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iREVIEWS

STATE-OF-THE-ART PAPER

Left Ventricular Remodeling in Heart Failure

Current Concepts in Clinical Significance and Assessment

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Ventricular remodeling, first described in animal models of left ventricular (LV) stress and injury, occurs progressively in untreated patients after large myocardial infarction and in those with dilated forms of cardiomyopathy. The gross pathologic changes of increased LV volume and perturbation in the normal elliptical LV chamber configuration is driven, on a histologic level, by myocyte hypertrophy and apoptosis and by increased interstitial collagen. Each of the techniques used for tracking this process—echocardiography, radionuclide ventriculography, and cardiac magnetic resonance—carries advantages and disadvantages. Numerous investigations have demonstrated the value of LV volume measurement at a single time-point and over time in predicting clinical outcomes in patients with heart failure and in those after myocardial infarction. The structural pattern of LV remodeling and evidence of scarring on cardiac magnetic resonance have additional prognostic value. Beyond the impact of abnormal cardiac structure on cardiovascular events, the relationship between LV remodeling and clinical outcomes is likely linked through common local and systemic factors driving vascular as well as myocardial pathology. As demonstrated by a recent meta-analysis of heart failure trials, LV volume stands out among surrogate markers as strongly correlating with the impact of a particular drug or device therapy on patient survival. These findings substantiate the importance of ventricular remodeling as central in the pathophysiology of advancing heart failure and support the role of measures of LV remodeling in the clinical investigation of novel heart failure treatments. (J Am Coll Cardiol Img 2011;4:98–108) © 2011 by the American College of Cardiology Foundation

Mechanisms and Characteristics of Ventricular Remodeling

The term *ventricular remodeling* refers to alteration in ventricular architecture, with associated increased volume and altered chamber configuration, driven on a histologic level by a combination of pathologic myocyte hypertrophy, myocyte apoptosis, myofibroblast proliferation, and interstitial fibrosis (1–3). Although originally described after myocardial infarction (MI), ventricular remodeling develops in response to a variety of forms of myocardial injury and increased wall stress (4,5).

Early work by Pfeffer and Braunwald (6) in a rodent MI model showed that a greater degree of myocardial injury was associated with a greater degree of chamber remodeling over

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time. Since that time, multiple studies have substantiated the relationship between infarct size and the extent of left ventricular (LV) remodeling (3,7,8). Solomon et al. (9) showed that patients with larger MIs, as evidenced by greater elevations in serum creatine kinase concentrations, manifest greater 90-day increases in LV end-diastolic volume (EDV) and greater reductions in left ventricular ejection fraction (LVEF) (Fig. 1).

The initial post-MI phase of LV remodeling results from fibrotic repair of the necrotic area with scar formation, elongation, and thinning of the infarcted zone (Fig. 2). LV volumes increase, a response that is sometimes considered adaptive, associated with stroke volume augmentation and maintenance of normal cardiac output (10). However, beyond this early stage, the remodeling process is driven predominantly by hypertrophic myocyte elongation in the noninfarcted zone, resulting in increased wall mass, chamber enlargement, and a shift from an elliptical to a more spherical chamber configuration (3,11–13). These changes, together with a decline in performance of the pathologically hypertrophied myocyte and interstitial fibrosis within the noninfarcted zone, result in progressive decline in ventricular performance. Left unchecked, LV hypertrophy, dilation, and contractile dysfunction appear to advance indefinitely, regardless of the initial inciting cause, as evidenced by progressive increases in LV volumes (12,14,15).

Pathologic LV remodeling is closely linked to activation of a series of neuroendocrine, paracrine, and autocrine factors, which are up-regulated after myocardial injury and in the setting of increased LV wall stress and hemodynamic derangement. Contributing factors include the renin-angiotensin-aldosterone axis, the adrenergic nervous system, increased oxidative stress, proinflammatory cytokines, and endothelin. Renin-angiotensin system inhibition (14–18) and beta-adrenergic blockade (19–23) have each been shown to markedly attenuate or reverse LV remodeling in patients with heart failure and LV dilation, although aldosterone blockade has yielded mixed results (24,25), and findings with antagonists of endothelin (26) and vasopressin (27) have been disappointing.

With continued application of imaging techniques within populations of patients with MI and/or heart failure, there has been increased understanding of the various macroscopic patterns of LV remodeling and their relationship to underlying etiology and prognosis. Verma et al. (28), examining patients with heart failure and/or LVEF ≤35% after MI, in the VALIANT (VALsartan In Acute myocardial iNfarcTion) echocardiographic study, defined 3 patterns of LV remodeling based on measurement of the LV mass index (LVMi) and relative wall thickness (RWT): concentric remodeling (normal LV mass index LVMi and increased RWT), eccentric hypertrophy (increased LVMi and normal RWT), concentric hypertrophy (increased LVMi and increased RWT) (Fig. 3) (28). Each of these patterns was associated with a higher risk of subsequent cardiovascular events than that of normal LV morphology, with each of these 3 patterns carrying progressively worse prognosis (see the "Relationship between LV remodeling and prognosis in patients with heart failure and decreased LVEF" section).

Techniques for Assessing Ventricular Remodeling

LVEF, the most common metric of cardiac performance in clinical practice, is influenced by the degree of LV remodeling more than by any other factor (29). Other, more precise metrics of remodeling, such as LV volumes and mass, have received greater focus in clinical trials than in clinical practice (30), yet these measurements relate more closely to prognosis and to the impact of therapy than does LVEF. For example, White et al. (31) demonstrated that within groups with various degrees of post-MI LV dysfunction defined by LVEF, analysis of LV end-systolic volume (ESV) further risk-stratified patients, suggesting that it is a more powerful metric for that purpose. At present, echocardiography remains the predominant clinically applicable noninvasive test of choice, based on broader availability, whereas alternative modalities, such as radionuclide imaging and cardiac magnetic resonance (CMR), also play an important role, with each modality offering advantages and disadvantages.

Two-dimensional (2D) and 3-dimensional (3D) echocardiography. 2D echocardiography is a widely available and well-established means of assessing LV remodeling. This technique can be performed in nearly all patients, including those who are critically ill, and is not associated with any radiation exposure. However, estimates of LV volumes derived from 2D images are subject to variability and error imposed by selection of the imaging plane, inaccuracies in identi-

ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional
3D = 3-dimensional
CMR = cardiac magnetic resonance
EDV = end-diastolic volume
ESV = end-systolic volume
LGE = late gadolinium enhancement
LV = left ventricular
LVEF = left ventricular ejection fraction
LVMi = left ventricular mass index
MI = myocardial infarction
RVG = radionuclide ventriculography
RWT = relative wall thickness

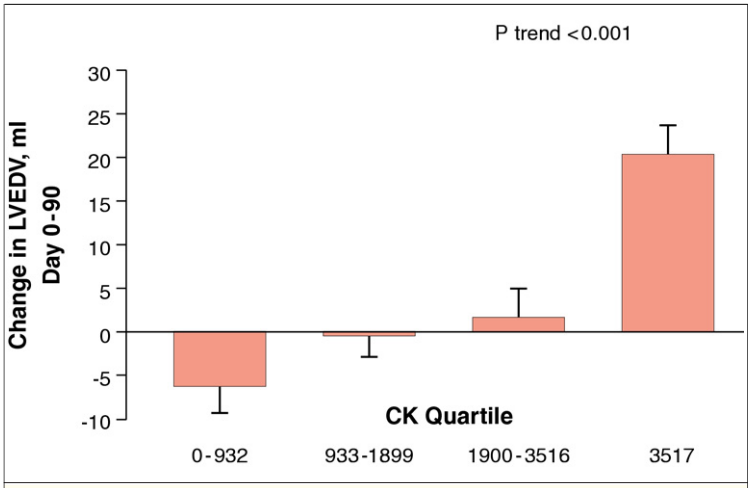

Figure 1. MI Size and Subsequent Remodeling

Patients with larger myocardial infarctions (MI), as reflected by higher serum creatine kinase (CK) levels, show greater 90-day increases in left ventricular end diastolic volume (LVEDV) than patients with smaller MI. Adapted, with permission, from Solomon et al. (57).

fying the endocardial border, geometric assumptions underlying the volumetric calculations, and beat-to-beat variation in LV volume and function.

Kober et al. (32) demonstrated the accuracy of echocardiographic LV volumes estimates, using the Simpson method when compared with in vitro canine measurements. A number of studies have demonstrated the superior reproducibility of 2D echocardiography over M mode for measuring LV mass in normal subjects (33,34) and those with abnormal LV geometry (35). Subsequently, harmonic imaging (36) and contrast echocardiography (37) have improved 2D echocardiographic image quality.

More recently, real-time 3D echocardiography has emerged as a clinically feasible method for quantifying ventricular volume and mass. 3D echocardiographic quantification of ventricular volumes and ejection fraction can be performed rapidly and avoids the geometric assumptions and problems of image plane position that are associated with 2D echocardiography. 3D echocardiography has superior accuracy and reproducibility for evaluation of ventricular chambers compared with 2D echocardiography, and several studies have observed that 3D echocardiographic assessments of ventricular volumes, mass, and ejection fraction correlate favorably with CMR (38–42).

Radionuclide ventriculography. Equilibrium-gated radionuclide ventriculography (RVG) has been used since the 1970s to assess right ventricular and LV function, with studies of ventricular volumes following soon thereafter. Because ventricular volumes are determined by changes in radionuclide counts, the RVG technique is independent of geometric assumptions and does not rely on operator-defined analysis of regional changes in wall motion or thickening throughout the cardiac cycle (30,43). This factor is especially advantageous over other imaging techniques in patients with ischemic cardiomyopathy, multiple wall motion abnormalities, and altered LV geometry. Because the radionuclide-based volumetric estimate integrates information from multiple cardiac cycles, the technique is not subject to error from individual beat-to-beat variation. Gating methodologies are designed to manage moderate cycle-length variability, although extreme variability, as when ventricular response to atrial fibrillation is excessively irregular, may introduce error into volumetric and functional estimates.

Multiple studies have demonstrated adequate reproducibility and low intraobserver and interobserver variability of RVG in estimating LV volumes in both normal subjects and those with heart disease. Studies comparing RVG with both contrast ventriculography (44,45) and visual estimation by 2D echocardiography (46) found that RVG is comparable to these 2 methods in estimating LVEF and has higher reproducibility.

Like any imaging modality, a high-quality, reproducible study is dependent on operator expertise in acquisition and analysis. Although LV volumes may not be routinely reported in many cardiac nuclear medicine laboratories, laboratories with qualified physicians and technologists can be trained to acquire high-quality data, and central data analysis will optimize accuracy and reproducibility of volumetric estimates for clinical trial purposes.

CMR. CMR is a 3D imaging technique producing images with high spatial and temporal resolution. The generation of thin, short-axis imaging slices with full ventricular coverage results in truly tomographic imaging without the limitation of geometric assumptions associated with 2D nontomographic imaging techniques. In addition, contemporary imaging sequences generate sharp contrast between the bright blood pool and dark myocardium, which results in accurate measurements of volume, mass, and wall thickness. A number of investigations have demonstrated strong correlations for LVEFs and volumes measured by CMR versus contrast angiography or echocardiography (47,48). CMR is now considered the reference for noninvasive measurements of functional and volumetric parameters. In addition, the supe-

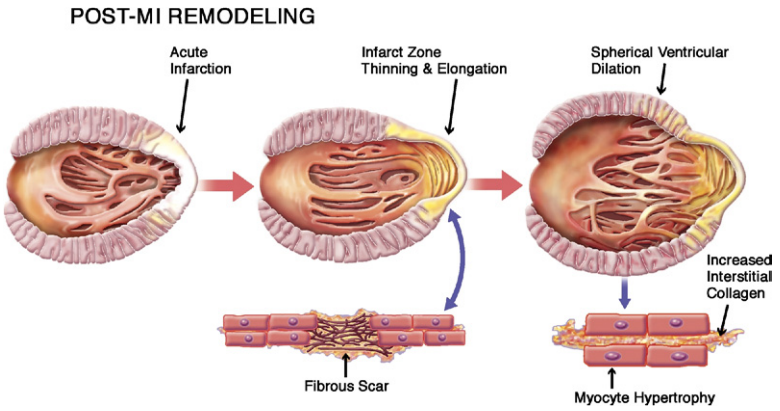

Figure 2. Ventricular Remodeling: Gross and Microscopic Architecture

Schematic representation of post-myocardial infarction (post-MI) left ventricular remodeling. The early phase is characterized by thinning and elongation of the fibrous scar within the infarcted zone. Subsequent left ventricular dilation, with transition from an elliptical to a more spherical configuration, is driven principally by diffuse myocyte hypertrophy associated with increased apoptosis (not shown) and increases in interstitial collagen. Figure illustration by Craig Skaggs.

rior reproducibility of these measurements with CMR facilitates application of CMR as a research tool for clinical investigation. For example, the sample size needed to demonstrate a given change in volume or mass with statistical confidence is substantially reduced with CMR compared with 2D echocardiography, a factor that may offset the increased cost of CMR by virtue of the savings from studying fewer patients per trial (49).

Beyond geometric measurements, contrast-enhanced CMR, with assessment of late gadolinium enhancement (LGE), has demonstrated the ability to predict patient risk of adverse remodeling post-MI (50–52). Due to the high spatial resolution, LGE, a marker of myocardial scarring, can identify acute and chronic MI with high accuracy and reproducibility (53). Areas of LGE can be planimetered, and the amount quantified and expressed as a percentage of the total LV mass or a percentage of the LV wall segment involved (50). This technique can also demonstrate microvascular obstruction, as evidenced by a central dark zone, surrounded by bright enhancement of the infarcted core (54), a finding that marks a greater risk of adverse LV remodeling post-MI.

Relationship Between LV Remodeling and Prognosis in Patients With Heart Failure and Decreased LVEF

Relationship between clinical outcomes and cross-sectional LV measurements. In 1987, White et al. (31) observed that LVEF measured 1 to 2 months after thrombolytic therapy for MI was a powerful predictor of prognosis, with LV ESV index (ESVi) providing additional predictive value. In a similar population, Migrino et al. (55) demonstrated a continuous relationship between ESVi and both mortality and the development of heart failure symptoms. In a population with symptomatic heart failure and decreased LVEF, Lee et al. (56) found that LV end-diastolic dimension index, measured with M-mode echocardiography, was an independent predictor of survival. In an echocardiographic

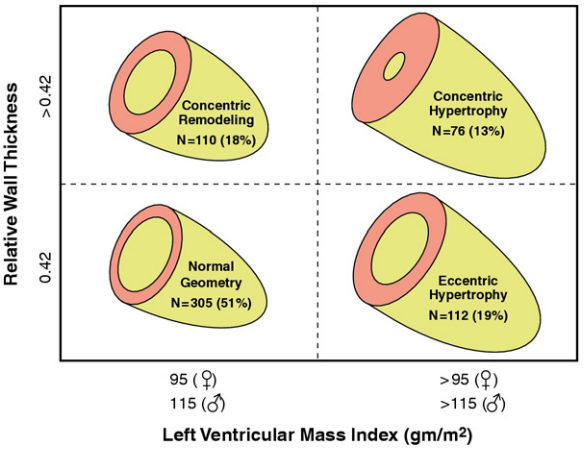

Figure 3. Patterns of Remodeling

The echocardiographic substudy of the VALIANT (VALsartan In Acute myocardial iNfarcTion) trial defined 3 patterns of left ventricular (LV) remodeling in patients with heart failure and/or LV ejection fraction ≤35%, based on measurement of left ventricular mass index (LVMi) and relative wall thickness (RWT): concentric remodeling (normal LVMi and increased RWT), eccentric hypertrophy (increased LVMi and normal RWT), concentric hypertrophy (increased LVMi and increased RWT). Reprinted, with permission, from Verma et al. (28).

substudy of the VALIANT (Valsartan in Acute Myocardial Infarction) study, Solomon et al. (57) demonstrated that baseline LVEF, EDV, and ESV were each independent predictors of the primary combined end point of death or heart failure hospitalization (Fig. 4).

Recently, investigators have begun to clarify the differential prognostic implication of different patterns of LV remodeling. In the VALIANT echocardiographic study, Verma et al. (28) found that, compared with patients without evidence of LV remodeling, patients with any of the patterns of LV remodeling post-MI had a greater risk of the composite of cardiovascular death, MI, heart failure, stroke, or resuscitated cardiac arrest. In addition, the patterns of concentric remodeling, eccentric hypertrophy, and concentric hypertrophy were associated with a progressively increased risk of the composite, with each of the individual outcome components following a pattern of risk similar to that of the overall composite (Fig. 5). Thus, although LV volumes remain powerful indicators of cardiovascular prognosis, additional information is contained within the specific pattern of LV remodeling.

These findings point to additional hypotheses related to the nature of the linkage between LV remodeling and cardiovascular events (29). First, the greater adverse implication of concentric hypertrophy suggests that antecedent hypertension of sufficient severity and duration to discernably affect LV structure carries an incremental risk in a patient with subsequent MI. Second, the similarity of risk patterns for subsequent MI and stroke, compared with that of heart failure and the overall composite end point, suggests that the mechanisms responsible for adverse outcomes are not simply operating through cardiac dysfunction and clinical heart failure. Rather, it is likely that LV remodeling represents a more global biomarker of systemic effects, such as that of hypertension and neurohormonal activation, on the entire cardiovascular system, with a likely association between LV remodeling and vascular changes responsible for coronary and cerebrovascular events.

The extent of LGE by CMR may also represent an important prognostic indicator. The number of LV segments with transmural (i.e., LGE occupying ≥75% of the LV segment) involvement post-MI is predictive of the extent of subsequent LV remodeling, as evidenced by increased LV volumes and decreased LVEF, independent of the magnitude of troponin increase (58). The extent of LGE also predicts the likelihood of functional recovery after either coronary revascularization or medical therapy. Those LV segments without LGE have approximately an 80% chance for improvement in function post-revascularization (52). Similarly, in patients with heart failure and decreased LVEF, systolic performance improved in more than half of LV segments without LGE, but in only rare segments with transmural LGE after 6 months of beta-blocker therapy (59). CMR evidence of microvascular obstruction post-MI predicts a greater likelihood of thinning and lack of functional recovery in a particular myocardial segment and a greater

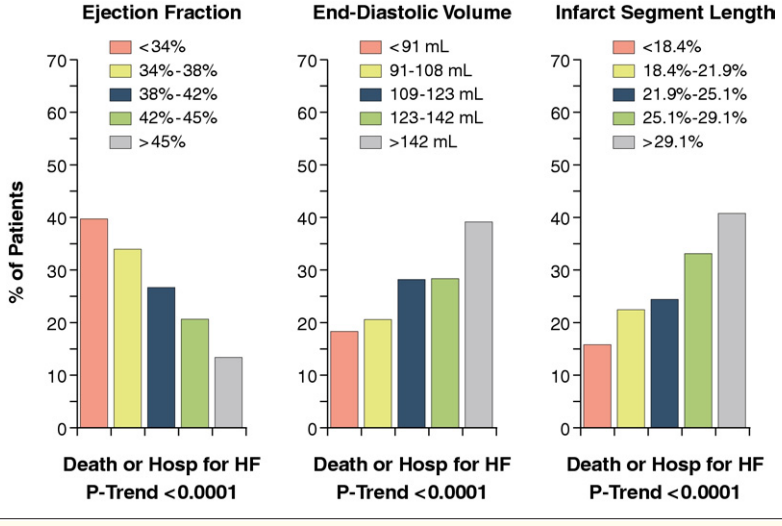

Figure 4. Ventricular Measurements and Prognosis

Relationship between echocardiographic parameters, ejection fraction, end-diastolic volume, and infarct segment length, and the combined outcome of death or hospitalization for heart failure (HF) after myocardial infarction. Reprinted, with permission, from Solomon et al. (57).

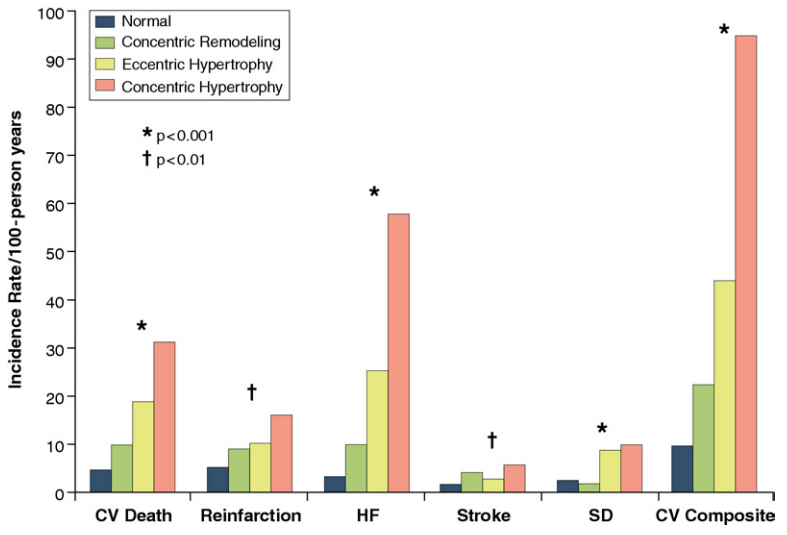

Figure 5. Remodeling Patterns and Cardiovascular Events

Compared with patients without evidence of left ventricular (LV) remodeling, patients with any of the patterns of LV remodeling post-myocardial infarction (MI) had a greater risk of the composite of cardiovascular (CV) death, MI, heart failure (HF), stroke, or resuscitated cardiac arrest. In addition, the patterns of concentric remodeling, eccentric hypertrophy, and concentric hypertrophy were associated with a progressively increased risk of the composite end point, with each of the individual outcome components following a risk pattern similar to that of the overall composite. SD = sudden death. Reprinted, with permission, from Verma et al. (28).

overall likelihood of future adverse cardiovascular events (60).

Although more work is needed in this area, it is likely that the combination of LV geometric indicators, such as volumes and overall patterns of remodeling, along with myocardial characteristics, such as LGE and microvascular obstruction, will together form a powerful constellation of findings predicting subsequent clinical outcomes.

Relationship between clinical outcomes and longitudinal LV measurements. A number of studies have supported the value of serial changes in parameters of LV remodeling for predicting clinical outcomes in patients with LV dilation and/or decreased LVEF. Data from the echocardiographic substudy of the SAVE (Studies of Ventricular Enlargement) trial demonstrated that longitudinal changes in LV area >1 year after MI significantly correlated with subsequent long-term rates of cardiovascular events, independent of randomization to either captopril or placebo (Fig. 6) (61). Similarly, echocardiographic data from the Val-HeFT (Valsartan Heart Failure Trial) in 5,010 patients with heart failure and both LVEF <40% and LV end-diastolic dimension index >2.9 cm/m^2, showed that both baseline LV end-diastolic dimension index and LVEF and changes in these parameters over time were independent predictors of patient outcome (62).

Relationship Between an Intervention's Effect on Remodeling and its Effect on Clinical Outcomes in Patients with Heart Failure and Decreased LVEF

Beyond mere prognostication, measures of LV remodeling have been used extensively to gauge the effect of drug and device interventions on cardiac structure and function. In a radionuclide ventricular

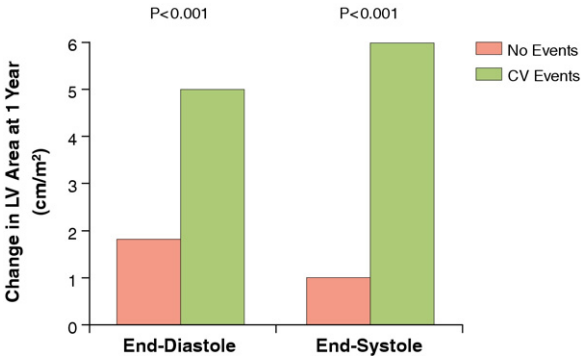

Figure 6. Longitudinal Ventricular Dilation and Prognosis

Changes in left ventricular (LV) area at end-systole and end-diastole over 1 year in patients after myocardial infarction with baseline left ventricular dysfunction, from the SAVE (Studies of Ventricular Enlargement) trial, compared in patients who sustained versus those who did not sustain adverse cardiovascular (CV) events. Patients experiencing events had a significantly greater increase in areas (i.e., more adverse remodeling) compared with those who had no events. Adapted, with permission, from St. John Sutton et al. (61).

function substudy of the SOLVD (Studies of Left Ventricular Dysfunction) trial, we demonstrated differences in serial measures of LV volumes for patients randomized to the angiotensin-converting enzyme inhibitor enalapril versus those randomized to placebo, which paralleled the enalapril effect on all-cause mortality and on heart failure hospitalization. We observed that enalapril prevented or reversed the progressive remodeling process seen in placebo-group patients with an LVEF ≤35%, either with (treatment trial) (14) or without (prevention trial) (15) heart failure symptoms (Fig. 7).

Numerous studies have shown favorable effects on parameters of LV remodeling for drugs that improve clinical outcomes in patients with decreased LVEF and LV dilation, notably angiotensin-converting enzyme inhibitors, beta-blockers, and angiotensin receptor blockers (14,15,18,57,63–69). Conversely, agents with neutral or adverse effects on remodeling, relative to a comparator, have often been found to be associated with neutral or adverse effects on clinical outcomes. Examples include omapatrilat (70,71) and ibopamine (72,73). In a head-to-head comparison of the angiotensin-converting enzyme inhibitor captopril, 150 mg daily, with the angiotensin receptor blocker losartan, 50 mg daily, we found a trend favoring captopril in the 1-year change in LV volumes (18), an effect that presaged the mortality findings in ELITE (Early Versus Late Intervention Trial With Estradiol) II (74). Yu et al. (75) showed that a decrease in LV ESV of ≥10% after cardiac resynchronization therapy predicted decreased long-term mortality and heart failure events, whereas symptomatic improvement did not. More recently, in separate trials, the vasopressin V2 receptor antagonist tolvaptan was shown to have a neutral effect on both ventricular remodeling and long-term clinical outcomes (27,76). In contrast, in 2001, Bozkurt et al. (77), examining 3-month changes in LVEF, EDV, and ESV, showed a dose-dependent, placebo-controlled reverse remodeling effect over 3 months with etanercept, an inhibitor of tumor necrosis factor-alpha. Three years later, a much larger, long-term study failed to show any long-term clinical outcome benefit (78). Conversely, we were unable to demonstrate a benefit of the aldosterone receptor blocker eplerenone on LV remodeling in a group of patients with class II and III heart failure and decreased LVEF (25), despite the favorable impact that this class of agent has exerted in select patient populations with heart failure and decreased LVEF (79,80). Nevertheless, it appears that in most, but not all, cases there is concordance between an intervention's effect on LV remodeling and heart failure–related clinical outcomes for patients with reduced LVEF, either post-MI or with chronic heart failure.

Recently, we performed a meta-analysis examining the relationship between drug- or device-induced changes in parameters of LV remodeling and the effects of the same interventions on mortality in

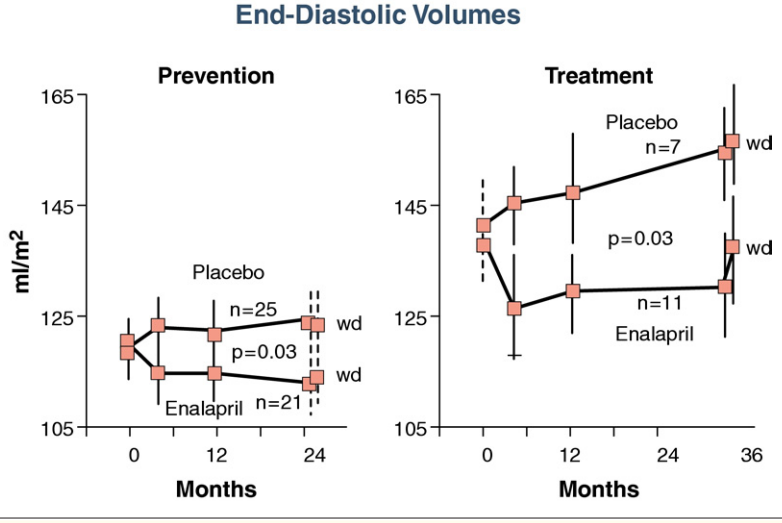

Figure 7. Angiotensin Converting Enzyme Inhibitor Effects on Ventricular Volumes

Changes in left ventricular end-diastolic volume over time in asymptomatic (Prevention) and symptomatic (Treatment) patients with decreased left ventricular ejection fraction while randomized to placebo or enalapril, from the SOLVD (Studies of Left Ventricular Dysfunction) trials. During long-term follow-up, patients randomized to placebo demonstrate evidence of progressive increase in left ventricular end-diastolic volume, whereas those randomized to enalapril showed reductions in left ventricular volume. wd = restudy after withdrawal of placebo or enalapril. Adapted, with permission, from Konstam et al. (14,15).

patients with heart failure and decreased LVEF (81). We classified 25 drug or device interventions as having favorable, neutral, or unfavorable effects on survival, estimating the odds ratio for death for each intervention compared with placebo based on large-scale, randomized, controlled outcome trials. We then examined the correlation between these odds ratios and the placebo-corrected change from baseline in LV volumes observed in 88 individual remodeling studies performed with each of these interventions (Fig. 8). We found significant correlations between longer term trial-level therapeutic effects on mortality and short-term trial-level therapeutic effects of a drug or device on LVEF ($r = -0.51$, $p = <0.001$), EDV ($r = 0.44$, $p = 0.002$), and ESV ($r = 0.48$, $p = 0.002$). Furthermore, these drug-/device-induced changes in ventricular remodeling reflect the probability of a categorical mortality outcome (favorable, neutral, or adverse) for those therapies. These findings provide the best support available linking interventional effects on the process of LV remodeling and on clinical outcomes in patients with decreased LVEF and heart failure and suggest that the placebo-corrected effect of a drug or device on the process of remodeling can serve as a probability signal of that intervention's potential effect on mortality. Certainly, an intervention might exert a favorable effect on clinical outcomes through mechanisms divorced from those responsible for LV remodeling. In the case of aldosterone receptor blockade, we postulate that at least some of the outcome benefit may be mediated through vascular effects. Conversely, off-target adverse effects may offset the clinical benefit derived from a drug's or device's favorable impact on the progression of myocardial pathology. Nevertheless, results of our meta-analysis support the use of remodeling data as a means of selecting agents to seek evidence of outcome benefit through larger scale investigation, focusing on clinical events. Further, although remodeling benefit cannot be taken as a definitive surrogate end point for survival, demonstrable remodeling benefit of a drug or device serves to substantiate and render more credible a survival signal observed with that intervention.

Conclusions

The process of ventricular remodeling is well established and well described in animal models of LV

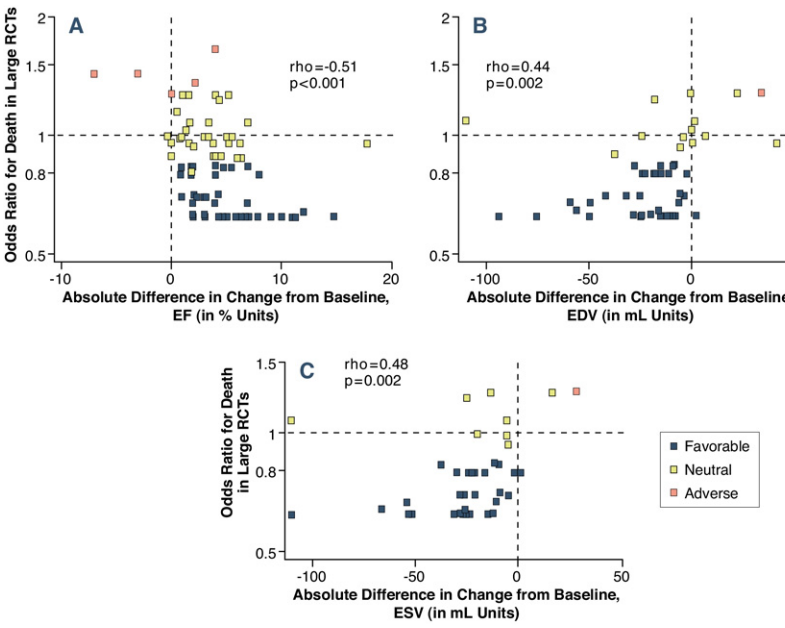

Figure 8. Correlation of an Intervention's Effect on Remodeling and on Mortality

Quantitative relationship between drug/device effects on ejection fraction (EF), end-diastolic volume (EDV), end-systolic volume (ESV), and mortality in patients with heart failure and left ventricular dysfunction. Each data point represents a placebo-corrected change in EF **(A)**, EDV **(B)**, or ESV **(C)** from an individual remodeling trial plotted against the mortality odds ratio for the specific therapy. Interventions were classified as favorable if the upper limit of the 95% confidence interval of the odds ratio for death from the mortality trials was <1, neutral if the confidence interval crossed 1, and adverse if the lower limit of the confidence interval was >1. There was a significant correlation between longer term therapeutic effect on mortality and short-term therapeutic effect on left ventricular EF ($r = -0.51$, $p <0.001$), EDV ($r = 0.44$, $p = 0.002$), and ESV ($r = 0.48$, $p = 0.002$). Remodeling data derived from analysis of 86 randomized, controlled trials (RCTs) of 25 interventions, including 19,092 total patients. Reprinted, with permission, from Kramer et al. (81).

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stress and injury and in patients after MI and other forms of dilated cardiomyopathy. Various techniques have been developed to explore the remodeling process in patients, each carrying advantages and disadvantages. These techniques have been extensively deployed in clinical trials, demonstrating the value of baseline LV volumes and change in LV dimension, area, and volume over time, for predicting subsequent clinical outcomes. Beyond LV volumes, the pattern of LV remodeling was recently shown to carry additional predictive value for vascular and heart failure-related events. These findings support the hypothesis that the linkage between LV remodeling and outcome occurs not merely through the adverse impact of cardiac pathology per se, but also via the role of LV morphologic change as a measure of concomitant vascular pathology. Finally, our recent meta-analysis correlating drug and device effects on LV volumes and on survival within a given population strengthens our understanding of the impact of remodeling changes on clinical outcomes in heart failure and provides support for the use of remodeling parameters to guide subsequent larger scale clinical investigation and to help substantiate a given outcome signal within a given population.

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