Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling

Jay N. Cohn, Roberto Ferrari, Norman Sharpe, and on Behalf of an International Forum on Cardiac Remodeling

J. Am. Coll. Cardiol. 2000;35;569-582

This information is current as of February 13, 2010

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://content.onlinejacc.org/cgi/content/full/35/3/569

JACC

JOURNAL *of the* AMERICAN COLLEGE *of* CARDIOLOGY

Cardiac Remodeling—Concepts and Clinical Implications: A Consensus Paper From an International Forum on Cardiac Remodeling

Jay N. Cohn, MD,* Roberto Ferrari, MD,† Norman Sharpe, MD,‡ on Behalf of an International Forum on Cardiac Remodeling

Minneapolis, Minnesota; Ferrara, Italy; and Auckland, New Zealand

Cardiac remodeling is generally accepted as a determinant of the clinical course of heart failure (HF). Defined as genome expression resulting in molecular, cellular and interstitial changes and manifested clinically as changes in size, shape and function of the heart resulting from cardiac load or injury, cardiac remodeling is influenced by hemodynamic load, neurohormonal activation and other factors still under investigation.

Although patients with major remodeling demonstrate progressive worsening of cardiac function, slowing or reversing remodeling has only recently become a goal of HF therapy. Mechanisms other than remodeling can also influence the course of heart disease, and disease progression may occur in other ways in the absence of cardiac remodeling.

Left ventricular end-diastolic and end-systolic volume and ejection fraction data provide support for the beneficial effects of therapeutic agents such as angiotensin-converting enzyme (ACE) inhibitors and beta-adrenergic blocking agents on the remodeling process. These agents also provide benefits in terms of morbidity and mortality. Although measurement of ejection fraction can reliably guide initiation of treatment in HF, opinions differ regarding the value of ejection fraction data in guiding ongoing therapy. The role of echocardiography or radionuclide imaging in the management and monitoring of HF is as yet unclear.

To fully appreciate the potential benefits of HF therapies, clinicians should understand the relationship between remodeling and HF progression. Their patients may then, in turn, acquire an improved understanding of their disease and the treatments they are given. (J Am Coll Cardiol 2000;35:569–82) © 2000 by the American College of Cardiology

Heart failure (HF) can no longer be considered a simple contractile disorder or a disease of the heart alone. Clinical manifestations are, in fact, the result of changes to the heart's cellular and molecular components and to mediators that drive homeostatic control. There is general acceptance that as heart disease progresses into HF, heart size increases, cardiac function deteriorates and symptoms of HF become evident. Although different terms have been used to describe it, cardiac remodeling encompasses many changes associated with progressive HF.

Therapeutic interventions aimed solely at correcting a low cardiac output or reduced blood flow—those offering symptomatic relief or improved cardiac emptying—do not necessarily slow HF progression or reduce mortality (1–3). Antineuroendocrine treatment with angiotensin-converting enzyme (ACE) inhibition, beta-adrenergic blocking agents and antialdosterone therapy are associated with significant reductions in morbidity and mortality in HF (4–12). Both ACE inhibition and beta-blockade are also known to slow, and in some cases even reverse, certain parameters of cardiac remodeling in HF patients (8,13–16). Cardiac remodeling is now recognized as an important aspect of cardiovascular disease progression and is, therefore, emerging as a therapeutic target in HF of all etiologies.

In April 1998, we held a meeting in Atlanta, Georgia, with the specific aim of examining the interrelationship between HF progression and cardiac remodeling. The *International Forum on Cardiac Remodeling* drew together interested physicians to discuss the basic mechanisms of cardiac remodeling, the potential link between cardiac remodeling and HF progression and the influence of therapeutic interventions on the remodeling process. This paper provides the consensus views on key concepts and definitions, supporting data and issues about cardiac remodeling which emerged from that meeting.

```
Abbreviations and Acronyms
ACE       = angiotensin-converting enzyme
AIRE      = Acute Infarction Ramipril Evaluation
            Study
ANP       = atrial natriuretic peptide
ANZ       = Australia/New Zealand Collaborative
            Group
CIBIS II  = Cardiac Insufficiency Bisoprolol Study
ECG       = electrocardiogram
HF        = heart failure
LV        = left ventricular
MDC       = Metropol Dilated Cardiomyopathy trial
MERIT-HF  = Metoprolol CR/XL Randomized
            Intervention Trial in Heart Failure
MI        = myocardial infarction
MRI       = magnetic resonance imaging
NO        = nitric oxide
RAS       = renin angiotensin system
SAVE      = Survival and Ventricular Enlargement
            Study
SNS       = sympathetic nervous system
SOLVD     = Studies of Left Ventricular
            Dysfunction
TBARS     = thiobarbituric acid reactive substances
TNF       = tumor necrosis factor
TRACE     = Trandolapril Cardiac Evaluation
            Study
V-HeFT I and
   V-HeFT II = Vasodilator Heart Failure Trials
```

Table 1. Processes Occurring in Ventricular Remodeling

Cardiomyocyte lengthening (21,24)
Ventricular wall thins (21,24,25)
Infarct expansion rather than extension occurs (20,21)
Inflammation and reabsorption of necrotic tissue (21)
Scar formation
Continued expansion of infarct zone (20)
Dilation and reshaping of the left ventricle (21,25–27)
Myocyte hypertrophy (21,24,25,27)
Ongoing myocyte loss
Excessive accumulation of collagen in the cardiac interstitium (28)

CONCEPTS OF CARDIAC REMODELING

CONSENSUS STATEMENT ONE

Cardiac remodeling may be defined as genome expression, molecular, cellular and interstitial changes that are manifested clinically as changes in size, shape and function of the heart after cardiac injury. The process of cardiac remodeling is influenced by hemodynamic load, neurohormonal activation and other factors still under investigation. The myocyte is the major cardiac cell involved in the remodeling process. Other components involved include the interstitium, fibroblasts, collagen and coronary vasculature; relevant processes also include ischemia, cell necrosis and apoptosis.

When does remodeling occur? Cardiac remodeling can be described as a physiologic and pathologic condition that may occur after myocardial infarction (MI), pressure overload (aortic stenosis, hypertension), inflammatory heart muscle disease (myocarditis), idiopathic dilated cardiomyopathy or volume overload (valvular regurgitation). Although the etiologies of these diseases are different, they share several pathways in terms of molecular, biochemical and mechanical events. Physiologic remodeling—compensatory changes in the proportions and function of the heart—is seen in athletes, but will not be discussed further in this paper.

In postinfarct models, the process of left ventricular (LV) remodeling begins rapidly—usually within the first few hours after an infarct—and continues to progress (17–19). The time course of events is influenced, however, by the severity of the underlying disease, secondary events (such as recurrent MI), other factors (such as ischemia or neuroendocrine activation), genotype and treatment (20–23). Animal studies also show that infarct expansion, regional dilation and thinning of the infarct zone can occur within one day of an MI (21). Severe impairment of global ventricular function—a functional and clinical phenomenon that can be differentiated clearly from LV remodeling—can be observed within two days of an insult (24). The changes that occur after an insult are summarized in Table 1 (20,21,24–28).

Although an exact picture of all the pathways and cells involved in LV remodeling is still unclear, the following scenario has been proposed at a molecular level. As myocytes stretch, local norepinephrine activity and angiotensin and endothelin release are increased; many other factors that are thought to be stimulated are currently being studied. These changes, in turn, stimulate expression of altered proteins and myocyte hypertrophy. The end result of this sequence of events is further deterioration in cardiac performance and increased neurohormonal activation. In addition, increased activation of aldosterone and cytokines may also stimulate collagen synthesis, thus leading to fibrosis and remodeling of the extracellular matrix.

Functional changes associated with remodeling. The initial remodeling phase leading to reparation of the necrotic area and to scar formation may, to some extent, be considered beneficial. This cellular rearrangement of the ventricular wall is associated with maintained or improved cardiac output but with significantly increased LV volumes. The magnitude of remodeling changes observed relates roughly to infarct size. After one month, large infarcts provoke greater dilation and greater increases in systolic and diastolic stress than small infarcts (24). In progressive postinfarction dilation, the end-systolic volume index increases progressively and ejection fraction declines. These are important predictors of mortality (26,29).

Gross changes to the heart. As the heart remodels, its geometry changes; it becomes less elliptical and more

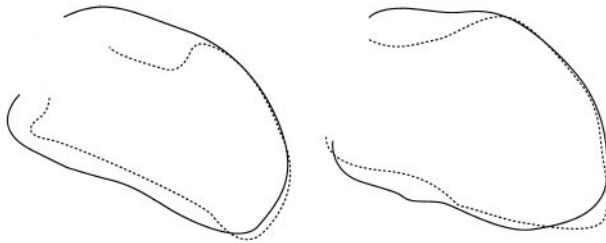| Parameter	3 weeks	1 year
End-diastolic volume	302ml	377ml
End-systolic volume	186ml	271ml
Circumference	59.5cm	62.8cm
Contractile segment	30.5cm	33.8cm
Non-contractile segment	23.7cm	23.5cm
Diastolic sphericity index	0.71	0.74
Systolic sphericity index	0.60	0.77

Figure 1. Late ventricular enlargement in a patients with anterior myocardial infarction. Marked increase in volume results from increased circumference and sphericity. The late change in circumference is due to lengthening of contractile tissue rather than further expansion of the infarcted, noncontractile segment. The increased sphericity results from a rounding out of the sharp abnormalities in contour at the margins of the infarct (reproduced with permission from reference 31).

Table 2. Pathophysiologic Changes in Response to an Ischemic Insult on the Myocardium

Immediate systolic and diastolic dysfunction
  Spontaneously reversible—the stunned myocardium
  Reversible upon restoration of flow—hibernating myocardium
  Irreversible (myocardial necrosis/apoptosis) (38)

Oxygen free radical formation
  Promotes myocardial ischemic damage, especially during reperfusion; also important in the pathology of HF (45)
  Causes oxidative stress which is closely linked to cytokines such as TNF, myocyte apoptosis and ventricular remodeling (46)

Increased neurohormonal activation
  Activation of the adrenergic nervous system early in HF results in an increased level of norepinephrine in the heart that initially provides support for the failing myocardium
  Continued activation of neurohormonal systems becomes deleterious to the heart leading to:
    Excessive vasoconstriction
    Volume expansion
    Continued deterioration of cardiac function
    Left ventricular remodeling
  Increased plasma levels of norepinephrine correlate with prognosis in HF (47)

HF = heart failure; TNF = tumor necrosis factor.

spherical (Fig. 1) (30,31). There are also changes in ventricular mass, composition and volume, all of which may adversely affect cardiac function (22,24–26,29,32,33) (for reviews see 28,34).

Cellular and molecular changes in remodeling. Remodeling encompasses cellular changes including myocyte hypertrophy, necrosis (35), apoptosis (36–38), fibrosis (39), increased fibrillar collagen (40) and fibroblast proliferation (41). Circulating or locally generated angiotensin II is also thought to play a role in altering gene expression, via activation of second messenger systems (42–44). Table 2 shows the pathophysiologic changes in response to an ischemic insult on the myocardium (38,45–47).

INFLUENCES ON CARDIAC REMODELING

Changes in hemodynamic load. Studies of global LV chamber volumes and muscle mass show that early LV dilation in patients with anterior wall MI may continue progressively and unabated; global compensatory (reactive) ventricular hypertrophy appears to be a delayed and limited adaptation during the first year (22). As a result of progressive ventricular dilation and insufficient development of reactive ventricular hypertrophy, global LV wall tension and stresses increase considerably during this period (reviewed by Rumberger [48]).

The importance of remodeling as a pathogenic mechanism is unclear, and the factors leading to remodeling may

be the major determinants of HF prognosis rather than ventricular dilation itself. If cardiac dilation persists without hypertrophy, myocardial wall stress is increased. A number of mechanisms may be stimulated by increased wall stress, and this may lead to further dilation of the heart. Without therapy to reduce ventricular dilation, decrease wall stress and promote a favorable neurohormonal pattern, this process progresses towards overt chronic HF (32).

Neurohormonal activation in HF. Neurohormonal activation in HF is known to mediate compensatory changes in response to falling cardiac output, but it is also a major component of disease progression and of the remodeling process (47,49–53).

Plasma norepinephrine levels, reflecting increased adrenergic activation, are elevated in HF patients (49,51) and relate to prognosis (47). Higher levels of circulating plasma norepinephrine correlate with a poorer long-term prognosis (47,50,54).

Increased plasma or tissue levels of other neurohormones also occur in patients with LV dysfunction and in asymptomatic patients post-MI without HF, with activation increasing further as overt HF ensues (50). Most recently, neurohormonal activation was shown to decrease progressively post-MI in patients with a good prognosis (54). Using measures of atrial natriuretic peptide (ANP), aldosterone, norepinephrine and plasma renin, asymptomatic patients who experienced an event within three months of MI had markedly elevated neurohormonal levels a mean of 10 days

after infarction (54). In contrast, post-MI patients who were without cardiovascular events during the 38-month mean follow-up of the study had lower neurohormonal levels that decreased further over time (54).

In cell culture, angiotensin II increases DNA synthesis in myocardial fibroblasts and increases protein synthesis in both fibroblasts and myocytes (43). It appears to be an important mediator of the cellular responses to stretch, with local production resulting in proliferation and growth (55). Angiotensin II also increases coronary artery permeability, allowing diffusion of growth factors into the myocardial interstitium (28). It is known to cause necrosis and fibrosis through its cytotoxic effect on cardiac myocytes (56). Increased aldosterone production as a result of increased angiotensin II has hemodynamic consequences and stimulates collagen synthesis by myocardial fibroblasts (57). Increased aldosterone levels may also play a role in myocyte death through their effect on electrolyte balance (58).

Additional factors that influence remodeling. The effects on remodeling of factors other than those related specifically to the renin angiotensin system (RAS) and the sympathetic nervous system (SNS) are currently under investigation and include endothelin, cytokines (tumor necrosis factors [TNF] and interleukins) and nitric oxide (NO) production and oxidative stress.

Endothelins are potent vasoconstrictor peptides, the levels of which are known to be elevated in HF (59). Endothelin blockade has been shown to be beneficial in animal models and patients with HF (60,61).

Cytokines are proteins secreted by cells in response to a variety of stimuli including environmental stress. Circulating levels of the cytokine TNF-alpha are known to be raised in cachectic patients with chronic HF. This elevation has been associated with the marked activation of the RAS seen in patients with end stage disease (51,62). Data from the Studies of Left Ventricular Dysfunction (SOLVD) indicated that proinflammatory cytokines increase in patients as their functional HF classification deteriorates (52). Data have also shown that stimulation with pathophysiologic concentrations of TNF-alpha provokes a time-dependent increase in LV remodeling in animal models of HF (63).

Oxidative stress is the term used to describe an imbalance between production of oxygen free radicals and antioxidant defenses (64), the importance of which is increasingly emerging with respect to LV dysfunction and HF progression (45,65–67; reviewed by Ferrari, et al. [46]). Cell viability depends on a complex interaction of inducers and suppressors of apoptosis, which are susceptible to modulation by cytokines such as TNF-alpha (68). Cytokines indirectly increase apoptosis through their effect on the death domain within the cytoplasmic portion of the TNF receptor-1. They also exert a direct cytotoxic effect leading to necrosis. Both apoptosis and necrosis cause further deterioration in the composition and function of the ventricle (46,68,69).

THE MAIN COMPONENTS OF CARDIAC REMODELING

Cardiac myocytes. Myocytes and other cardiac cell types are believed to be fundamentally involved in the remodeling process. Of all cardiovascular wall components, myocytes have received much attention in view of their contractile activity and numeric contribution to heart mass. As the result of an insult, myocyte numbers decrease and surviving myocytes become elongated or hypertrophied as part of an initial compensatory process to maintain stroke volume after the loss of contractile tissue. The thickness of the ventricular wall also increases (24). Altered loading conditions stretch cell membranes and may play a role in inducing the expression of hypertrophy-associated genes. In cardiac myocytes, this may lead to the synthesis of new contractile proteins and the assembly of new sarcomeres. It is thought that the pattern in which these are laid down determines whether the cardiac myocytes elongate or increase their diameter (70). Increased wall stress may precipitate energy imbalance and ischemia, which is one of the major determinants of myocardial oxygen demand. This is thought to lead to a vicious cycle of increased wall stress and wall thickness and further energy imbalance and ischemia (reviewed by Dhalla et al. [71]).

The role of fibroblast proliferation. Both fibroblasts and endothelial cells are activated in response to an ischemic insult. In human and animal models, fibroblast stimulation increases collagen synthesis and causes fibrosis of both the infarcted and noninfarcted regions of the ventricle, thus contributing to remodeling (72,73). The relative contribution of the interstitium to the remodeling process is, however, not clear.

The role of collagen degradation. The myocardium consists of myocytes tethered and supported by a connective tissue network composed largely of fibrillar collagen, which is synthesized and degraded by interstitial fibroblasts. Myocardial collagenase is thought to be an important proenzyme present in the inactive form in the ventricle (74,75). Its activation after myocardial injury contributes to an increase in chamber dimension in response to the distending pressure that is thought to be a possible cause of myocyte slippage, which some consider one contributor to chamber remodeling (24,27).

The role of apoptosis. A working hypothesis for the role of apoptosis in HF is that progressive LV dysfunction occurs, in part, as a result of ongoing myocyte cell death (36). The importance of this type of cell death in human cardiac remodeling is not yet firmly established, but it has been demonstrated to occur at an increased rate after injury due to ischemia, reperfusion and MI (38). Apoptosis may be an important regulatory mechanism involved in the adaptive response to pressure overload in which initial apoptosis is linked to cardiac hypertrophy (37). Other well-known triggers of apoptosis include cytokines (especially TNF-

alpha and the interleukins), oxidative stress and mitochondrial damage (46,76). Recent evidence suggests that myocytes may, in fact, reproduce within the mature heart and may do so at an increased rate in the injured heart (77). Clearly, if confirmed, such a process must be considered, as well as apoptosis, in the overall remodeling process.

CARDIAC REMODELING AND HEART FAILURE PROGRESSION

CONSENSUS STATEMENT TWO

Cardiac remodeling is generally an adverse sign and is linked to HF progression. Patients with major remodeling demonstrate progressive worsening of cardiac function, and it may underlie a sizeable proportion of cardiovascular morbidity and mortality. Mechanisms other than remodeling can, however, also influence the course of heart disease, and disease progression may occur in other ways in the absence of cardiac remodeling.

Adaptive versus maladaptive disease processes. Cardiac remodeling has been described as both an adaptive and a maladaptive process, with the adaptive component enabling the heart to maintain function in response to pressure or volume overloading in the acute phase of cardiac injury (78) (reviewed by Sabbah and Goldstein [79]). Increments in load, such as those seen in mitral insufficiency, modulate remodeling of the ventricle to maintain forward flow, but often after cardiac injury (such as MI), continued remodeling may not be necessary to maintain the integrity of the circulation. Under such circumstances, remodeling may be viewed as an adverse phenomenon that leads to progressive decompensation.

Progressive remodeling, irrespective of the criteria used to measure it, can always be considered deleterious and is associated with a poor prognosis (26,29). There are no data to indicate when the transition from possible adaptive to maladaptive remodeling occurs or how this might be identified in patients. The occurrence of such a transition and its time course may be expected to vary greatly. However, once established beyond a certain phase, it is likely that remodeling actually contributes to HF progression.

Measuring and monitoring cardiac remodeling. Current data do not allow an accurate determination of the proportion of cardiovascular mortality and morbidity directly attributable to cardiac remodeling. Understanding the extent of LV remodeling can, however, help to assess the prognosis of HF—the greater the extent of the remodeling, the poorer the prognosis. Relatively small increases in ventricular volume are associated with a major independent increase in the risk of death in patients with coronary artery disease, recent MI or HF (29,80,81). Measures to assess LV remodeling include heart size, shape and mass, ejection fraction, end-diastolic and end-systolic volumes and peak force of contraction (4). Each measure is indicative of a

different aspect of the disease state and none can currently be considered as definitive.

Heart size and shape. Although direct measurement of the size and shape of the heart might appear to be the most logical method of assessing the extent of remodeling, technical factors and differences of interpretation lead to variation in the results. For example, only 38% of hypertensive patients with anatomic LV hypertrophy on M-mode echocardiography showed LV hypertrophy when assessed using electrocardiography (ECG) (82). The ECG manifestation of LV hypertrophy appears to signify increased risk of cardiac failure, whether or not there is anatomical evidence of hypertrophy as assessed by echocardiography (83). Men, irrespective of age, have a higher risk of HF if LV hypertrophy is detected on both chest X-ray and ECG (83).

Measurement of myocardial hypertrophy, expressed as wall thickness indexes or myocardial mass, can provide some appreciation of changes in the overall structure of the myocardium. Such methods cannot, however, provide information on specific structural abnormalities, the degree of myocyte slippage or the relative contributions of myocyte hypertrophy and fibrosis (56).

LV volume and indexes of function. Left ventricular volumes and ejection fractions, linear dimensions and fractional shortening have all been measured in clinical trials (8,14,15,84–86). They have provided insight into long-term prognosis (4,85) and mortality rates (84) and have identified the extent of remodeling in HF patients (8). To appreciate fully what information these measures provide, an understanding of how they are derived is important.

The end-diastolic volume is a reflection of both structural remodeling and diastolic filling (end-diastolic myocyte fiber length). The end-systolic volume is influenced by both the end-diastolic volume and fiber shortening, but asymmetric contraction may make echocardiographically-derived measures of end-systolic volume inaccurate. Ejection fraction is derived from LV volume. Although heart rate and fiber shortening both affect ejection fraction, it is influenced to a far greater extent by end-diastolic volume because changes in stroke volume tend to be much smaller than changes in end-diastolic volume.

Reduced LV ejection fractions are associated with a poor prognosis in HF (84). In the post-MI population, LV volumes, particularly LV end-systolic volumes, are the strongest prognostic indicators (87). Post-MI patients experiencing subsequent morbid events had greater increases in LV diastolic and systolic volumes (measured using echocardiography) than patients without such events (85). By multivariate analysis, ejection fraction and stroke volume index at four days were among the significant predictors of progressive LV enlargement and chronic dysfunction (26).

Fractional shortening is derived from a single linear measure, the use of which is its greatest limitation. Fractional shortening attempts to use echocardiography to quantitate ventricular contractile function, thus providing an indicator of the extent of structural remodeling of the

ventricle. Although this is considered to be a good measure for remodeling, few studies have reported results on fractional shortening and disease progression or remodeling (86).

DIAGNOSTIC TOOLS AND THEIR CLINICAL VALUE

CONSENSUS STATEMENT THREE

Use of echocardiography or radionuclide imaging is standard practice in the identification of LV systolic dysfunction. Application of these diagnostic tools in management and monitoring needs to be more clearly defined. Opinions differ regarding the value of ejection fraction data in guiding therapy; measurement of ejection fraction can reliably guide initiation of treatment. At present, there are no data that definitely support the use of changes in ejection fraction as a basis for altering therapy.

Left ventricular systolic dysfunction is difficult to identify solely on the basis of symptoms and signs (88). An epidemiologic study of men and women randomly sampled from a geographically-defined urban population in Glasgow (Scotland, United Kingdom) showed LV systolic dysfunction in 2.9% of the population. Of these, approximately 50% were asymptomatic, i.e., remodeling had occurred but clinical symptoms had yet to develop (89). Symptoms alone are not a good indicator of the underlying disease state and physicians may need to look towards screening a population known to be at high risk for LV dysfunction (89,90).

Use of echocardiography or radionuclide imaging to measure remodeling. Radionuclide imaging and echocardiography provide a simple assessment of LV systolic function (88). However, although echocardiography is reliable in clinical trials, repeat measurements of LV mass and volume/ejection fraction may vary considerably (91), and methods are poorly standardized between centers. Its use may also be limited because good images can be difficult to obtain (e.g., in obese patients or those with airway disease, 92). Use of such methods for ongoing monitoring to guide management, therefore, requires caution. Although the use of magnetic resonance imaging (MRI) provides better accuracy and reliability than echocardiography (93), it is both difficult to access and is currently expensive for routine use.

Ejection fraction in management. Data from a primary care study showed that information generated from echocardiograms led to advice to change management in more than two-thirds of patients with, or suspected of having, HF who were referred for echocardiograms by general practitioners (92). Although ejection fraction is a good index of disease severity, its use is limited in the immediate post-MI period where LV dysfunction may be caused by large areas of hibernating or stunned myocardium.

The Vasodilator-Heart Failure Trials (V-HeFT I and V-HeFT II) also identified ejection fraction, measured using radionuclide imaging, as a powerful predictor of all-cause mortality in male HF patients (84). As ejection fraction fell, the mortality rate increased in a nonlinear fashion, such that in patients with ejection fractions below 25%, the mortality rate increased steeply (from V-HeFT II: 8% annual mortality with ejection fraction of 55% vs. 29% annual mortality with ejection fraction of 10%) (84). Improvements in ejection fraction have been linked to improved prognosis (84,94–96). The extent of the improvement in ejection fraction is important but must be considered in the context of other responses that may affect mortality. An analysis of the combined data from both V-HeFT studies showed that, although enalapril did not increase ejection fraction as much as hydralazine/isosorbide dinitrate, it was associated with an additional mortality reduction (97). The neurohormonal inhibiting effects of enalapril apparently conferred additional survival benefits.

The V-HeFT data also suggest that serial measurements of LV ejection fraction provided additional important prognostic information (97). Such findings suggest that there could be some merit associated with monitoring ejection fraction or chamber size to assess an individual's response to therapy and altering it accordingly. However, randomized clinical trials have yet to test this hypothesis prospectively.

Surrogate markers, such as ejection fraction, provide a general guide to the extent of cardiac remodeling and are useful clinical predictors of outcome. However, they do not provide a clear picture of changes in the underlying pathophysiology of the heart. New developments that may be useful to assess the extent of LV remodeling include imaging techniques for the quantitative evaluation of myocardial and nonmyocardial components and the measurement of plasma markers. Measurement of neurohormones known to be elevated in HF, perhaps combined with echocardiography, offers the possibility of more reliable detection of asymptomatic LV dysfunction and HF (54,98,99).

THE EFFECT OF THERAPEUTIC INTERVENTIONS ON THE CARDIAC REMODELING PROCESS IN HF

CONSENSUS STATEMENT FOUR

Although remodeling is generally accepted as a determinant of the clinical course of HF, slowing or reversing remodeling has not, until recently, been a recognized goal of HF therapy. The most convincing data demonstrating that therapeutic agents (e.g., ACE inhibitors and beta-blockers) modify the remodeling process are LV end-diastolic and end-systolic volume and ejection fraction data. The agents that affected remodeling did so in addition to other clinically relevant benefits in reducing morbidity and mortality in HF patients.

Heart failure therapy has traditionally concentrated largely on symptomatic relief rather than on addressing underlying disease processes. Cardiac dysfunction is ac-

Table 3. Effects of Therapeutic Approaches on Morbidity, Mortality and Parameters of LV Remodeling (Studies in Which the Results of at Least Two of These Three Categories Are Reported)

Class/Type	Specific Drug	Study Population	Impact on Mortality	Impact on Morbidity	Impact on Remodeling
Cardiac glycosides	Digoxin	HF (2)	=	? (decreased hospitalizations)	? Improved EF
Vasodilators	Hydralazine/ isosorbide dinitrate	HF (100)	+	?	Improved EF
	Prazosin	HF (100)	=	?	=
Calcium channel blockers	Diltiazem	HF (101)	−	−	?
	Felodipine	HF (102)	=	=	Short-term improved EF
Inotropic agents	Milrinone	HF (1)	−	−	?
ACE inhibitors	Captopril	Post MI (85, 103)	+	+	Improved EF; attenuation of LV dilation
	Enalapril	Post MI (104)	−	+	?
		Asymptomatic LV dysfunction, including post-MI (15)	+	+	Improved EF; attenuation of LV dilation
		HF (14, 105)	+	+	Improved EF; attenuation of LV dilation; improved ESV
	Ramipril	Post-MI with HF symptoms (106)	+	+	?
	Trandolapril	Post-MI (107)	+	+	=
	Lisinopril	Post-MI (108, 109)	+		No change in EF, decreased EDV, decreased ESV (nonsignificant)
Beta blockers	Bisoprolol	HF (12, 86, 110)	+	+	Improved fractional shortening and decreased ESV
	Carvedilol	HF (7, 8, 111–114)	+	+	Improved EF, decreased ESV and EDV and dimensions; improved sphericity index, EF, WMI
		Post-MI (115)	+	+	Improved EF, decreased ESV and EDV; improved WMI
	Metoprolol	HF (6,10)	+	+	Improved EF, decreased LV volumes; improved LV geometry
	Propranolol	Post-MI (116)	+		Improved EF
	Timolol	Post-MI (117)	+		Improved EF

+ positive benefit reported; − negative outcome reported; = no effect reported; ? effect not known. EF = ejection fraction; EDV = end-diastolic volume; ESV = end-systolic volume; HF = heart failure; MI = myocardial infarction; LV = left ventricular; WMI = wall motion index.

cepted as being progressive, even in the absence of clinical signs and symptoms of chronic HF. Patients with asymptomatic LV dysfunction and milder forms of HF are still at increased risk of sudden cardiac death (29,81). In addition to improving symptoms and reducing morbidity and mortality, preventing the progression of HF by slowing or reversing the remodeling process should be a target for therapy (Table 3) (1,2,6−8,10,12,14,15,85,86,100−117). Of the surrogate measures of remodeling, changes in ejection fraction, LV end-diastolic and end-systolic volumes have been assessed most frequently in large randomized studies. It is the chronic effects of therapies on these measurements (>4 months) that currently serves as a guide to the remodeling process.

Effects of vasodilators. The key to a mortality benefit is not related simply to an improvement in LV emptying, which would accompany peripheral vasodilation and reduced aortic impedance (118), but to regression of the LV remodeling with a structural reduction in chamber size. Thus, some vasodilator drugs, such as prazosin (100), diltiazem (101) and felodipine (102), do not reduce mortality or hospitalization rate, perhaps because they fail to influence the structural remodeling process. The combination of hydralazine and isosorbide dinitrate (100), however, does improve survival, probably because of a direct effect of nitrate on myocardial remodeling (119). Although ACE inhibitors exert vasodilator effects, their benefit on long-term outcome in HF relate importantly to their neurohormonal inhibiting effects, which contribute to their favorable action on remodeling (4).

Effects of inotropic agents. Similarly, positive inotropic drugs may exert favorable hemodynamic effects but adverse effects on survival. The phosphodiesterase inhibitor, milrinone, is widely used for hemodynamic support in advanced HF, but oral administration led to an increase in mortality in chronic HF (1). Flosequinan, pimobendan, ibopamine and vesnarinone, drugs with inotropic properties, also increased mortality in clinical trials (120–122). The mechanism of this adverse effect is unclear, but neurohormonal activation and ventricular arrhythmias are among the likely candidates.

Effects of ACE inhibition. *Effect on morbidity and mortality.* The Survival and Ventricular Enlargement (SAVE) (85), Acute Infarction Ramipril Evaluation (AIRE) (106) and Trandolapril Cardiac Evaluation (TRACE) (107) studies showed mortality benefits attributable to ACE inhibition in patients when started early after MI. A meta-analysis of ACE inhibitors in post-MI patients concluded that early intervention—within three to 16 days of infarction—can slow the progression of cardiovascular disease and improve the survival rate (123).

Angiotensin-converting enzyme inhibition relieved symptoms and significantly improved survival in patients with HF compared with placebo (Table 3) (4,5,9,105). These agents also favorably influence certain parameters of LV remodeling in both asymptomatic LV dysfunction post-MI and symptomatic patients with HF (4,14–16,124).

Effect on remodeling end points. In patients with LV dysfunction (ejection fraction <45%), administration of captopril one week after Q-wave MI resulted in significant reductions in the LV end-diastolic and end-systolic volume index and significant increases in ejection fraction and stroke volume index. In contrast, patients receiving furosemide or placebo showed significant increases in ventricular volumes, no change in stroke volume index and reductions in ejection fraction (103).

Using serial radionuclide ventriculograms, the SOLVD prevention trial showed that, compared with placebo, enalapril slowed or reversed LV dilation in patients with
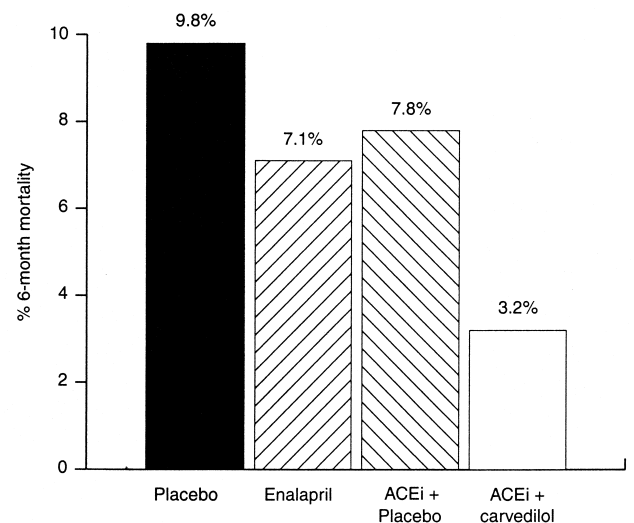

Figure 2. Cumulative benefit of beta-blockade in addition to angiotensin-converting enzyme inhibition in heart failure (5,7).

asymptomatic LV dysfunction but without clinical HF (ejection fraction ≤0.35) (15). Left ventricular volumes were reduced to a lesser degree by enalapril treatment in asymptomatic compared with symptomatic patients without HF (15). Although patient numbers were small (n = 56), a SOLVD treatment substudy showed that chronic administration of enalapril prevented progressive LV dilation and systolic dysfunction compared with placebo in patients with mild to moderate HF and reduced LV ejection fraction (≤0.35) (14). The findings of the above two studies were consolidated in a Doppler-echocardiographic evaluation of 301 patients recruited from both the prevention and treatment arms of SOLVD. This substudy showed that, compared with placebo, treatment with enalapril attenuated progressive increases in LV dilation and hypertrophy in patients with LV dysfunction, irrespective of the patient's symptomatic status (16).

Effects of beta-blockade. Multiple clinical trials have proved the benefits of beta-blockade in HF. In all these studies, beta-blockers were administered in conjunction with an ACE inhibitor and diuretics (6,7,10,12,110). Beta-blockade consistently improved LV function and provided clinical benefits over and above those achieved on standard therapy alone (Fig. 2) (5,7). However, the main aim of beta-blockade in chronic heart failure is not short-term relief of symptoms but improvement in LV function and long-term outcomes.

Effects on mortality and morbidity. Carvedilol, metoprolol or bisoprolol, when added to standard therapy including an ACE inhibitor, reduced mortality in large-scale studies of patients with ischemic and nonischemic HF (7,10,12,112). Carvedilol reduced the risk of all-cause mortality by 65% and produced a 27% reduction in the risk of hospitalization compared with placebo (7). The second Cardiac Insufficiency Bisoprolol Study (CIBIS II) demonstrated that

Table 4. Effect of ACE Inhibition With Enalapril and Beta-Blockade With Carvedilol on LV End-Diastolic and End-Systolic Volumes and Ejection Fraction (13, 16)

	Baseline	4 months	6 months	12 months	p Value
End-Diastolic Volume					
SOLVD placebo (ml)	200 ± 42	208 ± 43		210 ± 46	p = 0.025
SOLVD enalapril (ml)	196 ± 41	198 ± 37		197 ± 39	
ANZ placebo (including an ACE inhibitor) (ml)	175 ± 52	—	185 ± 58	194 ± 54	p = 0.0015
ANZ carvedilol (ml)	187 ± 72	—	179 ± 63	178 ± 63	
End-Systolic Volume					
SOLVD placebo (ml)	148 ± 38	155 ± 43		156 ± 42	p = 0.019
SOLVD enalapril (ml)	146 ± 38	147 ± 36		145 ± 38	
ANZ placebo (including an ACE inhibitor) (ml)	126 ± 49	—	133 ± 52	139 ± 47	p = 0.0001
ANZ carvedilol (ml)	136 ± 64	—	121 ± 56	121 ± 57	
Ejection Fraction (%)					
SOLVD placebo	26 ± 11	26 ± 11		26 ± 11	0.612
SOLVD enalapril	25 ± 11	26 ± 11		26 ± 11	
ANZ placebo (including an ACE inhibitor)	30.4 ± 9.1	—	29.3 ± 8.2	29.2 ± 7.8	
ANZ carvedilol	28.6 ± 7.1	—	33.5 ± 8.3	34.1 ± 9.7	

ACE = angiotensin-converting enzyme; ANZ = Australia/New Zealand Collaborative Group Study; SOLVD = Studies of Left Ventricular Dysfunction.

bisoprolol reduced all-cause mortality (the primary end point) by 34% compared with placebo (12). The Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF) which studied patients with moderate to severe HF was recently terminated early (10). At a mean follow-up of one year, a significant reduction in all-cause mortality of approximately 34% compared with placebo was reported (10).

In patients with idiopathic dilated cardiomyopathy, metoprolol, in addition to standard therapy including an ACE inhibitor, slowed clinical deterioration and improved symptoms and cardiac function (6). Similarly, in the first CIBIS study, bisoprolol conferred a functional benefit in severe HF with a greater benefit in idiopathic dilated cardiomyopathy (110). Neither the Metoprolol Dilated Cardiomyopathy trial nor the first CIBIS study was powered to detect any mortality benefit (6,110). Small-scale studies of bucindolol showed improvements in HF symptoms and resting cardiac function (113,125). The clinical progression of HF (defined as death or hospitalization for HF or an increase in medication for HF) was reduced in patients receiving carvedilol compared with those receiving placebo (111).

Effects on remodeling end points. Beta-blockade, in addition to ACE inhibition, consistently improves ejection fraction in both post-MI and HF patients irrespective of etiology (6,8,110–112,115,126,127). A small-scale study (n = 33) showed that when metoprolol treatment was

withdrawn after an average of 16 months' administration in patients with severe HF, LV function deteriorated in two-thirds of patients, and survivors benefited from read-ministration of the drug (128).

Data from an echocardiographic substudy of the Australia/New Zealand (ANZ) Collaborative Group show that carvedilol significantly decreased the LV end-diastolic and end-systolic volume index and increased LV ejection fraction compared with placebo (ACE inhibition alone), suggesting a sustained improvement in cardiac re-modeling (8). These improvements were apparent by 6 months and maintained at 12 months (13) (Table 4, Fig. 3) (13,16).

Smaller scale studies have also shown that beta-blockade with carvedilol (n = 44) and metoprolol (n = 26) has beneficial effects on LV geometry and mass (114,129).

An echocardiographic substudy from CIBIS I showed that after 5 months' treatment, LV fractional shortening increased and end-systolic dimensions were reduced significantly in the bisoprolol group compared with the placebo group (86); LV end-diastolic dimensions did not change significantly with bisoprolol therapy.

Although both bisoprolol and metoprolol have been shown to reduce mortality in HF, remodeling end points have been less extensively measured in association with these agents than in association with carvedilol. It has been postulated that antioxidant properties associated with some beta-blockers may contribute to their beneficial effects on
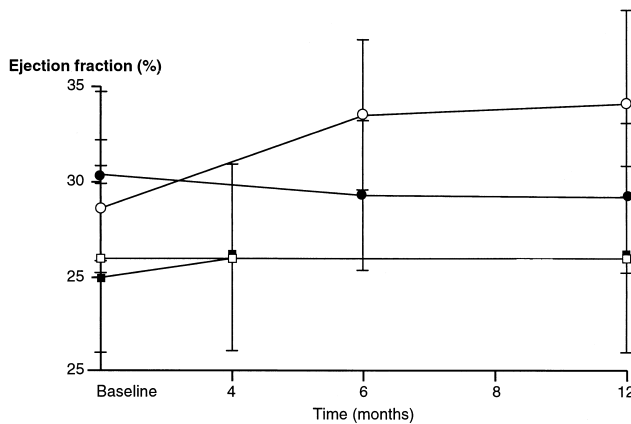
Figure 3. Effect of angiotensin-converting enzyme inhibition with enalapril and beta-blockade with carvedilol on left ventricular ejection fraction (13,16). ANZ = Australia/New Zealand Collaborative Group Study; LV = left ventricular dysfunction; SOLVD = Studies of Left Ventricular Dysfunction. **Solid circle** = ANZ substudy (placebo); **Open circle** = ANZ substudy (carvedilol); **solid square** = SOLVD substudy (enalapril); **Open square** = SOLVD substudy (placebo).

cardiac remodeling. In a comparative study of carvedilol and metoprolol in HF patients, assessment of thiobarbituric acid reactive substances (TBARS) was used to measure antioxidant effects. Both agents demonstrated significant antioxidant effects and improvements in ejection fraction over a six-month treatment period (130). Further studies are required to evaluate differences in the effects of individual beta-blockers on cardiac remodeling.

EDUCATIONAL IMPLICATIONS

CONSENSUS STATEMENT FIVE

It is desirable that clinicians, irrespective of specialty, understand the relationship between remodeling and HF progression; the messages to all clinician groups should be similar. Patients may benefit from receiving information about cardiac remodeling if it helps with compliance.

Physician education. Clinicians, whether specialists, general or primary care physicians, should understand and be aware of the association between cardiac remodeling and outcomes in HF. Such knowledge will enable clinicians to better understand the potential benefit of available therapies to ensure the most appropriate treatment for their patients. It is important to recognize that drugs useful for treating symptoms are not necessarily the most appropriate for long-term benefits (e.g., some positive inotropic drugs, despite hemodynamic benefits, showed negative effects on survival).

Studies such as SOLVD have demonstrated benefits of ACE inhibition on LV remodeling (14,15). More recently, the U.S. Carvedilol Heart Failure Trials Program, ANZ study, CIBIS II and MERIT-HF demonstrate that beta-

blockade provides additional benefits on mortality over and above those seen with ACE inhibition (7,8,10,12,126). One of the major issues associated with the use of beta-blocker therapy in patients with HF (particularly when symptoms are minimal) is that, if patients appear to be well compensated on current therapy, physicians are unwilling to administer another medication that may cause additional side effects. However, although symptoms may appear compensated, these patients should still be considered unstable since they are highly likely to experience clinical deterioration during the subsequent 12 months (131). Side-effects associated with beta-blockade are often associated with initial therapy and can be minimized with careful dose titration (6,128). In many cases, these events subside once dose titration is complete (132).

Patient education. Patients should be made aware of their condition in order for them to better understand the rationale for the therapy that they are receiving and its importance to their health and quality of life. Patients are most concerned about relief of symptoms and improvement in long-term outcomes as treatment aims, and long-term improvement may be achieved through preventing or delaying progression of remodeling. Indeed, when initiating treatment such as beta-blockade in HF, it is important for the patient to understand that they may not feel any particular immediate symptomatic benefit but that the overall benefit is associated with improved long-term outcome. Symptomatic improvement is generally not seen until after one to two months of chronic treatment. Such increased understanding may improve patient compliance.

Communicating information on remodeling to patients might also influence screening procedures and intervention programs for cardiovascular disease, if the importance of early detection and long-term therapy is made clear.

CLOSING STATEMENT

There is little doubt that remodeling and its role in disease progression are multimechanistic and complex. Few clinical trials have specifically addressed the role of remodeling in disease progression. Remodeling is, however, clinically relevant. Symptoms need not be the exclusive guide as to when therapy should be initiated, and the choice of therapy should take into account all the underlying components that contribute to disease progression with remodeling as a critical component within it.

The key next steps will be the determination of how the information generated from cellular and molecular models can be used, together with data from clinical trials, to ensure that patients receive optimal therapy at an appropriate time to slow disease progression. Reversing remodeling and preventing further remodeling is one way of slowing disease progression. Therapeutic approaches, such as ACE inhibition and beta-blockade, which reduce morbidity and mortality and, in some cases, improve a number of remodeling parameters, may offer such a therapeutic approach. The

challenge is to develop new and more specific treatments that may be even more effective in reversing the structural abnormalities in the left ventricle.

APPENDIX

The International Forum on Cardiac Remodeling includes:
Dr. Claudio Ceconi, University of Brescia, Italy; Dr. Jay N. Cohn, University of Minnesota Medical School, Minneapolis, Minnesota; Dr. Philip Currie, Royal Perth Hospital, Perth, Australia; Dr. Robert Doughty, University of Auckland, Auckland, New Zealand; Professor Helmut Drexler, Hannover Medical School, Hannover, Germany; Professor Roberto Ferrari, University of Brescia, Brescia, Italy; Dr. Drew Fitzpatrick, The Nepean Hospital, Penrith, New South Wales, Australia; Dr. Michael B. Fowler, Stanford University Medical Center, Stanford, California; Dr. Peter Gaudron, Heidelberg University, Mannheim, Germany; Dr. A. Martin Gerdes, University of South Dakota, Vermillion, South Dakota; Dr. Barry Greenberg, UCSD Medical Center, San Diego, California; Professor David J. Hearse, The Rayne Institute, London, United Kingdom; Professor Ake Hjalmarson, Goteborg, Sweden; Professor Garry Jennings, Heart Center at the Alfred, Prahran, Victoria, Australia; Professor Dr. John Kjekshus, Oslo, Norway; Dr. Marvin A. Konstam, New England Medical Center and Tufts University, Boston, Massachusetts; Dr. Peter Libby, Brigham and Women's Hospital, Boston, Massachusetts; Dr. Peter Liu, Toronto Hospital, Toronto, Canada; Dr. Jose L. Lopez-Sendon, Hospital Gregorio Maranon, Madrid, Spain; Dr. Tomas Luscher, University Hospital Zurich, Zurich, Switzerland; Professor John McMurray, University of Glasgow, Glasgow, United Kingdom; Professor Milton Packer, Columbia University College of Physicians and Surgeons, New York, New York; Professor Willem Remme, STICARES, Rotterdam, the Netherlands; Professor Mark Richards, Christchurch Hospital, Christchurch, New Zealand; Dr. Hani Sabbah, Henry Ford Hospital, Detroit, Michigan; Professor Norman Sharpe, University of Auckland School of Medicine, Auckland, New Zealand; Professor Jordi Soler-Soler, Barcelona, Spain; Dr. Yao Sun, University of Missouri-Columbia, Columbia, Missouri; Professor Karl Swedberg, Goteborg University, Goteborg, Sweden; Professor Luigi Tavazzi, IRCCS Policlinico San Matteo, Pavia, Italy; Dr. Christian Torp-Pedersen, Hellerup, Denmark.

Reprint requests and correspondence: Dr. Jay N. Cohn, Cardiovascular Division, Department of Medicine, University of Minnesota Medical School, 420 Delaware Street, SE—Box 508 UMHC, Minneapolis, Minnesota 55455.

REFERENCES

1. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. N Engl J Med 1991;325:1468–75.
2. The Digitalis Investigation Group. The effects of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525–33.
3. Massie BM, Fisher SG, Deedwania PC, Singh BN, Fletcher RD, Singh SN, for the CHF-STAT Investigation. Effect of amiodarone on clinical status and left ventricular function in patients with congestive heart failure. Circulation 1996;93:2128–34.
4. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303–10.
5. The SOLVD Investigators. The effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. N Engl J Med 1991;325:293–302.
6. Waagstein F, Bristow MR, Swedberg K, Camenini F, Fowler MB, Silver MA. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Lancet 1993;342:1441–6.
7. Packer M, Bristow MR, Cohn JN, for the US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996;334:1349–55.
8. Australia/New Zealand Heart Failure Research Collaborative Group. Randomized, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischemic heart disease. Lancet 1997;349:375–80.
9. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on morbidity and mortality in patients with heart failure: Collaborative Group on ACE-Inhibitor Trials. JAMA 1995;273:1450–6.
10. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomized intervention trial in congestive heart failure. Lancet 1999;353:2001–7.
11. Randomized Aldactone Evaluation Study (RALES) report presented at the American Heart Association meeting. November 14–16, 1998.
12. CIBIS II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomized trial. Lancet 1999;353: 9–13.
13. Doughty RN, Whalley GA, Gamble G, MacMahon S, Sharpe N. Left ventricular remodeling with carvedilol in patients with congestive heart failure due to ischemic heart disease. J Am Coll Cardiol 1997;29:1060–6.
14. Konstam MA, Rousseau MF, Kronenberg MW, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. Circulation 1992;86:431–8.
15. Konstam MA, Kronenberg MW, Rousseau MF, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. Circulation 1993;88:2277–83.
16. Greenberg B, Quinones M, Kolpillai C, et al. Effect of long-term enalapril on cardiac structure and function in patients with left ventricular dysfunction. Circulation 1995;91:2573–81.
17. Eaton LW, Bulkley BH. Expansion of acute myocardial infraction: its relationship to infarct morphology in a canine model. Circ Res 1981;49:80–8.
18. Hochman JS, Bulkley BH. Expansion of acute myocardial infarction; an experimental study. Circulation 1982;65:1446–50.
19. Korup E, Dalsgaard D, Nyvad O, Jensen TM, Toft E, Berning J. Comparisons of degrees of left ventricular dilation within 3 hours and up to 6 days after onset of first acute myocardial infarction. Am J Cardiol 1997;80:449.
20. Hutchins GM, Bulkley BH. Infarct expansion extension: two different complications of acute myocardial infarction. Am J Cardiol 1978;41:1127–33.
21. Weisman H, Bush DE, Mannisi JA, Bulkley BH. Global cardiac remodeling after acute myocardial infarction: a study in the rat model. Am J Cardiol 1985;5:1355–62.
22. Rumberger JA, Behrenbeck T, Breen JR, Reed JE, Gersh BJ. Nonparallel changes in global left ventricular chamber volume and muscle mass during the first year after transmural myocardial infarction in humans. J Am Coll Cardiol 1993;21:673–82.
23. Jugdutt BI. Effect of captopril and enalapril on left ventricular geometry, function and collagen during healing after anterior and inferior myocardial infarction in a dog model. J Am Coll Cardiol 1995;25:1718–25.
24. Anversa P, Olivetti G, Capasso JM. Cellular basis of ventricular

remodeling after myocardial infarction. Am J Cardiol 1991;68:7D–16D.

25. McKay RG, Pfeffer MA, Pasternak RC, Markis JE, Come PC, Nakao S. Left ventricular remodeling after myocardial infarction: a corollary to infarct expansion. Circulation 1986;74:693–702.

26. Gaudron P, Eilles C, Kugler I, Ertl G. Progressive left ventricular dysfunction and remodeling after myocardial infarction. Circulation 1993;87:755–63.

27. Olivetti G, Capasso JM, Sonnenblick EH, Anversa P. Side-to-side slippage of myocytes in ventricular wall remodeling acutely after myocardial infarction in rats. Circ Res 1990;67:23–34.

28. Weber KT, Brilla CG. Pathological hypertrophy and the cardiac interstitium: fibrosis and the renin-angiotensin-aldosterone system. Circulation 1991;83:1849–65.

29. White HD, Norris RM, Brown MA, Brandt PWT, Whitlock RML, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from endomyocardial infarction. Circulation 1987;76:44–51.

30. Douglas PS, Morrow R, Ioli A, Reichek N. Left ventricular shape, afterload and survival in idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1989;13:311–5.

31. Mitchell GF, Lamas GA, Vaughan DE, Pfeffer MA. Left ventricular remodeling in the year after first anterior myocardial infarction: a quantitative analysis of contractile segment lengths and ventricular shape. J Am Coll Cardiol 1992;19:1136–44.

32. Grossman W, Jones D, McLaurin LD. Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1975;56:56–64.

33. Hirose K, Shu NH, Reed JE, Rumberger JA. Right ventricular dilatation and remodeling the first year after an initial transmural wall left ventricular myocardial infarction. Am J Cardiol 1993;72:1126–30.

34. Struijker-Boudier HAJ, Smits JFM, DeMey JGR. Pharmacology of cardiac and vascular remodeling. Ann Rev Pharmacol Toxicol 1995;35:509–39.

35. Tan LB, Jalil JE, Pick R, Janicki JS, Weber KT. Cardiac myocyte necrosis induced by angiotensin II. Circ Res 1991;69:1185–95.

36. Sharov VG, Sabbah HN, Shimoyama H, Goussev AV, Lesch M, Goldstein S. Evidence of cardiocyte apoptosis in myocardium of dogs with chronic heart failure. Am J Pathol 1996;148:141–9.

37. Teiger E, Dam T-V, Richard L, et al. Apoptosis in pressure overload-induced heart hypertrophy in the rat. J Clin Invest 1996;97:2891–7.

38. Olivetti G, Abbi R, Quaini F, Kajstura J, Cheng W, Nitahara JA. Apoptosis in the failing human heart. N Engl J Med 1997;336:1131–41.

39. Anderson KR, Sutton MG, Lie JT. Histopathological types of cardiac fibrosis in myocardial disease. J Pathol 1978;128:79–85.

40. Weber KT, Pick R, Silver MA, Moe GW, Janicki JS, Zucker IH. Fibrillar collagen and remodeling of dilated canine left ventricle. Circulation 1990;82:1387–1401.

41. Villareal FJ, Kim NN, Ungab GD, Printz MP, Dillmann WH. Identification of functional angiotensin II receptors on rat cardiac fibroblasts. Circulation 1993;88:2849–61.

42. Reiss K, Capasso JM, Huang HE, Meggs LG, Li P, Anversa P. ANG II receptors, c-myc and c-jun in myocytes after myocardial infarction and ventricular failure. Am J Physiol 1993;264:H760–9.

43. Sadoshima J, Izumo S. Molecular characterization of angiotensin II-induced hypertrophy of cardiac myocytes and hyperplasia of cardiac fibroblasts. Critical role of the AT1 receptor subtype. Circ Res 1993;73:413–23.

44. Everett AD, Tufro-McReddie A, Fisher A, Gomez RA. Angiotensin receptor regulates cardiac hypertrophy and transforming growth factor-beta 1 expression. Hypertension 1994;23:587–92.

45. Belch JJF, Bridges AB, Scott N, Chopra M. Oxygen free radicals and congestive heart failure. Br Heart J 1991;65:245–8.

46. Ferrari R, Agnoletti L, Comini L, et al. Oxidative stress during myocardial ischemia and heart failure. Eur Heart J 1998;19 Suppl B:S138–41.

47. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984;311:819–23.

48. Rumberger JA. Ventricular dilation and remodeling after myocardial infarction. Mayo Clinic Proc 1994;69:664–74.

49. Chidsey C, Braunwald E, Morrow AG, Mason DT. Myocardial norepinephrine concentrations in man. N Engl J Med 1963;269:653–8.

50. Francis GS, Benedict C, Johnstone DE, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. Circulation 1990;82:1724–9.

51. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe heart failure. N Engl J Med 1990;323:236–41.

52. Torre-Amione G, Kapadia S, Benedict C, Oral H, Young JB, Mann DL. Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the Studies of Left Ventricular Dysfunction (SOLVD). J Am Coll Cardiol 1996;27:1201–6.

53. McClure S, Carunana L, Davie AP, et al. Cohort study of plasma natriuretic peptides for identifying left ventricular systolic dysfunction in primary care. BMJ 1998;317:516–9.

54. Vantrimpont P, Rouleau JL, Ciampi A, et al. Two-year course and significance of neurohumoral activation in the Survival and Ventricular Enlargement (SAVE) study. Eur Heart J 1998;19:1552–63.

55. Sadoshima J, Xu Y, Slayter HS, et al. Autocrine release of angiotensin II mediates stretch-induced hypertrophy of cardiac myocytes in vivo. Cell 1993;75:977–84.

56. Ollivier J-P, Bouchet VA. Prospects for cardioreparation. Am J Cardiol 1992;70:27–36C.

57. Brilla CG, Zhou G, Matsubara L, Weber KT. Collagen metabolism in cultured adult rat cardiac fibroblasts: response to angiotensin II and aldosterone. J Mol Cell Immunol 1994;26:809–20.

58. Sheehan JP, Seelig MS. Interactions of magnesium and potassium in the pathogenesis of cardiovascular disease. Magnesium 1984;3:301–14.

59. McMurray JJ, Ray SG, Abdullah I, Dargie HJ, Morton JJ. Plasma endothelin in chronic heart failure. Circulation 1992;85:1374–9.

60. Kiowski W, Sutsch G, Hunziker P, et al. Evidence for endothelin-1-mediated vasoconstriction in severe chronic heart failure. Lancet 1995;346:732–6.

61. Mulder P, Richard V, Bouchart F. Selective ET_A blockade prevents left ventricular remodeling and deterioration of cardiac function in experimental models of heart failure. Circ Res 1998;39:600–8.

62. McMurray J, Abdullah I, Dargie HJ, Shapiro D. Increased concentrations of tumour necrosis factor in cachectic patients with severe chronic heart failure. Br Heart J 1991;66:356–8.

63. Bozkurt B, Kribbs SB, Clubb FJ. Pathophysiologically relevant concentrations of tumor necrosis factor-alpha promote progressive left ventricular dysfunction and remodeling in rats. Circulation 1998;97:1382–91.

64. Ferrari R, Ceconi C, Curello S, Cargoni A, Pasini E, Visiolo O. The occurrence of oxidative stress during reperfusion in experimental animals and men. Cardiovasc Drug Ther 1991;5:277–88.

65. McMurray J, Chopra M, Abdullah I, Smith WE, Dargie HF. Evidence of oxidative stress in chronic heart failure in humans. Eur Heart J 1993;14:1493–8.

66. Singh N, Dhalla K, Seneviratne C, Singal PK. Oxidative stress and heart failure. Mol Cell Biochem 1995;147:77–81.

67. Hill MF, Singal PK. Antioxidant and oxidative stress changes during heart failure subsequent myocardial infarction in rats. Am J Pathol 1996;148:291–300.

68. Polunovsky VA, Wendt CH, Ingbar DH, Peterson MS, Bittermann PB. Induction of endothelial cell apoptosis by TNF alpha modulation by inhibitors of protein synthesis. Exp Cell Res 1994;214:584–94.

69. Hermann C, Zeiher AM, Dimmeler S. Sheer stress inhibits H_2O_2-induced apoptosis of human endothelial cells by modulation of the glutathione redox cycle and nitric oxide synthase. Arterioscler Throm Vasc Biol 1997;17:3588–92.

70. Francis GS, McDonald KM. Left ventricular hypertrophy: an initial response to myocardial injury. Am J Cardiol 1992;69:3G–6G.

71. Dhalla NS, Kaura D, Liu X, Beamish RE. Mechanisms of subcellular remodeling in postinfarct heart failure. In: Konstam M, editor. Myocardial Ischemia: Mechanisms, Reperfusion, Protection. Birkhauser Verlag Basel: Basel, Switzerland 1996:463–77.

72. Van Krimpen C, Smits JFM, Cleutjens JPN, et al. DNA synthesis in the noninfarcted cardiac interstitium after left coronary artery ligation in the rat: effect of captopril. J Mol Cell Cardiol 1991;23:1245–53.

73. Volders PGA, Willems IEMG, Cleutjens JPM, et al. Interstitial collagen is increased in the noninfarcted human myocardium after myocardial infarction. J Mol Cell Cardiol 1993;25:1317–23.

74. Tyagi SC, Matsubara L, Weber KT. Direct extraction and estimation of collagenase(s) activity by zymograph in microquantities of rat myocardium and uterus. Clin Biochem 1993;26:191–8.

75. Cleutjens JPM, Kandala JC, Guarda E, Guntaka RV, Weber KT. Regulation of collagen degradation in the rat myocardium after infarction. J Mol Cell Cardiol 1995;27:1281–92.

76. Delong MJ. Apoptosis: a modulator of cellular homeostasis and disease states. Ann NY Acad Sci 1998;842:82–90.

77. Kajstura J, Leri A, Finato N, di Loreto C, Bertrami CA, Anversa P. Myocyte proliferation in end stage cardiac failure in humans. Proc Natl Acad Sci 1998;95:8801–5.

78. Meerson FZ. The failing heart: adaptation and deadaptation: XVII. In: Katz J, Editor. Translated from Russian by Nicholas Bobrov and Leonid Levant. New York: Raven Press, 1983.

79. Sabbah HN, Goldstein S. Ventricular remodeling: consequences and therapy. Eur Heart J 1993;14 Suppl C:24–9.

80. Hammermeister KE, DeRouen TA, Dodge HT. Variables predictive of survival in patients with coronary disease. Selection by univariate and multivariate analyses from the clinical, electrocardiographic, exercise, arteriographic and quantitative angiographic values. Circulation 1979;59:421–30.

81. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Circulation 1990;81:1161–72.

82. Carr A, Prisant M, Watkins L. Detection of hypertensive left ventricular hypertrophy. Hypertension 1985;7:948–54.

83. Kannel WB. Need and prospects for prevention of heart failure. Eur J Clin Pharmacol 1996;49:S3–S9.

84. Cohn JN, Johnson GR, Shabetai R, et al. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias and plasma norepinephrine as determinants of prognosis in heart failure. Circulation 1993;87 Suppl VI:VI5–VI16.

85. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. N Engl J Med 1992;327:669–77.

86. Lechat P, Escolano S, Golmard JL. Prognostic value of bisoprolol-induced hemodynamic effects in heart failure during the Cardiac Insufficiency Bisoprolol Study (CIBIS). Circulation 1997;96:2197–205.

87. White HD, Norris RM, Brown MA, Brandt PWT, Whitlock RML, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987;76:44–51.

88. Cleland JGF, for the Task Force on Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis of heart failure. Eur Heart J 1995;16:741–51.

89. McDonagh TA, Morrison CE, Lawrence A, et al. Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. Lancet 1997;350:829–33.

90. McMurray JJV, Davie AP, McDonagh TA. Should we screen for asymptomatic left ventricular dysfunction to prevent heart failure? Eur Heart J 1998;19:842–6.

91. Gottdiener JS. Left ventricular mass, diastolic dysfunction and hypertension. Ann Intern Med 1993;38:31–56.

92. Francis CM, Caruna L, Kearney P, et al. Open access echocardiography in management of heart failure in the community. Br Med J 1995;310:634–6.

93. Krzesinski JM, Rorive G, Cauwenberge V. Hypertension and left ventricular hypertrophy. Acta Cardiologica 1996;51:143–54.

94. Gradman A, Deedwania P, Cody R, et al. Predictors of total mortality and sudden death in mild to moderate heart failure. J Am Coll Cardiol 1989;14:464–70.

95. Parameshwar J, Keegan J, Sparrow J, Sutton GC, Poole-Wilson PA. Predictors of prognosis in severe chronic heart failure. Am Heart J 1992;123:421–6.

96. Likoff MJ, Chandler SL, Kay HF. Clinical determinants of mortality in chronic congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy. Am J Cardiol 1987;59:634–8.

97. Cintron G, Johnson G, Francis G, Cobb F, Cohn JN, for the V-HeFT VA Cooperative Studies Group. Prognostic significance of

98. serial changes in left ventricular ejection fraction in patients with congestive heart failure. Circulation 1993;87 Suppl V:V17–VI23.

98. Cowie MR, Struthers AD, Wood DA. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. Lancet 1997;350:1349–53.

99. Ferrari R, Ceconi C. Neuroendocrine activation in left ventricular dysfunction [editorial]. Eur Heart J 1998;19:1423–4.

100. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. N Engl J Med 1986; 314:1547–52.

101. Goldstein RE, Boccuzzi SJ, Cruess D, Nattel S, the Adverse Experience Committee and the Multicenter Diltiazem Postinfarction Research Group. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. Circulation 1991;83:52–60.

102. Cohn JN, Ziesche S, Smith R, et al. Effect of the calcium antagonist felodipine as supplementary therapy in patients with chronic heart failure treated with enalapril: VHeFT III. Circulation 1997;96:856–63.

103. Sharpe N, Murphy J, Smith H, Hannan S. Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. Lancet 1988;1:253–9.

104. Swedberg K, Held P, Kjekshus J, Rasmussen K, Ryden L, Wedel H. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction: results of the Cooperative New Scandinavian Survival Study II (CONSENSUS II). N Engl J Med 1992;327:678–84.

105. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429–35.

106. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993;342:821–8.

107. Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 1995;333:1670–6.

108. GISSI 3 Study Group. GISSI 3: Effects of lisinopril and transdermal glyceryl trinitrate singly and together on six-week mortality and ventricular function after acute myocardial infarction. Lancet 1994; 343:1115–22.

109. Nicolosi GL, Latini R, Marino P, et al. The prognostic value of predischarge quantitative two-dimensional echocardiographic measurements and the effects if early lisinopril treatment on left ventricular structure and function after myocardial infarction in the GISSI-3 trial. Eur Heart J 1996;17:1646–56.

110. CIBIS Investigators and Committee. A randomized trial of beta-blockade in heart failure: the Cardiac Insufficiency Bisoprolol Study (CIBIS). Circulation 1994;90:1765–73.

111. Colucci WS, Packer M, Bristow MR, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. Circulation 1996;94:2800–6.

112. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. Circulation 1996;94:2807–16.

113. Gilbert EM, Anderson JL, Deitchman D, et al. Long-term beta-blocker vasodilator therapy improves cardiac function in idiopathic dilated cardiomyopathy: a double-blind randomized study of bucindolol versus placebo. Am J Med 1990;88:223–9.

114. Lowes BD, Gill EA, Abraham WT, et al. Effects of carvedilol on left ventricular mass, chamber geometry and mitral regurgitation in chronic heart failure. Am J Cardiol 1999;83:1201–5.

115. Basu S, Senior R, Raval U, van der Does R, Bruckner T, Lahiri A. Beneficial effects of intravenous and oral carvedilol treatment in acute myocardial infarction. A placebo-controlled randomized trial. Circulation 1997;96:183–91.

116. Beta-Blocker Heart Attack Trial Research Group. A Randomized trial of propranolol in patients with acute myocardial infarction. J Am Med Assoc 1982;247:1707–14.

117. The Norwegian Multicenter Study Group. Timolol-induced reduc-

tion in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981;304:801–7.

118. Cohn JN. Vasodilator therapy for heart failure: the influence of impedance on left ventricular performance. Circulation 1973;48:5–8.

119. McDonald KM, Francis GS, Matthews JH, Hunter D, Cohn JN. Long-term oral nitrate therapy prevents chronic ventricular remodeling in the dog. J Am Coll Cardiol 1993;21:514–22.

120. Lubsen J, Just H, Hjalmarsson AC, et al. Effect of pimobendan on exercise capacity in patients with heart failure: main results from the Pimobendan in Congestive Heart Failure (PICO) trial. Heart 1996;76:223–31.

121. Hampton JR, van Veldhuisen DJ, Kleber FX, et al., for the Second Prospective Randomized Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. Randomized study of effect of ibopamine on survival in patients with advanced severe heart failure. Lancet 1997;349:971–7.

122. Cohn JN, Goldstein SO, Greenberg BH, et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. N Engl J Med 1998;339:1810–6.

123. Beckwith C, Munger MA. Effect of angiotensin-converting enzyme inhibitors on ventricular remodeling and survival following myocardial infarction. Ann Pharmacother 1993;27:755–66.

124. Pfeffer MA, Lamas GA, Vaughan DE, Parisi AF, Braunwald E. Effect of captopril on progressive ventricular dilation after anterior myocardial infarction. N Engl J Med 1987;317:787–92.

125. Woodley SL, Gilbert EM, Anderson JL, et al. Beta-blockade with bucindolol in heart failure caused by ischemic versus idiopathic dilated cardiomyopathy. Circulation 1991;84:2426–41.

126. Packer M, Colucci WS, Sackner-Bernstein JD, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. THE PRECISE trial. Circulation 1996;94:2793–9.

127. Cohn JN, Fowler MB, Bristow MR, et al. Safety and efficacy of carvedilol in severe heart failure. J Card Fail 1997;3:173–9.

128. Waagstein F, Caidahl K, Wallentin I, Bergh CH, Hjalmarson A. Long-term beta-blockade in dilated cardiomyopathy. Effects of short and long-term metoprolol treatment followed by withdrawal and readministration of metoprolol. Circulation 1989;80:551–63.

129. Hall SA, Cigarroa CG, Marcoux L, Risser RC, Grayburn PA, Eichorn EJ. Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. J Am Coll Cardiol 1995;25:1154–61.

130. Kukin ML, Kalman J, Charney RH, et al. Prospective, randomized comparison of effect of long-term treatment with metoprolol or carvedilol on symptoms, exercise, ejection fraction and oxidative stress in heart failure. Circulation 1999;99:2645–51.

131. Packer M. Beta-adrenergic blockade in chronic heart failure: principles, progress and practice. Prog Cardiovasc Dis 1998;41 Suppl 1:39–52.

132. Sackner-Bernstein JD. Use of carvedilol in chronic heart failure: challenges of therapeutic management. Prog Cardiovasc Dis 1998;41 Suppl 1:53–8.

Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling

Jay N. Cohn, Roberto Ferrari, Norman Sharpe, and on Behalf of an International Forum on Cardiac Remodeling

J. Am. Coll. Cardiol. 2000;35;569-582

This information is current as of February 13, 2010

Updated Information & Services	including high-resolution figures, can be found at: http://content.onlinejacc.org/cgi/content/full/35/3/569
References	This article cites 120 articles, 73 of which you can access for free at: http://content.onlinejacc.org/cgi/content/full/35/3/569#BIBL
Citations	This article has been cited by 75 HighWire-hosted articles: http://content.onlinejacc.org/cgi/content/full/35/3/569#otherarticles
Rights & Permissions	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://content.onlinejacc.org/misc/permissions.dtl
Reprints	Information about ordering reprints can be found online: http://content.onlinejacc.org/misc/reprints.dtl