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Rationale for the Use of ß-Adrenergic Blockers in Patients with Systolic Heart Failure

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Our concepts of chronic heart failure have changed dramatically in the last 30 years. We have gone from viewing heart failure as an edematous state,to a view of heart failure in terms of a mechanical or hemodynamic paradigm, to a view of heart failure as a neurohormonal illness.[1]

When heart failure was viewed purely as a fluid-retaining state,we treated it with diuretics. However, while diuretics made patients feel better, they did not change the natural history of the syndrome. Subsequently,we viewed heart failure as a consequence of inadequate circulation to the systemic tissues. Therapy with inotropes and vasodilators was directed at improving pump performance. On the whole, these agents were disappointing because they produced a pharmacologic response of short-term hemodynamic improvement but ignored the basic biology of why heart failure progresses.[2] Inotropic agents improved symptoms but accelerated mortality.[3] With the exception of angiotensin-converting enzyme (ACE) inhibitors,many vasodilators improved symptoms but had little or no effect on survival.[4,5]

These therapies produced little improvement in the prognoses of heart failure patients because the underlying cellular mechanisms that contribute to progressively worsening cardiac function were not appreciated. We now know that left ventricular dysfunction activates compensatory neurohormonal responses involving the renin-angiotensin system, the adrenergic nervous system, vasopressin,inflammatory cytokines, and endothelins.

It should be noted that most of the agents that have been lumped into the broad category of neurohormones are not of neuronal origin, nor are they hormones in the conventional sense. Most are locally synthesized and locally acting autocrine/paracrine peptides for which the term *neurohormone* is inappropriate. Nevertheless, this designation is now in common usage and will be employed here.

These agents have short-term hemodynamic effects such as vasoconstriction, positive inotropic and chronotropic actions, and salt and water retention. They also have long-term, deleterious biological effects on myocardial growth and remodeling. These chronic deleterious effects lead to pathologic left ventricular remodeling and dilatation that, in turn, result in more left ventricular dysfunction, thereby establishing a vicious downward spiral. The way to treat heart failure is not to stimulate the dysfunctional pump but rather to remove the stimuli for progressive pump dysfunction – the offending neurohormones.

In the late 1980s and early 1990s, evidence began to emerge that neurohormonal antagonist therapy might have a beneficial effect on the natural history of left ventricular dysfunction or myocardial failure despite producing initial hemodynamic effects that were unimpressive or even adverse.[6] ACE inhibitors and ß-adrenergic blocking agents have changed our thinking about the potential of medical treatment of heart failure. Data generated from both clinical trials and model systems indicate that both types of therapy can slow or even reverse the progression of pump dysfunction and pathologic remodeling that characterizes the natural history of heart failure.

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It is important to emphasize that the benefit of these treatments is not their immediate pharmacologic effect on the cardiovascular system but their favorable influence on the biology of the failing heart.[2] It appears that these desirable effects on the natural history of heart failure are due to blockade of the deleterious growth and energetic effects of angiotensin II, norepinephrine, and cytokines. Heart failure should be viewed not as a purely hemodynamic illness but as an illness of abnormal cardiac growth and remodeling. In addition, the biologic improvements produced by ACE inhibition and ß-adrenergic blockade in patients with myocardial failure means that the heart-failure syndrome need no longer be viewed as an inexorably progressive process.[2]

Short-term compensatory mechanisms

Myocardial failure begins with an insult to pump function, such as a myocardial infarction, inflammation, severe hemodynamic overload from hypertensive or valvular disease, genetics, or idiopathic myocardial dysfunction. In response to as yet undefined signals that probably include arterial underfilling, tissue hypoperfusion, myocardial stretch, and central venous congestion, compensatory mechanisms are activated to support the failing heart.[7,8]

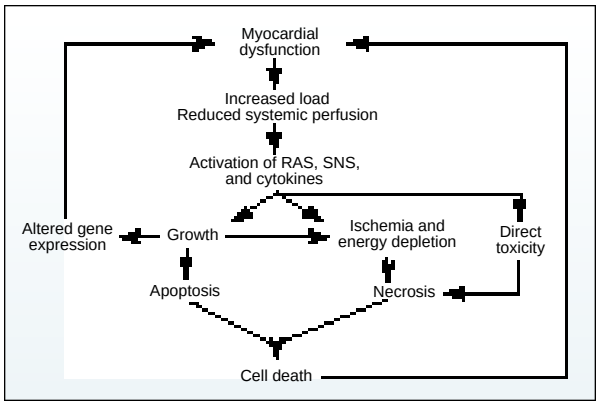
There are four physiologic elements that the heart can adjust to stabilize or to increase myocardial performance: pumping rate, contractility, preload volume, and contractile elements.[2,9] These four adjustments are largely accomplished by an increase in activity of a number of interrelated neurohormonal/autocrine-paracrine systems, the most prominent being the adrenergic and renin-angiotensin systems.[7,8] Activation of these systems has direct effects on the heart and vasculature and also indirect effects mediated by control of renal function and blood volume[10–12] that serve to stabilize central blood pressure; it also redistributes cardiac output to the brain and the heart, which have largely autoregulatory control of flow.

Although redistribution of fluid to these vital organs has obvious short-term advantages, the increase in peripheral resistance and left ventricular wall stress actually decreases myocardial performance, particularly in the presence of any degree of pump dysfunction. For this reason, as the adrenergic and renin-angiotensin systems are activated, there is coactivation of several counterregulatory elements, such as atrial natriuretic peptides[13] and vasodilator prostaglandins, that serve to minimize the effect of ß-adrenergic and angiotensin-II–mediated vasoconstriction.

Pathologic remodeling of the left ventricle

Despite the short-term hemodynamic benefits of activating the adrenergic nervous system and the renin-angiotensin system (RAS), the long-term effects of these regulatory systems on ventricular function and remodeling are deleterious (figure 1). Growth alterations within the myocyte (i.e., change in phenotype of contractile proteins) and in the interstitium (i.e., fibrosis), coupled with progressive cell death (i.e., apoptosis, necrosis) result in deterioration of left ventricular function.[2]

Figure 1: Relationship of neurohormonal activation and production of cardiac myocyte loss due to apoptosis/necrosis and altered gene expression. Cell loss and altered gene expression result in more myocardial dysfunction,and a downward spiral is established (from reference 2).



Eichhorn and Bristow. *Circulation* 1996;94:2285-2296

Angiotensin II and norepinephrine as growth promoters

Both angiotensin II and norepinephrine, as well as inflammatory cytokines and other peptide growth factors, can elicit a growth response in the heart.[2] Increased cardiac loading from heart failure results in myocardial stretch, which elicits local intramyocardial synthesis and release of several growth factors (e.g., angiotensin II[14] and tumor necrosis factor alpha[15]) at the tissue level. These factors act in a paracrine/autocrine fashion to promote growth in the heart.[14,16–23] Moreover, in the interstitium, angiotensin II promotes fibroblast proliferation and interstitial collagen formation.[19,20] Angiotensin II, acting locally within the heart and in the peripheral vasculature, also facilitates norepinephrine release by sympathetic nerves.[10,24–26] In response to norepinephrine release, both α- and ß-adrenergic receptors are activated to mediate both the positively inotropic and lusitropic effects of catecholamines on heart function and the myocardial growth-promoting effects of this catecholamine.[27,28]

Other so-called neurohormones might also be responsible for a growth response in the heart. These neurohormones include cytokines usually associated with the immune system[13,15,29] (such as tumor necrosis factor alpha [TNFα] and, perhaps,cardiotropin), endothelins,[13,30] and insulin-like growth factor-1 (IGF-1).[31] For example, TNFα, which can be elicited by myocyte stretch, has been shown[15] at physiologic concentrations in feline cardiac myocytes to increase protein synthesis, especially synthesis of the sarcomeric contractile proteins actin and myosin heavy chain.

Alterations in ventricular wall stress in the remodeling ventricle, combined with the specific effects on the myocardium of increased levels of catecholamines and the cytokines noted above, result in either abnormal cardiac myocyte growth or programmed cell death (apoptosis). The growth pattern of the failing myocyte is one of elongation due to contractile units being laid down in series.[32] This produces alterations in chamber geometry that increase its radius and mass with only a mild increase in its thickness. Stimulation of

cardiac non-myocyte cells, especially fibroblasts, results in the production of additional extracellular matrix to maintain structural integrity of the ventricular wall.[19,20] However, the presence of increased interstitial collagen might account for reduced capillary density and increased oxygen diffusion distance, which might contribute to metabolic stress or even overt ischemia.[33,34] All these effects contribute to a change in left ventricular geometry from a prolate ellipse to a larger, more spherical shape, resulting in an increase in meridional wall stress, abnormal distribution of fiber shortening, functional mitral regurgitation, worsened exercise tolerance, and poorer long-term survival.[2,35,36]

Neurohormonal activation and the myocyte

Neurohormonal activation has several deleterious effects on the heart, as outlined in table 1.

Downregulation of ß-receptors

In chronic heart failure, the number of ß-receptors and, in particular, the $ß_1$ subtype, is decreased (i.e., downregulated).[27] The amount of downregulation is proportional to coronary sinus norepinephrine blood levels, which are surrogate markers of adrenergic activity on the heart.[37] While the number of $ß_2$ subtype receptors is relatively preserved, these receptors are uncoupled from adenylate cyclase.[27] Thus, there is less cyclic AMP formation due to sympathetic stimulation in response to stress or exercise, resulting in an inadequate cardiac response when metabolic need is high.

Alteration in myocardial phenotype

While the process of hypertrophy increases the number of functioning contractile elements, alterations in gene expression involving calcium handling by the sarcoplasmic reticulum and changes in contractile proteins or their regulatory elements can produce an inefficient contractile element.[39–43] Some or all of these changes ultimately lead to progressive left ventricular dysfunction, best understood as a continued decline in systolic function.

Systolic dysfunction of individual cardiac myocytes is by definition due to a change in gene expression. Because humans do not exhibit major changes in gene expression during development,they do not exhibit the dramatic fetal program activation that characterizes hypertrophy or failure in experimental rodent models of human heart disease.[42] Nevertheless, there is upregulation of some fetal genes in human hearts (including that for atrial natriuretic peptide) and down-regulation of other genes, such as those for SR-calcium ATPase and a myosin heavy chain.[2,40–43]

Taken together, these adjustments can decrease systolic performance and compromise myocardial reserve in times of stress,such as during exercise.[2,6,44–47] Moreover, drugs typically used in heart failure, such as positive inotropic agents that act on the cyclic-AMP contractility-stimulating pathway, appear to cause depressed contractile function after they are withdrawn.[48] This effect might also be due to changes in gene expression, which contribute to a slowing of myocyte contraction and to disordered calcium handling.

Acceleration of cell death

In the adult myocyte, exposure to tropic agents such as angiotensin II, norepinephrine, endothelins, and inflammatory cytokines (e.g., TNFα, interleukin-6) not only stimulates altered growth patterns but also can accelerate cell death by two distinct processes: cell necrosis and apoptosis (table 2).[9,49]

Cell necrosis is an inflammatory process that is hypothesized to occur through either of two mechanisms: chamber remodeling and exposure to toxins.

Chamber remodeling leads to a larger, more spherical ventricle with elevated wall stress and left ventricular end-diastolic pressure. At the same time, the reduction in systolic performance leads to reduced stroke volume and aortic diastolic (and, thus, coronary perfusion) pressure. The reduction in coronary perfusion pressure and the elevation in left ventricular end-diastolic pressure results in a reduced epicardial-endocardial pressure gradient, leading to reduced endocardial blood flow. In addition, as noted above, interstitial remodeling can lead to increased interstitial collagen, reduced capillary density, and increased oxygen diffusion distance—factors that might contribute to metabolic stress or even overt ischemia within the remodeled ventricle.[33,34] Thus, overt ischemia can occur, resulting in myocyte cell necrosis.

Cell necrosis might also occur as a direct result of exposure to elevated levels of angiotensin II[44], norepinephrine[45], or other toxins.

In contrast to ischemia-induced myocyte necrosis, apoptosis is a non-inflammatory process of programmed cell self-

Table 1: Toxic effects of neurohormones on myocytes. Note that many "neurohormones" are neither of neuronal origin nor are they hormones in the conventional sense.

Toxic Effect	Responsible Neurohormone
ß-receptor down regulation	SNS
Altered chamber geometry	SNS, RAS, Cytokines
Energy Depletion	SNS, RAS, Cytokines
Direct depression LV function	Cytokines
Production of fetal phenotype	SNS, RAS, Cytokines
Reduced cell viability	SNS, RAS, Cytokines

SNS = sympathetic nervous system, RAS = renin-angiotensin system

Table 2: Modes of cell death in heart failure.

Necrosis	Apoptosis
• Result of acute cellular injury	• Results from withdrawal of cellular growth factors, activation of death receptors, or DNA damage
• Rapid cell swelling	• DNA degraded into fragments
• Lysis	• Loss of mitochondrial function
• Inflammatory response	• Membrane alterations signal phagocytes to digest the dying cell
	• No inflammatory response

destruction.[49] Apoptosis is a natural process used in fetal development to remodel the heart and great vessels. Within a cell type, control of cell number is determined by a balance between cell proliferation and cell death. Excessive cell proliferation can lead to malignancy, whereas excessive cell death can lead to organ dysfunction or death. Programmed cell death is characterized in part by condensation of cytoplasm,segmentation of the nucleus, and extensive degradation of chromosomal DNA (caused by activation of endogenous endonucleases) into oligomers of about 180 bp.[49]

Apoptosis within any cell can be initiated by a number of agents or pathways with relevance to the heart such as inflammatory cytokines, free radicals, excessive or absent growth-promoting signals, or oxygen free radicals, among others. Apoptosis has been reported[50] in heart-failure models in animals and recently was reported in human heart failure.[51] The extent to which accelerated apoptotic cell death contributes to myocardial remodeling,loss of functional contractile units, and heart failure is an area of active investigation.

Affecting remodeling with neurohormonal antagonists

The remodeling and myopathic processes can be affected in two ways: They can be attenuated by inhibiting the renin-angiotensin system, or they can be reversed or attenuated by ß-adrenergic blockade.

Inhibiting the renin-angiotensin system

Studies in animals have demonstrated that angiotensin is produced in the heart and is released in a paracrine/autocrine fashion in response to myocyte stretch.[14,17] ACE inhibitors retard the growth process induced by angiotensin II. The use of these agents produces regression of hypertrophy in the pressure-overload animal model[53] and can interfere with normal postnatal growth of the left ventricle.[54] ACE inhibitors can also slow the progressive remodeling process in rats after myocardial infarction, leading to prolonged survival.[55,56]

Recent work in a dog model of heart failure (induced by continuous, rapid ventricular pacing) has shown that an ACE inhibitor can affect three characteristics of ventricular remodeling in this animal model: It can attenuate the myocyte lengthening, reduce the velocity of shortening, and reduce the left ventricular ejection fraction.[57] This study highlights the close relationship between myocyte function, chamber function, and chamber architecture, and it emphasizes the benefit of an ACE inhibitor on all these elements. Other studies in canine heart failure models have demonstrated a slowing or reversal of the remodeling process with ACE-inhibitor therapy.[58,59] Thus, angiotensin II appears to play a critical role in the development of left ventricular hypertrophy, myocyte dysfunction, and chamber architecture. ACE inhibitors are able to reverse or to prevent the development of these changes in several animal models.

It is clear that, in humans, ACE inhibitors reduce mortality and retard the progression of the heart failure clinical syndrome in cases of chronic heart failure (table 3).[60,61] In addition, ACE inhibitor therapy prevents or retards the progressive remodeling process that occurs after myocardial infarction.[62,63,64]

Table 3: Effect of ACE inhibitors on survival in patients with left ventricular dysfunction.

	Mortality		
Trial	**ACEI**	**Controls**	**RR (95% CI)**
Chronic CHF			
Consensus I	50/127 (39%)	68/126 (54%)	0.56 (0.34-0.91)
SOLVD (Treatment)	452/1285 (35%)	510/1284 (40%)	0.82 (0.70-0.97)
SOLVD (Prevention)	313/2111 (15%)	334/2117(16%)	0.92 (0.79-1.08)
Post MI			
SAVE	228/1115 (20%)	275/1116 (25%)	0.81 (0.68-0.97)
AIRE	170/1004 (17%)	222/982 (23%)	0.73 (0.60-0.89)
TRACE	304/876 (35%)	369/873 (42%)	0.78 (0.67-0.91)
SMILE	38/772 (5%)	51/784 (6.5%)	0.75 (0.40-1.11)
Totals	1555/7290 (21%)	1829/7282 (25%)	

However, while ACE inhibitors retard the remodeling process, there is little evidence from clinical investigations that ACE-inhibitor therapy can lead to an actual reversal of this process or to improved intrinsic myocyte function. Although ACE inhibitors diminish the effects of the renin-angiotensin system on the myocyte, and despite the fact that ACE inhibitors initially reduce adrenergic activity,[26,65] plasma norepinephrine levels nevertheless increase over time.[65] These data suggest that progressive sympathetic nervous system activation occurs even in the presence of ACE inhibitors, and they enforce the need for a concomitant, adjunctive anti-adrenergic strategy to block the long-term sequelae of increased sympathetic nervous system activity.[66]

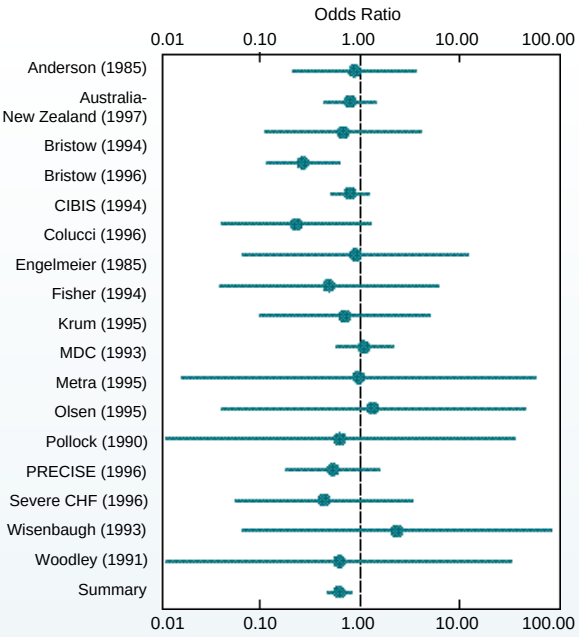
ß-adrenergic blockade

It is now clear from experimental animal and more recent human studies that ß-adrenergic blockade results in improvement of myocyte and chamber function in heart failure.[58,59,67,68] In a canine model of chronic mitral regurgitation, for example, atenolol resulted in restoration of ventricular (chamber) and myocyte contractile function due in large part to a biological improvement within the myocyte itself.[68]

My colleagues and I have examined the effect of ß-blockade in humans, most of whom had dilated cardiomyopathy.[69,70] ß-blockade resulted in improvement in ejection fraction and a reduction in ventricular volumes after 3 months of therapy. Using relatively load-independent measures of performance (such as the peak +dP/dt-end–diastolic volume relation) we demonstrated that the increase in ejection fraction was not attributable to an alteration in loading conditions, but that it was due to an improvement in left ventricular performance. These results demonstrate that mechanical work increased with ß-blockade, while the cost of performing that work, as measured by myocardial oxygen consumption, was not increased. This means that overall myocardial mechanical efficiency was increased.

To date, more than 15 placebo-controlled studies involving more than 2,000 patients with chronic heart failure from systolic dysfunction have examined the effect of ß-adrenergic

Figure 2: Controlled trials of ß-blockade.



Odds ratios (ORs) and 95% confidence intervals (CIs) for effect of beta-blockade on total mortality for 17 studies included in a meta-analysis.The summary OR is 0.69 (95% CI 0.54 to 0.88).CIBIS = Cardiac Insuffiency Bisoprolol Study; MDC = Metoprolol in Dilated Cardiomyopathy trial; PRECISE = Prospective Randomized Evaluation of Carvedilol in Symptoms and Exercise. (Adapted from Heidenreich PA, et al. *J Am Coll Cardiol.*1997;30:27-34

blockade on ventricular function,[38,71,72] some results of which are summarized in figure 2. In every study of more than one month duration, left ventricular ejection fraction has been consistently shown to increase with ß-blocker therapy.[38,71,72] No study of more than one month duration has produced negative results.

Our group recently demonstrated that, as expected in patients with heart failure due to systolic dysfunction, ß-blocking agents were found to depress ventricular function on the first day of therapy.[73] Although ejection fraction after one month of therapy was no better than at baseline, it increased significantly between one and three months of therapy. There appears to be continued improvement in left ventricular function between three and six months.[69] Despite this consistent improvement, however,[38,69–72] left ventricular architecture does not change until much later. For example, in a longer-term follow-up study by our group, continuous use of ß-blocking agents for 12–18 months started to reduce left ventricular mass and to remodel the heart into a more normal elliptical shape.[73]

This study highlights the underlying concept that ß-blockers improve ventricular function by a delayed biological effect on the myocyte.[2] The early reduction in ejection fraction is a pharmacologic effect of adrenergic withdrawal induced by the application of ß-blockade. It is for this reason that ß-blocking agents must be started at very low doses and slowly titrated upwards over many weeks.[74] In addition, not all ß-blockers are well tolerated, and early first-generation non-selective agents such as timolol and propranolol have high rates of intolerance.[6,74] Second-generation agents ($ß_1$ selective agents without ancillary properties) and third-generation agents (agents with ancillary properties such as vasodilation) are better tolerated.[74]

Table 4: Ongoing ß-blocker trials.

Trial	Pts	Drug(s)	NYHA	EF	Mean FU
BEST	2800	Bucindolol	III-IV	≤35%	36 mos
CIBIS II	2600	Bisoprolol	III-IV	≤35%	39 mos
MERIT-HF	3200	Metoprolol	II-IV	≤40%	24 mos
COPERNICUS	2000	Carvedilol	IIIb-IV	≤25%	36 mos
COMET	3000	Carv/Metop	II-IV	≤35%	36 mos
Total	13,600				

Clinical implications

Heart failure is a progressive syndrome of worsening ventricular function and symptoms that leads to death from pump failure and/or arrhythmias in the majority of cases. This downhill spiral is primarily due to worsening ventricular function caused by a combination of cell loss (necrosis and/or apoptosis), myocyte dysfunction due to altered gene expression and impaired energetics, and pathologic remodeling of the chamber.[2] The clinical objective for many years was to improve ejection fraction by pharmacologic manipulation of load or inotropic state. However,this strategy ignored the deleterious effects some of the agents had on the biology of the myocyte, and it sacrificed long-term benefits for short-term relief of symptoms—in fact, use of these agents resulted in little or no long-term increase in ejection fraction, which is a weak surrogate marker for left ventricular remodeling. In contrast, the use of neurohormonal antagonists (ACE inhibitors and ß-blockers) sacrifices short-term hemodynamic and symptomatic relief for long-term benefit. Thus therapy with these agents represents the antithesis of our previous concepts of chronic heart failure therapy.

Use of ACE inhibitors in patients with left ventricular dysfunction has produced a modest reduction in mortality.[60–62] The addition of ß-adrenergic blockade on top of ACE inhibition might result in a further reduction in mortality of 20–65%, although this has yet to be definitively proven.[71,75,76] The CIBIS trial demonstrated a 20% reduction in all-cause mortality with bisoprolol, but this trial did not yield statistically significant results due to its small size.[75] The US carvedilol program suggested a 65% reduction in mortality with carvedilol, but this program was limited by study design (as it was not a mortality study), the small number of morbid events, and the short follow-up of a selected group of patients.[76]

Data from additional ongoing clinical trials (table 4) should provide definitive information regarding whether ß-adrenergic blockade lowers mortality in chronic heart failure. The large amount of data presently available suggests that the mortality reduction seen with these drugs is related to improvement in myocardial biologic function.[77,78] Because of the additional therapeutic potential of biologic modification of the failing heart by ß-blocking agents, the National Institutes of Health and the Veterans Administration are jointly sponsoring a large mortality trial with bucindolol (the BEST trial).[79] Besides BEST, three other placebo-controlled

trials of ß-blockade are under way: the CIBIS II trial using bisoprolol, MERIT-HF using metoprolol, and COPERNICUS using carvedilol. These trials should help provide the definitive answer to the mortality question and will also help us understand which patients are most likely to benefit from such therapy.

One other trial, COMET, is a head-to-head study comparing metoprolol (a second-generation selective agent) with carvedilol (a third-generation, non-selective agent). As non-selective agents reduce adrenergic activity to the heart more than selective agents, differences might also exist with regard to their effects on sudden death and over-all mortality.[74] Thus COMET will help determine if such differences indeed do exist or whether beneficial effects on mortality are a class effect of all ß-adrenergic blockers.

Our ability to alter the biology of the failing heart through ß-blocker therapy strongly suggests that the future treatment of heart failure will involve identifying the adverse biological processes that result in pump failure, with the subsequent development of treatments that neutralize or normalize those adverse processes.

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Editor's note: The Brigham and Women's Hospital and Duke University are in the advanced planning phase for a large international trial to determine whether the use of an angiotensin receptor blocker would be as effective as the use of an ACE inhibitor in patients with a myocardial infarction with either symptoms of failure or a depressed ejection fraction. The trial will also evaluate whether the combination of these two inhibitors of the renin-angiotensin-system would lead to a survival benefit compared to ACE inhibitor alone. We seek the collaboration of experienced coronary care physicians with a commitment to investigative studies. If you are interested in receiving further information about this study, please contact Dr. Marc Pfeffer at: Brigham and Women's Hospital, Cardiovascular Division, 75 Francis Street, Boston, MA 02115; fax number: (617) 732-5291; or via e-mail: mapfeffer@bics.bwh.harvard.edu