitors of the renin-angiotensin system (Figure 2).

Figure 2. *Algorithm for the treatment of hypertension. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.*



African Americans appear to be particularly at risk of developing heart failure associated with hypertension as the putative cause of left ventricular dysfunction. More rigorous control of blood pressure has been advised for African Americans, and multiple drugs—up to 3 or 4 agents—may be required to effect meaningful blood pressure control.[8] It is suggested that antihypertensive therapy in all patients should include agents known to improve outcomes in heart failure.[2]

The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial compared the angiotensin receptor blocker (ARB) valsartan with the calcium channel blocker (CCB) amlodipine in hypertensive patients at risk for heart disease and failed to show an advantage of the ARB over the CCB.[9] Blood pressure control was better in the CCB arm, which further strengthens the argument that effective blood pressure control is the top-line goal in the prevention of cardiovascular complications.

In patients with a demonstrable burden of atherosclerosis and no history of hypertension, left ventricular dysfunction, or heart failure, the Heart Outcomes Prevention Evaluation (HOPE) trial identified a 17% reduction in episodes of new-onset heart failure in patients with established risk factors for heart disease who were treated preemptively with an angiotensin-converting enzyme (ACE) inhibitor.[10] Of note, the recent Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial failed to demonstrate a benefit of ACE inhibitors for low-risk patients with stable coronary artery disease and preserved left ventricular systolic function.[11] Because of the very low event rates, PEACE may have been underpowered to demonstrate an effect of the ACE inhibitor. It is, however, noted that patients in the PEACE trial had a higher rate of coronary artery revascularization and greater penetration of statin use, resulting in better control of low-density lipoprotein levels. Thus, ACE inhibitors are effective in patients at higher risk, especially those with diabetes, but when other risk factors are controlled and ventricular function is intact, the additional benefit of ACE inhibitors in nonhypertensive patients may be less apparent or perhaps not even realized.

The recent Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial failed to demonstrate a benefit of ACE inhibitors for low-risk patients with stable coronary artery disease and preserved left ventricular systolic function.

ACC/AHA Stage B Heart Failure

For patients with stage B heart failure (ie, those with structural heart disease but no symptoms of heart failure) the recommendation is to proceed with agents that are cardioprotective, especially ACE inhibitors and β-blockers. This category is largely populated by patients with post-myocardial infarction (MI) left ventricular dysfunction, and the recommendation is based on strong data using both ACE inhibitors and β-blockers in the post-MI setting. The landmark Survival and Ventricular Enlargement (SAVE) trial yielded convincing data that the consequences of post-MI left ventricular dysfunction can be ameliorated by the use of ACE inhibitors.[12] Similarly, the Valsartan in Acute Myocardial Infarction Trial (VALIANT) demonstrated a benefit similar to that of an ACE inhibitor for the ARB valsartan in the setting of post-MI left ventricular dysfunction.[13] The imputed mechanism of benefit for blockers of the renin-angiotensin system is a retardation of progressive ventricular remodeling.

The post-MI use of β-blockade is well established, but data regarding the use of β-blocker therapy for post-MI left ventricular dysfunction (left ventricular ejection fraction [LVEF] < 0.35) has been surprisingly sparse. The recently reported Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial established with a strong imperative that an evidence-based β-blocker appropriate for heart failure ameliorates the natural history of post-MI left ventricular dysfunction.[14] The addition of carvedilol to ACE inhibitors resulted in a 23% improvement in the risk of death (Figure 3). Taken together, these data would suggest a reasonable comfort level for the use of ACE inhibitors and β-blockers in patients with asymptomatic left ventricular dysfunction. These data are further extrapolated on a theoretical basis to apply to patients with asymptomatic nonischemic left ventricular

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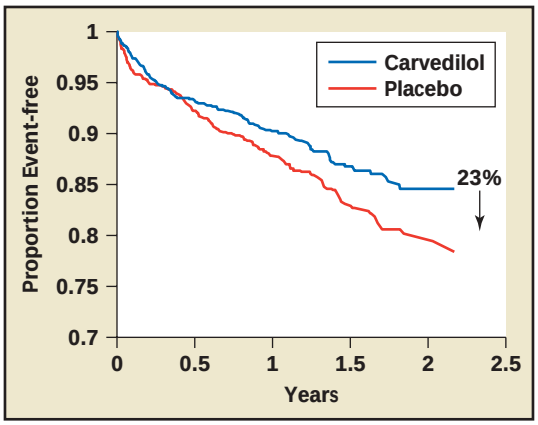

Figure 3. *All-cause mortality in the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial. Data from Dargie HJ.*[14]

dysfunction, those with familial cardiomyopathies, and perhaps those who have received cardiotoxic agents that have resulted in left ventricular dysfunction. Truly definitive strategies that prevent heart failure in at-risk patients still represent a need not yet fully addressed, thus providing a great opportunity for future research.

ACC/AHA Stage C Heart Failure

Stage C heart failure is the category that includes patients with structural heart disease and current or past symptoms of heart failure. For these patients, nonpharmacologic approaches including dietary sodium restrictions and avoidance of alcohol and tobacco are further expanded by the implementation of indicated medical therapy.[2] A multitude of medical options are currently available, including ACE inhibitors, angiotensin receptor antagonists, β-adrenergic receptor blockers, aldosterone antagonists, digoxin, diuretics, coumadin, ICDs, CRT, natriuretic peptides, and inotropes—all of which play a role in the correct context.

The data are quite compelling that both ACE inhibitors and β-blockers should be used in *all* patients with systolic dysfunction and heart failure unless there is an overt and important contraindication.[2] The aggregate impact of ACE inhibitors on symptomatic heart failure is a 15% to 20% improvement in the annual risk of death due to heart failure.[2,15] There are similar improvements in risk for hospitalization, increase in functional class, and recovery of quality of life. The mechanism of benefit of ACE inhibitors remains unclear as angiotensin II levels return to pretreatment levels just weeks after initiation of ACE inhibitors. Because ACE inhibitors act on both ACE and kininases, the potential benefit of increased bradykinin levels may be implicated as a mechanism of benefit for ACE inhibitors. The additional effects of ACE inhibitors on inflammation, oxidative stress, and protein expression represent plausible, but unproven, mechanisms of benefit (Figure 4).

Recently, the universality of ACE inhibitor efficacy has been questioned as both gender and racial variations in the responsiveness to ACE inhibitors for heart failure have been described.[16-19] A meta-analysis of pooled data from published heart failure trials using ACE inhibitors in women demonstrates only a 3% non–statistically significant benefit,[17] which is more likely the result of under-representation in clinical trials

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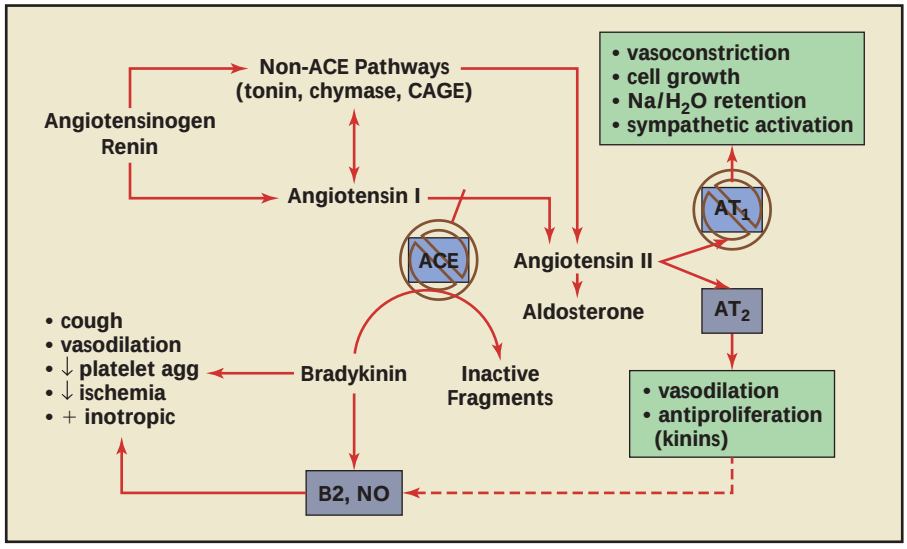
Figure 4. *The renin-angiotensin-aldosterone system. ACE, angiotensin-converting enzyme; agg, aggregation AT1, angiotensin II, type 1 receptor; AT2, angiotensin II, type 2 receptor; B2, bradykinin receptor; NO, nitric oxide.*



than a true biologic variation in the response to therapy. However, it is of some concern that definitive data regarding the efficacy of ACE inhibitors in women are lacking.[16] Based on a review of available clinical trial data, albeit retrospective, African Americans do appear to have a lesser response to ACE inhibitors.[18,19] Whether this can be overcome with higher doses is unknown but is suggested to be the case.[20] An explanation for variations in responsiveness to ACE inhibitors may invoke principles in genomic medicine. The dual deletion polymorphism of ACE is well described and appears to be associated with higher risk in some patient populations.[21] Similar variations in angiotensin receptors have been described as well.[22] Although this field remains incipient, it is likely to yield insights into variations in disease expression and responsiveness to medical therapy.

Since the original guideline generation process, important data regarding the use of ARBs have emerged. The Valsartan Heart Failure Trial (Val-HeFT) data tested the adjunctive benefit of valsartan added to an ACE inhibitor in a randomized placebo-controlled, double-blind trial in patients with principally class II heart failure. A mortality reduction was not realized in the trial, but a composite end point that included several clinical variables plus hospitalization for heart failure and all-cause mortality did yield a slight 13.2% risk reduction that was statistically significant.[23] Data derived from a subset analysis of Val-HeFT demonstrated that in the 7% of patients who were unable to tolerate an ACE inhibitor, the use of the ARB valsartan was associated with a 44% improvement in the combined outcomes of morbidity and mortality and an approximately 30% decline in the annual risk of death due to heart failure.[23] Based on this subset analysis, valsartan is indicated in the treatment of heart failure as a primary inhibitor of the renin-angiotensin system in ACE inhibitor–intolerant patients with heart failure.

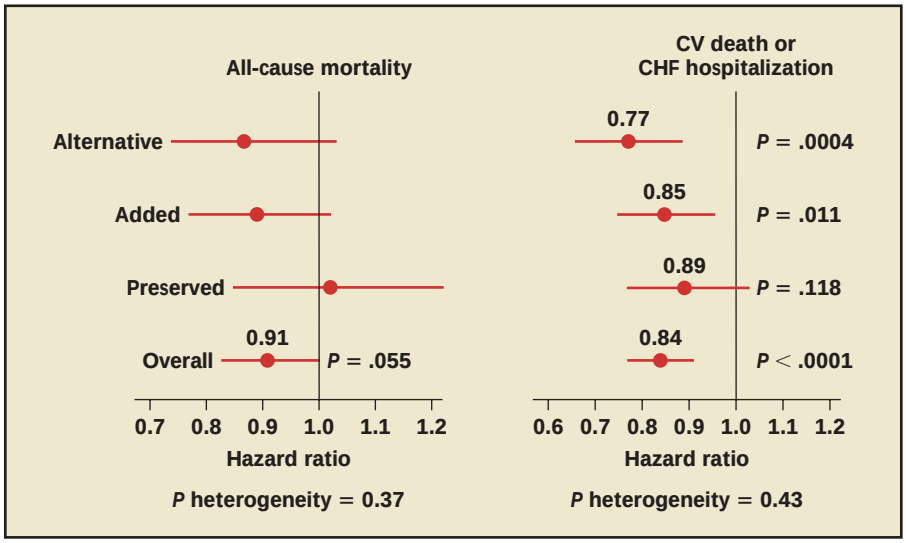


Figure 5. *Mortality and morbidity in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program.[24-27] CHF, congestive heart failure; CV, cardiovascular.*

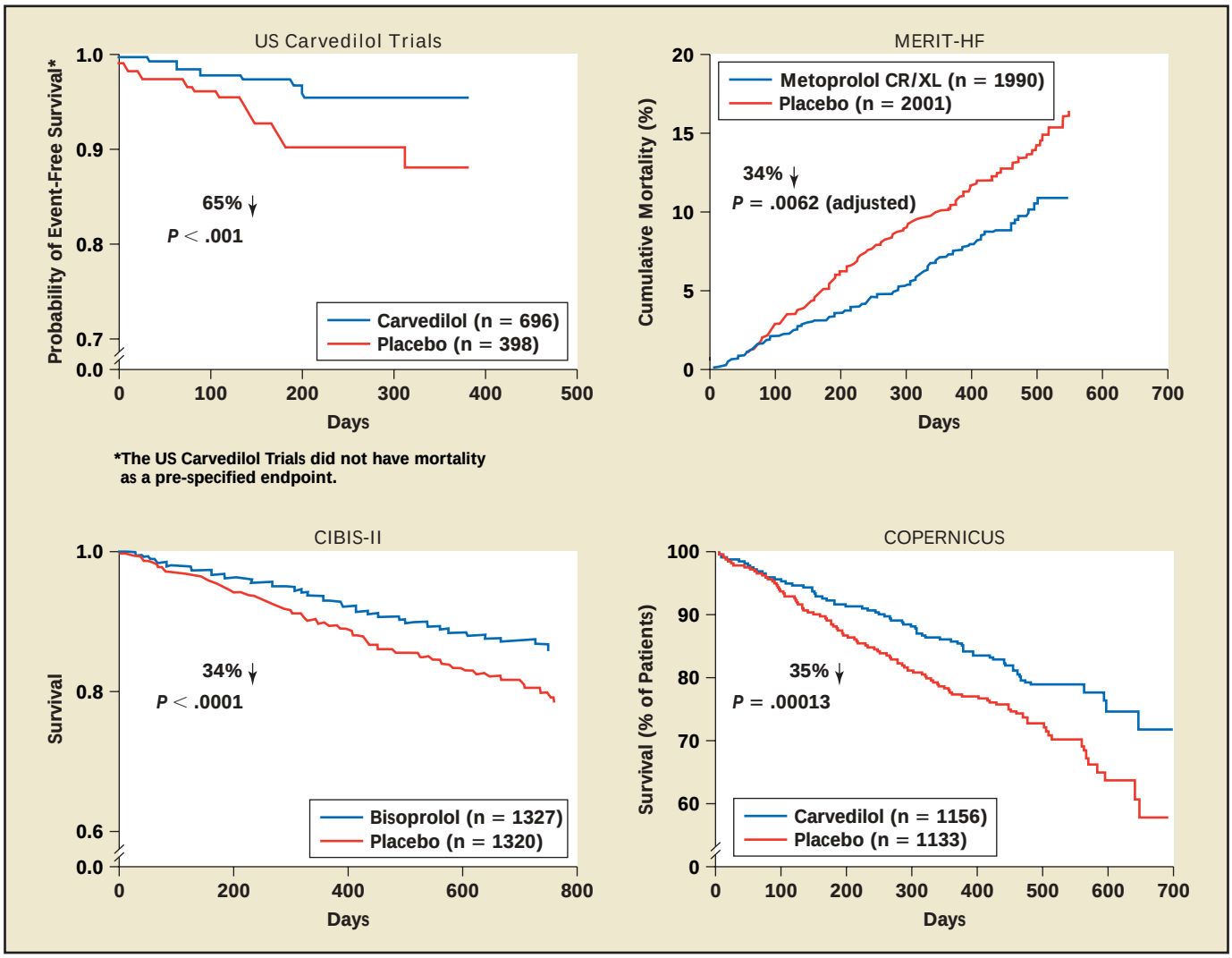
The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trial tested the benefit of candesartan in three scenarios: ACE inhibitor–intolerant patients with heart failure and systolic dysfunction; heart failure patients with systolic dysfunction on an ACE inhibitor; and symptomatic heart failure patients with preserved left ventricular systolic function not on an ACE inhibitor. This study of > 7000 patients with heart failure was intended to correctly position the use of ARBs in heart failure. The primary end point was all-cause mortality for the entire CHARM program (ie, all three trials). A non–statistically significant 9% reduction in all-cause mortality was observed for the overall program.[24-27] When an alternative endpoint of cardiovascular death or heart failure hospitalization was assessed, there was a 16% reduction for this composite in the overall CHARM program, varying from 11% for heart failure with preserved left ventricular systolic function to 23% for heart failure with impaired left ventricular systolic function and ACE inhibitor intolerance (Figure 5).[24-27] Thus, the use of an ARB is associated with a reduction in the combined endpoint of cardiovascular morbidity and mortality, whether used in ACE inhibitor–intolerant patients, in combination with an ACE inhibitor alone, or with an ACE inhibitor and β-blocker.

Aldosterone antagonists have now emerged as an effective treatment for patients with moderately severe heart failure and for those with left ventricular dysfunction complicating an acute MI.[28,29] Care must be observed to avoid administration of aldosterone antagonists to patients with significant renal insufficiency and/or those with borderline hyperkalemia. Recent data have suggested that since the release of the Randomized Aldactone Evaluation Study (RALES) trial, the incidence of hospitalizations for hyperkalemia and,

importantly, deaths attributable to hyperkalemia, have increased.[30] These observations indicate the need to be especially observant of renal function and to avoid the use of aldosterone antagonists in patients with significant renal insufficiency or in those who already have evidence of high-normal or elevated potassium levels. Conversely, the concerns regarding risks must be put in context, as the number of additional lives saved with the correct usage of these agents is not insignificant.[28,29] As a separate concern, there are few if any data, and none that have been prospectively acquired, regarding the use of aldosterone antagonists concomitant with ACE inhibitors, β-blockers, and angiotensin receptor antagonists. It would thus be prudent to avoid use of "quadruple" neurohormonal antagonism until data regarding safety and efficacy are available.

The cornerstone of improved outcomes in heart failure has come from the use of β-blockers. An activated sympathetic nervous system is especially injurious to the heart and predicts prognosis quite precisely. Impeding the activity of the sympathetic limb of the neurohormonal cascade is thus desirable. The addition of an evidence-based β-blocker to an ACE inhibitor has resulted in a 35% improvement in the annual risk of death due to chronic heart failure (Figure 6).[31] This benefit has been realized for all heart failure disease severities, both genders, all age ranges, and in African Americans.[32]

Figure 6. *Major placebo-controlled trials of β-blockade in heart failure. CIBIS-II, The Cardiac Insufficiency Bisoprolol Study II; COPERNICUS, Effect of Carvedilol on Survival in Severe Chronic Heart Failure; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure. Data from Packer M et al,[31,49] MERIT-HF Study Group,[50] and CIBIS-II Investigators.[51]*



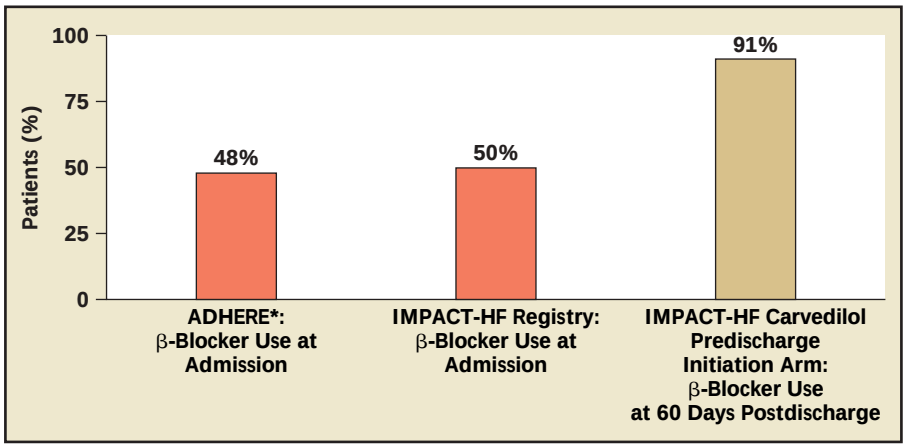


Figure 7. *β-Blocker use at admission and post discharge in the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial, IMPACT-HF Registry, and the Acute Decompensated Heart Failure National Registry (ADHERE).* $P < .0001$ *versus initiation postdischarge rate at 60 days (73%). Data from Gattis WA et al,*[35] *GlaxoSmithKline, Philadelphia, PA, and Scios Inc., Sunnyvale, CA.*

Concomitant improvements in the rate of hospitalization and quality of life are also associated with β-blocker therapy. A hallmark of β-blocker therapy for heart failure is an improvement in left ventricular systolic performance, and in patients who respond to β-blocker therapy, the expectation is an increase in ejection fraction of 5% to 10%; a few patients experience near normalization of ventricular function. There is a variation in response to β-blockers. At least part of this variation is a result of the distribution of single-nucleotide polymorphisms affecting adrenergic receptors. Loss-of-gain β_1-receptor polymorphisms have been discovered, as have very high–risk combinations of variants of the α-receptor and β_1-receptor that predispose to a high likelihood of developing heart failure.[33,34] The biggest hurdle to overcome in the use of β-blocker therapy is implementation. The Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial demonstrated that about 90% of patients discharged with a primary diagnosis of heart failure can be initiated on β-blocker therapy prior to hospital discharge, whereas the Acute Decompensated Heart Failure Registry (ADHERE) database now demonstrates that the use of β-blockers in appropriate patients is as low as 40% (Figure 7).[35,36] This gap in the utilization of evidence-based therapy for heart failure is unacceptable. For patients with mild to moderate disease, the number of patients needed to treat for 1 year to save a life is only 25 to 30, but for severe heart failure, the number falls to 14. The opportunity to treat patients with β-blocker therapy for symptomatic heart failure should not be missed.

The newest data regarding the medical treatment of heart failure have focused on an important cohort of the heart failure population: the African American patient. The best data now suggest that heart failure as it affects African Americans is a different illness with a different epidemiology, natural history, and responsiveness to proven medical treatment options.[37] Observations regarding events and responsiveness to therapy in this cohort have been especially difficult because the majority of the database emanates from retrospective reviews that are underpowered. Nevertheless, there was strong evidence from the earlier Vasodilator Heart Failure Trials (V-HeFT I and II) that African Americans respond in an especially robust manner when treated with isosorbide dinitrate and hydralazine.[19] Using a proprietary, fixed-dose combination of these two older drugs (BiDil; NitroMed, Bedford, MA), the African American Heart Failure Trial (A-HeFT) yielded noteworthy data. A 43% reduction in the risk of death due to heart failure was realized when BiDil was added to appropriate evidence-based medical therapy for heart failure (Figure 8).[38] The actual mechanism of benefit of this combination of a nitric oxide donor (isosorbide dinitrate) and antioxidant (hydralazine) is not entirely clear, but there is a strong implication that nitric oxide deficiency and increased oxidant stress may be operative in the development of heart failure in some individuals, and a compound that improves nitric oxide bioavailability would be beneficial.[38] It is anticipated that this compound will soon be commercially available. Whether it will be approved for heart failure broadly or heart failure only in African Americans remains to be seen. Even though A-HeFT was completed in an African American–only patient population, there is no reason to believe that the combination of isosorbide dinitrate and hydralazine would not be beneficial in other patients.

The emerging paradigm of natriuretic peptides has brought important diagnostic and therapeutic applications to the care and management of patients with heart failure. B-type natriuretic peptide (BNP) is a pleuripotent hormone that is produced by stress on the left and/or right ventricle. As such, it parallels

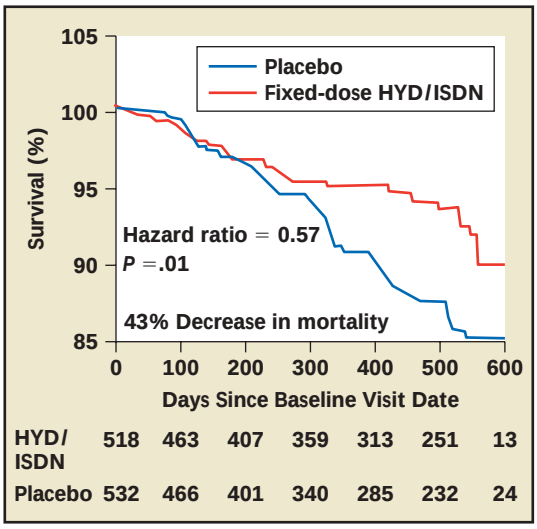
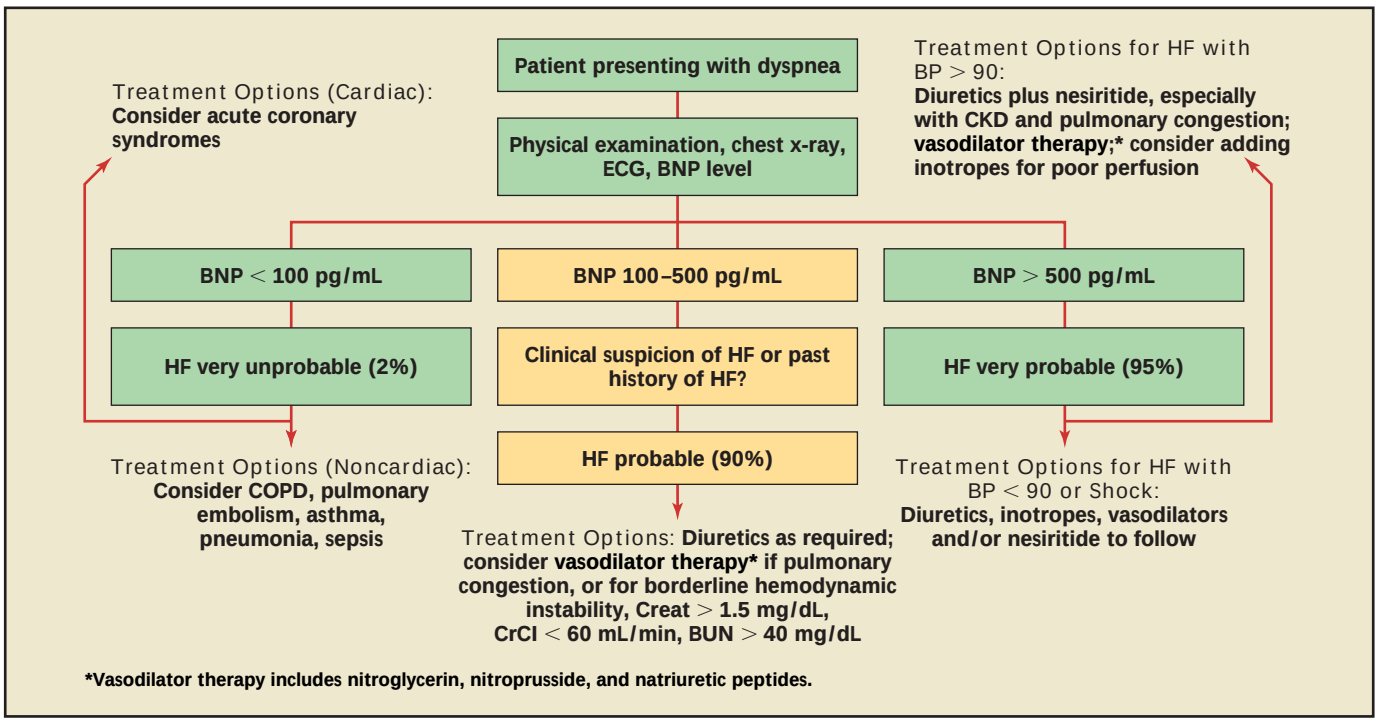


Figure 8. *Overall survival in the African American Heart Failure Trial (A-HeFT). This is the Kaplan-Meier curve that generated the recommendation of the Data Safety Monitoring Board. HYD, hydralazine; ISDN, isosorbide dinitrate. Adapted from Taylor AL et al.*[38]

neurohormonal activation and serves as a useful marker for heart failure (Figure 9).[39] As a diagnostic test, an assay for B-type natriuretic peptide is best applied when there is clinical ambiguity regarding a diagnosis of heart failure. BNP should not be surveyed in all patients, and it should be noted that several disease entities other than heart failure may lead to an elevated BNP, including pulmonary emboli, cor pulmonale, pneumonia, sepsis, and advanced age. The BNP assay may be elevated in the setting of chronic renal disease and lower than expected in the setting of obesity.[39]

Beyond its properties that promote natriuresis and diuresis, BNP is also a neurohormonal antagonist, as it provides central sympathoinhibition and antagonizes the release of aldosterone from adrenal cortical cells. In the periphery, it has important vasodilatory properties that indirectly result in an increase in cardiac output with minimal increase in heart rate, no increase in myocardial oxygen consumption, and no evidence of proarrhythmia.[39] This favorable profile has been applied to the treatment of acute decompensated heart failure (ADHF). The therapeutic application of BNP given as nesiritide demonstrates a more rapid resolution of symptoms, greater reduction in filling pressures, and a sustained period of benefit versus placebo (parenteral diuretics) or intravenous

Figure 9. *The evaluation and treatment of patients presenting with acute dyspnea. BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; Creat, creatinine; ECG, electrocardiogram; HF, heart failure. Adapted with permission from Silver et al.*[39] *Copyright 2004 by Lelacq Communications, Inc.*



nitroglycerin. To date, no untoward risks have been identified.[40] Clinical uncertainty remains regarding the best patient population to receive nesiritide in the setting of ADHF. In the opinion of this author, the compound is most appropriate for ADHF with overt volume overload, systolic blood pressure > 90 mm Hg, and clinical evidence of advanced disease, diuretic resistance, and/or the cardiorenal syndrome. Preliminary data now available suggest that it may be feasible to use nesiritide on an outpatient basis for patients with ACC/AHA stage C/D disease at risk for recurrent hospitalizations, but more definitive trials are ongoing and the outpatient use of natriuretic peptides cannot yet be fully embraced.[41]

ACC/AHA Stage D Heart Failure

Patients with ACC/AHA stage D heart failure are at high risk for repeat hospitalizations and premature death due to heart failure despite appropriate medical therapy. An enormous unmet need exists for the treatment of patients with stage D heart failure. Beyond ventricular replacement strategies, which include LVADs and heart transplantation, the portfolio of available treatment options is fairly thin. The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial randomized patients with ACC/AHA stage D heart failure who were not candidates for heart transplantation to optimal medical therapy versus an LVAD implanted as "destination therapy," with no plans to proceed with heart transplantation. The LVAD group realized an approximately 50% survival at 1 year and 25% at 2 years. The group on medical therapy realized a 75% mortality rate at 1 year and a nearly 90% mortality rate at 2 years.[42] Many of the patients in the optimal medical treatment arm were using long-term inotropes in the home setting, and the risk of these compounds may have contributed greatly to the success of the REMATCH trial.[43] REMATCH serves as a dramatic "proof-of-concept" trial, but easier-to-apply iterations of the LVAD are needed before widespread use of chronic mechanical support can become the norm. A more detailed discussion of emerging surgical treatments for heart failure (eg, surgical reverse remodeling and cardiac restraint devices) is beyond the scope of this review.

A major component of heart failure care, especially as it affects the patient with ACC/AHA stage D heart failure, is end-of-life decision making. Often, patients with stage D heart failure are older and have more comorbidities than patients in the other stages, and discussions regarding end-of-life issues may be fairly well received. Palliative care, home inotropes, hospice referral, and protocol participation are too infrequently considered but may be of great importance in the correct context.

Emerging Data: How Will the Treatment of Heart Failure Change?

A cornucopia of effective medical treatment options exist for symptomatic heart failure due to systolic dysfunction, but additional improvements in morbidity and mortality due to heart failure may be realized with the careful and appropriate application of device therapy. Patients with both left ventricular systolic dysfunction and a wide QRS duration consistent with a left bundle branch block have evidence of ventricular dyssynchrony that leads to inefficient cardiac contractions and significant mitral insufficiency. Correction of ventricular dyssynchrony with a cardiac resynchronization device has been proven to reduce the need for hospitalizations and when added to an implantable defibrillator, survival is likewise enhanced. The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) data clearly demonstrate that the combination ICD/CRT device leads to a statistically significant 39% decline in the combined endpoint of heart failure–related morbidity and all-cause mortality.[4]

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The Achilles' heel of heart failure has always been the inability to confidently modify the risk of sudden cardiac death (SCD), and, ironically, the greatest risk of heart failure–related SCD is in the stable, ambulatory NYHA class II or III heart failure patient. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) was completed in > 2500 patients, who were overwhelmingly represented by class II heart failure. The use of an implantable defibrillator resulted in a 23% reduction in mortality over 5 years, and the number of patients needed to treat to save 1 life over 5 years is only 14 (Figure 10).[3]

It is difficult and inappropriate to dismiss these noteworthy data

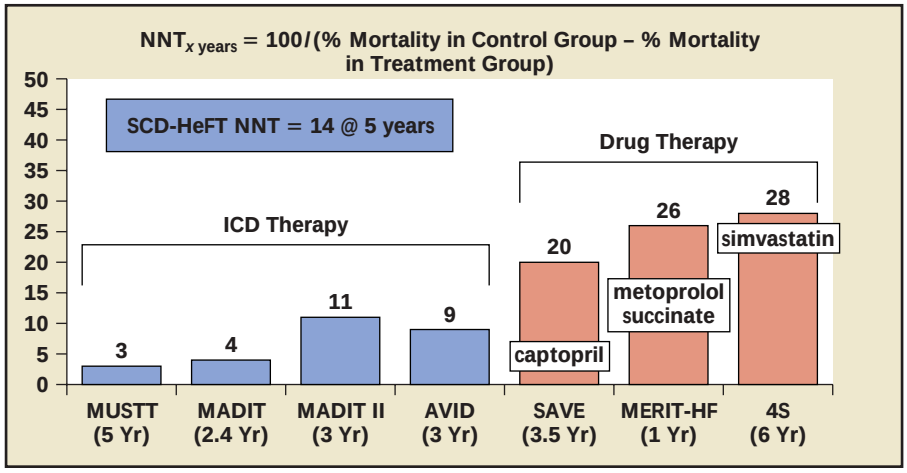


Figure 10. *Number needed to treat (NNT) in clinical trials of drug and implantable cardioverter-defibrillator (ICD) therapies. The NNT values in the major ICD trials have been superior to those in many important drug trials. NNT is a normalized measure of clinical effectiveness and efficiency that allows comparison among treatments/studies. NNT is calculated at a specific point in time. When comparable data are available, it is best to compare NNT for different therapies at the same point in time. Take the mortality estimate at a specific point in time from the survival/mortality curve if available. When crude mortality percentages are used, the average follow-up time is used. Multicenter Unsustained Tachycardia Trial (MUSTT) at 5 years from Kaplan-Meier (KM) curve: 55% to 24%, NNT = 3 (data from Buxton AE et al[53]); Multicenter Automatic Defibrillator Implantation Trial (MADIT) average follow-up of 2.4 years, crude mortality rate: 39% to 16%, NNT = 4 (data from Moss AJ et al[54]); MADIT-II at 3 years from KM curve: 31% to 22%, NNT = 11 (data from Moss AJ et al[55]); Antiarrhythmics Versus Implantable Defibrillators (AVID) trial at 3 years from the KM curve: 36% to 25%, NNT = 9 (data from the AVID Investigators[56]); Survival and Ventricular Enlargement (SAVE) trial (captopril, an angiotensin-converting enzyme inhibitor) crude rate with average follow-up of 42 months: 25% to 20%, NNT = 20 (data from Pfeffer MA et al[12]); Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF; metoprolol, a β-blocker in heart failure patients) at 1 year from KM curve: 11% to 7.2%, NNT = 26 (data from MERIT-HF study[50]); Scandinavian Simvastatin Survival Study (4S) at 6 years from KM curve: 12.3% to 8.7%, NNT = 28 (data from 4S study[57]); amiodarone meta-analysis of 15 trials at average follow-up of 2 years: 19.2% to 16.5%, NNT = 37 (data from Sim I et al[58]). SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.*

regarding device therapy, and it is critical to acknowledge that all of the demonstrated benefit of device therapy has been in the context of appropriate medical therapy. Thus, device therapy for heart failure does not supplant medical therapy; rather, it is complementary. It is anticipated that the next version of the ACC/AHA guidelines for chronic heart failure will address device therapy. The Center for Medicare and Medicaid Services (CMS) has posted its decisions regarding coverage of devices[44]:

> CMS has determined that the evidence is adequate to conclude that an implantable cardioverter-defibrillator (ICD) is reasonable and necessary for the following:
>
> - Patients with ischemic dilated cardiomyopathy (IDCM), documented prior myocardial infarction (MI), New York Heart Association (NYHA) class II and III heart failure, and measured left ventricular ejection fraction (LVEF) ≤ 35%
> - Patients with nonischemic dilated cardiomyopathy (NIDCM) > 9 months, NYHA class II and III heart failure, and measured LVEF ≤ 35%
> - Patients who meet all current CMS coverage requirements for a cardiac resynchronization therapy (CRT) device and have NYHA class IV heart failure

In a cost effectiveness analysis of ICD therapy from the recent SCD-HeFT trial presented at the 2004 scientific session of the AHA, Dr. Daniel Mark of the Duke University Research Institute, Durham, NC, showed definitively that amiodarone therapy was more expensive but no more effective than placebo. Single-chamber ICD treatment was also more expensive than placebo but was correspondingly more effective as well. Economic benchmark analysis concludes that a cost greater than $100,000 per life-year saved is not attractive, whereas a cost less than $50,000 per life-year saved is attractive. The cost per life year saved in SCD-HeFT was $27,718 (undiscounted) and $33,192 (discounted at 3%). Favorable cost effectiveness was observed for a wide range of prespecified subgroups including patients in NYHA Classes II and III, those with ejection fractions above and below 30%, age both above and below 65 years, and QRS duration less than or greater than 120 msec. The presenter concluded that "ICD therapy is both more effective and more expensive but represents an economically attractive way to increase societal health benefits."

Future Directions of Heart Failure Therapy

Several intriguing medication adjuncts are likely to arrive soon and enter the heart failure treatment milieu. The early data regarding the use of arginine vasopression (AVP) antagonists are promising, particularly for patients with renal insufficiency.[45] These agents appear to restore the ability to secrete concentrated urine and, in clinical practice, function as aquaretics. In keeping with one of the presumed benefits of AVP antagonists, hyponatremia appears to be an excellent marker for AVP antagonist therapy. Other promising therapeutic agents/classes include calcium-sensitizing agents (eg, levosimendan)[46]

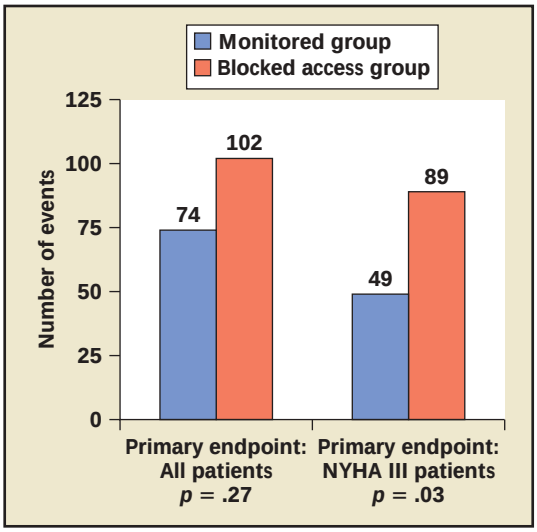


Figure 11. *Results of the COMPASS-HF Trial. At 6 months, heart failure patients treated utilizing data from hemodynamic monitoring systems (monitored group) required 21% fewer hospitalizations than those treated without monitoring information (blocked access group). Reproduced with permission from www.cardiosource.com. Accessed April 6, 2005.*

substrate utilization agents (eg, ranolazine)[47] and erythropoietin analogues—several of which are under intense investigation.[48]

Similarly, newer devices are quickly becoming available, including implantable hemodynamic monitoring, more easily applied left ventricular leads to facilitate CRT, and smaller LVAD platforms. At the 2005 Scientific Sessions of the American College of Cardiology, Dr. Robert Bourge presented results of the Chronicle Offers Management to Patients With Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) Trial (Figure 11). Patients were implanted with a hemodynamic monitoring system (Chronicle; Medtronic, Inc., Minneapolis, MN). This trial was the first large scale evaluation of the impact of continuous ambulatory intracardiac pressure monitoring on heart failure morbidity added to maximal medical management. The investigators found a significant 21% reduction in HF hospitalizations in the device-monitored group.

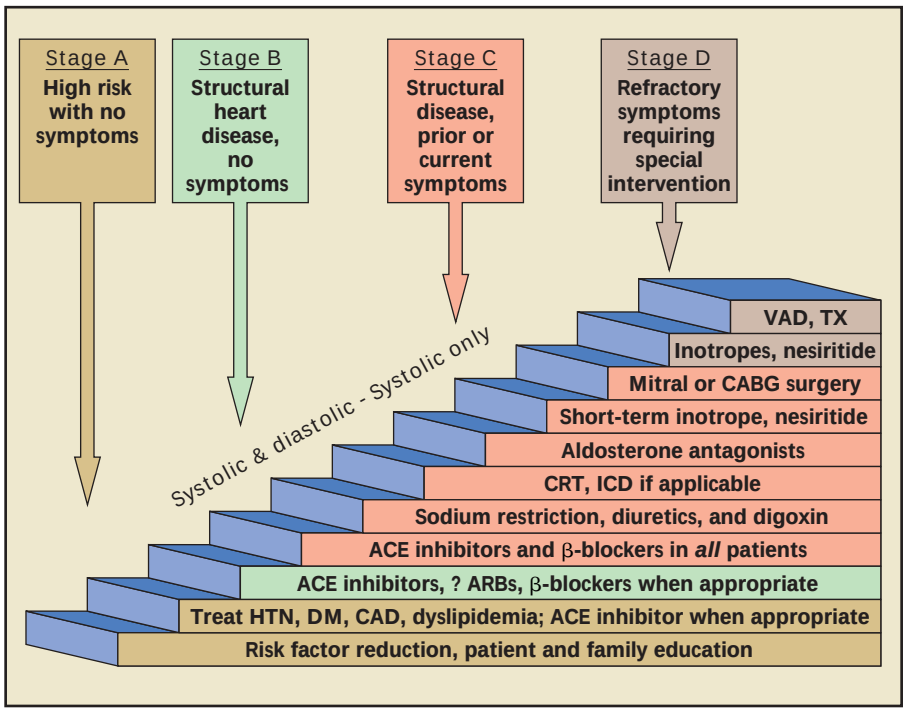
The future is quite exciting. It is anticipated that pharmacogenomics will allow for true tailored therapy so that patients are treated with personalized medical regimens. The promise of biologic regeneration of myocytes may eventually obviate the need for transplantation, and future devices may rely on real-time data inputs to modify cardiac performance and reduce the need for medical therapy or may administer medical therapy in a more physiologic manner.

Several important questions remain: How is heart failure with preserved systolic function best treated? Can clinical trials be done in the setting of ADHF that will generate treatment guidelines? How can the current evidence-based therapies, both medical and device, be more fully implemented? Within the sea of current treatment options, what are the best practices? These and other questions must be resolved if progress is to continue.

Conclusions

It is apparent that the treatment of heart failure is no longer associated with poor outcomes and limited treatment options. Even though future discoveries are required for our continued success, a larger problem has to do with adherence to

Figure 12. *Stages of congestive heart failure and steps of treatment. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CABG, coronary artery bypass graft; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; HTN, hypertension; ICD, implantable cardioverter-defibrillator; TX, thromboxane; VAD, ventricular assist device. Courtesy of Mariell Jessup, MD.*



evidence-based guidelines and published data. Startling data now demonstrate that compliance with evidence-based strategies is well below acceptable thresholds, negatively affecting quality of care. The implementation of well-refereed guidelines is one opportunity to improve the quality of care, whereas the increasing application of dedicated disease management programs is yet another mechanism to increase compliance with known effective therapies for heart failure. How one constructs an effective treatment regimen and considers the information on which choices are made may greatly affect morbidity and mortality in heart failure (see Figure 12 for a proposed treatment algorithm).

With the correct application of proven therapies, specifically pharmaceuticals and device platforms, the burden of heart failure can be reduced. This should be the challenge and the calling of all physicians who treat heart failure. ■

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Main Points

- The American College of Cardiology/American Heart Association (ACC/AHA) staging nomenclature for heart failure was proposed to more adequately address disease severity. Whereas the New York Heart Association classification system focuses on symptom status, the ACC/AHA staging scheme addresses disease progression, particularly for hypertension.
- For patients who have stage A heart failure, aggressive prevention and treatment strategies are advised.
- For patients with stage B heart failure (ie, those with structural heart disease but no symptoms of heart failure) the recommendation is to proceed with agents that are cardioprotective, especially angiotensin-converting enzyme (ACE) inhibitors and β-blockers.
- For patients with stage C heart failure (ie, those with structural heart disease and current or past symptoms of heart failure) nonpharmacologic approaches including dietary sodium restrictions and avoidance of alcohol and tobacco are further expanded by the implementation of indicated medical and device therapies.
- The Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial demonstrated that about 90% of patients discharged with a primary diagnosis of heart failure can be initiated on β-blocker therapy prior to hospital discharge, whereas the Acute Decompensated Heart Failure Registry (ADHERE) database now demonstrates that the use of β-blockers in appropriate patients is as low as 40%.
- Patients with stage D heart failure are at high risk for repeat hospitalizations and premature death due to heart failure despite appropriate medical therapy. Beyond ventricular replacement strategies, which include left ventricular assist devices and heart transplantation, the portfolio of available treatment options is fairly thin. End-of-life discussions are appropriate at this stage.
- Correction of ventricular dyssynchrony with a cardiac resynchronization device has been proven to reduce the need for hospitalizations, and when added to an implantable defibrillator, survival is likewise enhanced.

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