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MANAGEMENT OF CONGESTIVE HEART FAILURE IN THE 21ST CENTURY: *BEYOND* ACE-INHIBITORS AND BETA-BLOCKERS

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OBJECTIVES:

A) To review current outcomes in congestive heart failure
B) To establish a "best practice" approach to heart failure based on currently available treatment options for heart failure including treatment preferences of the UTSW Congestive Heart Failure Service
C) To introduce several new potential treatment options based on an expanded neurohormonal perspective of the pathophysiology of heart failure

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PARTICULAR INTERESTS:

Congestive Heart Failure
    -esp., development of new therapies
Cardiac Transplantation
Critical Care Medicine
Invasive Hemodynamics/Cardiac Catheterization
American Heart Association
Texas Coalition on Heart Disease and Stroke

MANAGEMENT OF CONGESTIVE HEART FAILURE IN THE 21ST CENTURY: *BEYOND* ACE-INHIBITORS AND BETA-BLOCKERS

I. OUTCOMES IN CONGESTIVE HEART FAILURE

Congestive heart failure continues to represent an increasing cardiovascular problem. As morbidity and mortality rates due to myocardial infarction continue to decline, the incidence of heart failure is escalating. Currently, >5 million Americans are affected with heart failure. Of these, 70% are >60 years of age. This burden coupled with an estimated one million annual hospitalizations for heart failure and an annual expenditure of >30 billion dollars (>$8000/patient/year) makes this problem of heart failure one of our leading public health concerns[1].

Congestive heart failure is a clinical syndrome of circulatory insufficiency characterized by impaired ventricular function, either systolic or diastolic, with a resultant mismatch between cardiac performance and cardiac requirements --- all of which occurs in an environment characterized by complex interactions of activated neurohormonal systems. Previously known to be a dismal diagnosis, congestive heart failure has reaped major advantage from advances in basic and clinical research. These improved outcomes in congestive heart failure have come from: a shift in the paradigm of heart failure; improvements in morbidity and mortality from the wider applications of available therapies; and improved management of end-stage heart disease.

Over the past 30 years there has been a dramatic *shift in the paradigm* of heart failure. (See Figure 1.) The original hypothesis was that of a biomechanical problem explained solely on the basis of impaired contractility with a resultant increase in filling pressures in accord with Starling's law. The clinical expression of this hypothesis was backward and forward failure and the therapy was focused on diuretics and inotropes. Although useful in the relief of symptoms, this approach actually led to *increased* mortality rates. In the mid to late eighties, the heart failure hypothesis evolved to encompass a hemodynamic model based on abnormal loading conditions, i.e., increased afterload and preload. It became apparent that vasodilators given to euvolemic patients, even with marginal blood pressures, can result in an increase in cardiac performance without further detriment in blood pressure. Unfortunately, the clinical use of pure vasodilators has been *inconsistent*, with only one regimen demonstrating only modest survival advantage[2]. The greatest advantages have been realized with the evolution of the heart failure hypothesis to include the current neurohormonal hypothesis along with an increasing understanding of cardiac pathobiology. The development of specific antagonists of the neurohormonal system and other biological targets has yielded the greatest impact on survival in heart failure. These biological antagonists have not consistently demonstrated dramatic symptom relief suggesting that there is a discontinuity between hemodynamic presentations of heart failure and abnormal cardiac pathology in heart failure. As we approach the 21st century, our model of heart

failure will almost assuredly change yet again. The future focus will be on mechanisms of abnormal growth which result in remodeling of the left ventricle. Our ability to understand mechanisms of remodeling and to effectively manipulate those systems (i.e., "reverse remodeling") will represent the crux of future investigation and clinical management of heart failure.

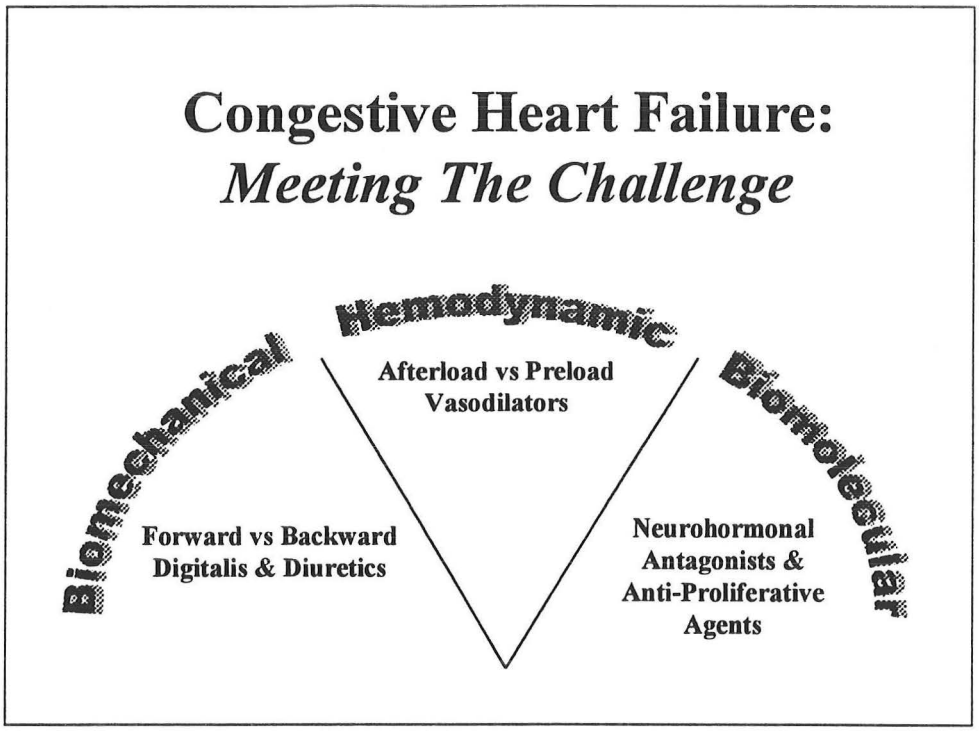

Figure 1

Mortality data on heart failure is finally beginning to show improvements. For the first four decades of follow-up in the Framingham Study, there was no decline in mortality due to heart failure. However, analysis of 1980-1995 [i.e., vasodilator vs. ACE-I era] national mortality statistics demonstrate a decrease in age-adjusted death rates for heart failure beginning in 1988. There has been a 1-3% annual decline in death rates due to heart failure irrespective of gender or race. The largest decline of 3% has been in black men and the smallest decline of 0.5% has been in white women. Age-adjusted death rates for heart failure vary widely among states. For persons aged >65, Texas has an age-adjusted death rate of 112.5 deaths per 100,000 population. This compares to 146/100,000 in Louisiana and 30.7/100,000 in New Hampshire. The lower death rate in black patients is attributable to better management of hypertension. Overall, the decline in death rates is likely due to widespread use of ACE-I therapy[1]. Although ACE-I therapy is still not applied to all patients, current estimates suggest that ~70% of suitable heart failure patients are being exposed to ACE-inhibitors. With the introduction of beta-blockers suitable for the management of heart failure, it is anticipated that the death rates for heart failure will continue to decline, perhaps at a faster rate.

The *management of end-stage congestive heart failure* has also improved considerably over the last decade. Tailored therapy is a treatment strategy for advanced heart failure based on aggressive dosing of conventional agents for heart failure guided by invasive monitoring of hemodynamic targets[3]. By utilizing parenteral diuretics and vasoactive drugs (e.g., nitroprusside or dobutamine), "normal hemodynamics" are achieved. (See Table I.) An attempt is then made to maintain adequate hemodynamic responses to heart failure with high dose oral therapy. If such can be accomplished, the outcomes in these patients are comparable to those patients undergoing transplantation. This strategy is best applied by physicians experienced in heart failure management and is appropriate for the class IIIb or IV patient. An NHLBI-sponsored trial [ESCAPE] is being established to evaluate the potential benefit of aggressive medical therapy vs. conventional therapy for advanced heart failure.

TABLE I:
TAILORED THERAPY GOALS

HEMODYNAMIC END-POINT:	USUAL DRUG THERAPY:
PCWP <18 mmHg	diuretics; long acting oral nitrates
cardiac index >2.2 L/min/m^2	maximal tolerable dose of ACE-I
CVP <12 mmHg	Diuretics
SVR >800<1200 & systemic BP >85 mmHg systolic	vasodilators as required

Heart transplantation is no longer an experimental intervention to be applied "when there is nothing to lose". The national survival data are 85% at one year and 60% at five years[4]. Individual centers (e.g., UT Southwestern/St. Paul Medical Center and UT Southwestern/Baylor University Medical Center, Dallas, TX) are now consistently reporting one-year survivals of 90%. Several multicenter databases (e.g., Transplant Lipid Registry Database) that rely on input from major university-based transplant programs are now reporting survival statistics of nearly 95% at one year[5]. Transplantation should be considered as a part of the expected treatment algorithm in appropriate patients. The application of cardiac transplantation remains limited, however, due to the chronic shortage in available donors. Future strategies will involve enhanced donor awareness, more selective transplant criteria and xenotransplantation.

An increasing number of non-transplant surgical options/mechanical therapies for end-stage heart disease have been developed. Intracardiac defibrillators are being used increasingly as definitive management for those patients at highest risk for sudden cardiac death. An ongoing NIH-sponsored trial, SCD-HeFT [Sudden Cardiac Death in Heart Failure] is evaluating the survival advantage of implantable defibrillators placed prophylactically in heart failure patients irrespective of the presence of ventricular tachycardia. Pneumatic-driven left ventricular assist devices (LVADs) are FDA approved, and fully implantable electronic devices that use external battery packs have been recently approved (October, 1998). This latter modality would allow <u>outpatient</u> use of LVADs -- either as a bridge to transplantation or as definitive therapy. The enthusiasm for left ventriculectomy (Batista operation) has waned some due to the excess morbidity and mortality that has been seen in this country. For patients with

chronic ischemic heart disease that have objective evidence of ischemia and are not suitable candidates for conventional bypass surgery, transmyocardial laser revascularization (either intraoperative or percutaneous) is a promising strategy. It is based on the creation of very small full-thickness microchannels within the left ventricle. It is thought that these microchannels encourage angiogenesis.

Lesser options include: dynamic cardiomyoplasty, which is the use of the latissimus dorsi as an endogenous left ventricular assist after wrapping the latissimus dorsi around the ventricle and training it with chronic pacing; triple chamber pacing with optimization of atrial emptying, heart rate, pacing site and left/right ventricular interactions; and high risk mitral valve repair in patients with dilated ventricles and severe mitral insufficiency.

The development of an improved understanding of the mechanisms of heart failure, wider application of available treatment options and a number of very effective but aggressive strategies for end-stage heart disease has indeed resulted in improved overall outcomes in heart failure management.

II. CURRENT BEST PRACTICE IN HEART FAILURE

Based on exhaustive reviews of the literature, there has been a clear mandate established that **all patients with heart failure due to systolic dysfunction should be on triple drug therapy** to include -- a loop diuretic; an ACE-inhibitor; and digoxin.

Although data on the use of digoxin in heart failure remain debatable, many CHF specialists continue to advocate the use of digoxin, especially in patients with advanced heart failure, severe left ventricular dysfunction and concomitant atrial arrhythmias. The recently completed DIG trial (Digoxin Investigators Group) established benefits for digoxin: reduction of hospitalizations by nearly 30%; improvement of cardiovascular mortality in severe LV dysfunction; and improvement of outcomes in elderly patients with diastolic heart failure (LVEF >0.45)[6].

[*The reasons for this improvement in diastolic dysfunction are not clear, but it has been hypothesized that the real role of digoxin is as a neurohormonal antagonist that reduces the central nervous system sympathetic outflow and NOT as an inotrope. Reduced efferent sympathetic nerve traffic may be beneficial in promoting reverse remodeling of hypertrophic ventricles such as were present in the DIG trial.*]

ACE-inhibitors remain the mainstay of therapy for heart failure. Currently five drugs have FDA approved indications for heart failure: enalapril, captopril, lisinopril, quinapril and fosinopril. The approval of ramipril is anticipated based on the results of the AIRE[7] and AIREX[8] trials both of which showed survival advantage using ramipril in patients with heart failure as a complication of an acute myocardial infarction. Survival advantage was seen at 30 days s/p infarction (AIRE trial) and seen again at 2-4 years of follow-up (AIREX trial). The selection of the best ACE-inhibitor should be based on use of one of the approved agents and on physician/patient preference. For

patients with advanced heart failure, the most compelling survival data are with the use of enalapril (CONSENSUS I[9] and SOLVD[10]) thus it appears appropriate to utilize enalapril in class III, IIIb or IV patients. There has been much rhetoric regarding the use of ACE-inhibitors in doses that parallel those used in the major survival trials. The recently reported ATLAS trial compared the use of lisinopril at 5 mg/day vs. 30 mg/day in 3164 patients with chronic class II-IV CHF[11]. At a mean follow-up of 46 months, all cause mortality was 8% lower in the high dose ACE-I group compared to the low dose group (p=0.128 or **ns**). Cardiovascular mortality was 3% lower (40.2 % vs. 37.2%) which did reach statistical significance (p=0.007). Hospitalizations were reduced by 24% in the high dose group. These data would suggest that there is incremental benefit of higher dose ACE-inhibitor therapy, but this must be weighed against patient tolerance, side effects, and cost. As the complexity of heart failure regimens increase, it may be reassuring to realize that even low doses of ACE inhibitors may be beneficial. It is expected that ACE inhibitor therapy will continue to be integral to the management of heart failure in the 21st century.

Much enthusiasm has been generated by the potential advantage of angiotensin receptor blockers [ARBs] in heart failure. The potential benefits include: true once-a-day therapy; complete antagonism of all the known biological effects of angiotensin II irrespective of whether it emanates via converting enzyme or non-converting enzyme pathways; and avoidance of an ACE inhibitor induced cough – thought to be due to increased levels of bradykinin associated with ACE-inhibitor use (due to its anti-kininase property) and not seen with ARBs. The ELITE trial[12] evaluated the use of losartan in heart failure in a unique patient population. The ELITE trial randomized 722 elderly patients, >65 years old, with heart failure not previously on an ACE-inhibitor to losartan vs. captopril. The primary end-point was renal insufficiency and the secondary endpoint was the composite of death or CHF admission. There was no difference in serum creatinine determinations. No losartan treated patient withdrew due to cough but 14 captopril patients developed intolerable cough (3.7% of ACE inhibitor treated patients). There was a 32% trend towards risk reduction of death in patients treated with losartan vs. captopril (p=0.075; 95% CI -4% to 55%). A true survival trial is underway, ELITE II, to attempt to detect any real advantages of losartan over ACE-inhibitors in heart failure. A separate trial, RAAS, [Randomized Angiotensin Receptor Antagonist-Angiotensin-Converting Enzyme Inhibitor Study][13] is comparing the combination of losartan and ACE-inhibitors to ACE-inhibitors alone. A not yet published trial, RESOLVED, (Randomized Evaluation of Strategies for Left Ventricular Dysfunction)[14] evaluated a different ARB, candesartan, vs. enalapril in 769 patients with class II-IV CHF and systolic dysfunction (LVEF <0.40). After 6 months, 450 of the patients were then randomized to also receive metoprolol or placebo. There was no early survival advantage of the ARB over the ACE-inhibitor, but when a beta-blocker was added, there was a trend towards increased survival. Additional data will be forthcoming from this trial.

This triple drug strategy of digoxin, diuretics and ACE-inhibitors/ARBs is soon to be expanded to four drugs or "quadruple therapy" with the next broad category being the use of beta-blockers. The most compelling data for the use of beta-blockers comes from: the MDC (Metoprolol in Dilated Cardiomyopathy)[15] trial; the U.S. Heart Failure Trials Program[16]; and CIBIS I[17] & CIBIS II (Cardiac Insufficiency Bisoprolol Studies)[18].

The MDC trial evaluated the efficacy of metoprolol, a cardio-selective beta-blocker, in a randomized double blind trial of 383 patients with a dilated cardiomyopathy and class III or worse heart failure sufficient to warrant referral for consideration of transplantation who were already on appropriate therapy with digoxin, diuretics and vasodilators. The end-point was death or the need for transplantation. The initial results at one year demonstrated a trend towards improvement in the combined end-point of death or need for transplantation ($p=0.058$). However, all of the early benefit came from a reduction in the need for transplantation with no effect on mortality. A follow-up analysis has been completed and assesses survival at 3 years. The data demonstrate significant improvement in survival ($p=0.051$) and thus support the hypothesis that beta-blockade in chronic heart failure reduces mortality. Importantly, the beta-blockade and standard therapy curves did not diverge until >1 year of therapy had elapsed.

The U.S. Heart Failure Trials program evaluated the efficacy of carvedilol, a new nonselective vasodilating beta-blocker with beta-1, beta-2 and alpha-1 antagonism as well as a significant anti-oxidant property. This complex study involved four arms: mild CHF, two moderate CHF arms (PRECISE & MOCHA), and severe CHF[16]. Survival was not a defined end-point, but was one of the safety criteria that was continually assessed. Over 1000 patients were randomized to standard therapy (digoxin/diuretics/ACE-inhibitors) vs. standard therapy plus carvedilol. This trial was prematurely terminated due to a survival advantage seen in those patients on carvedilol. At 7 months follow-up, there was a striking 65% reduction in mortality in patients treated with carvedilol. As well, dramatic reductions in the need for hospitalization and/or adjustment in heart failure medications were likewise observed. These data are flawed by the relatively short follow-up, the predominance of patients with milder forms of heart failure, class II & III, and the concerns that it was not a designed mortality trial. Nevertheless, no other treatment strategy to-date has demonstrated outcomes of this magnitude in heart failure management. Tables II & III summarize the appropriate use of Carvedilol in heart failure.

TABLE II

CANDIDATE SELECTION FOR USE OF CARVEDILOL IN HEART FAILURE
Who is NOT appropriate for carvedilol therapy?
• -class IV CHF, decompensated or "wet" CHF
• -concomitant use of inotropes
• -known contraindication to beta-blocker therapy, esp., conduction system disease and asthma
• -not already on standard, triple drug therapy for heart failure
Who IS appropriate for carvedilol therapy?
❖ -ambulatory, class II or III CHF
❖ -compliant patients
❖ -clinically compensated and euvolemic patients

TABLE III

HOW TO ADMINISTER CARVEDILOL IN HEART FAILURE?
❖ Initial BP >90 mmHg & HR >60 bpm
❖ Start at 3.125 mg BID; give first dose in the office; monitor X 90 min
❖ Telephone follow-up at 3 days; return visit q 2 weeks for up-titration
❖ Double the dose at each follow-up visit provided HR >60 & BP >90
❖ Target dose is 25 mg BID if <200 lbs. and 50 mg BID if >200 lbs. or max tolerated dose
POTENTIAL PROBLEMS IN THE USE OF CARVEDILOL
Bradycardia: due to beta-blocking action; may also be due to drug-drug interactions with digoxin since carvedilol does increase digoxin levels; managed by checking digoxin levels and, if necessary, reducing beta-blocker dose
Worsening CHF: due to initial negative inotropic properties; managed with temporary increase in diuretics
Orthostasis: due to significant first pass metabolism by the liver with marked alpha-1 blockade effect; can be limited by taking medication with food; usually transient and resolves within 30-60 minutes

The pattern established with carvedilol will be the model for future beta-blockers, i.e., start low and titrate slowly with therapy limited to compensated patients. Every effort should be made to continue beta-blockers even when mild side effects occur. The potential advantages appear to outweigh the early difficulties with establishing therapy.

At present, the most convincing evidence in support of beta-blocker use in heart failure comes from the CIBIS I & II studies. In CIBIS I, 641 patients with class II/III CHF who were taking ACE-inhibitors were randomized to bisoprolol or placebo[17]. Once again, this study was not designed as a mortality trial and thus was not sufficiently powered to detect a mortality difference. Nevertheless, there was a trend observed towards a 20% reduction in mortality in patients on bisoprolol compared to standard therapy

with an ACE-inhibitor. When those patients with non-ischemic etiologies of heart failure were analyzed, the survival advantage did reach statistical significance. The follow-up study, CIBIS II, was a designed mortality trial and was recently reported in August, '98 after it was stopped prematurely due to an observed survival advantage of bisoprolol. CIBIS II enrolled 2647 patients with CHF, class III or IV, on diuretics and ACE-inhibitors with systolic left ventricular dysfunction (LVEF <0.35). Patients were randomized to bisoprolol vs. placebo and follow-up was >1 year. Bisoprolol treatment significantly reduced all-cause mortality by 32% (11.8% vs. 17.3%; p<0.001) when compared to placebo and reduced all cause hospitalizations by 15% (33.6% vs. 39.8%; p<0.001) compared to placebo. In the opinion of the investigators, "all ambulatory patients with heart failure should be on both an ACE-inhibitor and a Beta-blocker"[18].

A recently reported meta-analysis of all 18 published double-blind, randomized trials of beta-blockers in heart failure demonstrated remarkable clinical benefit of beta-blockers in the management of CHF[19]. The greatest effect of the drugs was to increase left ventricular ejection fraction and to improve the combined endpoint of deaths and hospitalizations. LVEF increased by 29% with the use of beta-blockers and the combined risk of death and hospitalization improved by 37%. The effect on functional class was minimal. The greatest reduction in mortality was seen with the non-selective beta-blockers (e.g., carvedilol), 49% vs. 18% for the selective beta-blockers (e.g., metoprolol). It is apparent that beta-blockers will represent standard therapy for heart failure in the 21st century.

Table IV lists ongoing beta-blocker trials, the drugs being evaluated and the design of the study[20]. These additional data should be available just after the year 2000 and will greatly enlighten our understanding of the use of beta-blockers in heart failure. There is particular optimism for the BEST trial, which is evaluating the use of bucindolol which is also a nonselective, vasodilating beta-blocker. This drug in smaller studies has already demonstrated the ability to promote reverse remodeling of the left ventricle and to improve myocardial metabolism.

TABLE IV

ONGOING BETA-BLOCKER TRIALS			
Trial	***# of Patients***	***Drug(s) studied***	***Design***
BEST	2800 class III &IV	Bucindolol	Survival
COMET	3000 II-IV	Metoprolol vs. carvedilol	Survival
COPERNICUS	2000 IIIb & IV	Carvedilol in severe CHF	Survival
MERIT-HF	3200 II-IV	Metoprolol	Survival

An important component of any best practice strategy in heart failure is the realization that 70% of heart failure in this country is due to ischemic heart disease. There are few if any data available to warrant the use of aggressive revascularization strategies in chronic heart failure management primarily because patients with overt heart failure have been excluded from most revascularization trials. As such there are few guidelines to direct the management of heart failure due to chronic ischemic heart disease. The AHCPR guidelines for managing heart failure (Agency for Health Care

Policy and Research – part of the US Dept. of Health and Human Services) emphasized the potential benefit of revascularization and suggested the following strategy[21]. Any heart failure patient with angina should undergo cardiac catheterization and revascularization if the anatomy is suitable. In the absence of angina, multiple positive risk factors and/or a history of a myocardial infarction should prompt a physiological test of ischemia with a cardiac catheterization completed for a positive test. Revascularization would follow if the anatomy were suitable and if the risk-benefit ratio were felt to be clinically within reason for a given patient. A combined American College of Cardiology/American Heart Association task force published its Guidelines for the Evaluation and Management of Heart Failure and also emphasized the importance of coronary revascularization in patients with congestive heart failure due to ischemic heart disease[22]. The benefit appears greatest in patients with angina and is less clear for those patients without angina. It would appear prudent to be aggressive in the evaluation of ischemic heart disease and cautious in the use of revascularization as specific therapy for heart failure.

Ideally, the best therapy for heart failure is to *never get heart failure* through application of effective preventive strategies. The use of diuretics in the SHEP (Systolic Hypertension in the Elderly) trial[23] was associated with a decreased incidence of heart failure in elderly patients with hypertensive heart disease. The 4S trial (the Scandinavian Simvastatin Survival Study)[24] demonstrated a remarkable decrease in the incidence of heart failure in those patients s/p myocardial infarction treated with lipid-lowering therapy. The effect appears to be independent of the decrease in future myocardial infarctions. This observation lacks explanation. Finally, the use of post-MI ACE-inhibitors and post-MI beta-blockers in patients without heart failure but with asymptomatic left ventricular dysfunction has not only been associated with a decrease in the incidence of heart failure but also with a survival advantage[25,26]. It is inexplicable that all patients s/p myocardial infarction with residual left ventricular dysfunction are not treated with ACE-inhibitors and beta-blockers. There is no debate on the efficacy of these strategies.

The current treatment algorithm for heart failure used by the UT Southwestern Congestive Heart Failure Service ("the pump docs") is outlined in Table V.

TABLE V

MANAGEMENT OF HEART FAILURE AT UT SOUTHWESTERN
1. Prior to any decisions regarding treatment options, all patients are re-evaluated to determine the etiology of heart failure, systolic vs. diastolic dysfunction, and the presence of coronary artery disease.
2. Nonpharmacological strategies are utilized in all patients and include: patient and family education; salt restriction; avoidance of alcohol; daily weights; and cardiac rehab as tolerated.
3. All patients with heart failure and systolic dysfunction are treated with triple drug therapy. ACE-inhibitors are given to all patients unless there is an overt ACE-I allergy; Digoxin therapy is used in all patients with systolic dysfunction.
4. Beta-blockers are attempted in all appropriate patients that are not protocol candidates.
5. ARBs are utilized only in patients with definite ACE-I intolerance; N.B., most cough in heart failure is due to pulmonary congestion and not due to ACE-I therapy.
6. Calcium channel blockers are avoided. Amlodipine or felodipine are used only for patients with persistent hypertension after maximal CHF therapy has been achieved.
7. Amiodarone is used for patients with chronic atrial fibrillation that is not otherwise well-controlled. Patients with nonsustained ventricular tachycardia are treated with amiodarone if they are asymptomatic. Symptomatic nonsustained VT and nonsustained VT in the setting of ischemic heart disease are evaluated by the EP service.
8. Defibrillator therapy is aggressively utilized in those patients with sustained ventricular tachycardia, symptomatic VT, and positive EP evaluations.
9. Class IV CHF is subjected to "tailored therapy" utilizing pulmonary artery catheters and targeted hemodynamic endpoints; Chronic intermittent outpatient inotropic support is not utilized routinely for class IV patients and is limited strictly to those patients with end-stage disease, short life expectancy, and a lack of any other treatment option. Home inotropic therapy is not used.
10. Adjunctive therapy consists of electrolyte supplements. Coumadin is used sparingly and only in those patients with embolic risks other than a dilated left ventricle.
11. As many patients as possible are enrolled in active clinical protocols.
12. Transplantation referral is exercised in any appropriate patient with advanced and/or persistently symptomatic heart failure with poor prognostic indicators.

III. LIMITATIONS OF CURRENTLY AVAILABLE TREATMENT STRATEGIES FOR HEART FAILURE

It would appear from the foregoing discussion that the management of heart failure is a *fait accompli*. Angiotensin converting enzyme inhibitors have established a proven track record of effectiveness and the potential improvement in survival and hospitalization rates with beta-blockers is substantial. Indeed, if all appropriate patients with heart failure were maximally treated with ACE-inhibitors and beta-blockers, the decline in morbidity and mortality would be significant.

Unfortunately, this utopian state can not yet be realized. In truth ACE-inhibitors are only modestly effective in heart failure. For every 100 patients treated, the number of lives saved would be less than 5 and for each individual patient the average extension of survival may be as little as six months. The cost of these drugs and the myriad of choices, not all of which have supporting data to justify their use in heart failure, also complicates management. Beta-blockers are limited as well. In the CIBIS studies, 20%[17] of patients did not realize a benefit from beta-blocker therapy. In a most worrisome way, those patients who did not realize an increase in their left ventricular ejection fraction with beta-blockers experienced an ***excessive*** mortality rate compared to placebo therapy, i.e., standard ACE-I therapy. In the U.S. Heart Failure Trials program, 30%[16] of treated patients experienced side effects from the use of carvedilol including worsening of heart failure (only 1% required withdrawal of therapy). It is still not clear which patient is likely to tolerate therapy and which patients are likely to have adverse events related to beta-blockade.

Even when best therapies can be tolerated and patients realize the intended benefits of therapy, there is still a concern over this increasingly complex polypharmacy. This is particularly of concern given that the majority of heart failure patients are elderly and medication errors are not uncommon. In an increasingly cost-sensitive environment, labor intensive disease management algorithms such as heart failure are falling under the purview of physician extenders (e.g., advanced practice nurses, nurse practitioners, physician assistants). This involves more training and worrisome issues of liability.

For those patients who move on to protocol therapy, they are exposed to uncertain risks. Certainly, the most aggressive strategy of tailored therapy utilizing pulmonary artery catheters is invasive, costly and is associated with some risk. The long-term benefits of this approach have not yet been identified which is also an issue. Transplantation and advanced surgical/mechanical interventions are truly invasive, costly and frankly not an option for the majority of heart failure patients.

As a consequence of these observations, it is clear that the ideal or optimal regimen to treat heart failure has not yet been established and that in the 21st century, it will be necessary to go beyond ACE-inhibitor and beta-blocker use in the management of congestive heart failure.

IV. EVOLVING TREATMENT STRATEGIES

The already established neurohormonal hypothesis of heart failure serves as a framework for the development of future treatment strategies, especially over the near term. It is important to identify "neurohormones". This term is used to characterize virtually any compound found in the circulation, the properties of which can impact the vascular system. In truth, these substances either have autocrine effects, i.e., produced by an organ/cell and exerting an effect on that same organ/cell, or paracrine (a.k.a. endocrine) effect, i.e., produced by one organ/cell for an effect on another organ/cell distant from the site of production[27]. By convention, "neurohormone" encompasses all of these properties. The potential benefit of any of the new agents will not only be defined by clinical criteria but will rely heavily on the ability of those agents to alter the abnormal biology of heart failure. The evolution of the heart failure hypothesis has progressed now to not only emphasize the role of activated neurohormones but also the role of unregulated growth factors that stimulate myocardial growth in an environment where the cardiac cell is already terminally differentiated. Thus myocyte hypertrophy ensues and the ventricle becomes reshaped with concomitant reductions in left ventricular function and an increased propensity for arrhythmias. Treatment strategies associated with a reduction in ventricular size, e.g., ACE-inhibitors and beta-blockers, have had the most effect in heart failure. More specific growth inhibitors may yield even greater improvements in outcomes and this represents the current target of new drug development.

The sympathetic nervous system represents a principle target for neurohormonal manipulation and to-date beta-blockers have been the preferred antagonists by interfering with adrenergic receptors in the periphery. An alternative approach might be to decrease sympathetic nervous system activity centrally. It has been well established that sympathetic nervous system activity (i.e., nerve traffic) is increased in heart failure and is responsible for cardiac hypertrophy, enhanced thrombosis, platelet aggregation, progression of atherosclerosis and renal underperfusion (which can then stimulate the renin-angiotensin system). The incidence of ventricular arrhythmias and sudden death is also increased by an overactive sympathetic nervous system.

Centrally acting sympathetic nervous system inhibitors have been available for some time. Clonidine represents the prototype. It modulates brain stem activity by stimulating central alpha-2 adrenoceptors resulting in a decrease in peripheral sympathetic tone. It also slows the heart rate, decreases reflex tachycardia, suppresses plasma renin activity, and regresses left ventricular hypertrophy. These features would be desirable in the management of heart failure. A small trial of clonidine use in heart failure was completed and did demonstrate favorable trends towards reductions in heart rate, increases in ejection fraction and improvement in functional status[28]. However, the side effect profile of clonidine limits its further applications in this area.

Moxonidine is a centrally acting sympathetic nervous system inhibitor that works on the recently discovered sympathoinhibitory imidazoline receptors[29]. These receptors

are distant from the alpha-2 receptors. The receptors are located in the lateral reticular formation of the medulla whereas the alpha-2 receptors are located in the pontomedullary region. When stimulated the imidazoline receptors are associated with a reduction in blood pressure and heart rate. These receptors do not appear to promote sedation, dry mouth or impotence[29]. Moxonidine has an affinity for the imidazoline receptors that is 35 times greater than its affinity for the alpha-2 adrenoceptors and thus is free of the side effect profile associated with clonidine. Plasma norepinephrine levels are significantly reduced while cardiac output is preserved. Another potential advantage of moxonidine's stimulation of the imidazoline receptor is the potential antiarrhythmic role that these receptors may have. Moxonidine has been shown to suppress episodes of tachycardia and in animals it has been demonstrated to have anti-arrhythmic properties. Moxonidine also causes regression of left ventricular hypertrophy and via activation of imidazoline receptors in the kidney it causes natriuresis[29]. These properties of moxonidine make it a candidate drug for management of heart failure in the 21st century.

The MOXCON trial has been initiated to test the efficacy of moxonidine in a survival trial of heart failure. There is much enthusiasm that this may be a preferable approach to the use of beta-blockers since the introduction of therapy may be better tolerated and the dosing schedule will not need to be quite so arduous as in the use of beta blockers.

It is apparent that the abnormal growth and remodeling phenomenon in heart failure is not limited to the myocardium. Scarred myocardium at necropsy contains nearly 70% fibrous tissue with a dramatic increase in types I & III collagen[30]. Cardiac myofibroblasts are stimulated by angiotensin II, transforming growth factor-beta, and endothelins and they are inhibited by prostaglandin E2, bradykinin and nitric oxide. Angiotensin II is associated with the expression of type I collagen mRNA and aldosterone is associated with the expression of types I & III procollagen mRNA. Interference with not only the production of angiotensin II and aldosterone but also the activity of myofibroblasts would be beneficial in promoting reverse remodeling and decreasing the stimulus for abnormal growth in heart failure[31]. Dual metalloprotease inhibitors possess the property of both renin-angiotensin-aldosterone antagonism and neutral endopeptidase (NEP) antagonism. This latter role of NEP antagonism is associated with enhanced vasodilatory, natriuretic, and anti-proliferative effects via inhibition of the breakdown of natriuretic peptides and bradykinin. The recently completed IMPRESS trial evaluated the effectiveness of this treatment strategy vs. ACE-inhibitor therapy in a randomized trial of class II/III heart failure patients with an endpoint of functional capacity. The results are pending but if the data are encouraging, a survival trial may be forthcoming. This approach may represent a "better ACE-I" and could well be a candidate drug for management of heart failure in the 21st century.

Elevated aldosterone levels in heart failure are yet another expression of the activated neurohormonal environment in CHF[32]. In much the same way that angiotensin II can be produced by non-converting enzyme mechanisms, aldosterone may escape ACE-inhibition, i.e., other mechanisms may lead to the production of aldosterone. In

particular, corticotropin, atrial natriuretic peptide and potassium may stimulate aldosterone production without involving angiotensin II. A remarkable finding has been that there is an inverse relationship between serum high-density lipoprotein levels and aldosterone. Patients with low HDL levels may be at higher risk for heart failure due to increased production of aldosterone despite ACE-inhibition.

(This may explain the observed benefit of statin therapy to reduce heart failure episodes in patients with ischemic heart disease and hyperlipidemia apart from any decrease in re-infarction rates)

Preliminary data on the use of spironolactone, an aldosterone antagonist, with ACE-inhibitors has demonstrated a fall in N-terminal pro-atrial natriuretic peptide levels. Hyperkalemia is a concern when the two drugs are given together. The RALES mortality trial (Randomized Aldactone Evaluation Study)[33] will evaluate 1400 patients with heart failure due to systolic dysfunction (LVEF <0.40) who are treated with an ACE-inhibitor and then randomized to placebo vs. aldactone. These data will be available within the next 3-5 years and may provide additional benefit in heart failure management in the 21st century.

Another extension of the neurohormonal hypothesis is the production of endogenous vasodilators and natriuretic compounds that counterbalance the vasoconstriction and sodium retention of the renin-angiotensin-aldosterone system, sympathetic nervous system and arginine vasopressin. These endogenous substances are known as natriuretic peptides and are in fact produced by the heart (thus satisfying the definition of an *endocrine* organ). They have significant natriuretic, diuretic, and vasodilatory properties. There are three types of natriuretic peptides: atrial natriuretic peptide (ANP); brain natriuretic peptide (BNP); and C-type natriuretic peptide (CNP). Atrial natriuretic peptide is produced by atrial tissue and brain natriuretic peptide is produced by the ventricle (although it was originally isolated from brain tissue). C-type natriuretic peptide is a much less potent diuretic and its expression in brain tissue is 70-fold that of ANP or BNP. The natriuretic peptides exert their actions via natriuretic peptide receptors of which there are three, NPR-A, -B, and –C. NPR-A and NPR-B receptors utilize guanylate cyclase/cGMP as a second messenger pathway. NPR-A is activated by ANP and BNP but not CNP, while NPR-B is not affected by ANP or BNP but is significantly stimulated by CNP. NPR-C is responsible for clearance of the natriuretic peptides and has a greater affinity for ANP over BNP. The natriuretic peptides are also cleared by the action of neutral endopeptidase[34].

Secretion of ANP occurs in response to increased atrial transmural pressures. It has been suggested that for each 1 mmHg rise in transmural atrial pressure, there is an increase in ANP of 14 pmol/L. Supraventricular tachycardia and atrial fibrillation also stimulates the production of ANP. BNP is secreted by the ventricle but the relationship to increased ventricular pressure is not as clear. Since levels of BNP are elevated in clinical syndromes associated with dilated ventricles, it appears that some parameter of left ventricular dysfunction stimulates the production of BNP. Elevated concentrations of angiotensin-II and endothelin stimulate both ANP and BNP production. ANP and

BNP act to inhibit production of catecholamines, angiotensin-II, aldosterone, and endothelin. ANP inhibits cardiac fibroblasts reducing collagen deposition and ANP also induces cardiac myocyte apoptosis thus limiting the hypertrophic response to injury.

The levels of ANP and BNP are both elevated in heart failure. ANP is increased even in mild CHF while BNP is increased in more severe clinical syndromes. In patients with class IV heart failure, the increase in ANP and BNP may be as much as 30-fold over baseline. ANP is strongly related to pulmonary artery pressures and elevated pulmonary capillary wedge pressures while BNP is closely correlated to prognosis.

Because of the important role that ANP and BNP play in heart failure, there is some enthusiasm that exogenous infusions of ANP or BNP may be of clinical benefit in heart failure. Experimental studies have demonstrated increased urine flow and favorable hemodynamic profiles, but there appears to be a down-regulation of NPR-A and thus the benefit of ANP infusion is blunted. Concomitant administration of a phosphodiesterase inhibitor restores ANP effect suggesting that part of the blunted response may be related to cGMP degradation. In humans with heart failure, infusion of ANP, 0.1 μg/kg/min, was associated with a drop in pulmonary capillary wedge pressure, increase in cardiac index and a drop in peripheral vascular resistance. BNP may be more beneficial. Infusions of 0.1 μg/kg/min also reduced PCWP and peripheral vascular resistance. The use of BNP has been associated with a significant reduction in isovolumic relaxation time suggesting an additional ability to improve diastolic function. Additionally, plasma aldosterone is decreased by BNP. However, renal resistance to BNP has been demonstrated. A synthetic BNP has been developed, Natrecor™, and is under active investigation[35].

A novel approach to exploit the potential benefit of ANP and BNP while avoiding the blunted effects seen has been to use inhibitors of neutral endopeptidase thus inhibiting the breakdown of ANP and BNP. Neutral endopeptidase is also active against angiotensin I & II, and bradykinin. Candoxatrilat is a prototype neutral endopeptidase inhibitor that has been associated with increased sodium excretion in heart failure[36].

The use of either exogenous ANP or BNP and/or the development of neutral endopeptidase inhibitors may serve as useful alternatives to diuretics and pure vasodilators in the management of heart failure in the 21st century.

Endothelin is a potent vasoconstrictor, perhaps the most potent vasoconstrictor yet identified. It induces extremely long-lasting vasoconstriction[37]. Additionally it has potent effects on myocardial cell growth and expression of a fetal phyenotype. It also affects synthesis of the extracellular matrix. Thus it may be an important mediator of ventricular remodeling. It is synthesized in the vasculature and myocardium (thus it has both autocrine and paracrine functions) and exerts its actions via endothelin-A and endothelin-B receptors. Endothelin-A receptors stimulate vasoconstriction and endothelin-B receptors stimulate vasodilation. The vasoconstrictor effects predominate in man.

(In heart transplant recipients with transplant coronary disease, endothelin-B receptors appear to mediate vasoconstriction and contribute to the pathology of chronic rejection.)

The role of endothelin in heart failure may be considerable. Plasma levels of endothelin and big endothelin-1 (a precursor of endothelin) are increased in heart failure and parallel the severity of the disease. The plasma levels are most closely correlated with pulmonary artery pressures and this is in keeping with the pulmonary vasculature being the major site of endothelin production[38]. The use of an endothelin antagonist, either a receptor blocker or an endothelin converting enzyme-inhibitor, may be particularly useful in the management of heart failure.

Bosentan is a non-selective endothelin receptor antagonist that blocks both ET-A & ET-B receptors[38]. In animal studies, Bosentan has exhibited increased survival in CHF models, inhibition of cardiac remodeling, and prevention of cardiac hypertrophy. In animal models it is synergistic with ACE-inhibitors. Limited human studies have demonstrated a reduction in left and right ventricular filling pressures, an increase in cardiac index and a drop in pulmonary vascular resistance, perhaps because of the correlation between endothelin levels and pulmonary hypertension. The effects are long lasting and tachyphylaxis does not seem to be a problem. A large multicenter trial has been put together to evaluate the mortality benefits of Bosentan, but ongoing concerns regarding drug toxicity have hampered the initiation of the study. Nevertheless, this is a very promising strategy that has potential benefit in the management of heart failure in the 21st century.

Having established that the heart in addition to its hemodynamic role is also an endocrine organ, the model can be pushed even further to state that the heart is an *immunological* organ and that chronic heart failure may be characterized by a chronic low-grade inflammation. This is supported by the observation that heart failure is associated with the presence of pro-inflammatory cytokines, especially TNF-α, that appear to play a role in the perpetuation of the heart failure syndrome. The effects of the inflammatory cytokines appear to be mediated by increased production of nitric oxide within the myocardium.

NO, nitric oxide, is an endogenous vasodilator previously felt to have been endothelium-derived relaxing factor (EDRF)[39]. It mediates vasodilation by activation of guanylyl cyclase with production of cGMP thus leading to smooth muscle relaxation. This is the same mechanism of vasodilation seen with NO donors such as nitroglycerin. NO is synthesized from the conversion of L-arginine to L-citrulline. There are several kinds of NO syntheses: neuronal NOS or nNOS; endothelial NOS or eNOS; and inducible NOS or iNOS. Endothelial NOS (eNOS) is the principle source of endogenously generated NO within the myocardium. It is involved in the regulation of smooth muscle tone, vascular permeability and contractile function. Inducible NOS (iNOS) is the principle target of inflammatory cytokines and significant amounts of NO can be expressed via iNOS. The actions of NO are mediated via the production of cGMP. This is a complex system that can promote the activity of adenyl cyclase with

low levels of NO by inhibiting phosphodiesterase activity (type 3PDE) leading to *increased levels of cAMP.* Or, it can reduce cAMP content by stimulating phosphodiesterase activity (type 2 PDE) with *high levels of NO* leading to the *breakdown of cAMP.* Sustained elevations of cAMP, as seen with exogenous catecholamine or phosphodiesterase inhibitor administration, diminish eNOS transcription which has the effect of decreasing parasympathetic nervous system control of calcium channels and thus leads to arrhythmogenesis[40].

Inducible NOS (iNOS) is stimulated by the proinflammatory cytokines: tumor necrosis factor, interferon gamma, interleukin-1 and interleukin-6. Both the inflammatory cytokines and NO have been shown to stimulate myocyte apoptosis, promote the expression of the fetal phenotype and promote the extracellular matrix by activation of metalloproteinases. Tumor necrosis factor (TNF) is elevated in severe heart failure and represents what was previously known as cachectin. It is associated with decreased contractility, pulmonary edema, left ventricular remodeling and the development of cardiomyopathy. It is produced by activated mononuclear cells in response to stress and may be an important component of the injury response (remodeling) in heart failure. It acts via TNF receptors, TNFR-1 and TNFR-2. These receptors are increased in heart failure, but along with the increase in TNFRs, there is the production of TNF-α binding proteins which act as a buffer to neutralize the negative inotropic effects of TNF-α[41].

Clinical manipulation of this complex system has just begun. The early enthusiasm generated by the use of vesnarinone in heart failure was fueled in part by the discovery that it inhibited the production of TNF-α. Unfortunately, it was associated with excess mortality in the definitive mortality trial, VEST [the Vesnarinone Survival Trial][42]. This is likely due to its effect on positive inotropy due to its partial phosphodiesterase inhibition. A more physiological approach may be through the use of TNF antagonists. Receptor-based antagonists have been developed that consist of soluble TNF receptors linked to the Fc portion of human IgG, TNFR:Fc. This protein binds to and inactivates TNF-α. The prototype is <u>etanercept or Enbrel</u>™. In clinical studies, TNFR:Fc infusion is associated with improvement in the ejection fraction and an increase in functional status as measured by six minute walks[41]. It is now available in a subcutaneous form and is undergoing active investigation as a new therapy for heart failure in the 21st century.

The PRAISE trial [Prospective Randomized Amlodipine Survival Evaluation Trial][43] demonstrated potential survival benefit with the use of <u>amlodipine</u> in addition to ACE-inhibitor therapy in chronic heart failure. In general, calcium antagonists are contraindicated in heart failure due to their negative inotropic properties and the attendant reflex tachycardia they generate. This benefit of amlodipine has been difficult to explain. In vitro data are now available that show that amlodipine reduces NO production. Additional data show that dihydropyridine calcium channel blockers inhibit NO production by inhibiting iNOS. This may represent yet another potential treatment strategy for heart failure in the 21st century.

The newest theory is that oxidative stress is increased in congestive heart failure. Markers of lipid peroxidation are high in patients with heart failure due to ischemic heart disease or dilated cardiomyopathies. This would imply a decrease in antioxidant systems in heart failure or an increase in reactive oxygen species (ROS). ROS can be stimulated by inflammatory cytokines and like cytokines, ROS can exert negative inotropic effects on the ventricle. ROS also promotes ventricular remodeling by stimulating myocyte apoptosis and by causing expression of the fetal phenotype in myocardial cells. These observations would suggest that anti-oxidant therapy might be beneficial in heart failure management. No convincing data are available but it is extremely curious that carvedilol possesses marked anti-oxidant properties and has been associated with dramatic improvements in left ventricular function and survival. Metoprolol may also reduce oxidative stress and ACE-inhibitors have been shown to scavenge free radicals[44].

V. SUMMARY

Indeed the paradigm of heart failure has clearly shifted from a simpler biomechanical and hemodynamic definition of the pathology of heart failure to a biological model. Figure 2 summarizes the known neurohormonal systems that are active in heart failure and their potential antagonists or agonists that would be beneficial in heart failure management.

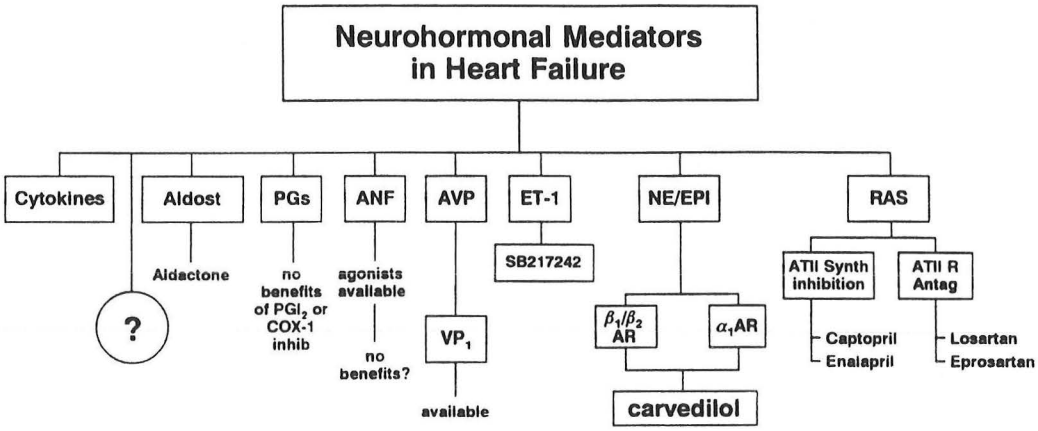

Figure 2

As the neurohormonal and growth hypotheses are investigated further, even newer modalities of therapy will be realized. Current treatments only improve outcomes to a modest extent while the newest drugs, especially beta-blockers, appear to greatly improve outcomes in heart failure. See Figures 3 and 4.

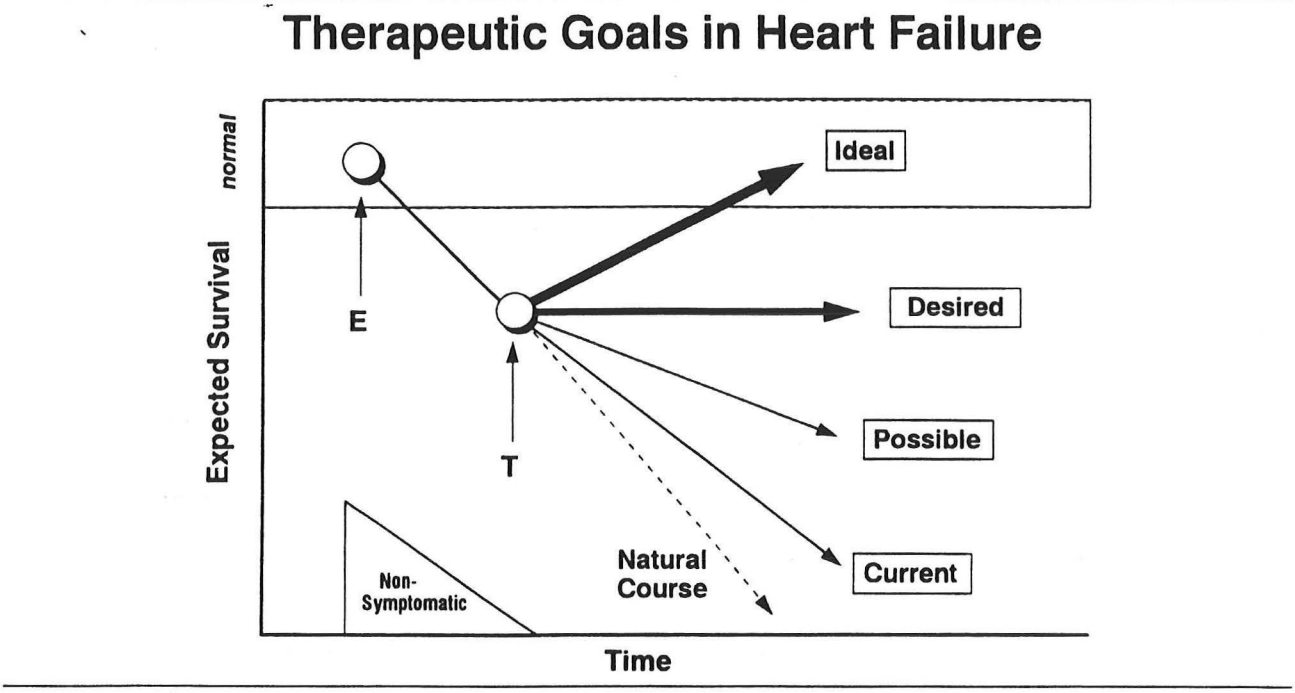

Figure 3

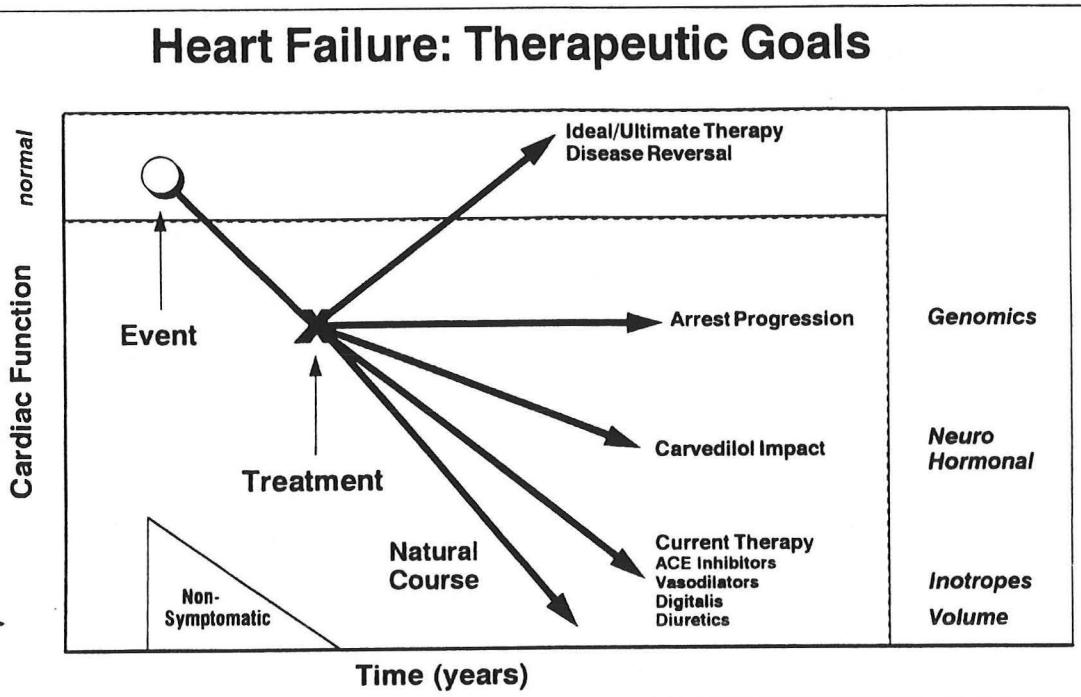

Figure 4

To achieve the desired improvements in management including the ultimate goal of complete reversal of the disease process, discoveries in genomic medicine will undoubtedly be required. Despite the burgeoning enthusiasm for newer therapy, there is concern that only epiphenomena are being identified as opposed to the true pathobiology of heart failure. Thus these new strategies will only be evolutionary. No dramatic improvements in heart failure management will occur until we truly understand the basic mechanisms of congestive heart failure.

An even greater challenge in heart failure management will be the ensuing public health crisis of managing an ever-increasing number of elderly patients with heart failure. How many different medicines, devices or operations, at what costs, can be given to heart failure patients? Who will care for those patients and how will they be reimbursed?

These are the challenges that are anticipated in the management of heart failure in the 21st century.

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