

# Heart Failure

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# The evolving rationale of heart failure therapy

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*Current heart failure rationales bear little resemblance to the pump failure model that prevailed in the 1970s, prompting prescriptions of digitalis to potentiate myocardial contractility and diuretics to decrease fluid retention. First, the 1980s focused on the feature of diffuse vasoconstriction and added vasodilators to the therapeutic regimen. Then a conceptual leap in the 1990s revealed the role of regulatory system hyperactivity, inspiring a range of renin-angiotensin-aldosterone and adrenergic system modulators with multifaceted and still unexhausted pharmacodynamic potential. Models, medicines, and an increasing wealth of devices have since driven each other forward to create the current plethora of complementary rationales. The macroscopic ventricular remodeling responsible for deteriorating ventricular dysfunction is related to microscopic disruption of the connective tissue matrix, since both features respond to angiotensin-converting enzyme therapy. Other models, each with an actual or, more often, potential therapeutic correlate, include the early role of diastolic dysfunction, ventricular desynchronization, the contribution of myocardial small vessel and endothelial disease revealed in hypertensive and diabetic heart failure, and the critical impact of cardiomyopathy genes and their differential expression depending on clinical circumstance. Unfortunately, these interdigitating narratives have yet to be generally mirrored in a seamless system of efficient heart failure care.*

Schematically, over the last 30 years, there have been at least three different models for interpreting heart failure, which have led to different approaches to the treatment of this syndrome.<sup>1</sup> In the 1970s, heart failure was seen as the clinical manifestation of heart pump failure causing a drop in renal blood flow, thus resulting in water retention. Therapy was based on drugs that could potentiate myocardial contractility (digitalis) and limit fluid retention (diuretics). In the 1980s, the prevailing interpretation was that heart pump failure caused diffuse vasoconstriction. The resulting blood flow limitation increased the work of the heart and compromised the function of organs and peripheral districts. Treatment, therefore, placed the emphasis on vasodilators, in addition to diuretics and digitalis. New classes of drugs emerged, among which the phosphodiesterase inhibitors (amrinone, milrinone, etc). These drugs were capable of both stimulating myocardial contractility and dilating the vessels. However, they appeared to be more harmful than beneficial in long-term treatment. In the 1990s, attention focused on the hyperactivity of regulatory systems, such as the renin-angiotensin-aldosterone system (RAAS) and the adrenergic system, which were ascribed a major pathophysiological role in heart failure.

Although these systems provide effective short-term protection of cardiocirculatory function in the presence of dehydration or hemorrhage, they were shown to be deleterious in the long term. The 1990s also saw the beginning of systematic evaluation of drug efficacy and safety in clinical trials conducted on large populations, which confirmed without the slightest doubt the clinical efficacy of RAAS and adrenergic system modulation. Thus, heart failure today is understood as the ultimate common outcome of many forms of heart disease at the advanced stage. This implies a great complexity in the pathogenesis and evolution of the heart failure process, in which two main features play an essential role: (i) ventricular remodeling, which causes progressively worsening systolic and diastolic ventricular dysfunction; and (ii) activation of a series of biological responses to ventricular dysfunction, which contribute to determining the clinical expression and

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**SELECTED ABBREVIATIONS AND ACRONYMS**

<b>ARB</b>	angiotensin-receptor blocker
<b>CHARM</b>	Candesartan in Heart failure Assessment in Reduction of Mortality
<b>CONSENSUS I</b>	First COoperative North Scandinavian ENalapril SURvival Study
<b>CRP</b>	C-reactive protein
<b>DCM</b>	dilated cardiomyopathy
<b>DEFINITE</b>	DEFibrillators In Non-Ischemic cardiomyopathy Treatment Evaluation
<b>EF</b>	ejection fraction
<b>EUROPA</b>	EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease
<b>HCM</b>	hypertrophic cardiomyopathy
<b>HOPE</b>	Heart Outcomes Prevention Evaluation
<b>ICD</b>	implantable cardioverter defibrillator
<b>LVEF</b>	left ventricular ejection fraction
<b>MI</b>	myocardial infarction
<b>PUFA</b>	polyunsaturated fatty acid
<b>QUASAR</b>	QUinapril Anti-ischemia and Symptoms of Angina Reduction
<b>QUO VADIS</b>	Effect of QUinapril On Vascular ACE and Determinants of ISchemia
<b>RAAS</b>	renin-angiotensin-aldosterone system
<b>RCM</b>	restrictive cardiomyopathy
<b>REVIVE</b>	Randomized, multicenter, Evaluation of Intravenous leVosimendan Efficacy vs placebo in the short-term treatment of decompensated chronic heart failure
<b>SCD-HeFT</b>	Sudden Cardiac Death in Heart Failure Trial
<b>SOLVD</b>	Studies Of Left Ventricular Dysfunction
<b>SURVIVE</b>	Multicenter, parallel-group randomized, double-blind, double-dummy study in patients with acutely decompensated heart failure comparing the efficacy of levosimendan with that of dobutamine
<b>TNF-<math>\alpha</math></b>	tumor necrosis factor- $\alpha$

evolution of heart failure. The current treatment of heart failure, laid down in the guidelines of the major international Cardiology Societies, addresses the latest pathophysiological concepts. Nevertheless, clinical

and scientific experience over the past several years has highlighted the limitations as well as the benefits of the current therapeutic approach and of the conceptual model on which it is based.

**HOW EFFECTIVE IS THERAPY?**

The most common way of reporting the benefit of treatment in mortality trials is the reduction in deaths occurring during the observation period, either in absolute terms (number of deaths less for every 100 subjects in 1 year and/or during the observation period) or in relative terms (percentage of deaths less in the treated population in relation to control subjects). There is much talk of lives saved and of the number of subjects needed to treat to prevent 1 death (NNT). It would sometimes appear as though this life were saved "for ever!" Obviously, this is not the case. Heart failure usually persists and life has only been prolonged. By how much? This is the real question to ask. To answer this, we need to know how long all the patients, both treated and untreated, live. Furthermore, since control patients will also be treated, at the end of the study, if the treatment is shown to be effective, the mean difference in survival of the two groups reflects the efficacy of the treatment during the period of the study, when the treatment was randomized. In this context, the First COoperative North Scandinavian ENalapril SURvival Study (CONSENSUS I) reported an average of 9 months additional life over a mean period of treatment with captopril of less than 1 year.<sup>2</sup> This was a dramatic finding in view of the severity of heart failure in the patients enrolled in CONSENSUS, in whom the annual mortality rate was about 50%. Curiously, similar results were found when estimating the increase in survival of patients enrolled in the treatment arm of the Studies Of Left Ventricular Dysfunction (SOLVD-treatment), with an ejection fraction (EF) <35% and symptoms of heart failure, and in the prevention arm (SOLVD-prevention) (with EF <35% without symptoms of heart failure) trials.<sup>3</sup> This was only an estimate, with wide confidence limits, and not a measurement, since when the calculation was carried out, 12 years after the start of the study, not all the patients had died. The estimate showed that SOLVD conferred an average of about 9 additional months of life on patients treated with enalapril for a mean period of randomized treatment of 3 years. Taking into account the fact that after the first months<sup>2</sup> or the first year<sup>3</sup> of randomized treatment the survival curves of patients treated with ACE inhibitors and of the controls tended to become parallel, what we can reasonably expect from angiotensin-converting enzyme (ACE) inhibitor treatment



in heart failure from these two trials is under 1 extra year of life. It should be noted that these patients were not treated with  $\beta$ -blockers.

Similar considerations also apply to device-based treatment, particularly in the case of implantable defibrillators, whose only function is, precisely, the prevention of sudden arrhythmic death. The only study carried out to date in patients with heart failure is the still unpublished Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). In this study, the reduction of mortality was about 1.7%/year in absolute values for a total of about 8 deaths less over an observation period of approximately 5 years. How much longer these patients lived (in relation to their natural destiny) is unknown. We do, however, know that, over 5 years, 92 patients out of 100 derived no benefit from the treatment despite being exposed to the risk of possible complications or inappropriate shocks delivered by the device. Thus, for example, the recently published DEFibrillators In Non-Ischemic cardiomyopathy Treatment Evaluation (DEFINITE) study recorded inappropriate shocks in 46 patients and appropriate shocks in 41 patients<sup>4</sup>). We mention SCD-HeFT not because it is the only trial of its kind in heart failure patients, but also because of its relatively long observation period. As Salucke et al recently pointed out, studies with relatively short observation periods can lead to underestimation of the real benefit of defibrillators.<sup>5</sup> Identification of patients at genuine high risk is clearly critical for an appropriate indication for defibrillator use. In other words, prognostic stratification needs to be improved.

### PROGNOSTIC STRATIFICATION

The fact that heart failure guidelines contain only a few inconclusive lines on prognostic stratification is no mere oversight. European guidelines list a series of supposedly independent prognostic predictors.<sup>6</sup> However, despite the many prognostic indicators and algorithms that have been proposed,<sup>7</sup> our ability to provide satisfactory prognostic evaluation remains extremely limited. A number of explanations for our impotence have been put forward.<sup>6</sup> I will briefly discuss several of these.

- The numerous pathologies that lead to heart failure evolve in their own specific way. This fact, which necessarily affects the progression of the cardiac syndrome, is not taken into account by the indicators usually used in the prognostic stratification of heart failure.
- Associated comorbid conditions, in particular in the elderly, can produce clinical profiles and disease evo-

lutions that are not consistent with the algorithms based on trial data, inasmuch as patients with comorbid diseases are usually excluded from trials.

- Investigation of the biological systems involved in the progression of heart failure is limited by our ability to measure the key variables of these very systems. At most, we measure the blood concentrations of the mediators, but many of them have paracrine functions and very short lives. As only a small fraction of these mediators enters the circulation, blood concentrations do not reflect levels of activity in the tissues.
- The activation of many biological systems and their impact on organs and tissues in heart failure is not gradual and constant over time. Furthermore, the prognostic power of indicators can differ in relation to the stage of evolution of the syndrome. Powerful indicators at earlier stages of the syndrome (eg, left ventricular ejection fraction [LVEF]), lose some of their predictive strength at more advanced stages, while others assume greater importance (eg, organ damage indicators or right ventricular dysfunction). Clinical destabilization may occur abruptly and regress rapidly. Prognostic stratification yields very different results depending on whether the patient is in a stable or unstable phase. Therefore, one set of predictive algorithms should be used for making immediate decisions during acute phases and different one for defining long-term strategies during stable periods.
- About half of the deaths in patients with heart failure are sudden and can occur at any stage of the syndrome's evolution, a fact that traditional algorithms fail to address. In other words, we lack strong indicators for sudden death.
- The introduction of new treatments into clinical practice can have a marked effect of both outcome and symptoms, but not necessarily simultaneously. For this reason, algorithms for prognostic stratification should be updated in relation to the treatments used and the individual application of algorithms should take into account the therapy used in the individual patient.

Alongside these general methodological considerations, others concern individual aspects of prognostic studies reported in the literature, including more or less restrictive inclusion criteria, numerically inadequate series, and the restriction of parameters included in multivariate analyses, such that the independent value of the prognostic indicators selected is often questionable.

Obviously, prognostic limitations in turn impose a substantial limitation on the successful identification of the potential responders to available treatments. It will

not have escaped attentive clinicians that although guidelines were issued recommending the prescription of ACE inhibitors and  $\beta$ -blockers to all patients, no formal recommendations could be given regarding neurohormonal prognostic predictors usable in clinical practice. Brain natriuretic peptide (BNP) is a cardiac hormone that is only indirectly involved in modulating the major systemic regulatory systems. This may not be very relevant for some treatments targeted at the fundamental pathophysiological mechanisms of heart failure, in particular those shown to be effective in both the prevention and treatment of heart failure whatever the severity, but it certainly is relevant for those treatments reserved to patients with specific risk factors, typically of sudden death. Since it is generally thought that the risk of sudden arrhythmic death is relatively higher in the numerous patients with heart failure in the less advanced New York Heart Associated (NYHA) classes, although recent data contradict this assumption,<sup>8</sup> a reliable definition of the risk of sudden death is essential. Thus, prognostic stratification, based on databases of randomized trials, and particularly, of registries and observational studies, must be considered a primary aim.

**TREATMENT PRIORITIES:  
THE HEART, THE REGULATORY  
SYSTEMS, OTHER ORGANS,  
OR COMPROMISED TISSUES?**

The obvious answer, "all," is not the correct one. Priorities should be strictly based on benefits versus risks, new drugs should be developed with compliance as a major goal, and therapeutic research should focus attention and resources on clearly defined objectives.

**The heart**

As far as the heart is concerned, *Table I* lists what I believe are the fundamental mechanisms of pump failure, together with their respective therapeutic implications. The most obvious pathophysiological aspect is pump failure associated with the *inability of myocytes to generate a force* sufficient to ensure efficient and appropriate circulation of the blood to meet the needs of the body. Treatment should increase the contractile force of myocytes without causing notable side effects. So far, however, all tested long-term oral inotropic drugs have invariably increased mortality. As for intravenous inotropic drugs (whether  $\beta$ -receptor stimulators such as dobutamine or phosphodiesterase III inhibitors such as milrinone and amiodarone), their most significant limitation is due to the fact that their inotropic action

is expressed through increased availability of intracellular calcium. Since calcium also has important electrophysiological actions, any increase in the concentration of calcium causes changes in ion flows, facilitating the onset of potentially fatal arrhythmias. A new class of drugs, the calcium sensitizers—prototype: levosimendan—claims to increase myocardial inotropism without inducing dangerous ionic imbalances. Initial clinical trial data appear to support this hope.<sup>9,10</sup> Two large prospective mortality-morbidity trials with levosimendan, the first versus placebo (REVIVE [Randomized, multicenter, Evaluation of Intravenous leVosimendan Efficacy vs placebo in the short-term treatment of decompensated chronic heart failure]), the second versus dobutamine (SURVIVE), are currently under way and should provide a definitive answer.

The aspect that I believe has been less clearly appreciated so far is *disruption of the connective tissue matrix*. This is a fundamental mechanism of heart failure in most cases of hereditary dilated cardiomyopathies (DCMs), which definitely also plays an important role in ischemic cardiomyopathy. It leads to an increase (not a decrease) in ventricular compliance, shifting the entire ventricular pressure-volume curve to the right, resulting in greater dilatation of the chamber for smaller pressure loads. Although Starling's law should fully apply in this case, the problem is that part of the force generated by the myocytes is not transmitted because of changes in intercellular connective tissue bridges, and is therefore lost because it does not contribute to producing the overall mechanical energy expressed by the ventricles. We do not have drugs "designed" to counteract disruption of the connective tissue matrix, but it is likely that some of the benefit of drugs modifying the renin-angiotensin system and of antialdosterone drugs is linked to this mechanism.

The third mechanism of heart failure is *ventricular dyssynchrony*. The severely compromised ventricular mechanics leading to heart failure can be characterized by functional desynchronization of the two ventricles due to a disorder of intraventricular conduction (usually left bundle branch block) or to changes in the mechanical coordination of the left ventricle. Under these conditions, myocardial regions contracting against each other early waste energy in inefficient movements, and regions that do so late waste it in overcoming the unduly high resistances. The therapeutic approach is ventricular resynchronization by elective multisite stimulation.

The fourth form of heart deficit is *ventricular diastolic dysfunction*. It has now become essential to differenti-



Mechanism	Effect	Treatment
<ul style="list-style-type: none"> <li>Bioenergetic decline of myocytes</li> <li>Disruption of the collagen matrix</li> </ul>	<ul style="list-style-type: none"> <li>Loss of contractile function</li> <li>“Too” compliant ventricles Inadequate/erratic transmission of the force generated by the myocytes</li> </ul>	<ul style="list-style-type: none"> <li>Inotropic drugs</li> <li>No specific treatment, neurohormonal agents?</li> </ul>
<ul style="list-style-type: none"> <li>Cardiac dyssynchrony</li> </ul>	<ul style="list-style-type: none"> <li>Atrioventricular inter/intraventricular incoordination</li> </ul>	<ul style="list-style-type: none"> <li>Multisite pacing</li> </ul>
<ul style="list-style-type: none"> <li>Alterations of relaxation and elastic properties</li> </ul>	<ul style="list-style-type: none"> <li>Poorly relaxing, stiff ventricles, limited ventricular filling</li> </ul>	<ul style="list-style-type: none"> <li>Unloading, atrial contribution, and adequate diastolic interval</li> </ul>

**Table 1.** Mechanisms, effects, and treatment of major cardiac function alterations in chronic heart failure.

ate heart failure into forms with depressed left ventricular systolic function and those with preserved left ventricular function, that is, with an EF less than or greater than  $\approx 45\%$ , respectively. Whether therapy should be radically different in relation to ventricular systolic function, in practice in relation to left ventricular ejection fraction, is not yet clear. Apart from the results of the Candesartan in Heart failure Assessment in Reduction of Mortality (CHARM)-preserved study (which did not show any added value of the angiotensin receptor blockers [ARBs]),<sup>11</sup> data from the various ongoing trials testing different classes of drugs in heart failure with preserved systolic function are not yet available. The clinical profile of these patients seems to be relatively specific: higher prevalence among the elderly, women, hypertensive, diabetics with a relatively good functional class in stable conditions, but with a tendency to abrupt destabilizations during which left ventricular EF tends to remain almost normal; these patients may be relieved relatively easily with the administration of diuretics and vasodilators. The prognostic data are consistent with this profile: less mortality than among patients with a low EF, but a similar incidence of hospital admissions. It is probable that ongoing studies will show that pharmacological control of the regulatory systems needs not be very different from that in patients with a reduced EF, but that direct interventions to the heart should differ. Drugs that prevent progressive fibrosis of the heart (the antialdosterones?) could also, or above all, be particularly effective in these forms. Furthermore, it seems essential to prevent destabilizations, prevalently caused by pulmonary congestion, which does, in fact, dominate this clinical picture. Since the left ventricle is less elastic (in the first phase of diastole) and less compliant (in the late phase of diastole) than normal, it adapts poorly to volume loads. A modest increase in volume load is not accepted by the rigid left ventricle, causing a considerable increase

in pulmonary pressure, which can trigger acute pulmonary edema. Relieving the congestion with a moderate dose of intravenous diuretics can rapidly resolve the destabilization, which in turn can reduce the risk associated with these episodes and contribute to a less severe prognosis.

Why should the diastolic properties of the heart be prevalently altered in some diseases? Do alterations in small vessel function play an important role? Hypertension is a disease of the arteries that secondarily affects the heart. When and why, as well as in whom, hypertension becomes a cardiac disease is still far from clear. The scope for prevention might be enormous if research would focus on the heart and small myocardial vessels as well as on the arteries. New perspectives should include existing drugs and new molecular players in hypertrophy and remodeling, such as melusin, a protein whose absence in the hypertrophic heart seems to condition dilation and heart failure.<sup>12</sup> The microcirculation also represents a major research field and substrate of treatment in diabetic patients. Diabetes-related heart disease is currently considered as the result of coronary artery disease (CAD) electively complicating the natural history of diabetes. Furthermore, although more than twenty genetically different types of diabetes are known, our current approach only groups patients into those affected by insulin-dependent or non-insulin-dependent diabetes, mostly because treatments are exclusively based on either insulin or oral hypoglycemic drugs.

Small-vessel disease and endothelial dysfunction are major contributors to myocardial damage in both hypertension and diabetes. The increasing use of positron emission tomography (PET) scan could increase our knowledge of small-vessel disease and open up new areas of research for protecting the myocardium. Small-

vessel disease may either contribute to left ventricular hypertrophy via an imbalance between myocyte hypertrophy, hyperplasia, and apoptosis or impaired myocardial perfusion. Prevention of heart failure should therefore be based on the preservation of structural and functional integrity of the myocardial tissue. Systolic dysfunction comes later and its improvement is a late strategy. Elucidation of the role of small-vessel disease in myocyte apoptosis and collagen production and turnover may initiate a translational paradigm shift in clinical practice.

### **The regulatory systems**

As already mentioned, among the various regulatory systems, we are able to therapeutically manipulate the RAAS and the adrenergic system. One of the ways of doing this is to modulate some of the many functions of the endothelium. Analysis of the clinical effects produced by ACE inhibitors in ischemic heart disease, the most common cause of heart failure, gives a clear indication of the extent to which the counterregulatory actions of drugs can be selective.

The pharmacological treatment of stable angina has two major purposes. The first is to prevent myocardial infarction (MI) and death and thereby increase the quantity (duration) of life. The second is to reduce the symptoms of angina and the occurrence of ischemia, which should improve the quality of life. Accordingly, there are two categories of treatment: those prescribed to prevent death and MI and those with antianginal and anti-ischemic effects aimed at alleviating symptoms and reducing ischemia.<sup>13</sup> Obviously the two categories partially overlap. The first group of drugs includes antiplatelet agents, antithrombotic therapy, antihypertensive agents, lipid-lowering agents, and ACE inhibitors; the second group includes  $\beta$ -blockers, calcium antagonists, and nitrates.

After having been tested with success in heart failure, systemic hypertension, and acute and subacute MI, the ACE inhibitors were tried in patients considered to be at risk for cardiovascular events in both the Heart Outcomes Prevention Evaluation (HOPE)<sup>14</sup> and European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA)<sup>15</sup> trials. The effectiveness and safety of ramipril and perindopril, respectively, were clearly demonstrated, even in patients who were not hypertensive. The EUROPA trial is particularly relevant in this context because it specifically enrolled patients with chronic ischemic heart disease, since the criterion for inclusion in the study

was confirmed presence of CAD associated with any level of risk. Given that some ACE inhibitors (ramipril and perindopril) have been shown to effectively prevent the clinical progression of coronary atherosclerosis, one may wonder whether these drugs are also effective in reducing the ischemic burden of patients with CAD and inducible myocardial ischemia. About twenty small published studies suggest that these drugs are indeed effective in this context. However, two recent randomized studies demonstrated the opposite. The QUinapril Anti-ischemia and Symptoms of Angina Reduction (QUASAR) trial<sup>16</sup> sought to determine whether an ACE inhibitor prevents transient ischemia (exertional and spontaneous) in patients with CAD and stable angina. Three hundred and thirty-six patients without hypertension, left ventricular dysfunction, or previous MI were randomly assigned to quinapril or placebo groups. After 8 weeks, the groups did not differ at all in terms of indices assessing myocardial ischemia, such as ischemic threshold during exercise, ischemic burden from ambulatory recordings, and scores on the Seattle Angina Questionnaire. These findings match those from another trial, the Effect of QUinapril On Vascular ACE and Determinants of ISchemia (QUO VADIS) study,<sup>17</sup> carried out in 149 patients with ischemic heart disease randomized to quinapril or placebo 4 weeks before elective bypass surgery and then followed for 1 year. Again, no differences in ischemic measures were observed between the two groups. Although clinical events were obviously not end points in this small trial, it is interesting to note that fewer adverse cardiovascular events were recorded in the quinapril group than in the placebo group (4% vs 15%,  $P=0.02$ ). Though the absence of any effect of quinapril on ischemic parameters may be related to the dose of the drug, or to different effects (or lack of effects) of different ACE inhibitors, the complex scenario of the action of ACE inhibitors in ischemic heart disease suggests that there is a clear distinction between antianginal and anti-atherosclerotic-antithrombotic drugs, the former being effective in reducing the ischemic burden, but having little or no effect on progression of the coronary artery disease, the latter having little or no effect on the ischemic burden, but significantly modulating the progression of the coronary artery disease.

The other major system activated in heart failure, the immune-inflammatory system, is not currently controllable. This system is partly also responsible for the progression of ischemic heart disease, and thus relevant in heart failure secondary to ischemic heart disease. Vasan et al recently explored the predictive value of interleukin 6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and



C-reactive protein (CRP) on the onset of congestive heart failure in older subjects without previous MI.<sup>18</sup> They showed a strong predictive value for all the markers, particularly for IL-6. Similar findings were reported by Koukkunen et al<sup>19</sup> and Cesari et al<sup>20</sup> exploring the prognostic value of these three inflammatory markers in older patients with CHD, perhaps, because of their wide range of actions including effects on platelets, endothelium, and factors of metabolism and coagulation. TNF- $\alpha$  and IL-6 levels are associated with the severity of left ventricular dysfunction and with the degree of activation of the sympathetic and renin-angiotensin systems. It has also been reported that proinflammatory cytokines might depress myocardial contractility. Over the past years, a series of multicenter clinical trials using “targeted” approaches to neutralize cytokines in patients with heart failure have been conducted. These trials failed to show any substantial benefit in heart failure.<sup>21,22</sup> These results raise important questions about the role that cytokines play in the pathogenesis of heart failure. Are higher levels of inflammatory markers part of the pathophysiological pathway leading to cardiovascular disease or just an indirect measure of subclinical disease? If the latter is shown to be true, treatment aimed at depressing inflammation might be useless. The increase in cytokines such as TNF- $\alpha$ , endothelin, and interleukins cannot be controlled by agents specifically blocking one or the other of these biological mediators. It is possible that the activation of a complex, multifaceted system like the immune-inflammatory system (the cytokine family alone is formed of scores of different molecules), and one that certainly contains redundancies as do all biological systems essential to life, cannot be modulated by blocking a single component of the system. The system must probably be manipulated more upstream or with a different approach. This is part of the rationale that led to the design of an ongoing trial in Italy, the Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza cardiaca–Heart Failure (GISSI-HF) trial,<sup>23</sup> to test the effects of n-3 PUFA (polyunsaturated fatty acids) in heart failure (demonstrated to be effective in preventing sudden death in the GISSI-Prevention trial<sup>24</sup>), as well as of a statin, rosuvastatin, which, like all statins, is endowed with a powerful anti-inflammatory effect.

### Other compromised organs and tissues

Focusing on clinical aspects such as anemia and renal dysfunction, considered marginal until a few years ago, has highlighted their prognostic relevance and led to greater consideration of the changes that heart failure causes in organs and tissues other than the heart. The

alterations in skeletal muscles, liver, and lungs may become critical and play driving roles in the clinical evolution of the syndrome.

For example, *anemia*, common in patients with advanced heart failure,<sup>25,26</sup> can be due to occult bleeding from a damaged gastrointestinal tract and/or to the use of drugs, including antiplatelet agents and anticoagulants—which, for some reason or another, about 80% of patients with heart failure take—but can also be due to inhibition of the production of erythropoietin and its action on the bone marrow (mainly through cytokines). A 1-point reduction in hematocrit in patients with marked anemia increases the probability of death by 15%.<sup>27</sup> It seems that treatment with erythropoietin and substances necessary for erythrocyte production, such as iron, can be effective.<sup>28</sup> Methodologically appropriate trials are currently verifying this hypothesis.

*Renal dysfunction* is also a relevant prognostic factor in heart failure.<sup>29-31</sup> The observation that renal failure does not develop in all patients with advanced heart failure is interesting. Heart failure can unmask renal dysfunction in patients with structural alterations and/or functional changes, which are often an associated effect of the disease that has caused the heart failure. Thus, an increase in creatinemia is a sign of both the severity of the heart failure and of the pathogenic penetration of the underlying disease. The kidney is increasingly becoming a therapeutic target in heart failure. There are solid data demonstrating that modulating the RAAS is effective in controlling the renal dysfunction of heart failure. Among diabetic subjects, ACE inhibitors in insulin-dependent patients and ARBs in non-insulin-dependent patients have been shown to be particularly effective in preventing renal damage. Data also confirm the good tolerance of  $\beta$ -blockers in heart failure patients with renal dysfunction. Trials are under way to evaluate the clinical efficacy of drugs blocking the receptors of vasopressin, adenosine, and other molecules acting on the kidney.

### ACUTE HEART FAILURE

Acute heart failure has long been banished to the sidelines by the international cardiological community. The European Society of Cardiology has finally produced the first, long overdue, guidelines on acute heart failure.<sup>32</sup> The growing awareness of the relevance of this clinical problem (which has led among other things to a greater willingness on the part of scientific journals to publish articles dealing with this topic), more attention to methodology (not least by regulatory bodies),

and above all the increasing investment in this field by some companies, should facilitate a rapid increase in knowledge and more rational and diversified therapeutic approaches. Currently, the drug most frequently used (as infusion) in acute heart failure is dobutamine, a drug many consider more harmful than useful in terms of survival and which has been given a 2B recommendation in the European guidelines. This gives an idea of just how rudimentary our management of acute heart failure is.

## THE ERA OF DEVICES

### Electrical devices

As mentioned, simultaneous electrical stimulation of the two ventricles can overcome interventricular desynchronization, and stimulation of the left ventricle, usually applied to the posterolateral wall (with a catheter placed in the coronary sinus), can reduce intraventricular desynchronization by modifying the ventricular excitation-contraction sequence. In some randomized trials, this therapy has improved symptoms and exercise capacity, reduced ventricular volumes and mitral regurgitation, improved ventricular systolic function, and reduced morbidity.<sup>33,34</sup> There are promising, though not definitive, data on its effect on mortality.<sup>35</sup>

Resynchronization therapy has been used in patients in NYHA classes III-IV with electrocardiographic evidence of desynchronization (usually diagnosed from the presence of an intraventricular conduction delay, QRS >130 ms) and with severe ventricular systolic dysfunction (LVEF <40%). It has been reported that about 30% of patients receiving biventricular stimulation derive no benefit from the treatment.<sup>36</sup> The identification of candidates for this therapy is, therefore, very important and is still being defined.

As mentioned above, only one randomized study on the use of implantable cardioverter defibrillators (ICDs) has been carried out to date specifically in patients with heart failure, the still unpublished SCD-HeFT trial. Other controlled studies have not specifically looked at the efficacy of ICDs in patients with heart failure. Nevertheless, in some of these studies, a considerable proportion of the enrolled population did have signs or symptoms of heart failure in addition to advanced left ventricular systolic dysfunction.<sup>4,37,38</sup> There is thus substantial experience confirming that therapy with ICD improves the survival and need for new hospital admissions in patients who have survived a heart attack or who have sustained poorly tolerated ventricular

tachycardia. The greatest benefit is seen among patients with advanced heart disease and multiple risk factors, eg, a long QRS in addition to a low EF.<sup>37</sup>

### The future of devices

Preclinical and clinical evaluations of numerous mechanical devices to control left ventricular dilation are under way. These devices can be applied to the exterior of the heart or placed within the left ventricle. Continuous refinements are being made to devices supporting left ventricular or biventricular mechanical function as a bridge to transplantation or as destination therapy in patients with end-stage heart failure. Newer-generation models are less bulky, more easily managed, less prone to infections, made of more resistant materials, and less likely to cause thrombotic complications. The artificial mechanical heart, although still in an embryonic stage of clinical experimentation, has taken its first steps along the path that should lead to greater applicability and acceptability within a reasonable period of time. Electrical current suppliers are being studied; these could potentiate mechanical efficacy when applied to ventricular myocardium or modulate the activity of the nervous system to produce an antiarrhythmic effect when applied to appropriate neural sites.

Diagnostic and monitoring devices are also being designed. These range from the small implantable electrocardiographic monitoring instruments already in current use for diagnostic purposes, to functions connected with pacemakers and ICDs that allow continuous real-time measurements of various biological parameters such as heart rate, heart rate variability, state of hydration and thus pulmonary congestion, some characteristics of cardiac or pulmonary blood flow expressing the mechanical function of the heart, the patient's motor activity, and other variables of clinical interest. The dramatic acceleration in the refinement and miniaturization of computer technology and the production of new materials is opening up many very promising avenues for patients with heart failure.

## NEXT TARGET: PREVENTION

### Secondary heart failure

Until a few years ago the epidemiological data on heart failure, in particular concerning hospital admissions for, or with accompanying, heart failure were increasing at an astonishing rate, about 50% in the decade 1990-2000 in several countries (though incidence did not seem to increase similarly<sup>39</sup>). However, more recent



data suggest that the spread of the heart failure epidemic seems to have been halted.<sup>40</sup> It is possible that part of the increase recorded in the last few decades is artificial, linked to changes in coding systems, greater diagnostic attention (which could have increased sensitivity to the problem, though perhaps not the accuracy of diagnosis), and changes in doctors' behaviors with greater use of hospital admissions. However, it seems certain that the increased prevalence of heart failure is for the most part real. The possible causes of this phenomenon have been repeatedly analyzed, and it is more interesting to determine why the trend seems to have now halted, at least in the Western world. Is treatment, and above all prevention, managing to have an epidemiologically measurable impact on public health? This is probably the case. The decrease in hospital admissions seen in numerous trials with various drugs and the growing, though still only partial, adherence to guidelines, make the recently noted evolution in the clinical epidemiology of heart failure plausible. In particular, it is suggested by the decreased incidence of heart failure in hypertensive subjects treated with various drugs,<sup>41,42</sup> in patients with ischemic heart disease with or without ventricular systolic dysfunction treated with ACE inhibitors,<sup>15</sup> with ARBs,<sup>43</sup> or with carvedilol,<sup>44</sup> in subjects at high risk of atherosclerotic events, but who do not necessarily have heart disease and who are treated with ACE inhibitors,<sup>14</sup> and in subjects with renal dysfunction treated with ARBs.<sup>45</sup> These data, together with the reduction in the incidence of diabetes and atrial fibrillation observed in some trials testing both ACE inhibitors<sup>46</sup> and ARBs,<sup>47</sup> indicate that besides intervening favorably on the progression of ventricular dysfunction to decompensation and on the clinical evolution of the heart failure, we can also reduce the incidence of risk factors for heart failure, thus correcting the roots of the chain of events that eventually culminate in cardiac insufficiency. In fact, given that heart failure is a clinical phenotype shared by the majority of cardiovascular diseases in their late natural history, primary prevention and treatment imply prevention of the underlying disease. We will only be able to ensure a substantial reduction in the clinical and social dimensions of heart failure if we are able to better control systemic hypertension, ischemic heart disease, and diabetes.

### **Familial cardiomyopathies**

#### ***Dilated cardiomyopathy***

The development and exploitation of knowledge on the molecular genetics of familial dilated cardiomyopathy (DCM) has taken more time than expected a decade

ago. This is due to the complexity of the matter, and probably also depends on: (i) the phenotype (which looks similar in the majority of cases of DCM); (ii) families and the potential role of endocrine, infectious, and systemic factors that may have either a genetic basis or predisposing roles; and (iii) the absence of clear phenotypic markers that may address screening to likely genes/loci. In this complex field, the high costs of screening serial populations of patients, the lack of high throughput tools, and the fact that the clinical benefits are still unclear, all severely limit the translation of knowledge from bench to bedside. Centralized genotype studies enable the prevalence of genotypes to be determined, but provide practical clinical benefits only to a very limited number of patients and families.<sup>48,49</sup>

Clinical genetics, relying on family pedigrees and studies, have shown that familial DCM is a genetically heterogeneous disease, inherited as an autosomal dominant trait in the vast majority of cases. Recessive forms are rare, and difficult to prove, unless the parents of affected siblings are consanguineous, or more generations of living family members are tested. X-linked cardiomyopathies affecting males include dystrophin-related cardiomyopathies, Barth Syndrome, X-linked infantile spongiform cardiomyopathy (the latter two are caused by a defect of the gene encoding tafazzins), and Emery-Dreyfus DCM.<sup>50,51</sup> Mitochondrial DNA mutations are found in a limited proportion of DCM patients when serial screening is performed in consecutive patients (about 3%).<sup>52</sup> Genetic testing is restricted to the gene defect that causes the disease in the proband. In the majority of familial DCM, however, the genetic defect remains undetected because although the known number of disease genes is high, the proportion of genotyped patients is still low. The genes that have been found to recur in familial DCM include *LMNA*<sup>53</sup> and dystrophin in males,<sup>54</sup> and mitochondrial DNA.<sup>55</sup> The majority of all other disease-genes have been exceptionally found to be mutated in familial DCM (*ACTC* and desmin) and serial family screening has excluded the recurrence of mutations in patients with DCM.<sup>56</sup> The few exceptions of familial DCM with associated cardiac or noncardiac markers (eg, atrioventricular-block in *LMNA* defect-associated familial DCM, increase in serum creatine phosphokinase (CPK) blood levels in X-linked cardiomyopathies, or hearing loss and other noncardiac phenotypes that may recur in mitochondrial DNA defects) have proven to be more successful than the less specific isolated idiopathic DCM. A large number of linkage studies have identified further disease loci that have never been confirmed, and no disease gene has been mapped in these loci.<sup>57</sup>

A novel source of knowledge and potential area of intervention in gene-related cardiomyopathies is emerging from the strategy of screening relatives of probands with familial cardiomyopathies.<sup>58</sup> The studies are providing evidence that 6% to 10% of relatives of patients with familial DCM are affected, though still asymptomatic. Screening is based on clinical, electrocardiographic, and echocardiographic evaluation of all informed relatives who agree to the evaluation. Blood testing includes measurement of serum CPK.<sup>59</sup>

The benefits of these studies include presymptomatic diagnosis and identification of instrumental noninvasive markers that may predict the development of the disease, and whose role should be assessed in large clinical series. These markers include abnormal left ventricular diastolic dimension, systolic fractional shortening, left bundle branch block, and atrioventricular delay or block. When identified in healthy relatives of probands, these markers should be monitored in re-screening studies.<sup>60</sup> Preliminary data show that an increase in end-diastolic dimension is a promising marker that predicts the development of DCM in about 30% of cases. In our experience, at an average follow-up of 32 months from the first screening, only 2% of relatives who were healthy at the first screening turned out to be fully affected: their echocardiographic data at the first screening were either normal or abnormal. An intriguing observation in our series was that a number of subjects who had abnormal echocardiographic parameters at the first screening had normalized at re-screening. Therefore, additional efforts should be carried out to validate the role of instrumental preclinical markers: tissue Doppler echocardiography is a promising tool. While waiting for large clinical series to become available for genotype-phenotype correlation, a search for clinical markers should be implemented. A further benefit of clinical screening and re-screening studies is of course the prospect of early treatment; however, whether early treatment modifies the natural history of the disease is unknown. Clinical monitoring may prevent sudden life-threatening events, help to introduce drugs, and encourage lifestyle modification.

### **Hypertrophic cardiomyopathy**

Hypertrophic cardiomyopathy (HCM) is an instructive model for heart failure investigation as it is a monofactorial model of diastolic heart failure. In about 10% of cases, it evolves toward DCM, thus mimicking that disease. The proportion of HCM with dilated evolution is low, but the number of patients with HCM is high: 1:500 is the estimated prevalence of the disease by the age of 30 to 40 years.<sup>61,62</sup> Therefore, of the 2000 patients

per million subjects expected to be affected, 200 will evolve to dilation and heart failure. This means that the clinical importance of HCM is high given that the majority of HCMs are familial (70%), inherited as autosomal dominant traits, with 50% of relatives expected to be affected and possibly develop the disease. More than 10 disease-genes are known to cause the phenotype: three have a particularly high frequency (*MYBPC3*, *beta-MHC*, *TNNT2*: up to 60% of cases), while mutations of the remaining genes are rare. Genotype-phenotype correlation studies have provided preliminary evidence that HCM caused by *beta-MHC* (beta-myosin heavy chain) defects is associated with more severe hypertrophy, higher arrhythmogenic risk, and higher and earlier penetrance than that caused ie, by *MYBPC3* gene defects, and that *TNNT2* defects cause a mild hypertrophic phenotype with high arrhythmogenic risk. These observations need confirmation on large consecutive series of patients. There are no studies addressing the risk of evolution to heart failure. The molecular basis of penetrance complications is far from elucidated. Modifier genes are probably involved, complex genotypes (double or compound heterozygosity) could explain this inheritance complication. To further increase the complexity of the clinical translation from bench to bedside of the molecular genetics of HCM, hypertrophy may be absent: this is a paradox supported by the documentation of genetically affected, but phenotypically healthy, family members, especially in *TNNT2* defect carriers.<sup>63</sup> Genotypically affected subjects are at risk of sudden death independently of the phenotype.

Besides molecular genetic analysis, clinical screening is a key strategy of prevention in HCM. The low, incomplete, and variable penetrance (a nonpenetrant phenotype in a parent of an affected son with an affected uncle is the typical example) is a complication that does not limit the value of clinical family screening. The screening identifies affected asymptomatic relatives of the proband, and provides the basis for early treatment and arrhythmogenic risk stratification. Whether early  $\beta$ -blockade may modify the natural history of the disease is still unknown. The majority of the past efforts have sought to identify disease-genes, collect large, informative families for linkage, and start genotyping of series of patients. The majority of these studies do not inform on the true prevalence of genotypes in the whole HCM patient population, since they have been performed in nonconsecutive series representing the sum of the historical collections of the large families in which disease genes have been mapped. The genotype is clinically relevant: if the disease-gene



mutations are the sole cause of the disease then their identification implies that, sometime during the course of their life (unless the penetrance limits or abates the expectancies at an unknown rate) the mutation carriers will develop the disease. What room is there for prevention, and what is its target: arrhythmias or heart failure? The strategy of screening relatives of probands is equally or even more useful than in familial DCM: HCM may be symptom-free during its entire natural history, or may cause life-threatening arrhythmias at first onset.

#### **“Pure restrictive” cardiomyopathy phenotype**

As for the most rare form of cardiomyopathy—the “pure restrictive” cardiomyopathy (RCM) phenotype—new targets for prevention should rely on knowledge that is now available.<sup>64</sup> Restrictive phenotypes include primary RCM, both isolated and associated with atrioventricular block or with myopathy or with systemic diseases such as amyloidosis. The only known disease genes associated with RCM are desmin (autosomal dominant in the majority of cases, causing desmin accumulation with atrioventricular block<sup>65,66</sup>) and  $\alpha$ B-crystallin,<sup>67</sup> which causes a phenotype similar to that of desmin accumulation, but with associated cataract. The natural history of these diseases evolves, over a variable range of time, to end-stage heart failure, and at present there is nothing that can be done about prevention. Remaining RCMs are orphan diseases that still need to be assigned to specific disease genes.

In the RCM setting, the most frequent and likely cause is amyloidosis. Identification of amyloidogenic protein conditions therapeutic decision-making. ApoA1 amyloid RCM can be transplanted with low risk of recurrence. Transthyretin (TTR) amyloid RCM requires heart and liver transplantation. Primary amyloid RCM, with either  $\kappa$  or  $\lambda$  chains, can be either pharmacologically treated, when the diagnosis is early, or transplanted with combined marrow or stem cell transplantation. Serum amyloid A (SAA) amyloidosis requires treatment of the underlying inflammatory or autoimmune disease, and  $\beta_2$ -microglobulin amyloidosis does not affect the heart.<sup>68</sup> Therefore, in the setting of RCM there is a lot that can be done.

In summary, new targets of prevention in cardiomyopathies should concern mostly early and preclinical diagnosis and rely on cardiological instruments such as screening and rescreening as well as on molecular genetics—this, however, is costly, time-consuming, and still limited to less than 1% of the European population.

## LOOKING TOWARD THE FUTURE

Every single biological process of the body is controlled by the expression of largely unknown genes and genetic programs. Comparative embryology has identified some forms of congenital heart disease as the expression of genetic programs characteristic of ontogenetically more primitive animal species (such as amphibians, reptiles, etc). We know that greater or lesser expression of key enzyme activities following stimuli such as cellular stretching can direct the cardiomyocytes toward hypertrophy or apoptosis. Genetic analyses carried out on biopsy samples of human myocardium taken during application of ventricular mechanical assistance in patients with end-stage heart failure and on the same hearts explanted during heart transplant operations have shown that gene expression is radically different depending on the ischemic or non-ischemic etiology of the heart disease, and equally dramatic changes are induced by prolonged unloading following mechanical assistance.<sup>48</sup> Many other examples could be mentioned.

Every therapeutic intervention involves biological sequences governed by genes that the therapy directly or indirectly activates or inhibits. Therapeutic research is moving, albeit tentatively, in this direction. It is now conceivable that we could, thanks to current technology, obtain cells capable of producing mediators that would be more useful, with fewer undesirable effects in given pathological conditions, or engineered in such a way as to produce new molecules, such as the “autologous drugs,” or “supercontractile” myocytes, etc. The ability to mitigate myocardial hypertrophy by directly influencing the natural responses of the myocytes to a given workload level, initiation of apoptotic mechanisms, and activation of cell repair mechanisms could become feasible therapeutic pathways. One concrete example is the last aforementioned mechanism: a repair approach to cardiological therapy rather than a modulatory or replacement approach.

One of the most important recent breakthroughs in medicine is the prospect of using the regenerative potential of the human body for therapeutic purposes. Obviously, this is of particular interest in chronic diseases characterized by a progressive decline in the structure and function of organs or tissues that the available therapy is unable to stop. Various working hypotheses were offered in a recent review in the *Lancet*, the essential points of which are discussed below.<sup>49</sup>

### **Reactivation of postmitotic cardiomyocyte replication**

The genetic program for reinitiating DNA synthesis exists in cardiomyocytes, but there is also a program that protects against uncontrolled proliferation of contracting cardiomyocytes, which is probably related to continuous active suppression of cell-cycling activity (or to an absence of expression of cell-cycle promoting factors). Cell-cycling can be reinitiated by overexpressing cell-cycle promoting factors, but this seems to lead to immediate cardiomyocyte apoptosis. The possibility of reactivating safe cell-cycling and whether this process would be sufficient to meet clinical needs is uncharted territory.

### **Cloning of artificial organs**

The lack of natural organs available for transplantation is a well-known fact, and there is no reason to anticipate any significant increase in organ supply in the future. In contrast, an increased demand for transplantable organs is very likely. Therapeutic cloning might meet this need. The most obvious way would be to inject a nucleus taken by a skin biopsy into an enucleated donor oocyte, then to modulate the multiplication and differentiation of the resulting cells into cardiomyocytes. These clone cardiomyocytes would then be reinjected as such or used in conjunction with a biodegradable scaffold to generate an artificial heart. This process is theoretically feasible, but there is no evidence so far that it really works. Moreover, the use of embryonic cells is still matter of strong debate.

### **Organ regeneration via stem cells**

There are strong data to suggest that autologous progenitor cells can home to myocardial tissue and differentiate into myocytes, smooth muscle cells, or endothelial cells. The autologous cells may be mononuclear bone marrow cells or, alternatively, muscle satellite cells.

Clinical experience in this field is promising, and further clinical research is ongoing. Satellite cells, able to proliferate and become committed to the myocyte lineage when stressed by workload, have recently been reported to be present in the human myocardium. If this is confirmed and the number of such local pluripotent cells is sufficient to generate a clinically significant regenerative process, a new method of endogenous myocardial repair would be available. The authors of the *Lancet* review, acknowledging that many fundamental questions are still open, suggested both "healthy skepticism" and "cautious optimism."<sup>49</sup> This is an honest position worthy of being shared. However, sooner or later, cell therapy for heart failure will come to stay.

### **IN THE MEANTIME, THE ROLE OF DISEASE MANAGEMENT AND COMMON SENSE**

In daily practice, it is abundantly clear to the cardiologist and hospital internist that the continuous flow of hospital admissions of patients with heart failure is partly due to the limited efficacy of available therapies, and to their suboptimal use, but above all to a rigidly compartmentalized care system that imposes a stranglehold on hospital and community doctors, as well as to the lack of patient education and assistance in the community. There are no population studies on this subject, but very encouraging, reasonably sized, randomized studies exist.<sup>69-74</sup> The difficulty lies mainly in having to coordinate the often conflicting priorities of doctors/specialists and health care authorities. The latter are obsessed with economic problems and more intent on ensuring immediate control of expenses than on achieving long-term public health care program goals. In other words, although we know (more or less) what to do, we are unable to organize ourselves accordingly. However, we must not give up, because so many of the health care issues of patients with heart failure depend, at least for the present, on our success.



### THREE KEY QUESTIONS

Heart failure therapy is an area of constant change par excellence: change made unavoidable in order to keep pace with the increasingly numerous and complex pathophysiological mechanisms involved in heart failure that have been discovered over the past 30 years. Probably one of the most enlightening insights is the current understanding of heart failure as the ultimate common outcome of an impressive array of disorders and diseases. To date, three main models have been successively described to explain the causes and consequences of pump failure: (i) pump failure causing decreased renal blood flow and fluid retention; (ii) pump failure causing diffuse vasoconstriction, restricting the blood flow and resulting in increased cardiac work and peripheral target organ dysfunction; and (iii) the latest player in the field: pump failure caused by hyperactivity of the neurohormonal regulatory systems. This pathophysiological complexity is naturally mirrored by the similar complexity of the therapeutic range of medicines, devices, and interventions available, the most drastic and bold of which is, of course, the old-for-new swap—transplantation. In the following section, our Experts identify three of the fastest-moving aspects of heart failure therapy. CRT (cardiac resynchronization therapy) is an increasingly popular method for treating ventricular dyssynchrony. Many devices and techniques have already been developed and used, prompting Angelo Auricchio and Cecilia Fantoni to ask: “**Cardiac resynchronization therapy in heart failure: which type and for whom?**” The answer to neurohormonal hyperactivity is, logically enough, neurohormonal modulation. Michal Komajda takes stock of the therapeutic offer and asks: “**Multiple hormonal modulation: what are the most effective combinations?**” So successful did neurohormonal modulation prove to be that the catchword was soon “the more, the better.” That this is not the case, and why, inspires a question by Helmut Drexler and Kai C. Wollert: “**Why are we unable to completely control the activation of neurohormonal systems in chronic heart failure—and should we?**” Much still remains to be done to gain an ever-deeper understanding of the mechanisms leading to and arising from heart failure, and to make new therapeutic discoveries. Just as important, however, is putting to more effective and economically sound use what is already available, as Luigi Tavazzi concludes in the Lead article.

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# Cardiac resynchronization therapy in heart failure: which type and for whom?

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*Cardiac resynchronization therapy (CRT) offers a new therapeutic approach for patients with ventricular dyssynchrony and moderate-to-severe heart failure who have dilated cardiomyopathy, regardless of etiology, with depressed systolic function and a QRS  $\geq 120$  ms.*

*Clinical trials have shown that it is safe and effective, achieving significant improvement in clinical symptoms, multiple measures of functional status, and exercise capacity. Furthermore, CRT has reduced morbidity and mortality in patients with heart failure. Conclusive cost-effectiveness data are not yet available. Whether or not heart failure patients should be implanted with a CRT plus defibrillator (CRT-D) device versus CRT alone remains debatable, although growing evidence is pointing to extensive use of implantable cardioverter defibrillators (ICDs) in this population.*

Over the past decade, treatment of heart failure (HF) has markedly improved; mortality due to pump failure and sudden death has declined significantly.<sup>1,2</sup> Hospitalizations for severe symptoms of HF have also decreased after use of angiotensin-converting enzyme (ACE) inhibitors,  $\beta$ -blockers, diuretics, digoxin, and most recently, spironolactone. However, despite better medical treatment, a significant number of patients remain symptomatic. Until recently, the mainstay of treatment for advanced HF was pharmacological, with very small number of patients considered for heart transplantation or left ventricular (LV) assist devices. While cardiac transplantation can be an extremely effective therapy, its availability is severely limited by lack of donor organs—and there is still the unresolved issue of tissue rejection after transplantation. Mechanical devices to augment cardiac output are currently only suitable for short-term use and the financial cost of

these devices is likely to limit their widespread application. Against this background, cardiac resynchronization therapy (CRT) has emerged as a promising treatment option for some patients with HF.

## MECHANICAL AND STRUCTURAL CONSEQUENCES OF VENTRICULAR CONDUCTION DISTURBANCES

A complex blend of structural, functional, and biological abnormalities is found in patients with HF and dilated cardiomyopathy of various etiologies. Significant QRS prolongation is present in approximately 30% of patients with HF. Electrical delays generate abnormal atrioventricular timing and dyssynchronous contraction of left, right, or both ventricles. Furthermore, prolongation of atrioventricular timing delays atrial contraction relative to the onset of ventricular systole and reduces the efficiency of atrial systole for ventricular filling.

**Keywords:** heart failure; ventricular conduction disturbance; left bundle branch block; cardiac resynchronization therapy; implantable cardioverter-defibrillator

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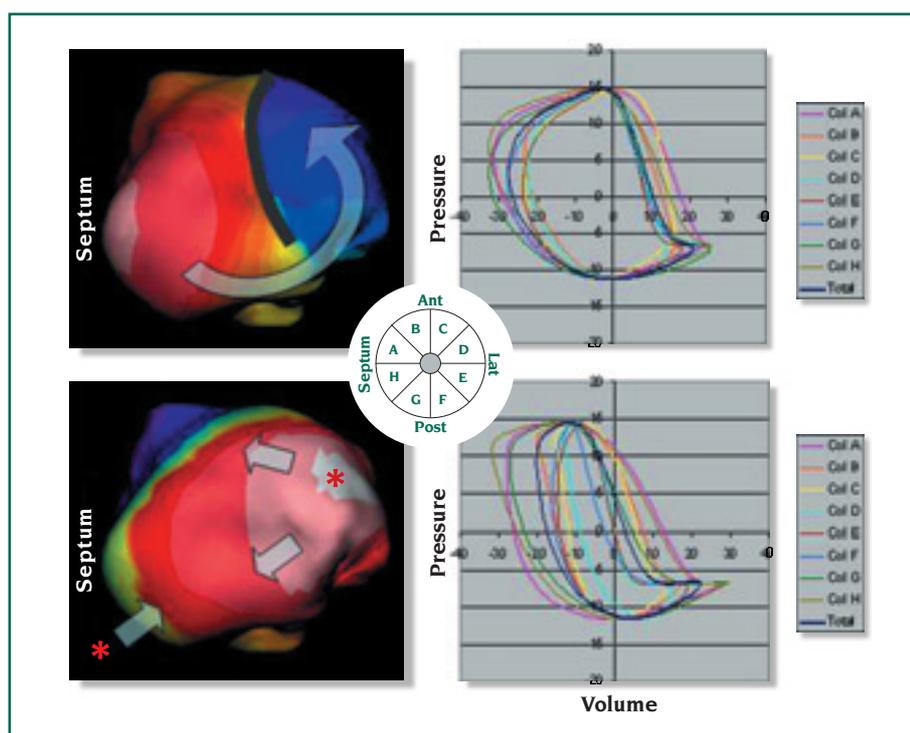
### SELECTED ABBREVIATIONS AND ACRONYMS

<b>COMPANION</b>	COmparison of Medical therapy, Pacing And defibrillatioN In chrONic heart failure
<b>CRT</b>	cardiac resynchronization therapy
<b>HF</b>	heart failure
<b>ICD</b>	implantable cardioverter defibrillator
<b>SCD-HeFT</b>	Sudden Cardiac Death–Heart Failure Trial
<b>TDI</b>	tissue Doppler imaging

Left bundle branch block is the most common ventricular cause of delay reported in patients with impaired pump function. This conduction disturbance affects cardiac mechanics by altering right-left ventricular systolic and diastolic timing, causing abnormal ventricular contraction and relaxation, worsening

have to contract against a preexisting stiffened portion of the ventricular wall (the septum). This phenomenon has been termed mechanical dyssynchrony (Figure 1). Mechanical dyssynchrony generates increased wall stress with increased cardiac work, which may contribute to myocyte damage and to the develop-

cardiac performance by reducing inter- and intraventricular mechanical dyssynchrony, thereby reducing myocardial oxygen consumption. In order to achieve this, the regions of the LV that are activated latest during sinus rhythm are stimulated early by delivery of a pacing stimulus, usually simultaneously with the



**Figure 1.** Recording of electrical activation (10-ms isochronous line) in a patient with dilated cardiomyopathy and left bundle branch block. The upper panels show electrical (left) and mechanical (pressure-volume, right) activation during left bundle branch block. A U-shaped activation sequence of the left ventricle (LV) is noted; the regional pressure-volume loops show large mechanical dyssynchrony. The lower panels present the effect of biventricular stimulation by pacing (asterisk) the apex of the right ventricle (not shown) and the free wall of the LV. The electrical activation sequence (left) shows two fronts, one coming from right and the other from left colliding over the septum. The pressure-volume loop (right) is now larger and shows a more homogeneous distribution of regional stroke work. The pie-shaped circle in the middle shows the 8 LV segments (lettered A to H) corresponding to the same-lettered regional pressure-volume recordings in the right panels.

the underlying systolic and diastolic performance and increasing cardiac energy requirements. Basically, at the beginning of the LV ventricular systole, the region of earliest ventricular activation (usually the interventricular septum) contracts against minimal workload because the remaining ventricular myocardium (usually the lateral and posterolateral LV region) is still in the relaxation or in a non-activated phase (Figure 1). The regions of early ventricular activation waste contraction energy as no effective intraventricular pressure can develop. On the other hand, the region of late ventricular activation and the lateral and posterolateral ventricular regions

ment of fibrous tissue, regional hypertrophy, and regional apoptosis.<sup>3</sup> All these functional and structural changes caused by left bundle branch block may be associated with poor prognosis and increased morbidity.<sup>4</sup>

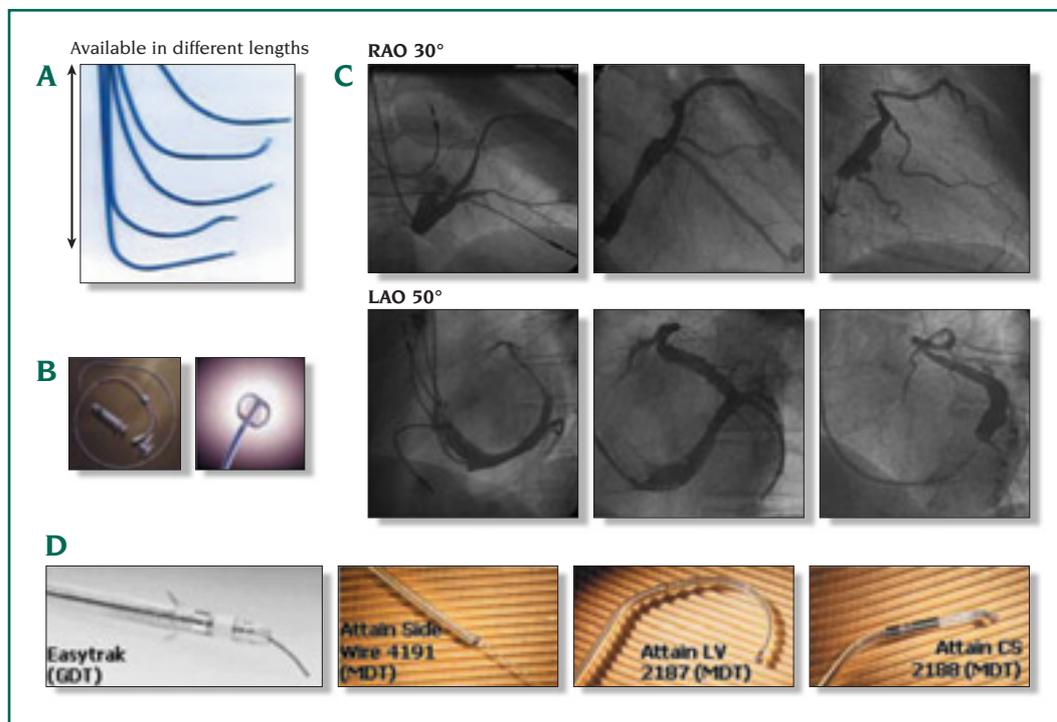
### CARDIAC RESYNCHRONIZATION THERAPY

CRT is a novel nonpharmacological option for symptomatic patients with HF who have wide QRS complexes (>120 ms) on the 12-lead surface electrocardiogram (ECG) and who are refractory to medical therapy. The aim of CRT is to improve

right ventricle (RV) via a separate pacing lead, thus reducing the total activation time for the ventricles. In patients with sinus rhythm, the pacemaker system will sense the atrial electrical activation via a right atrial lead and stimulate the ventricles at a programmed atrioventricular time that is less than the intrinsic atrioventricular conduction time in order to ensure full ventricular capture.

### Implantation technique

The implantation technique is similar to a standard dual chamber sequential pacemaker or implantable cardioverter defibrillator (ICD). The most challenging aspect for achiev-



**Figure 2.** A family of catheters for selective cannulation of the coronary sinus is presented in **panel A**. After cannulation of the coronary sinus, a balloon occlusion using a standard Swan-Ganz catheter (**panel B**) is performed, followed by contrast dye injection. **Panel C** shows the large variability of the coronary veins. According to the differences in coronary venous anatomy, different pacing electrodes may be implanted (**panel D**).

ing resynchronization therapy is placing a permanent LV lead. The transvenous or thoracotomic approach can be used. The transvenous approach requires retrograde cannulation of the coronary sinus, selective angiography of the coronary sinus to delineate the venous anatomy (*Figure 2*), and final introduction into a coronary vein, which lies over the epicardial surface of

the LV, of a specifically designed pacing lead. *Figure 3* shows the typical configuration of pacing leads in a biventricular system implanted either transvenously or via limited lateral thoracotomy.

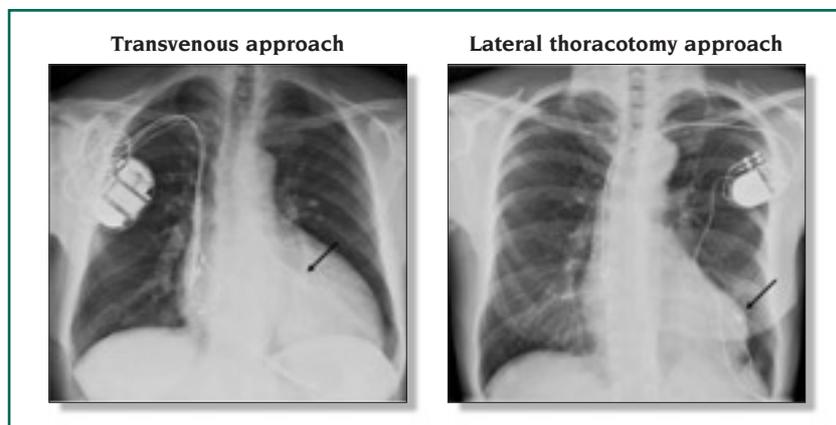
The transvenous approach may be a difficult and time-consuming technique. The major limitation is that options for lead placement are gov-

erned largely by the patient's venous anatomy, which shows considerable interindividual variability. In about 10% to 15% of cases, it is not possible to achieve a satisfactory LV pacing position, or left phrenic nerve stimulation may occur, thus causing an unpleasant sensation due to diaphragmatic contraction.

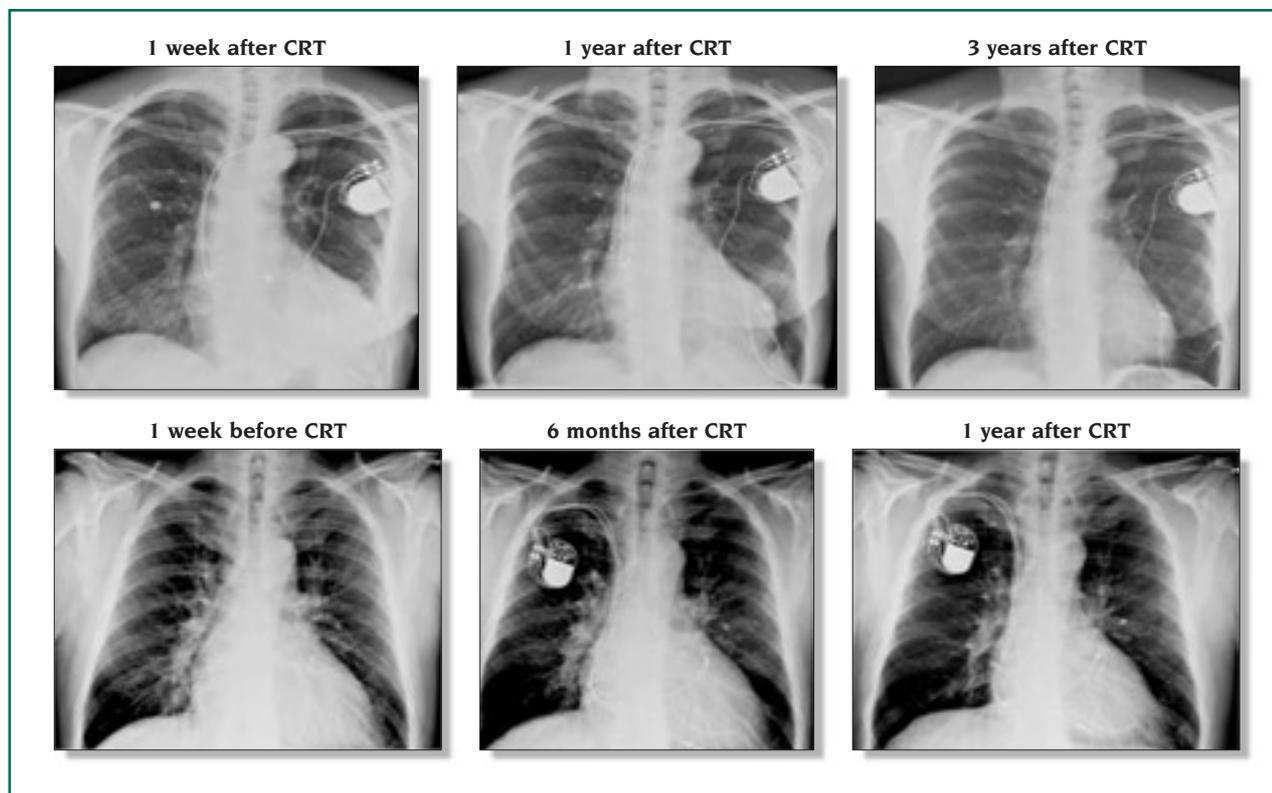
### Clinical efficacy

The beneficial effects of CRT include improvement in exercise tolerance and quality of life. Furthermore, CRT reduces ventricular volumes and mitral regurgitation, and improves left ventricular ejection fraction (*Figure 4*, page 228).<sup>5-7</sup> CRT has recently been shown to improve mortality and hospitalization in a large randomized trial.<sup>8</sup>

Most clinical trials have included patients with moderate or severe (New York Heart Association [NYHA] functional class III or IV) chronic HF due to ischemic or nonischemic cardiomyopathy and widened QRS



**Figure 3.** Two examples of implantation of cardiac resynchronization devices. In both cases, the atrial pacing lead and the right ventricular pacing lead are placed as in a conventional DDD pacemaker of an implantable defibrillator. The lead for the left ventricle (arrow) may be inserted transvenously as indicated in *Figure 2* or via a minimal lateral thoracotomy.



**Figure 4.** Reverse remodeling in two patients implanted with a cardiac resynchronization device.

duration on the surface electrocardiogram. A QRS duration of 120 ms or more has been the typical selection threshold.<sup>9</sup> *Table I* summarizes clinical criteria for patients selected for CRT and current clinical evidence supports the value of CRT for these patients.

Few data have been collected on CRT in patients with NYHA class II, and currently this patient group is not routinely recommended for CRT. Insufficient data are available for patients with atrial fibrillation; although preliminary data support the efficacy of CRT in this setting, definitive data are lacking. Similarly, the question of whether heart failure patients with a standard pacemaker indication for bradycardia benefit from CRT is still unanswered. In contrast, there is increasing evidence that the implantation of CRT instead of a standard single-chamber or dual-chamber pacemaker

may be appropriate for patients with paroxysmal or permanent rapidly conducting atrial fibrillation who undergo His bundle ablation.

<b>AHA/ACC/NASPE Guidelines</b>	
Pacing recommendations (Class IIa Indication)	
•	Medically refractory heart failure
•	Functional New York Heart Association Class III or IV
•	Idiopathic dilated or ischemic cardiomyopathy
•	QRS duration $\geq 130$ ms
•	Left ventricular ejection fraction $\leq 35\%$
•	Left ventricular end-diastolic diameter $\geq 55$ mm

**Table I.** Inclusion criteria listed in the recently published AHA/ACC/NASPE guidelines for cardiac resynchronization therapy.

**Abbreviations:** ACC, American College of Cardiology; AHA, American Heart Association; NASPE, North American Society for Pacing and Electrophysiology.

### IDENTIFYING INDIVIDUAL RESPONDERS

All randomized clinical CRT trials have used statistical techniques to define the response of groups of patients to CRT. No technique is available to predict reliably the clinical response of a given individual. The large clinical improvement observed in some individuals after CRT (the so called “Lazarus” effect) has created the perception that patients who do not exhibit such improvement are not responding positively to CRT. However, many patients who do not show overt improvement may nevertheless benefit from a less observable slowing of disease progression by living longer and remaining out of the hospital. Since these benefits can only be determined for populations, it may be inappropriate to withhold CRT from patients who meet mortality and morbidity trial indications, but



who do not have indicators predicting individual functional improvement. With this caveat, various factors that may influence the clinical impact of CRT in individual patients are described below.

### QRS duration

Duration of the QRS complex is one of the simplest ways to measure timing abnormalities that may have a mechanical correlate. Indeed, all randomized studies to date have used this variable to select patients. Basal QRS duration has been shown to be associated with the degree of mechanical dyssynchrony and with the short-term clinical improvement obtained from CRT (*Figure 1*). Clinical trials have consistently shown that in patients with QRS complex >150 ms, functional capacity, quality of life, and exercise tolerance are significantly improved after a few months of CRT. In contrast, patients with a shorter QRS complex (120-150 ms) show less or no significant changes in functional capacity, quality of life, and exercise tolerance.<sup>10</sup> However, preliminary evidence indicates that patients with shorter QRS also may improve after CRT longer than 6 months, suggesting a time-dependency effect of CRT based on the baseline QRS width. The effect of CRT on disease progression in these two subgroups of patients, as evaluated by reverse remodeling, morbidity, or mortality is still unknown. However, CRT has been shown to decrease hospitalization and all-cause mortality in NYHA class III/IV patients with QRS >120 ms.

### Echocardiographic assessment

In patients with HF and ventricular conduction delay, four different levels of ventricular asynchrony have been recognized: atrioventricular delay, interventricular and intraven-

tricular delay, and intramural delay. Some patients with HF with depressed LV ejection fraction despite normal duration of the QRS complex may present with echocardiographically assessed mechanical dyssynchrony of similar magnitude as patients with considerably prolonged QRS duration. The reasons for this "electromechanical dissociation" are not clear, but possible explanations include the relatively poor representation on the surface ECG of electrical impulses from diseased areas of the LV and "uncoupling" of mechanical contraction from electrical stimulation due to abnormalities of calcium homeostasis in cardiac myocytes. Although preliminary data suggest that patients with mechanical dyssynchrony despite normal QRS may benefit, CRT should not be extended to this group without prospective randomized studies.

With the exception of intramural delay, conventional or Doppler echocardiography allows a direct quantification of the degree of mechanical asynchrony. Some of the echocardiography-guided indices are based on timing abnormalities of specific LV regions, others explore the mechanics of the entire LV, and others evaluate a difference in timing between the right and left ventricles. Although pilot studies are promising, the validity of these mechanical indices of dyssynchrony to predict outcome after CRT has not been prospectively established. These indices also may not help identifying the patients who would benefit from the potential preventative effect of CRT in stopping progression of dyssynchrony and its associated negative effects on cardiac function, hypertrophy, and remodeling. However, measures of mechanical resynchronization may help optimize therapy by determining best lead position and proper atrioventricular delay programming.

### Mechanical abnormalities detected by conventional echocardiography

Interventricular delay time is usually defined as the time difference between the onset of pulmonary artery flow and the onset of aortic flow with respect to the beginning of the QRS complex. A delay >40 ms is considered indicative of significant dyssynchrony. Because the time to ejection of the RV and LV could be influenced by several factors, the predictive utility of such interventricular delay has been questioned. Intraventricular delay is considered the most important one for identifying patients who will experience the largest short-term clinical responses by CRT, and is defined as the mechanical dispersion of motion of the LV. M-mode echo-imaging has been used to determine the delay exclusively between the initial septal inward motion, and posterior wall motion. This delay time has been correlated with chronic improvement in LV diameters after CRT. The major limitation of this index is that it does not account for delays possibly located elsewhere in the LV. Heterogeneous regional wall motion synchrony with left bundle branch block QRS morphology has also been demonstrated by 2-D echocardiography.

### Mechanical abnormalities detected by tissue Doppler imaging

Regional systolic and diastolic synchrony can be evaluated by tissue Doppler imaging (TDI) by comparing the time to peak systolic contraction and early diastolic relaxation of multiple segments. TDI appears to offer a comprehensive assessment of cardiac mechanical synchrony. Although improvement of interventricular dyssynchrony after CRT has been demonstrated by TDI, TDI pa-

rameters of interventricular delay have not been shown to predict the improvement of cardiac function.

A number of parameters based on TDI have been proposed to evaluate intraventricular dyssynchrony. These parameters examine either the time to peak myocardial systolic contraction (Ts) between two or more segments or the dispersion (standard deviation) of Ts (Ts-SD) over multiple segments in the LV, typically 12.

A Ts-SD >33 ms has been shown to strongly predict short-term reverse remodeling. Other proposed indices of systolic dyssynchrony include counting the number of segments with postsystolic shortening and possibly strain rate parameters. The former parameter has been observed to correlate with a beneficial change in systolic function. However, a recent comprehensive analysis suggested that assessment of Ts-SD is the best predictor of reverse remodeling. This may be the best current candidate to replace QRS with an index of mechanical dyssynchrony for the selection of new patients in expanded CRT trials.

### **PROTECTION FROM SUDDEN CARDIAC DEATH BY IMPLANTABLE CARDIOVERTER DEFIBRILLATOR**

Sudden cardiac death is a catastrophic event, the annual incidence of which increases from 2% to 6% per year in patients with NYHA class II symptoms up to 24% per year for patients with class III to IV symptoms.<sup>11</sup> Ventricular tachycardia or fibrillation is the predominant mode of death. It has been shown that the implantable cardioverter defibrillator (ICD) is the most powerful—and therefore first-line—therapeutic approach for secondary as well as primary prevention for

sudden death. The recently concluded Sudden Cardiac Death–Heart Failure Trial (SCD-HeFT), has provided further evidence that ICD implantation in addition to the best pharmacological therapy (including ACE inhibitors, angiotensin II type 1 (AT<sub>1</sub>) receptor blockers,  $\beta$ -blockers, diuretics, and spironolactone) is the most effective long-term (at 5 years) therapy compared with conventional optimal therapy alone or with amiodarone given on top of the best medical therapy for prolonging life in patients with HF.

The rationale for the use of ICD in CRT devices is primarily based on the assumption that sudden death prevention in patients with HF will provide mortality benefits above those of CRT alone. The Comparison of Medical therapy, Pacing And defibrillation In chrONic heart failure (COMPANION) study has shown marked reduction in combined measures of morbidity and mortality as well as for mortality with CRT alone and with CRT plus defibrillator therapies (CRT-D). The morbidity data from COMPANION indicated a near-equal 1-year benefit for both groups (with and without an ICD); in contrast to CRT alone, which demonstrated a relative risk reduction in all-cause mortality of about 24% ( $P=0.060$ ), CRT-D provided a larger (36%) relative risk reduction in mortality compared with optimal drug therapy ( $P=0.003$ ). A reduction in all-cause mortality and hospitalization for HF by 40% following CRT suggests a substantial reduction in the use of medical resources. These findings are supported by other CRT trials.<sup>12</sup>

The important issue raised by the COMPANION study is whether all patients with HF indicated for CRT should be treated with an additional ICD. Therefore, despite the fact that the CRT-D device has larger

initial cost, and may require more extensive follow-up than CRT alone, this strategy may be most cost-effective particularly when measured in terms of quality-adjusted life-years gained. However, longer-term data are not available and a direct comparison between CRT and CRT-D has not been performed yet.

### **MONITORING FEATURES OF CRT DEVICES**

The monitoring features of conventional pacemakers or ICDs mainly focus on device-related parameters such as pacing threshold, impedance, R-wave amplitude, and storage of intracardiac electrograms. Careful hemodynamic control and electrical monitoring is now implemented into CRT devices. Hemodynamic parameters can be either directly or indirectly monitored via the implanted devices. Specific sensors of the maximum pressure derivative are already implemented.

Furthermore, heart rate and heart rate variability can also be continuously monitored with an implanted CRT device. Finally, recording of accelerometer signals, which usually reflect the patient's physical activity, is already used in pacemakers and implantable cardioverter-defibrillators. This is now used for monitoring the HF-treated patient activity, as well. Initial experience with recording of patient activity tracked by accelerometer has shown that activity monitored by accelerometers is highly sensitive and specific in detecting the patient's physical activity. However, the accuracy of monitoring chronic hemodynamics, lung water content, heart rate, and physical activity changes in patients with HF has yet to be determined. It is also unknown whether major cardiac events can be forecasted by monitoring one or more of these parameters.



## SUMMARY

Cardiac resynchronization therapy is now proven to be a valuable adjunctive treatment to standard pharmacological therapy for patients with HF with dyssynchrony. This therapy has demonstrated large symptomatic improvements as well as a strong impact on disease progression. The likelihood is that the indication for device implantation will expand in the future, so that patient selection techniques need to improve to ensure that the overwhelming majority of patients receiving this therapy also benefit from it. QRS duration remains the most practical and validated means for selecting patients for CRT, because it is clinically simple to measure and widely available, and its value as a selection criterion has been proven in large, randomized outcome trials demonstrating a mortality and hospitalization benefit with CRT.

The predictive value of QRS duration may derive from a close correlation of long QRS and a corresponding mechanical dyssynchrony, which increasingly is believed to be the main substrate for CRT efficacy. Evidence that QRS duration is an imperfect indicator of mechanical dyssynchrony, added to the desire to identify individual patients likely to experience immediate large improvements in clinical condition with CRT, has led to a search for other noninvasive techniques, based mainly on imaging, that directly measure mechanical dyssynchrony.

However, particular indices of mechanical dyssynchrony that best predict clinical improvement have not been established, and it is unclear whether CRT is preventing disease progression in patients with prolonged QRS before severe mechanical dyssynchrony is apparent.

At the present time, evidence-based medicine supports the use of prolonged QRS (>120 ms) as an indicator of patients with severe HF who should be prescribed CRT. Noninvasive imaging techniques can be used to verify that resynchronization has been achieved.

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# Multiple neurohormonal modulation: what are the most effective combinations?

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*Numerous clinical trials on neurohormonal modulation have shown that angiotensin-converting enzyme (ACE) inhibition combined with  $\beta$ -adrenergic blockade improves all-cause cardiovascular mortality, sudden cardiac death, and hospitalization rate, including in patients with depressed systolic function. International guidelines now recommend dual neurohormonal inhibition in post-myocardial infarction left ventricular dysfunction and in all symptomatic patients. In patients intolerant to, or with contraindication to, one of these compounds, angiotensin II receptor blockers (ARBs) are a good alternative. In symptomatic patients, addition of an ARB or/and aldosterone antagonist to the ACE inhibitor and  $\beta$ -blocker can improve the outcome. Other options, such as vasopeptidase inhibitors, endothelin receptor antagonists, and arginine-vasopressin antagonists are currently under evaluation.*

**Keywords:** neurohormonal modulation; chronic heart failure; treatment; ACE inhibitor;  $\beta$ -blocker; aldosterone antagonist; angiotensin II receptor antagonist; polypharmacy

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Chronic heart failure (CHF) is a major burden for health care systems due to its growing incidence, particularly in elderly and very elderly patients, and to the high mortality and morbidity associated with this condition.

The concept of neurohormonal stimulation as a key component of the onset and progression of heart failure was developed in the 1980s and proved to be a major breakthrough in the understanding and clinical management of this condition. The body of evidence supporting neurohormonal modulation as a major medical goal in heart failure is immense, and is based on numerous, large, and well-conducted clinical trials that have enrolled more than 100 000 patients exposed to various neurohormonal modulators.

Historically, this scientific period can be divided into three distinct eras:

- The demonstration of the beneficial effect of angiotensin-converting enzyme (ACE) inhibitors on top of conventional treatment, consisting in diuretics and digitalis  $\pm$  vasodilators.
- The use of  $\beta$ -blockade on top of ACE inhibitors and diuretics  $\pm$  digitalis.
- The more recent use of other neurohormonal modulators, including angiotensin II receptor antagonists (ARBs, or sartans) and aldosterone antagonists, such as spironolactone and eplerenone.

The aim of this review is to discuss the best neurohormonal antagonist combinations, the order of initiation of these various antagonists, and to define the patient profiles for which this medical approach is most effective. Due to the lack of data in heart failure with preserved systolic function ("diastolic" heart failure), most of the evidence reviewed here focuses on heart failure with depressed systolic function.

## ACE INHIBITION AND $\beta$ -BLOCKADE: THE GOLD STANDARD OF NEUROHORMONAL MODULATION IN CHF

The first trial showing a benefit of neurohormonal modulation in severe heart failure was the COoperative North Scandinavian ENalapril SURvival Study (CONSENSUS), which showed a substantial 28% reduction in mortality in New York Heart Association (NYHA) class IV CHF patients.<sup>1</sup> In 1991, two landmark trials established the benefit of ACE inhibition on top of conventional therapy (Studies Of Left Ventricular Dysfunction, SOLVD)<sup>2</sup> or compared with conventional vasodilator treatment (Vasodilator-Heart Failure Trial II, V-HeFT II).<sup>3</sup> In SOLVD, ACE inhibition was associated with a relative risk reduction of 16% in all-cause mortality, of 22% in heart failure death, and of 26% in death or hospitalizations for heart failure in patients with NYHA class II and III



CHF. In V-HeFT II, there was an 18% reduction in mortality, and a substantial number of sudden cardiac deaths were avoided by ACE inhibition in comparison with a combination of hydralazine and nitrates. Following these two trials, it was further demonstrated that ACE inhibitors were also beneficial in post-myocardial infarction mortality in patients with reduced ejection fraction <40% (Survival And Ventricular Enlargement [SAVE] trial)<sup>4</sup> and that they slowed the progression of the disease to overt heart failure and decreased the number of related hospitalizations in asymptomatic left ventricular dysfunction (SOLVD-prevention).<sup>5</sup> These observations, followed by other confirmatory trials, led to the recommendation of the use of ACE inhibitors in a broad

spectrum of patients with left ventricular dysfunction, NYHA Class II, III, or IV, in the guidelines published by the European Society of Cardiology (ESC).<sup>6</sup> Five ACE inhibitors are recommended in the treatment of CHF in these guidelines: enalapril, captopril, perindopril, lisinopril, and ramipril.

The demonstration of the benefit of  $\beta$ -blockers was made in three trials published in 1996 and 1999 (Carvedilol US program<sup>7</sup>; Cardiac Insufficiency Bisoprolol Study II [CIBIS II]<sup>8</sup>; METoprolol controlled release Randomized Intervention Trial in Heart Failure [MERIT-HF]<sup>9</sup>). The  $\beta$ -blockers carvedilol, bisoprolol, and metoprolol succinate, given on top of a combination therapy consisting of diuretics, ACE inhibitors  $\pm$  digitalis

and vasodilators, resulted in a substantial reduction in all-cause mortality, heart failure hospitalizations, and/or sudden cardiac death. The results were so dramatic that they led to the early termination of the three trials. One of the most remarkable results of these trials was the magnitude of the effect observed on mortality and hospitalizations: the relative risk reduction in all-cause mortality was 65% with carvedilol and 34% with metoprolol and bisoprolol. Similarly, all-cause hospitalizations were reduced by 20% in CIBIS II, whereas mortality or hospitalization for worsening heart failure was reduced by 32% in MERIT-HF. A significant 34% reduction in all-cause mortality was also demonstrated in patients with severer CHF in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial<sup>10</sup> and of 23% in post-myocardial infarction with left ventricular dysfunction in the Carvedilol Postinfarction survival Controlled evaluation (CAPRICORN) trial.<sup>11</sup>

These results were embodied in the ESC guidelines, which recommend the use of dual neurohormonal inhibition in all stable NYHA class II, III and IV patients, together with diuretics (Class IA recommendation). This regimen is also recommended in patients with post-myocardial infarction with left ventricular dysfunction (Class IB recommendation). Thus, there is no longer any controversy on the need for dual neurohormonal therapy using ACE inhibitors and  $\beta$ -blockers in CHF.

### IS DUAL NEUROHORMONAL INHIBITION USED IN PRACTICE?

A number of surveys have been carried out, both at national and international levels, to determine to what extent CHF guidelines are implemented in daily practice. All these

#### SELECTED ABBREVIATIONS AND ACRONYMS

<b>ARB</b>	angiotensin receptor blocker
<b>AT<sub>1</sub></b>	angiotensin II type 1 receptor
<b>CAPRICORN</b>	Carvedilol Postinfarction survival Controlled evaluation
<b>CHARM</b>	Candesartan in Heart failure Assessment of Reduction in Mortality
<b>CHF</b>	chronic heart failure
<b>CIBIS II</b>	Cardiac Insufficiency Bisoprolol Study II
<b>CONSENSUS</b>	COoperative North Scandinavian ENalapril SURvival Study
<b>COPERNICUS</b>	Carvedilol Prospective Randomized Cumulative Survival
<b>ELITE II</b>	Evaluation of Losartan In The Elderly II
<b>EPHESUS</b>	Eplerenone Post-AMI Heart failure Efficacy and Survival Study
<b>MERIT-HF</b>	MEtoprolol controlled release Randomized Intervention Trial in Heart Failure
<b>OPTIMAAL</b>	OPTimal Trial In Myocardial infarction with Angiotensin II Antagonist Losartan
<b>RALES</b>	Randomized ALdactone Evaluation Study
<b>RAS</b>	renin-angiotensin system
<b>SAVE</b>	Survival And Ventricular Enlargement
<b>SOLVD</b>	Studies Of Left Ventricular Dysfunction
<b>Val-HeFT</b>	Valsartan in Heart Failure Trial
<b>VALIANT</b>	VALsartan In Acute myocardial INfarcTion

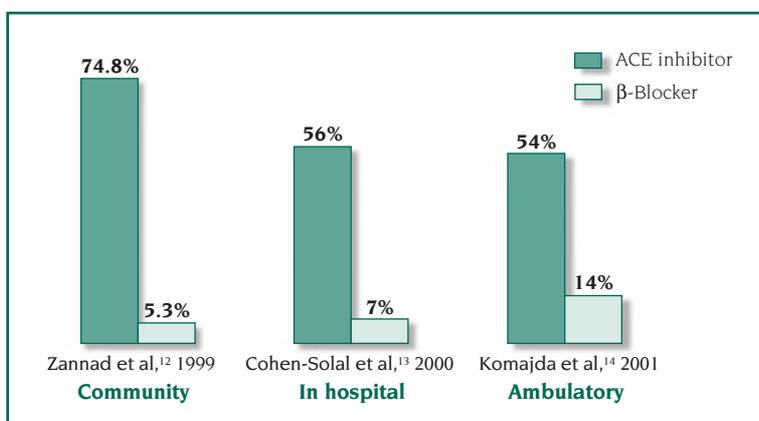
**Multiple neurohormonal modulation: what are the most effective combinations? - Komajda**

surveys show similar results, ie, a worrying underuse of ACE inhibitors and even more of  $\beta$ -blockers in CHF patients. Surveys conducted in the community, in hospital patients, or in ambulatory patients at the time of the publication of the updated version of the ESC guidelines, reveal an overall rate of prescription of ACE inhibitors in the range of 60% and less than 15% for  $\beta$ -blockers (Figure 1).<sup>12-14</sup> The Euro Heart Failure Survey (2001-2002), which en-

cept” drugs; contraindications or side effects; and difficulty to adhere to the time-consuming stepwise uptitration required for  $\beta$ -blockers. Whatever the reason, the upshot is that, in practice, fewer than 50% of patients who ought to be on both ACE inhibitors and  $\beta$ -blockers actually receive them. Of note, the Euro Heart Failure Survey suggests that elderly patients (>70 years) are less likely to receive the dual neurohormonal therapy.

Below is a brief discussion of the findings from large randomized, controlled outcome studies performed over the past 5 years in the wake of several pilot studies.

- ARB-mediated neuromodulation using losartan 50 mg/day was not found to be superior to ACE inhibition in terms of mortality and various outcome measures in CHF and post-myocardial infarction (Evaluation of Losartan In The Elderly II [ELITE II]<sup>16</sup>; OPTimal Trial In Myocardial infarction with Angiotensin II Antagonist Losartan [OPTIMAAL]<sup>17</sup>).
- In myocardial infarction with heart failure, left ventricular dysfunction, or both, the effect of valsartan on mortality was not inferior to that of captopril (VALsartan In Acute myocardial INfarcTion [VALIANT]<sup>18</sup>).
- In patients not receiving an ACE inhibitor due to intolerance, the magnitude of the beneficial effect on morbidity and mortality is similar to the effect observed with ACE inhibitors (Candesartan in Heart failure Assessment of Reduction in Mortality [CHARM-alternative]<sup>19</sup>).
- In combination with ACE inhibitors, ARBs significantly reduce heart failure hospitalizations (Valsartan-Heart Failure Trial [Val-HeFT]<sup>20</sup>; CHARM-added<sup>21</sup>) or cardiovascular death (CHARM-added). The beneficial effect of comprehensive RAS inhibition by the combination of ACE inhibitors and ARBs seems particularly important in patients not receiving a  $\beta$ -blocker.<sup>22</sup>
- The potential negative interaction of triple inhibition using ACE inhibitors, ARBs, and  $\beta$ -blockers, which was discussed in the first trials (ELITE II, Val-HeFT) was not confirmed subsequently and might have been a chance occurrence.
- A dose effect is discussed, as doses used in “positive” trials such as CHARM, VALIANT were high, whereas in ELITE II or OPTIMAAL—which failed to demonstrate superiority



**Figure 1.** Rate of prescription of angiotensin-converting enzyme (ACE) inhibitors and  $\beta$ -blockers in three national surveys.

rolled more than 11 000 in-hospital patients across 24 ESC countries indicates that, overall, only 63% and 37% of patients were on ACE inhibitors and  $\beta$ -blockers, respectively, at discharge, and that daily dosage of  $\beta$ -blockers was markedly below the target dose used in randomized trials.<sup>15</sup> Even in the subgroup of patients with depressed systolic function did the rate of prescription of  $\beta$ -blockers remain below 50%. These consistent observations suggest that dual neurohormonal inhibition, although strongly recommended, remains poorly implemented in real life both in terms of rate of prescription and daily dosage.

The reasons for this gap between current practice and guidelines are many and include educational issues; reluctance to use “new con-

### ALTERNATIVES TO DUAL NEUROHORMONAL THERAPY AND MULTIPLE NEUROHORMONAL THERAPY

#### Angiotensin II type I receptor antagonists (ARBs)

The development of new modulators of the renin-angiotensin system (RAS)—the angiotensin II type I receptor blockers (ARBs, aka sartans)—has raised new hopes for the treatment of heart failure. In theory, a potential advantage of sartans over ACE inhibitors would be to block the effect of “alternative” angiotensin II generation pathways that bypass ACE inhibition, such as the chymase pathway, by blocking the angiotensin II type I (AT<sub>1</sub>) receptor.



or noninferiority compared with ACE inhibitors—the doses of losartan used were rather low (approximately 50 mg/day).

### Aldosterone antagonists

The Randomized ALdactone Evaluation Study (RALES) was performed in patients with severe CHF, NYHA Class III or IV, and a history of class IV in the 6 months prior to randomization, with a severely depressed ejection fraction below 30%.<sup>23</sup> It compared the addition of spironolactone 25 to 50 mg/day on top of diuretics, ACE inhibitors, and in most instances, digitalis to this background therapy. The study was prematurely terminated due to the magnitude of the benefit observed in the spironolactone arm on mortality (-30%) and on hospitalizations, particularly heart failure hospitalizations (-35%). More recently, the selective aldosterone blocker eplerenone, 25 to 50 mg/day, was evaluated in acute myocardial infarction complicated by left ventricular dysfunction and heart failure, showing a significant 15% risk reduction in all-cause mortality and a 13% reduction in cardiovascular death or hospitalizations.<sup>24</sup>

These two trials therefore suggest that aldosterone blockade is another successful approach to improving outcome both in chronic heart failure and in high-risk myocardial infarction. In this context, it is relevant to examine the background therapy used in these two trials with regard to  $\beta$ -blockers: in RALES, only 11% of the patients were on  $\beta$ -blockers, in contrast to 75% of the patients enrolled in the Eplerenone Post-AMI Heart failure Efficacy and SURvival Study (EPHESUS). This suggests that, for historical reasons, the benefit observed with spironolactone did not fall within the context of recommended “modern”

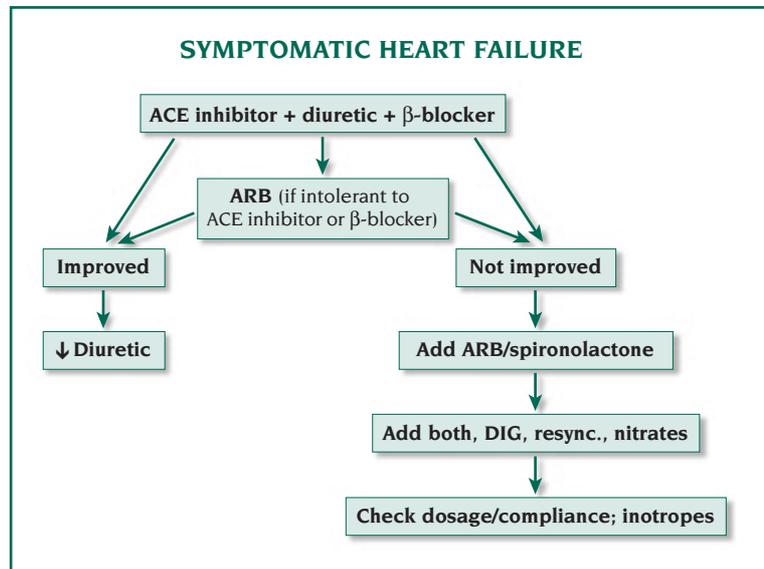
neurohormonal modulation, as opposed to eplerenone, for which the benefit was demonstrated in the context of current treatment guidelines for myocardial infarction.

### MULTIPLE NEUROHORMONAL MODULATION IN PRACTICE

Based on the evidence reviewed above, the following recommendations can be made:

Neurohormonal blockade applies only to patients with depressed systolic function defined by an ejection fraction below 35% to 40%. The level of evidence regarding heart failure with preserved systolic function is poor, outside of CHARM-preserved, which enrolled patients with an ejection fraction of 40% or more, a threshold that already suggests a somewhat altered ejection fraction). Indeed, CHARM-preserved suggested that the ARB candesartan led to a reduction in the number of heart failure hospitalizations, but the trial fell short of demonstrating improved survival, possibly due to insufficient power.

Patients with asymptomatic left ventricular dysfunction should receive an ACE inhibitor and, in the context of post-myocardial infarction, a  $\beta$ -blocker. Symptomatic CHF patients should receive an ACE inhibitor, a  $\beta$ -blocker unless contraindicated, and a diuretic (Figure 2). If the patient improves, the diuretic should be downtitrated to the lowest dosage compatible with a good quality of life in order to avoid potential harmful effects of high diuretic dosage on the RAS. Conversely, every effort should be made to uptitrate both ACE inhibitors and  $\beta$ -blockers to the maximal tolerated dose close to the target dose used in clinical trials. Although there are few data to support this practice, many experts prefer to give ACE inhibitors and  $\beta$ -blockers at a “medium” dosage in order to ensure simultaneous good tolerance of both drugs, rather than giving the maximal dose of ACE inhibitor, which might limit the introduction and uptitration of the  $\beta$ -blocker. The order of prescription remains ACE inhibitor first, followed by the  $\beta$ -blocker when the patient is in stable condition, as all  $\beta$ -blocker trials have been designed with a



**Figure 2.** Algorithm for the combination of neurohormonal modulators in symptomatic patients with CHF. Resync., resynchronization therapy.

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background therapy of ACE inhibitors. However, some data suggest that the introduction of the  $\beta$ -blocker first is just as well tolerated.<sup>25</sup> If the patient is intolerant to ACE inhibition or  $\beta$ -blockers, an ARB should be introduced early on in combination with an ACE inhibitor or a  $\beta$ -blocker. If the patient remains symptomatic despite this dual neurohormonal inhibition, a third neurohormonal modulator should then be used. Given the fact that in CHARM-added patients were in a less severe category and were more often treated with  $\beta$ -blockers than in RALES, one might give the preference to ARBs in chronic heart failure. Conversely, more patients in CHARM-added had to be withdrawn from the trial for serious adverse reactions (24%), including hypotension and increase in creatinine or hyperkalemia, than in RALES (8%).

In post-myocardial infarction with heart failure or left ventricular dysfunction, use of an aldosterone antagonist such as eplerenone (not yet licensed in many countries) can be recommended. If the patient remains severely symptomatic despite triple neurohormonal therapy, then the use of four neuromodulators should be considered (ACE inhibitor +  $\beta$ -blocker + ARB + aldosterone antagonist). Due to the potential risk of hypotension, hyperkalemia, and renal dysfunction in this situation, regular monitoring of blood pressure, serum potassium, and serum creatinine is mandatory upon initiation and during follow-up. Another option at this stage is to consider resynchronization therapy.

**LIMITATIONS AND FUTURE OPTIONS FOR NEUROHORMONAL MODULATION**

One of the limitations of long-term neurohormonal modulation is suggested by the findings of the 12-year

follow-up of SOLVD patients: the absolute risk reduction in all-cause mortality in the symptomatic patients initially treated with the ACE inhibitor enalapril was only 1%, and 4 out of 5 patients had died at the end of follow-up.<sup>26</sup> This illustrates that although active therapy did slow down the mortality rate, in the end, a majority of symptomatic died at 12 years, particularly due to noncardiac reasons. Conversely, the 12-year absolute risk reduction in mortality remained substantial in the asymptomatic patients (5.5%), suggesting that the earlier the neurohormonal modulation, the better.

Other therapeutic options have recently been tested in CHF. Interest focused on endothelin antagonists, but, despite theoretical potential advantages, these agents failed to demonstrate any clinical benefit on top of ACE inhibitors and  $\beta$ -blockers. Among the various hypotheses raised to explain this failure, one is that a ceiling of neurohormonal blockade is reached with the successful combination of an ACE inhibitor and a  $\beta$ -blocker or an ARB and a  $\beta$ -blocker, leaving very little room for further improvement with additional blockade.

Similarly, the dual ACE/neutral endopeptidase inhibitor omapatrilate failed to demonstrate any benefit against captopril, thus suggesting that, so far, this complex type of neurohormonal modulation is not better than simple ACE inhibition.<sup>27</sup>

Finally, several ongoing studies are currently assessing the role of arginine-vasopressin antagonists in heart failure with hyponatremia.

To conclude, the story of multiple neurohormonal modulation as a key player in CHF management is not over and exciting future developments can be anticipated.

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# Why are we unable to completely control the activation of neurohormonal systems in chronic heart failure—and should we?

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*The neurohumoral hypothesis provided the rationale for treating heart failure with angiotensin-converting enzyme (ACE) inhibitors, aldosterone blockers, and  $\beta$ -blockers. Backed by the cytokine hypothesis, the case for incremental benefit from neurohumoral and cytokine blockade appeared made. However, the pendulum may have swung too far. Clinical trials are releasing evidence of hypotension, renal insufficiency, and critical loss of adrenergic support. ACE inhibitors and  $\beta$ -blockers are already so successful that added treatments do not automatically confer added benefits. More is not necessarily better. Neurohormonal activation is, at least in part, a healthy response to the low cardiac output that defines heart failure. Although its partial blockade remains an effective treatment, we are only just beginning to understand why at the receptor, postreceptor, and cardiovascular cell type level.*

**Keywords:** neurohormonal activation; chronic heart failure; ACE inhibitor; aldosterone blocker;  $\beta$ -blocker; cytokine

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The introduction of angiotensin-converting enzyme (ACE) inhibitors, aldosterone blockers, and  $\beta$ -blockers in the treatment of chronic heart failure (HF) represents one of the great success stories of modern medicine. The neurohormonal hypothesis provided the scientific rationale for these therapies. According to this concept, persistent activation of neurohormonal systems, such as the renin-angiotensin-aldosterone (RAAS) system, the sympathetic nervous system, or the endothelin system, exerts a deleterious effect

on the heart that is independent of the hemodynamic actions of these endogenous mechanisms. Therapeutic interventions that block the effects of these neurohormonal systems are therefore predicted to favorably alter the natural history of HF.<sup>1</sup> More recently, it has become apparent that, in addition to neurohormones, cytokines are also overexpressed in HF. According to the cytokine hypothesis, cytokines, much like the neurohormones, represent another class of biologically active molecules that are responsible for the progression of HF.<sup>2</sup> Several lines

## SELECTED ABBREVIATIONS AND ACRONYMS

<b>ATLAS</b>	Assessment of Treatment with Lisinopril And Survival
<b>BEST</b>	Beta-blocker Evaluation of Survival Trial
<b>CHARM</b>	Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity
<b>EARTH</b>	Endothelin <sub>A</sub> Receptor antagonist Trial in Heart failure
<b>EPHESUS</b>	Eplerenone Post-acute myocardial infarction Heart failure Efficacy and SURvival Study
<b>HF</b>	heart failure
<b>NEP</b>	neutral endopeptidase
<b>OVERTURE</b>	Omapatrilat Versus Enalapril Randomized Trial of Utility in Reversing Events
<b>RAAS</b>	renin-angiotensin-aldosterone system
<b>RALES</b>	Randomized ALdactone Evaluation Study
<b>TNF-<math>\alpha</math></b>	tumor necrosis factor- $\alpha$
<b>Val-HeFT</b>	Valsartan in Heart Failure Trial
<b>VALIANT</b>	VALsartan In Acute myocardial iNfarction Trial



of evidence indicate that neurohormonal and cytokine activation is detrimental in HF. Angiotensin II, norepinephrine, endothelin, and tumor necrosis factor (TNF)- $\alpha$  are directly cytotoxic to cardiomyocytes and promote adverse myocardial and remodeling in experimental models.<sup>3</sup> In patients with HF, activation of these systems is proportional to disease severity, increases with the progression of the disease, and is related to prognosis.<sup>4</sup> Moreover, changes in neurohormonal activation over time occurring either spontaneously or in response to pharmacologic therapy are associated with proportional changes in subsequent morbidity and mortality.<sup>5</sup> The success accrued from inhibiting the RAAS and sympathetic nervous system has led to the proposition that a concerted approach to inhibit every single neurohormonal and cytokine system may provide incremental benefits. However, recent clinical trial data evaluating this all-encompassing strategy have yielded start-lingly disappointing results and indicate that there may be limits to the classic neurohormonal and cytokine models, and that too much neurohormonal blockade may even be harmful.<sup>4,6</sup>

### **MORE COMPLETE ACE INHIBITION**

The first hints that we may have reached a therapeutic ceiling in our efforts to achieve more and more complete neurohormonal blockade have emerged from clinical studies comparing high-dose versus low-dose ACE inhibition in HF patients. In the Assessment of Treatment with Lisinopril And Survival (ATLAS) trial, patients with symptomatic HF and a left ventricular ejection fraction below 30% were randomly assigned to a high (target dose 35 mg daily) or low dose (5 mg) of lisinopril.<sup>7</sup> Patients in the high-dose

group experienced 24% fewer hospitalizations for HF. However, high-dose ACE inhibition was associated only with a nonsignificant 8% lower mortality rate, the primary end point of the ATLAS trial. At the same time, renal insufficiency and dizziness were observed more frequently in the high-dose group, confirming that ACE plays a supportive role in maintaining kidney function and blood pressure in HF.<sup>7</sup> A study comparing a very high dose of enalapril (60 mg) with a standard dose (20 mg) in patients with advanced HF did not find significant differences in survival and clinical end points between the two groups.<sup>8</sup> However, tolerability of the high-dose regimen was limited, as evidenced by an excessive withdrawal rate.<sup>8</sup> The lack of benefit of high-dose ACE inhibition may be related to the phenomenon of angiotensin II and aldosterone escape.<sup>9,10</sup> Indeed, high-dose enalapril (40 mg) does not provide greater suppression of circulating angiotensin II and aldosterone levels in HF patients compared with low-dose enalapril (5 mg).<sup>10</sup>

### **MORE COMPLETE RAAS INHIBITION**

According to the neurohormonal hypothesis, addition of angiotensin receptor blockers or aldosterone blockers to a stable regimen of ACE inhibitors and  $\beta$ -blockers would be expected to provide additional therapeutic benefit by counteracting the angiotensin II and aldosterone escape, thereby providing more complete neurohormonal coverage.<sup>11</sup> Indeed, two large clinical trials conducted either in patients with severe HF (Randomized ALdactone Evaluation Study, RALES) or in patients with acute myocardial infarction, reduced left ventricular ejection fraction, and HF symptoms (Eplerenone Post-acute myocardial infarction Heart failure Efficacy and SURvival

Study, EPHEsus) have demonstrated that treatment with aldosterone blockers results in a further reduction in all-cause mortality (-30% in RALES, -15% in EPHEsus).<sup>12-14</sup> Nonjudicious use of aldosterone blockers in HF, however, may lead to life-threatening episodes of hyperkalemia, indicating that aldosterone plays an important role in maintaining potassium homeostasis, especially in HF patients already receiving an ACE inhibitor (many of whom display some degree of renal insufficiency), and that close monitoring of serum potassium levels is mandatory when using aldosterone blockers in HF.<sup>15</sup> Combination of ACE inhibitors and angiotensin receptor blockers has been cheered as a means to overcome the angiotensin II escape observed with ACE inhibitors alone, and to achieve incremental benefits in HF.<sup>11</sup> However, studies investigating whether angiotensin receptor blockers on top of ACE inhibitors and  $\beta$ -blockers provide additional benefit have provided quite disappointing results. In the Valsartan in Heart Failure Trial (Val-HeFT), addition of valsartan did not affect overall mortality (relative risk 1.02) and had only a modest effect on a composite mortality and morbidity end point (relative risk 0.87) in HF patients already being treated with ACE inhibitors (93%) and  $\beta$ -blockers (35%).<sup>16</sup> Subgroup analyses revealed that this benefit was greatest in patients not taking an ACE inhibitor and was no longer statistically significant among those who were on ACE inhibitor and angiotensin receptor blocker combination therapy.<sup>16,17</sup> Although valsartan was generally well tolerated, hypotension and renal impairment were noted more frequently in the valsartan group.<sup>16</sup> Not surprisingly so, because the AT<sub>1</sub> receptor is critical for blood pressure control and kidney function, also in HF!

In the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM)-added trial, treatment with candesartan in patients receiving ACE inhibitors (100%) and  $\beta$ -blockers (55%) exerted a modest beneficial effect on the primary end point of combined cardiovascular death or hospital admission with HF (hazard ratio 0.85), but did not significantly reduce all-cause mortality (hazard ratio 0.89).<sup>18</sup> Increases in creatinine and hyperkalemia were observed more frequently in candesartan-treated patients.<sup>18</sup> In the VALsartan In Acute myocardial infarction Trial (VALIANT), patients with myocardial infarction complicated by left ventricular systolic dysfunction and/or HF were randomly assigned to captopril, valsartan, or captopril and valsartan.<sup>19</sup> Although valsartan was not inferior to captopril in reducing all-cause mortality, combination therapy with valsartan and captopril did not provide any additional benefits on mortality and morbidity beyond monotherapy with either agent.<sup>19</sup> Similar to Val-HeFT, hypotension and renal insufficiency were observed more frequently in patients receiving combination therapy.<sup>19</sup>

### **MORE COMPLETE SYMPATHETIC NERVOUS SYSTEM INHIBITION**

Little information is available regarding the dose dependency of the effects of  $\beta$ -blockers in HF. In one study, patients with mild to moderate HF were randomized to receive low-dose (6.25 mg bid), medium-dose (12.5 mg bid), or high-dose (25 mg bid) carvedilol treatment (the "high dose" actually represents the recommended target dose for carvedilol in HF patients). In this study, carvedilol produced dose-related improvements in left ventricular function and dose-related reductions in mortality and hospitalization rate.<sup>20</sup>

Additional clues may be derived by looking at some early  $\beta$ -blocker trials that have used relatively low doses of  $\beta$ -blockers and did not demonstrate as impressive benefits as later trials using the now recommended doses of the same agents.<sup>17,21</sup> Surprisingly, in the Beta-blocker Evaluation of Survival Trial (BEST), class IV patients receiving bucindolol who had a marked decrease in circulating norepinephrine levels from baseline experienced an increase in mortality, as compared with patients who had no significant change in norepinephrine levels.<sup>22,23</sup> Moreover, the observation that moxonidine, a centrally-acting sympatholytic agent, decreases plasma norepinephrine levels, but adversely affects survival in HF patients, has raised concerns regarding the efficacy of a generalized sympathetic inhibition in HF.<sup>24</sup> This may suggest, that excessive inhibition of the sympathetic nervous system results in a critical loss of adrenergic support and adverse outcomes in HF patients.

### **INHIBITION OF ADDITIONAL NEUROHORMONAL/CYTOKINE SYSTEMS**

It has recently been attempted to expand the benefits derived from ACE inhibitors by combining ACE inhibition with inhibition of other peptidases such as neutral endopeptidase (NEP) in a single molecule, a strategy known as vasopeptidase inhibition. NEP metabolizes natriuretic peptides, and NEP inhibition offers the prospect of combining the benefits of increased vasodilatory natriuretic peptide levels with those of ACE inhibition. However, NEP also converts angiotensin I to the vasodilatory angiotensin (1-7) peptide and metabolizes angiotensin II and endothelin. Addition of NEP inhibition to ACE inhibition there-

fore reduces angiotensin (1-7) levels, and may increase angiotensin II and endothelin levels. These additional consequences of combined ACE/NEP inhibition may counteract any benefit of ACE inhibition.<sup>25</sup>

In the OVERTURE trial (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) the vasopeptidase inhibitor omapatrilat was found not to be superior to enalapril with regard to the primary combined end point of risk of death or hospitalization for HF requiring intravenous treatment.<sup>26</sup> Hypotension and dizziness were reported more frequently with omapatrilat, especially in patients with low pretreatment systolic blood pressure.<sup>26</sup> This is another example that the occurrence of hypotension may limit our efforts at more aggressive neurohormonal blockade.

Endothelin has been suggested to contribute to the pathophysiology of HF very much like angiotensin II and norepinephrine. However, several studies have failed to demonstrate that endothelin antagonists provide clinical benefit. The mixed  $ET_A$  and  $ET_B$  receptor blocker bosentan promoted early worsening of HF, but later symptomatic improvement, when given at a high dose; low-dose bosentan, however, did not improve clinical outcome (reviewed in reference 4). Because selective  $ET_B$  receptor blockade may worsen hemodynamics in HF patients,<sup>27</sup> it was suggested that selective  $ET_A$  receptor blockade may be more effective than mixed  $ET_A$  and  $ET_B$  blockade. However, in the recently completed Endothelin<sub>A</sub> Receptor antagonist Trial in Heart failure (EARTH), the  $ET_A$  receptor blocker darusentan did not add incremental benefit in patients already receiving an ACE inhibitor (98%) and a  $\beta$ -blocker (80%).<sup>4,28</sup> Studies in experimental models and preliminary



clinical experience suggested a possible therapeutic role for the soluble TNF- $\alpha$  antagonist etanercept in HF. However, etanercept had no effect on clinical status and a combined death or HF hospitalization end point in two recently completed clinical trials.<sup>29</sup> Although one interpretation of these disappointing results is that TNF- $\alpha$  is not a viable target in HF in patients already receiving ACE inhibitors and  $\beta$ -blockers, a countervailing point of view is that we have not targeted TNF- $\alpha$  with the right agent, or alternatively, that targeting a single component of the inflammatory cascade is not sufficient in a disease as complex as HF. Moreover, these trials do not exclude the possibility that there exists a select group of patients in whom TNF- $\alpha$  antagonism may be beneficial.<sup>29</sup>

### WHY MORE IS NOT NECESSARILY BETTER

Why did our recent attempts at more complete neurohormonal and cytokine blockade fail to significantly impact on the prognosis of HF? First of all, it should be noted that recent strategies were tested in patients many of whom were already receiving effective ACE inhibitor and  $\beta$ -blocker therapy. Any potential survival benefit of a new agent therefore had to be demonstrated on top of these extremely successful treatments. We will never know whether newer therapies are in fact, as good as, or even better than ACE inhibitors or  $\beta$ -blockers alone.

Secondly, ACE inhibitors and  $\beta$ -blockers are already extremely efficacious in reducing morbidity and mortality in HF. Consider, for example, the subgroup of patients in the Val-HeFT trial receiving both an ACE inhibitor and a  $\beta$ -blocker: this subgroup experienced an annual mortality rate of only 5.7%. Thus,

at least in the setting of clinical trials, effective use of ACE inhibitors and  $\beta$ -blockers has already reduced the mortality rate of patients with moderate to severe HF to a remarkably low level, considering that, according to the National Vital Statistics Report, the annual mortality rate in white American men aged 65 years without HF is approximately 3%.<sup>4</sup> It is possible that angiotensin receptor blockers, vaso-peptidase inhibitors, or endothelin antagonists would provide greater therapeutic benefit if they were used as first-line treatments in HF patients (as they did in experimental models).<sup>30-32</sup>

Thirdly, we may have to revise our thinking that neurohormonal activation is entirely harmful in the setting of HF. Despite the recent refinements in our understanding of the cellular, molecular, genetic, and inflammatory alterations in HF, low cardiac output remains the pathophysiological basis of the disease. Neurohormonal activation represents an ancient defense system to maintain blood pressure, blood volume, water and electrolyte homeostasis, and renal function during acute or chronic volume loss (eg, after trauma or starvation). It is the reduction of cardiac output in HF that leads to neurohormonal activation. Not surprisingly, hypotension, renal dysfunction, and hyperkalemia are encountered in many patients where maximum neurohormonal blockade is attempted, and the body's own homeostatic mechanisms are undermined.

Finally, let's be honest, we do not really understand why neurohormonal blockade is so effective in HF. We are only beginning to appreciate what neurohormonal antagonists do at the receptor and postreceptor level, and what the consequences at the (post)transcriptional level are in distinct cardiovascular cell types.<sup>33</sup>

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# Trails of Discovery

## *Class III antiarrhythmic agents: serendipity or drug design?*

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The classification of antiarrhythmic drugs proposed by Singh and Vaughan Williams in 1970<sup>1,2</sup> relied on the differential actions of these agents on the profile of the transmembrane action potential in isolated myocardial tissue from different species. Despite the dramatic advances over the last 15 years in understanding the molecular and ionic basis, which determine the profile of the transmembrane action potential, the original classification persists in both the clinical and government regulatory spheres. The field of Class III antiarrhythmic drug research has been illuminated by numerous publications in a most fruitful manner over the last 30 years by Professor Braham Singh, who provides an elegant example of what is now translational medicine, ie, applying data from the laboratory to the bedside. This essay is largely based on Professor Singh's seminal work.<sup>3-7</sup>

### **FIRST-GENERATION CLASS III AGENTS: AMIODARONE AND SOTALOL**

Amiodarone and sotalol provide striking examples of the role of serendipity in drug discovery. Amiodarone was initially developed as a selective coronary

vasodilator for the treatment of angina pectoris, and sotalol was a nonselective  $\beta$ -blocker first synthesized at the same time as the classic  $\beta$ -blockers pronethalol and propranolol (1959-1962).

### **DISCOVERY OF AMIODARONE**

Amiodarone was one of a large number of benzofuran analogs synthesized in the Labaz Laboratories in Belgium between 1958-1966.<sup>8,9</sup> The rationale for the synthetic program was based on the natural product, khellin, which was used in the Middle East as a diuretic and antispasmodic. Khellin was isolated from the seeds of the plant *Ammi visnaga*, called in Arabic "khella." The first paper from the Labaz Laboratories describes the coronary vasodilator properties of a series of benzofurans derived from the furanochromone structure of khellin.<sup>9</sup> In regard to the rationale for the research program, the paper quotes the work of Anrep et al<sup>10</sup> published in 1945, which concluded that khellin (120 mg daily) was effective in 36 of 38 anginal patients. The Labaz paper also notes that Greiner et al<sup>11</sup> had failed to confirm Anrep's observations. Nevertheless, the Labaz scientists appear to have concluded that the proof of concept of the antianginal action of khellin was established. Furthermore, the khellin preparation was marketed by Smith-Kline in the early 1950s and is still classified in the Martindale *Extra Pharmacopoeia* under Supplementary Drugs and Other Substances.<sup>12</sup>

Eighty-one benzofurane analogs were synthesized and tested in vitro for their antispasmodic activity on smooth muscle as well as their coronary dilating action in the isolated, fibrillating, rabbit heart. In these in vitro tests, khellin was used as the benchmark coronary vasodilator.<sup>9</sup> Compound L2329 (Amplivix®, benziodarone) was developed for clinical studies in angina pectoris.<sup>13,14</sup>

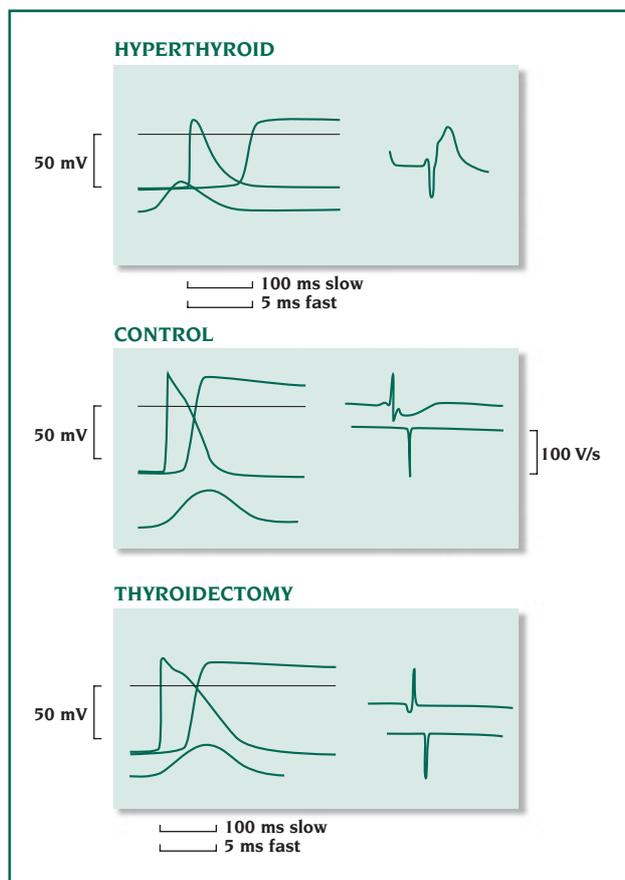
Clinical trials in the early 1960s showed that it was effective in reducing the number of anginal attacks and increasing exercise tolerance. It was also observed that it slowed the heart rate. A paper from the Labaz Laboratories in 1969<sup>15</sup> states that a clinical investigator had observed that amiodarone had antiarrhythmic properties. The published paper<sup>14</sup> does not refer to a reduction of arrhythmias, but only of heart rate in anginal patients treated with amiodarone 600 mg daily for a month. Interestingly, the paper reports that "the depolarization complex of the ECG showed no change." The introduction to the paper by Charlier et al<sup>15</sup> refers to "a chance observation of normalization of cardiac rhythm in an anesthetized dog following amiodarone 10 mg/kg/ IV," although the paper they quote contains only clinical studies in anginal patients.

Nevertheless, the Labaz scientists re-evaluated amiodarone in several experimental arrhythmia models and attributed their positive findings to a combination of the sympatholytic and quinidine-like actions of amiodarone.<sup>15</sup>

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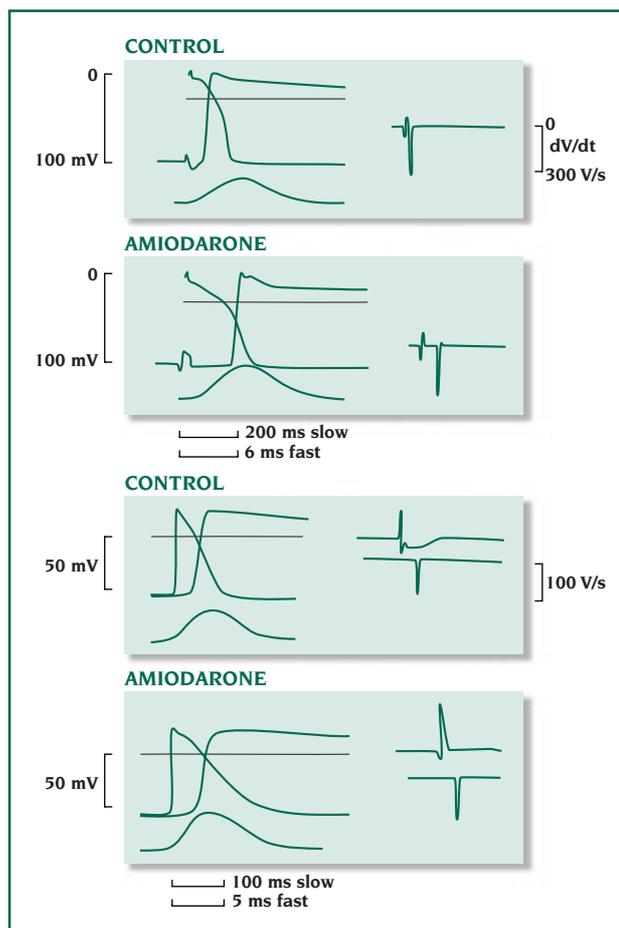
**Figure 1a.** The effect of thyroid state on cardiac intracellular potentials. The horizontal line in each frame indicates the zero potential and the superimposed traces record intracellular action potentials at both slow and fast sweep speeds. The lowest trace records the contractile response.

From reference 16: Freedberg AS, Papp J, Vaughan Williams EM. The effect of altered thyroid state on atrial intracellular potentials. *J Physiol Lond.* 1970;207:357-370. Copyright © 1970, Blackwell Publishing.

During this same period, Vaughan Williams' group in Oxford published a series of papers examining the effects of different drugs on the myocardial transmembrane action potential. These studies resulted in a proposal to classify antiarrhythmic drugs into at least three categories.<sup>2</sup> His group had also observed the effects of experimental hypothyroidism on the transmembrane action potential in rabbits and showed that six weeks after thyroidectomy the action potential duration was significantly prolonged (*Figure 1a*).<sup>16</sup>

Dr Bramah Singh, who was a Commonwealth Fellow born in Fiji and trained in medicine in Otago University, New

Zealand, joined Professor Vaughan Williams group in the late 1960s in order to do a PhD degree. The topic chosen was "The study of the pharmacological actions of certain drugs and hormones with a particular reference to cardiac muscle." Included in this research program was an evaluation of the effects of chronic amiodarone treatment on the transmembrane action potential after chronic administration (20 mg/kg IP) to rabbits. He showed that amiodarone specifically prolonged the action potential duration (APD) without significant effects on the resting potential or the rate of rise of the action potential (*Figure 1b*). The precise rationale for selecting amiodarone



**Figure 1b.** The effects of 6 weeks treatment with amiodarone (20 mg/kg/IP daily) in rabbit atrial muscle, above, and in ventricular muscle, below.

From reference 3: Singh BN, Vaughan Williams EM. The effects of amiodarone, a new anti-anginal drug, on cardiac muscle. *Br J Pharmacol.* 1970;39:657-667. Copyright © 1970, Nature Publishing Group.

for study is not stated in the published papers or the thesis. One may speculate that it was the di-iodo substitution in amiodarone that was the stimulus for its selection, though it was claimed at the time to have no effect on thyroid function. In addition, amiodarone had complex effects on the autonomic system, causing an atropine-resistant bradycardia in dogs and inhibition of sympathetic nerve stimulation and catecholamines, but not due to specific blockade of  $\alpha$  or  $\beta$  adrenoceptors.<sup>17</sup>

This combination of pharmacological attributes made it an interesting tool for exploring the mode of action of antiarrhythmic compounds.



Site of ADR	Number of trials reporting	Number affected in amiodarone group	Number affected in placebo group	Peto odds ratio (25% CI)	P-value
Heart	6	98/2087	43/2066	2.40 (1.69, 3.41)	<0.00001
Thyroid	5	74/2038	12/2014	4.19 (2.72, 6.45)	<0.00001
Respiratory	6	76/2087	42/2066	1.78 (1.23, 2.58)	0.002
Nervous system	5	48/1782	19/1758	2.40 (1.48, 3.89)	0.0004
Liver	5	30/1782	14/1758	1.95 (1.07, 3.56)	0.03
Gastrointestinal tract	5	66/2038	47/2014	1.32 (0.9, 1.94)	0.15
Eyes	4	23/1702	6/1676	3.05 (1.46, 6.38)	0.003
Skin	6	24/2087	12/2066	1.93 (1.00, 3.72)	0.05

**Table I.** Meta-analysis of adverse effects of amiodarone in six randomized controlled trials.

*Modified from reference 20: Loke YK, Derrey S, Aronson JK. A comparison of three different sources of data in assessing the frequencies of adverse reactions to amiodarone. Br J Clin Pharmacol. 2004;57:616-621. Copyright © 2004, Blackwell Publishing.*

## CLINICAL STUDIES

The major clinical utility of amiodarone is in the prophylactic control of supra-ventricular and ventricular arrhythmias. Parenteral amiodarone (5 mg/kg by slow injection) slows the ventricular response in atrial flutter and fibrillation. Observational studies suggest that it is also effective acutely in the control of life-threatening ventricular arrhythmias.<sup>18</sup> Its major utility is as chronic therapy (200-400 mg daily), firstly to control the ventricular response in atrial flutter and fibrillation both at rest and on exercise. Secondly, amiodarone has had a major impact on the treatment of recurrent life-threatening ventricular tachyarrhythmias. It is currently the drug of choice for this indication. Remarkably, it has much less proarrhythmic activity than many other antiarrhythmic drugs.<sup>19</sup> The most serious unwanted effect is pulmonary toxicity, which occurs in 2% to 17% of patients and is observed with doses higher than 300 mg daily. Between 2% and 10% of patients receiving amiodarone have alterations in thyroid function, and given the arrhythmogenic potential of thyrotoxicosis, can reverse the antiarrhythmic effects of chronic amiodarone therapy (Table I).<sup>20</sup>

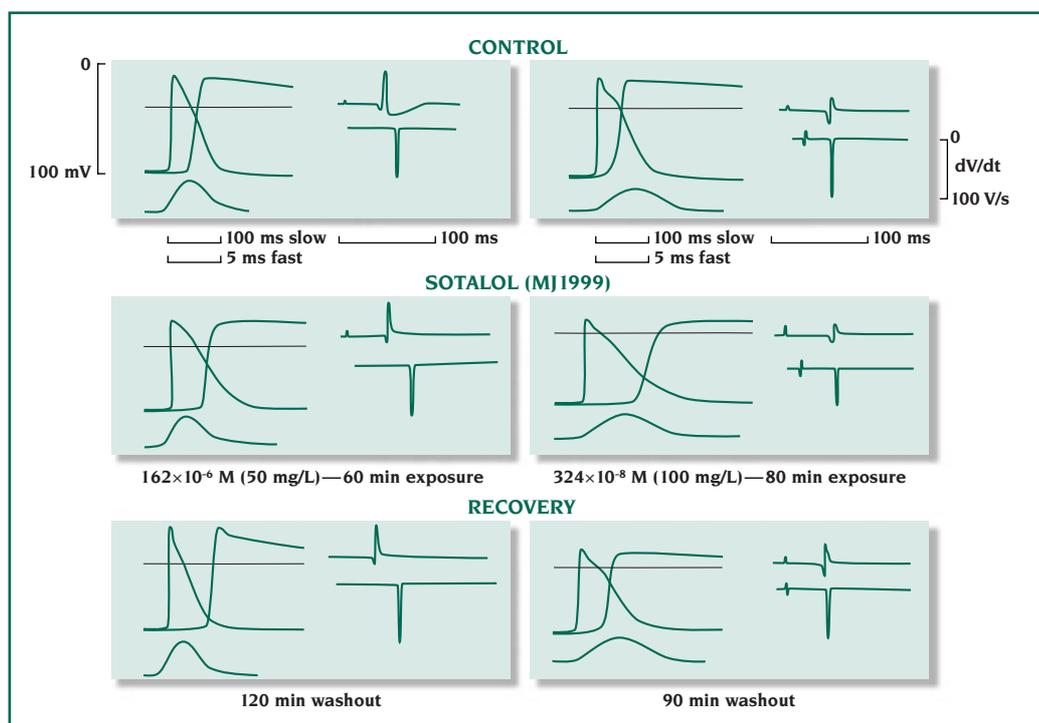
## THE DISCOVERY OF SOTALOL

This compound was synthesized in about 1960 by the Mead Johnson Company, in Indiana, USA.<sup>21</sup> It was one of a series of analogs submitted to the US Patent Office in January 1962, the patent was subsequently abandoned and then refiled and finally completed in 1965. The patent made broad claims including "vasopressors, vasodepressors, analgesics, bronchodilators,  $\alpha$ -receptor stimulants,  $\beta$ -receptor stimulants,  $\alpha$ -receptor blocking agents,  $\beta$ -receptor blocking agents, and papaverine-like smooth muscle depressants." DL-Sotalol was compound No. 11 in this patent, but the preferred compound was No. 3, possessing "strong and selective adrenergic vasoconstrictor emphasized activity." Thus the  $\beta$ -blocking properties of sotalol (Compound 11) are not described in the initial patent.<sup>22</sup> Ironically, sotalol would have been synthesized at the same time as pronethalol and propranolol in the ICI laboratories by Crowther and Black (1958-1964), but sotalol's potential therapeutic utility was not initially recognized, although eventually extensive clinical studies were undertaken.<sup>23</sup> It was shown that sotalol had a more attractive pharmacokinetic and phar-

macodynamic profile than propranolol. Unlike propranolol, it was not extensively metabolized and 80% was excreted unchanged in the urine while having a half-life of about 10 hours compared with propranolol's half-life of 2 hours. In addition, it had much less brain penetration. Perhaps more importantly, it did not have significant "membrane-stabilizing properties" or quinidine-like actions and had much less direct myocardial depressant properties.

The unique property of sotalol in prolonging action potential duration in cat papillary muscle was first published by Kaumann and Olson in 1968.<sup>24</sup> They showed that sotalol (MJ1999) in a concentration of  $6 \times 10^{-4}$  M lengthened APD from  $401.3 \pm 46.4$  ms (control) to  $1209.4 \pm 290$  ms at 90% repolarization. In the conclusion of their paper, they attribute its antifibrillatory properties in experimental canine infarction<sup>25</sup> to the fact that "It appears that the antifibrillatory activity of sotalol, unlike that of other presently-known antiarrhythmic agents, is attributable to the marked prolongation of the ventricular action potential."

In 1970, Singh and Vaughan Williams published their findings on the effects of MJ1999 on the transmembrane ac-



**Figure 1c.** The effect of sotalol (MJ1999) on intracellularly recorded potentials of rabbit atria.

From reference 2:  
Vaughan Williams EM. Classification of antiarrhythmic drugs. In: Sandoe E, Flensted-Jensen E, Olesen KH, eds. Symposium on Cardiac Arrhythmias. Sodertalje, Sweden: AB Astra; 1970: 449-469. Copyright © 1970, Astra. All rights reserved.

tion potential in isolated ventricular and atrial muscle and confirmed that it greatly prolonged the duration of the action potential (Figure 1c).<sup>17</sup> In their discussion, they also made the point that “the main interest of the delay in repolarization produced by MJ1999 is that it is an immediate effect, apparent after a few minutes exposure to the drug in vitro, whereas the effect produced by thyroidectomy and amiodarone takes several weeks to develop.”<sup>1</sup> Several years later it was shown that sotalol prolonged the monophasic action potential duration in man, as well as an acute increase in effective refractory period.

In an elegant study, Creamer et al compared the effects of acute and chronic administration of sotalol with those of propranolol in patients with programmable pacemakers. Sotalol prolonged the QT interval by 11.5% after 1 month's oral treatment, with a lesser effect of 6.5% following acute parenteral administration. Propranolol did not cause any change in the QT interval.<sup>27</sup> Extensive clinical studies with DL-so-

talol showed that it is effective in controlling both supraventricular and ventricular arrhythmias. The balance of evidence suggested that the dual effects of  $\beta$ -blockade (Class II) and prolongation of APD (Class III) gave the best clinical results.<sup>28</sup> This may be important for the prevention of sudden death in postinfarction patients, where the Class III agent D-sotalol was shown to be less effective than placebo.<sup>29</sup> It is not the purpose of this article to review the comparative effectiveness of different classes of antiarrhythmic drugs, but rather to describe the subsequent impact on cardiovascular research strategies within the pharmaceutical industry of the initial discovery of the selective specific prolongation of action potential duration (Class III drugs).

#### SUBSEQUENT DEVELOPMENTS IN CLASS III DRUG RESEARCH

The potential therapeutic utility of selective prolongation of APD was widely recognized.<sup>30</sup> The perceived disadvan-

tages of amiodarone included poor bioavailability, complex pharmacological profile, and unacceptable side effects. Thus, research was directed toward finding patentable, potent, highly selective Class III compounds. There were two assumptions underlying this strategy. Firstly, the beneficial antiarrhythmic effects of amiodarone were attributed almost entirely to its Class III properties and secondly, high specificity for the major ion channel involved in APD prolongation, namely,  $I_{Kr}$ , enabled in vitro testing to proceed rapidly.

The research strategy was highly successful, in that at least 18 pharmaceutical companies initiated research programs designed to discover improved Class III antiarrhythmic agents (Figures 2a and 2b, page 247 and 248). Such programs would be dominated by medical chemistry conceptual skills, using one or more of the four original Class III chemical templates, namely, sotalol, isopropyl nitrophenylethanolamine (INPEA), *N*-acetyl procainamide (a metabolite of procaine with selective Class III actions), and



amiodarone. The majority of research groups synthesized chemical series in which the methanesulfonamidophenyl group, present in sotalol, was retained (Figure 2b). For example, this substitution in a structure based on *N*-acetyl procainamide (NAPA) resulted in the development of sematilide (Berlex). Similarly, Pfizer chemists prepared a large chemical series based on the sotalol structure, resulting in 21 published patents and the development

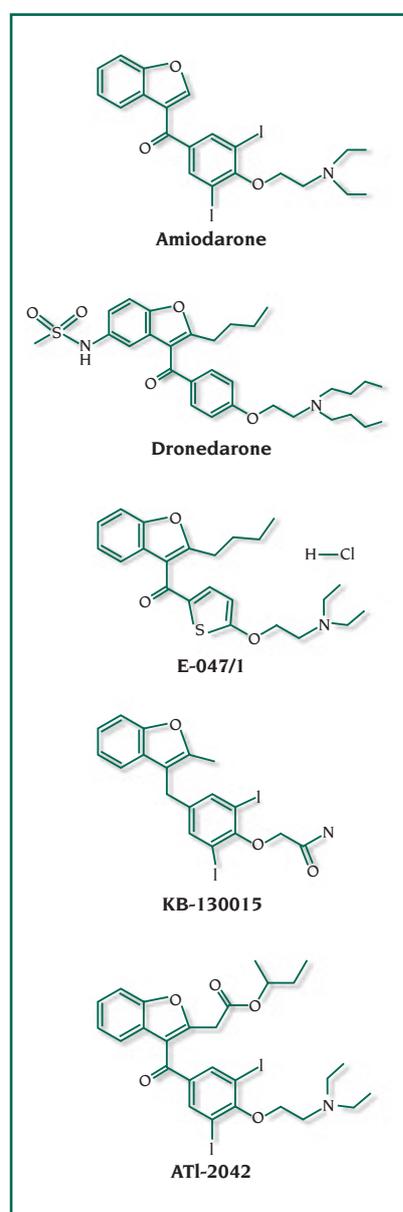


Figure 2a. Chemical structures of amiodarone and benzofuran analogs.

Drug	Cardiac channel	Dose range (mg)	T <sub>1/2</sub> (h)	Excretion
Dofetilide	$I_{Kr}$	0.125-0.5 PO bid	8	Kidney ≈80%
Sematilide	$I_{Kr}$	100-150 PO tid	3-8	Kidney ≈75%
Ibutilide	$I_{Kr}$ slow Na current	0.5-2 IV	6	Liver
Azimilide	$I_{Kr}$ $I_{Ksr}$ $I_{Ca(L)}$	100-125 PO od	100-120	Liver
Dronedarone	$I_{Kr}$ $I_{to}$ $I_{K(Ach)}$ $I_{Ks}$ $I_{Ca(L)}$	400 PO bid	150	Liver
Tedisamil	$I_{to}$ $I_{Kr}$	100 PO bid	16	Kidney

Table II. Cardiac and pharmacokinetic properties of newer "Class III" drugs.

of dofetilide (UK68798). The overall result of this intense drug research activity is somewhat limited in proportion to the enormous investment (Table II).

At present, the only Class III antiarrhythmic drugs approved for parenteral and oral use are dofetilide (Pfizer), indicated for the conversion (parenteral) or maintenance (oral) of sinus rhythm in patients with atrial fibrillation. As dofetilide also causes QT prolongation and, in some instances, torsades de pointes, treatment should be initiated in hospital, titrating the dose in relation to both the QT interval and the status of renal function.<sup>31</sup>

The other Class III compound is ibutilide, approved only for parenteral use for acute chemical conversion of atrial fibrillation or atrial flutter, as a possible alternative to DC cardioversion. In addition to blocking the  $I_{Kr}$  channel, it activates a sustained sodium channel, which must be distinguished from the "fast" sodium channel.<sup>32</sup>

There are three other Class III agents in phase 3 clinical trials: tedesamil, azimilide, and dronedarone, none of which block solely the  $I_{Kr}$  channel.

At this point, it is perhaps worth reflecting how advances in the understanding of the molecular mechanisms underlying the genesis of the cardiac action potential have influenced the approach to devising improved antiarrhythmic agents. In the context of

prolonging APD in order to prolong the refractory period, at least seven potassium channels may play a role (Table III, page 249).<sup>33</sup> A further difficulty for "pure"  $I_{Kr}$  blockers is that the prolongation of APD induced by them is reduced at rapid heart rates, a clinical situation that often requires efficacy in antiarrhythmic therapy at high heart rates. This phenomenon is termed "reverse use dependence."<sup>34</sup>

An additional disadvantage of their greater blocking efficacy at slow heart rates is that excess APD prolongation may trigger early afterdepolarizations, possibly leading to torsades de pointes. It is now apparent that the voltage-gated "delayed rectifier" potassium current ( $I_K$ ) is composed of two different currents carried by different ion channel species, namely, the "slow" component  $I_{Ks}$  comprising a major subunit (KCNQ1) and a minor unit (KCNE1). The rapid component ( $I_{Kr}$ ) is composed of the HERG (human ether-a-go-go-related gene) protein as the major subunit and KCNE2 as the accessory subunit. At high heart rates (high depolarization frequencies), the  $I_{Ks}$  outward current becomes the major one and selective blockade of  $I_{Kr}$  has little effect on APD in this setting. The chronic administration of amiodarone significantly decreases both  $I_{Kr}$  and  $I_{Ks}$  so that the APD prolongation does not show reverse use dependence. The lower incidence of torsades de pointes on amiodarone therapy has been attributed to this dual action.

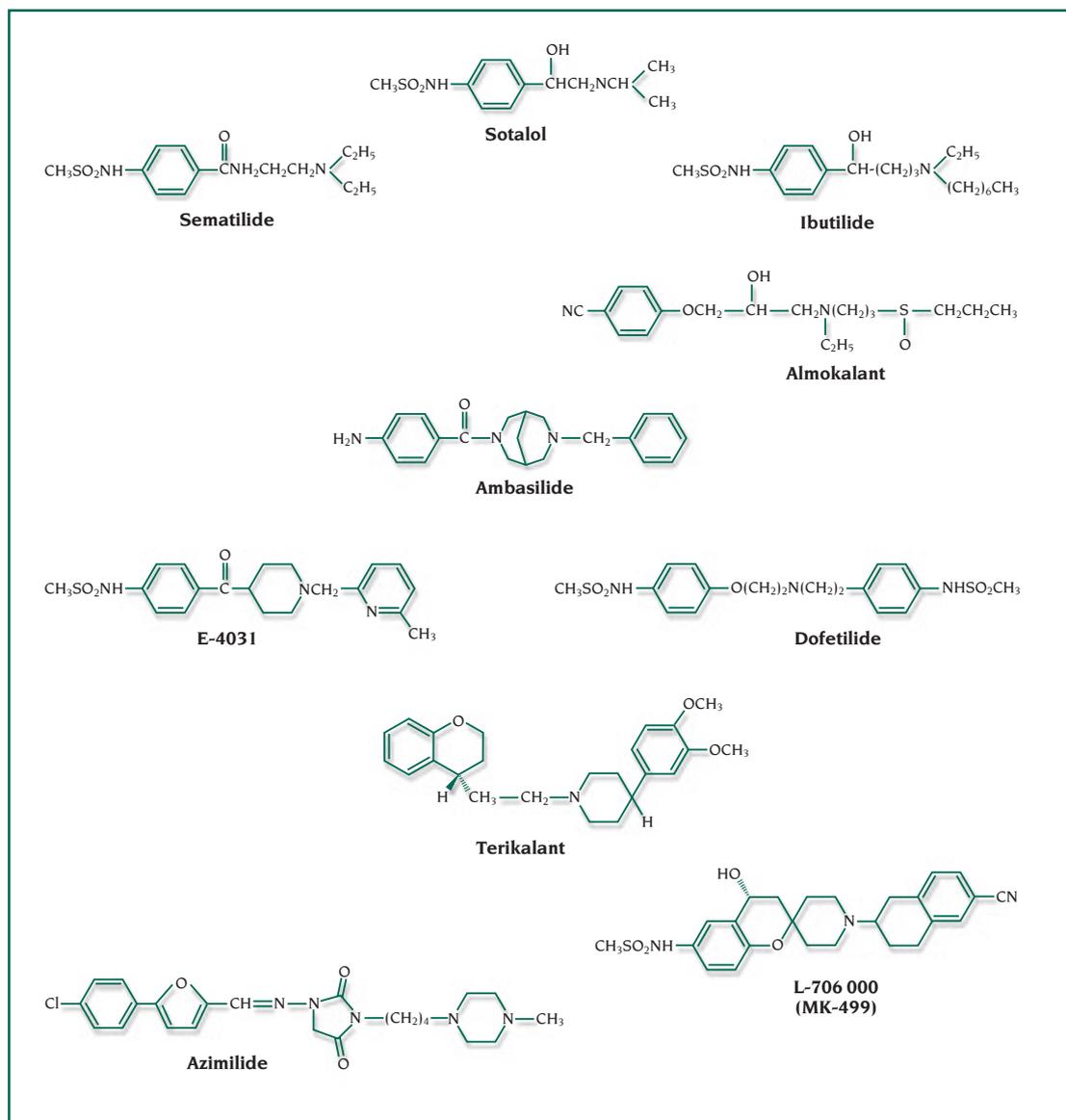


Figure 2b. Chemical structures of Class III agents based on the sotalol template.

It is perhaps ironical that potent binding to the HERG protein in the  $I_{Kr}$  channel is now perceived as a disadvantageous property of Class III agents because of proarrhythmia potential. Regulatory agencies now require data on the effects of any novel compound on the HERG channel prior to human exposure. In retrospect, perhaps drug researchers seeking an improved amiodarone were somewhat misled by assuming that its major desirable property was prolongation of APD solely by selective  $I_{Kr}$  blockade.

### THE SEARCH FOR AN IMPROVED AMIODARONE

The cardiac channel actions of amiodarone include potent inhibition of the  $K_r/K_s$  channels, moderate inhibition of the cardiac  $\alpha$  and  $\beta$  receptors, as well as of the  $L-C_a$  channel and the fast sodium channel. The challenge in seeking an improvement on amiodarone is to decide how many of these properties contribute to its antiarrhythmic efficacy. Amiodarone is more efficacious than all other antiarrhythmic

drugs in treating atrial fibrillation, and is better than placebo or lidocaine for treating ventricular fibrillation. The electrophysiological properties of acutely administered amiodarone are markedly different from those observed following chronic oral therapy, which results in APD prolongation. It is noteworthy that the original studies by Singh involved the study the effects of long-term intraperitoneal administration to rabbits for prolonged periods followed by ex vivo studies on the atria and ventricles. A single parenteral dose of



Channel name	Abbreviation	Gene	A-subunits	Selective blocker
Rapid delayed rectifier	$I_{Kr}$	<i>KCNH2</i>	ERG1	Class III (agents)
Slow delayed rectifier	$I_{Ks}$	<i>KCMQ1</i>	$K_V$ LQT (Mink)	Class III (agents)
Inward rectifier	$I_{K1}$	<i>KCMJ4</i>	$K_{IR}$ 2.3	Tertiapin (venom)
ATP-gated channel	$I_{K-ATP}$	<i>KCNJ8</i> <i>KCNJ11</i>	$K_{IR}$ 6.1/6.2	↑ ATP
Muscarinic	$I_{K-Ach}$	<i>KCNJ3</i> <i>KCNJ5</i>	$K_{IR}$ 3.1 $K_{IR}$ 3.4	Atropine
Transient outward current	$I_{to1}$	<i>KCND3</i> <i>JCNA4</i>	$K_V$ 2/4.2 $K_V$ 21.4	
Ultrarapid delayed rectifier	$I_{Kur}$	?	$K_V$ 1.5 (human) $K_V$ 1.3 (canine)	

**Table III.** Selected voltage-gated cardiac potassium ion channels.  $K^+$  channels consist of pore-forming ( $\alpha$ ) transmembrane subunits and accessory units that can markedly alter the properties of the channel.

amiodarone (5 mg/kg) causes only a significant lengthening of the AH interval and atrioventricular nodal effective refractory period, with no effect on the heart rate or the QTc interval. There is thus a marked disparity between the electrophysiological effects of acutely administered amiodarone and those observed after long-term treatment (Table IV).<sup>35</sup> The explanation for these differences is not clearly understood,

but possibly the interaction of amiodarone (and its major metabolite desethylamiodarone) with thyroid hormones may be important.<sup>36</sup> Amiodarone treatment causes a dose-dependent decrease in the expression of several  $T_3$ -dependent genes. The main metabolite, desethylamiodarone, inhibits the binding of  $T_3$  to its nuclear receptors. It is a competitive inhibitor at the  $\alpha_1$  thyroid hormone receptor

( $TR_{\alpha 1}$ ) and a noncompetitive inhibitor at the  $\beta_1$  thyroid hormone receptor ( $TR_{\beta 1}$ ). An additional complexity regarding the mode of action of amiodarone is that the contribution of the systemic and coronary vasodilator actions of amiodarone to its overall antiarrhythmic efficacy is not clearly established, though there is reason to believe that these effects are also beneficial.

The major shortcomings of amiodarone relate, firstly, to its suboptimal pharmacokinetics properties. It is variably absorbed from the gut and is widely distributed, accumulating in muscle and fat. It has an average half-life in humans of 50 days, ranging between 20 to 100 days. Its effects persist for up to 1 month after stopping therapy. Secondly, amiodarone treatment can be associated with a range of adverse effects involving multiple organ systems (Table II). These adverse events may be due in part to the iodine content of the molecule (ie, changes in thyroid status and ocular deposits), but the mechanism of the hepatic, skin, and pulmonary effects is not understood.<sup>20</sup>

Several research strategies have been adopted in seeking agents with an efficacy similar to amiodarone, but with better tolerability and pharmacokinetics. Close analogs of amiodarone have been made by one group, preserving both the benzofuran and di-iodo structures, but substituting ester homologs, in order to achieve better kinetics and more rapid onset of effect. The lead compound (ATI 2042) is in phase 2 clinical trials. It has a half-life in humans of 100 hours instead of the 50-day half-life of amiodarone. Experimental studies in isolated guinea pig hearts show that ATI 2042 increases atrial conduction time by 70% and APD and QTc by 10%.<sup>37</sup> It is not easy to understand the logic of this group's research strategy because of the widespread assumption that the iodo substitution in amiodarone, which is also present in ATI 2042, is a major contributor to its un-

Electrophysiological parameter	Acute	Chronic
Increase in: RR interval	±	+++*
PR interval	++	+++
QT/QTc	±	++++
AH interval	++	+++
QRS interval (rate-related)	++	+++
Atrial ERP	+	++++
AV nodal ERP	+++	++++
Ventricular ERP	±	++++
His-Purkinje ERP	±	+++
Bypass tracts (anterograde/retrograde)	±	++++

\* Sympatholytic action.

**Table IV.** Comparison of the electrophysiological effects of acute versus chronic amiodarone administration in man.

**Abbreviations:** AV, atrioventricular; ERP, effective refractory period.

**Class III antiarrhythmic agents: serendipity or drug design? - Fitzgerald**

wanted side effects. The compound KBI 30015, produced by Karo Bio AB (Sweden), also retains the benzofuran and di-iodo substitutions, but the hypothesis is that amiodarone's action on chronic administration is mediated by inhibition of thyroid hormone action on the heart. KBI 30015 is an antagonist at both the human  $\alpha$  and  $\beta$  thyroid receptors ( $IC_{50}$  2.2 and 4.1 micro, respectively.<sup>7</sup> However, the electrophysiological effects in acute administration studies show that it reduces the cardiac sodium and  $I_{CaL}$  channels.<sup>38</sup> It seems unlikely that the acute effects are due to modification of thyroid hormone action on the heart.

An alternative strategy adopted by the scientists in the Sanofi laboratories had been to synthesize noniodinated analogs of amiodarone, preserving the benzofuran structure. The most advanced compound is dronedarone (SR 33589), which is in phase 3 clinical trials in atrial fibrillation.<sup>39</sup> The literature on the electrophysiological effects of dronedarone provides differing profiles, depending upon the animal species, whether the studies are in vitro or in vivo or are acute or chronic. Specifically, its effects in prolonging APD were not observed following acute administration to anesthetized dogs, but APD and QTc were significantly prolonged following chronic treatment ( $2 \times 20$  mg/kg/day) in a canine model of atrioventricular block.<sup>40</sup>

While the electrophysiological properties of dronedarone are not finally agreed upon, the dose-ranging trial in atrial fibrillation (postconversion) indicates that in a dose of 800 mg/day, it increased the time to recurrence of fibrillation from 5 days on placebo to 60 days on therapy.<sup>39</sup> Two additional phase 3 clinical trials are in progress (EURIDIS [EUROPEAN trial In atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm] and ADONIS [American-Australian-African trial with Drone-

darONE In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm), but the results are not currently available. A trial of its antiarrhythmic effects in moderate-to-severe chronic heart failure (ANDROMEDA [Antiarrhythmic trial with DRonedarone in Moderate to severe CHF Evaluating morbidity Decrease]) showed an excess of deaths (24 vs 10) in the treated group. The trial was stopped. On balance, it seems likely that dronedarone will be as effective as amiodarone, but its overall risk:benefit profile remains to be clearly established.

E-0471 is another analog of amiodarone in which the di-iodophenyl is replaced by a thiophin. Studies in guinea pig myocytes show that it has effects not only in depressing the  $I_{Kr}$  channel, but also the slow and fast components of the delayed rectifier current as well as blocking the L-type Ca channel. An open pilot clinical study showed beneficial effects in patients with atrial arrhythmias.<sup>41,42</sup>

### COMMENTARY

This essay has described the evolution of the Class III antiarrhythmic drugs from their inception in the late 1960s until the present time. The story illustrates the continuing importance of serendipity and clinical observations in the drug discovery process. For example, sotalol was not originally synthesized as a  $\beta$ -blocker, but as part of a structure/function study on the incorporation of alkylsulfonamido groups into the benzene ring of phenylethanolamines.<sup>21</sup> The attractive properties of DL-sotalol for arrhythmia control by a Class III action, as well as for treating angina pectoris and hyperthyroidism, due to its  $\beta$ -blocking properties, were entirely serendipitous observations. Similarly, the amiodarone research program seeking an improved antianginal agent was based on the unsubstantiated efficacy of khellin in angina pectoris.<sup>10</sup> Its Class III actions were

only observed after chronic oral administration to rabbits, necessitated by the poor solubility of amiodarone for acute in vitro studies on cardiac electrophysiology.<sup>4</sup> Furthermore, the reversal of its effects on prolonging action potential duration in rabbit heart by coadministration of thyroxine, as well as its slow onset of effect following oral dosing, are not fully explained even today.<sup>35</sup> Its antiarrhythmic effects were first detected in the clinic and only subsequently did the research scientists in Labaz Laboratories study its acute effects in experimental arrhythmias.<sup>15</sup>

The next phase of the Class III drug evolution was designed drug discovery, based on the reasonable assumption that potent, specific blockade of the  $I_{Kr}$  channel would provide improved antiarrhythmic therapy. This target was made possible by the advances in electrophysiology and patch-clamp technology. Furthermore, the availability of D-sotalol as a chemical template, as well as amiodarone, provided the medicinal chemists with ample opportunities. The currently approved Class III agents (dofetilide/ibutilide) are effective in atrial arrhythmias, but are less effective in controlling serious ventricular arrhythmias.

Nevertheless, Class III agents are more attractive than Class I and Class II because they have minimal negative hemodynamic effects and can be given both orally and parenterally.<sup>43</sup> However, potent highly selective blockade of only the  $I_{Kr}$  channel with concomitant reverse use dependency can be associated with potentially lethal torsades de pointes. The newer antiarrhythmic agents, while termed Class III, have actions on one or more additional cardiac channels (*see Table I*), so the research goals are moving away from pure  $I_{Kr}$  blockade. Perhaps an important lesson to be learned, with application to the whole field of drug discovery, is the pitfall of our tendency



to oversimplify the biological targets, in this case selective  $I_{Kr}$  blockade. This field, like so many others in drug discovery, requires a deeper understanding of the complexity of biological systems.<sup>44</sup> Until this is more feasible, serendipity and translational research, both animal<sup>45</sup> and human,<sup>46</sup> will continue to play a major role.

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## Familial dilated cardiomyopathy: from clinical presentation to molecular genetics

E. Arbustini, P. Morbini, A. Gavazzi, L. Tavazzi

*Eur Heart J.* 2000;21:1825-1832

This Clinical Perspective article outlines the clinical decisions and potential problems in diagnosis facing clinicians when a patient presents with a possible family history of dilated cardiomyopathy. Although diagnosis of dilated cardiomyopathy by clinical examination, electrocardiography, echocardiography, and angiography is relatively straightforward, family pedigree, noninvasive screening of informed consenting relatives, and possibly genetic analysis of affected subjects is required to accurately diagnose familial dilated cardiomyopathy. The article describes basic Mendelian and matrilinear law-driven methods for characterizing the disease by tracing the familial pedigree to understand the pattern of inheritance: for example, when a father, son, and daughter are all affected, an autosomal dominant disorder would be suspected, and X-linked, or recessive disease could be excluded. Similar familial formulae can be applied to diagnose autosomal dominant, recessive, and X-linked recessive disease. However, this is only the first step in a genetic approach to the disease. The diagnosis of familial cardiomyopathy is only the start of a detailed, and sometimes frustrating, investigative pathway. The etiopathogenic background of the disorder can be further dissected by examining a number of pertinent clinical signs.

In this article, Arbustini et al describe eight different phenotypes, detailing the clinical scenarios and outlining the steps necessary for their effective clinical and pathological identification. In their explanation of the diagnoses, the authors outline possible pitfalls in the methodology and the numerous problems associated with precise sampling when dealing with inheritable disorders of this type. This article further suggests an important link between the physician, the clinical staff, the pathology laboratory, and the research groups specializing in these disorders, since much of the diagnosis involves complex molecular investigation and can involve family members in order to precisely pinpoint the origins of the disease.

At present, though, it is recommended that information on patients should not rely on molecular genetics, but rather

on established clinical examination, assessment of the familial condition of the disease, identification of preclinical signs and asymptomatic patients, prevention of ventricular arrhythmias, and counseling.

Despite the fact that the knowledge on the molecular genetics of this disease is growing, the number of diagnoses that can be provided to patients is still limited to a few cardiomyopathies and rare general myopathies with heart involvement. The literature, currently, only contains a few articles about this subject and it is clear that major multi-center research projects are required if cardiologists are to plan properly for the prevention and eventual cure of familial dilated cardiomyopathy.

The authors of this article conclude by suggesting that a major scientific society, such as the European Society of Cardiology, should promote research in this field and provide the information needed to plan for useful preventive care strategies for dilated cardiomyopathy.

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2000

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After 15 years as world chess champion,  
Gary Kasparov is beaten by his  
25-year-old protégé, Vladimir Kramnik;  
thousands march in Berlin in memory  
of the 1938 anti-Jewish pogrom that presaged  
the Holocaust; and an alcoholic brew mixed  
with methanol to make it stronger kills  
126 Kenyans and leaves a further 500  
requiring hospital treatment



## Randomized trial of an education and support intervention to prevent readmission of patients with heart failure

H. M. Krumholz, J. Amatruda, G. L. Smith, J. A. Mattera, S. A. Roumanis, M. J. Radford, P. Crombie, V. Vaccarino

*J Am Coll Cardiol.* 2002;39:83-89

One of the less frequently addressed issues in the management of heart failure is the high readmission rate to hospital after an initial inpatient episode. The authors quote a rate of readmission of up to 44% within 6 months of discharge. Among the causes of this high rate are poor compliance with medication and delays in seeking preventative care. This paper describes an intervention that teaches patients to understand their illness better and respond appropriately if deteriorating, with the aim of reducing the frequency of readmissions.

Consecutive admissions to the study hospital were screened for the presence of heart failure according to clinical or radiological parameters. Eighty-eight patients were enrolled into the study, and randomized to the study group or to the control group of usual medical care. Five educational domains were addressed, patient knowledge of the illness, the relationship between medications and illness, the relationship between health behavior and illness, knowledge of the early features of decompensation, and practicalities of obtaining necessary assistance. There were two phases of the intervention. In the first, an interview was conducted by an experienced cardiac nurse shortly after hospital discharge to identify the level of the patients' understanding of the above issues, thus providing a framework for future education. The second phase involved phone calls, initially weekly, but of reducing frequency, down to monthly, during which the nurse could reinforce education in the areas previously described. This contact was maintained over 12 months. In neither stage was an attempt made to perform extra clinical assessments, although, if appropriate, patients were advised to see their physician.

In comparing the study and control groups, the readmission rates were 56.8% and 81.8%, respectively (relative risk 0.69,  $P=0.01$ ), and there was a similar reduction in the rate of multiple readmissions. A nonsignificant reduction in the death rate was observed in the treatment group. The Kaplan-Meier curves representing time to all-cause admission or death diverge early on, and the median times to such an event were 193 days in the treatment group and

126 days in the control cohort (relative risk 0.56,  $P=0.03$ ). An estimate of the potential economic impact of this intervention was made, and although this intervention involves extra costs, these were heavily outweighed by the reduction in readmissions, with mean savings of nearly \$7000 per patient.

The key difference between this intervention and other previously described related strategies in the treatment of heart failure is that previous such studies have involved a more intensive provision of medical supervision. It appears that patient education and empowerment produce levels of benefit that approach those of more reactive programs of physician- or nurse-led therapeutic adjustment.

This study leaves some questions open. It is not clear how long the support needs to continue, nor whether there is an ongoing benefit to patients beyond 1 year. However, it is clear that there are very significant gains in terms of patient morbidity/mortality and cost savings, which are the result of a straightforward education program. As such, it seems reasonable to conclude that such initiatives could and should be introduced more widely, and form part of the standard management of patients hospitalized with heart failure.

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2002

Horror writer Stephen King announces  
he will retire when his contract expires after  
the publication of five more books;  
Argentina appoints its fifth President in two weeks;  
and US reporter Pearl disappears while  
investigating alleged shoe bomber Richard Reid's  
ties to Moslem fundamentalists in Pakistan

## Long-term trends in the incidence of and survival with heart failure

D. Levy, S. Kenchaiah, M. G. Larson, E. J. Benjamin, M. J. Kupka, K. K. Ho, J. M. Murabito, R. S. Vasan

*N Engl J Med.* 2002;347:1397-1402

Over recent decades, there have been significant advances in the treatment of hypertension, historically the leading cause of heart failure. In addition, the treatment of heart failure itself has witnessed major advances, with numerous randomized trials indicating the medications that reduce mortality. However, there has been a lack of clear evidence that these benefits have been translated into improvements in outcomes in the “real world.” In this paper, temporal trends among the Framingham study population are examined with regard to incidence of and survival with heart failure. This allows a longitudinal examination of these parameters over a 50-year period, with the inherent advantage that, in the Framingham study, a uniform set of diagnostic criteria and assessment has been utilized throughout.

The study began in 1948 with the enrollment of all members of the Framingham population aged 28 to 62 years. This cohort has been evaluated at 2-yearly intervals, and, in 1971, the descendants and their spouses were also enrolled, with reviews taking place slightly less frequently. The age-adjusted incidence of heart failure was higher at all times in males than females. In the former, the initial incidence was 627 per 100 000 person-years, compared with 420/100 000. The authors found little change in the incidence of heart failure in men over the last 50 years, while it has dropped by about one third in women. After controlling for various other risk factors, the risk of death has fallen by approximately one third over the same period in both sexes, with an overall trend of reduction in risk of death of 12% per decade (*P* for trend, 0.01 in men and 0.02 in women). Nevertheless, this leaves heart failure as a significant public health problem, and it remains a disease with a high mortality. The median 5-year survival rate in men in the 1990s was under 4 years, and in women it was 6 years, an improvement over the 2 and 4 years, respectively, seen in the 1950s.

In addressing the disparity between the sexes, the authors suggest that the falling incidence among women may relate to hypertension as a more frequent etiological factor in

women, with ischemic heart disease more common among men. There has been success in targeting and treating hypertension, but improvements in the treatment of myocardial infarction may have increased the number of survivors without affecting the numbers surviving with impaired left ventricular function. This, the authors suggest, is because there are now more survivors with residual damage, who are thus at risk of heart failure.

Three recent hospital-based studies of the mortality after hospitalization with heart failure have shown more substantial reductions in mortality than in this series. The authors highlight that in this study hospitalization was not a criterion for enrollment. They also suggest that hospital-based studies are open to a number of biases. Improved technology may result in lead-time bias, by allowing diagnosis at a less severe stage. The nature of diagnosis-based reimbursements to hospitals may influence the nature and number of diagnoses made.

There were some limitations to this study, including the predominance of whites among the subjects, meaning that one may not necessarily extrapolate these results to other racial groups. Patients in the Framingham Heart Study may have had better medical access than other patients, leading to better outcomes. Despite these concerns, one may conclude that the incidence of heart failure among women has decreased and that improved survival has occurred in both sexes over the last 50 years.

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2002

A study on animal intelligence reveals that Californian sea lions may have the best memory of all nonhuman creatures; the Pope canonizes Opus Dei founder Josemaria Escrivá de Balaguer; and a masked gunman in Queens, New York, shoots run-DMC D. J. Jason Mizell aka Jam Master Jay



## Differential gene expression and genomic patient stratification following left ventricular assist device support

B. C. Blaxall, B. M. Tschannen-Moran, C. A. Milano, W. J. Koch

*J Am Coll Cardiol.* 2003;41:1096-1106

Donor organs required for heart transplantation are in limited supply and for many patients the wait for transplant surgery proves too long, with fatal deterioration before organ availability. A treatment to help maintain an adequate circulation is the use of a left ventricular assist device (LVAD). LVADs have previously been shown to reduce mortality and are thought to lead to reverse remodeling of myocardial structure and function.

This article seeks to determine whether mechanically unloading the failing human heart with an LVAD results in significant change in left ventricular gene expression using gene microarray technology. Previous reports have looked at the expression of particular genes in response to this treatment and have led to the understanding that this useful therapy can lead to significant changes in gene and protein expression. However, using oligonucleotide microarray technology, which can detect approximately 6800 genes or novel clones with homology to known genes, the authors were able to examine many more genetic pathways, thus gaining a greater insight into some of the molecular mechanisms that may be involved in LVAD-mediated myocardial recovery.

Statistical analysis of gene arrays from 6 male patients at the time of LVAD placement and at myocardial explantation revealed a large number of genes that were upregulated or downregulated in response to treatment. Interestingly, further statistical analysis revealed a clear demarcation between gene expression profiles pre-LVAD and post-LVAD, and also identified two distinct groups among the pre-LVAD failing hearts depending on their etiology, determined both clinically and pathologically after explantation. In particular, the pre-LVAD patients with nonischemic, idiopathic dilated cardiomyopathy had distinctly different myocardial gene expression post-LVAD, whereas those patients exhibiting ischemic cardiomyopathy had similar gene profiles both pre-LVAD and post-LVAD. Examination of this phenomenon revealed that out of the 900 or so genes whose expression was modified during the treatment, only 16 were shared between these two groups. This underscores the divergent

baseline phenotypes and responses to LVAD-mediated reverse remodeling that occur in ischemic and nonischemic cardiomyopathies.

In addition, genes determined to have been significantly regulated were sorted according to their biological function. Although the data obtained were not shown to be statistically different, it is of interest that there was an enhancement in the percentage of metabolic genes changed significantly following LVAD support, thus supporting the authors' hypothesis that LVAD enhances reverse myocardial remodeling.

This study demonstrates the ability to distinguish patients' LVAD status and heart failure etiology using oligonucleotide microarrays. The differential gene expression identified in the study further demonstrates that phenotypic changes that occur following LVAD support are associated with genotypic changes in the form of significantly altered myocardial gene expression profiles. Importantly, in their closing remarks, the authors suggest that microarray technology might be used to facilitate the prediction of an individual patient's response to LVAD therapy.

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2003

Islamic cleric sheik Abdel Majid al-Khoei, a prominent Shiite, is murdered at the Najaf mosque a week after returning to Iraq from exile; scientists at the British Columbia Cancer Agency decipher the SARS genome, demonstrating it to be a completely new coronavirus; and the Rijksmuseum in Amsterdam is closed for an indefinite period after asbestos is found in the building during a routine inspection

## Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure

A. Nohria, S. W. Tsang, J. C. Fang, E. F. Lewis, J. A. Jarcho, G. H. Mudge, L. W. Stevenson

*J Am Coll Cardiol.* 2003;41:1797-1804

Despite the introduction of many new therapies for the treatment of chronic heart failure, morbidity and mortality remain high. It is clear, however, that patients with this condition form a heterogeneous group and various strategies have been employed to distinguish between those at different levels of risk. Many of these strategies use measures that have inherent limitations. Peak oxygen consumption is demanding to record, and most suited to use in the assessment of the stable, moderately effected patient. The New York Heart Association (NYHA) classification, based on symptoms, is intrinsically subjective. Laboratory markers such as neurohormonal peptides have been demonstrated to be of predictive value at a population level, but their role in guiding individual management is less clear.

In 1976, Forrester et al described 4 hemodynamic profiles based on pulmonary artery (PA) catheterization parameters. These profiles segregated patients according to the presence or absence of congestion (pulmonary capillary wedge pressure threshold of 18 mm Hg), and adequacy of perfusion (cardiac index threshold 2.2 L/min/m<sup>2</sup>). Forrester's original paper demonstrated that the prognosis of patients post-acute myocardial infarction correlated with their subgroup. The hypothesis examined in Nohria's paper is that a similar classification based on clinical examination might be useful in guiding management.

Of the 452 patients enrolled into the study, the majority were admitted with decompensation of heart failure (49%), but there were significant numbers admitted with arrhythmias, angina, and for heart transplantation evaluation. Patients were categorized according to the presence of congestion and adequacy of perfusion. Congestion (wet) was defined by the presence of recent history of orthopnea, elevation of the jugular venous pressure, hepatojugular reflux, peripheral edema, leftward radiation of the pulmonary heart sounds, or a square-wave blood pressure response to a Valsalva maneuver. Impaired perfusion (cold) was defined by the presence of a narrow proportional pulse pressure (pulse pressure/SBP <25%), pulsus alternans, symptomatic hypotension, cool extremities, or impaired cognitive

function. This defined 4 groups: dry-warm (A), wet-warm (B), wet-cold (C), and dry-cold (L). Follow-up was for at least 12 months, with end points of time to death and the combined end point of time to death or heart transplantation.

There were clear and significant differences between the different groups, (although group L was too small to allow statistical analysis). Compared with group A, the hazard ratios were 3.66 for group C ( $P < 0.001$ ) and 2.10 for group B ( $P < 0.003$ ). Further stratification of these groups using the NYHA classification showed that groups B and C tended to co-segregate with classes III and IV. However, these clinical profiles were independent predictors of mortality. In a subset of patients investigated using the PA catheter, there was good correlation with the clinical groups.

The authors propose that these profiles may aid in the selection of appropriate therapy, in the same way that the PA catheter does, although accepting that there are no data to support this strategy. For example, profile A (dry-warm) may be likely to tolerate the introduction and uptitration of  $\beta$ -blockers, whereas, in group B, one would not do this until the patient had stabilized and returned to group A, and in Group C, one might consider reduction or cessation of such drugs. In addition, it is proposed that since these profiles are independent predictors of outcome, they may prove useful tools in the selection of patients for clinical trials.

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### 2003

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Scientists create a mule, named Idaho Gem, from a cell from a mule fetus and a horse egg; the Old Man of the Mountain, a 700-ton granite formation, falls from its perch at New Hampshire's Franconia Notch; and the military regime in Burma announces that Aung San Suu Kyi and other members of Burma's National League for Democracy are in protective custody



## Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study

P. Jong, S. Yusuf, M. F. Rousseau, S. A. Ahn, S. I. Bangdiwala

*Lancet.* 2003;361:1843-1848

This paper describes the long-term outcomes of patients recruited into the Studies Of Left Ventricular Dysfunction (SOLVD). The original study recruited patients with left ventricular (LV) dysfunction (ejection fraction  $\leq 35\%$ ) and compared outcomes on enalapril vs placebo in patients with and without overt heart failure. Although short-term benefits of angiotensin-converting enzyme (ACE) inhibitors in the treatment of LV dysfunction had been observed, the longer-term effects were unknown. Furthermore, it was unclear whether such a benefit could be enhanced by initiating treatment prior to the development of symptoms.

A total of roughly 7000 patients were entered into the treatment or prevention arm based on whether or not they were already receiving heart failure therapy or had symptoms of heart failure. All were randomized to enalapril or placebo, and followed for a mean duration of 3.2 years.

The prevention trial showed a relative risk reduction in the combined end point of death or development of heart failure of 29%, ( $P < 0.001$ ). There was no significant reduction in mortality alone in this asymptomatic group, whereas in the treatment group, the death rate was reduced by 16% ( $P = 0.0036$ ). It was suggested that those treated with enalapril for heart failure gained 0.4 years of life expectancy.

The current manuscript reviews the outcomes after 12 years of follow-up. Despite this long follow-up period, outcomes were known in 99.8% of the original participants. In the prevention study, death occurred in 56.4% in the placebo group, compared with 50.9% in the enalapril group ( $P = 0.001$ ), with an increase in median survival from 10.3 to 11.1 years ( $P = 0.05$ ). Furthermore, the survival curves continued to diverge for the whole period even though patients were not necessarily on their assigned study medication after the end of the trial. In the treatment study, the death rate was slightly lower in the enalapril group than the placebo, but most patients were dead (79.8% and 80.8%, respectively). The survival curves, though initially inevitably diverging, converged toward the end of follow-up, as shown by the median survival (5.5 and 4.8 years, respectively). There were

no differences in survival among the prespecified subgroups according to age, gender, ethnicity, cause of LV dysfunction, hypertension, diabetes mellitus, and New York Heart Association class at baseline. The benefit was seen to be greater in those with lower ejection fractions.

This extension of the original study has shown a benefit in the prevention arm, and suggests that 56 deaths could be prevented by the treatment of 1000 patients for 3 years. It is noted that after the first phase of the trial, patients were in many cases started on ACE inhibitors, as recommended by the trial committee, with a probable reduction in the difference observed between treated and placebo groups. The reduction in mortality with enalapril is felt to be possibly due to a reduction in the rate of nonfatal myocardial infarction during the initial study, with subsequently reduced risk of progression to heart failure. The authors discuss the convergence of the survival curves in the treatment group and offer a number of suggestions. There was a significant reduction in the number of cardiac deaths and a similar excess of noncardiac deaths, so they postulate that when cardiac death is prevented, there may be exposure to alternative competing causes of death.

The authors conclude that treatment for 4 years with enalapril in all patients with LV dysfunction reduces the risk of death over the long term

### 2003

Indian Prime Minister Atal Bihari Vajpayee restores civilian air travel between his country and Pakistan in an effort to ease tensions;  
more than 800 000 French public workers stage a 1-day strike to protest pension reforms;  
and Nepal confers honorary citizenship on Sir Edmund Hillary to mark the golden jubilee of the first ascent of Mount Everest

## Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL)

D. L. Mann, J. J. McMurray, M. Packer, K. Swedberg, J. S. Borer, W. S. Colucci, J. Dijan, H. Drexler, A. Feldman, L. Kober, et al

*Circulation.* 2004;109:1594-1602

Observation of elevated levels of tumor necrosis factor (TNF) in heart failure led to investigations into its possible role in the pathophysiology of the condition. A heart failure phenotype is seen when TNF is administered to experimental animals and in transgenic animals that overexpress TNF. High levels of TNF have been observed in a number of disparate conditions, including ankylosing spondylitis, rheumatoid arthritis, and psoriasis. Etanercept is a recombinant human TNF receptor that binds to soluble (circulating) TNF, causing functional inactivation by preventing the binding of TNF to cell surface receptors. Trials of it in the inflammatory conditions mentioned above resulted in clinical improvements, leading to trials in heart failure. Small studies suggested that there was a benefit in terms of left ventricular function, and thus larger clinical trials were designed.

This paper reports on the combined results of two studies designed to determine the effects on patients' functional capacity and morbidity/mortality. The studies had similar designs, differing mainly by geographical locality: RECOVER took place in Europe, Australasia, and Israel, while RENAISSANCE was undertaken in North America. Patients with ischemic or nonischemic heart failure graded between New York Heart Association class II and IV, with ejection fraction  $\leq 30\%$ , were assigned to receive placebo or etanercept 25 mg SC once, twice, or three times a week. Both studies were terminated early (RECOVER after 6 months; RENAISSANCE after 12 months), due to failure to demonstrate benefit. There was no evidence of an excess mortality in the etanercept groups, but there was certainly no benefit. Among prespecified subgroups, no differences were observed in the effects of etanercept.

To offer some possible explanation for this apparent lack of benefit, the authors briefly discussed the possibility that TNF is not important in the pathogenesis of heart failure, and the elevated levels are a consequence of heart failure, or of chance. Second, although the conditions described above have been seen to improve with anti-TNF therapy, others associated with elevated levels, including Crohn's

disease and systemic sepsis, do not respond. This implies that there may be a more complicated network of cytokines, and the removal of a single component may be insufficient to result in benefit. This could be assessed by the measurement of TNF bioactivity, as well as the levels of other circulating cytokines. This would also be useful in investigating whether the dose of antagonist was sufficient to neutralize the effects of TNF. The authors observed that among those patients who worsened, disproportionately represented were the patients who had been exposed to etanercept for the longest duration. They wondered whether there is an early period of benefit, as seen in the pilot studies, followed by a period where continuation of etanercept is detrimental. This might be caused by a phenomenon whereby etanercept stabilizes a biologically active (trimeric) form of TNF and thus paradoxically acts as a TNF potentiator. The final possibility is that TNF might play a useful role in maintaining cardiovascular stability, and prolonged blockade might therefore be deleterious.

Infliximab is a monoclonal antibody to TNF, recently employed in the Anti-TNF- $\alpha$  in Congestive Heart Failure (ATTACH) study. Circulating TNF was neutralized, and cell-bound TNF resulted in cell lysis. This study reported an increase in death and heart failure hospitalization. Although infliximab and etanercept act in different ways, there must now be concern over the targeting of TNF in this way. Future therapies are likely to be directed at other components of the inflammatory cascade, or at multiple components.

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### 2004

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The discovery of a cat buried with its owner in a Neolithic grave on Cyprus suggests domestication of cats began at least 9500 years ago; the popular search engine "Google" announces it will offer shares to the public in late 2004; and the African National Congress wins South Africa's general election claiming about 70% of the vote



## Regenerative capacity of the myocardium: implications for treatment of heart failure

R. von Harsdorf, P. A. Poole-Wilson, R. Dietz

*Lancet.* 2004;363:1306-1313

This review article describes in some depth novel approaches to the management of heart failure and discusses the rationale for, as well as the limitations of, each treatment. Von Harsdorf et al introduce a fictitious, but clinically typical, patient: a 46-year-old man with a recent diagnosis of acute myocardial infarction (MI). Having survived the acute period of MI the patient has substantial irreversible myocardial damage and exhibits symptoms of heart failure due to the remodeling process. This is characterized by structural changes within the healthy area of the heart both adjacent to, and remote from, the damaged area. The authors go on to describe possible options for the patient's treatment and outline four possible alternatives: conventional drug therapy; cardiomyocyte replication therapy; cloning of artificial organs, and organ regeneration via stem cells.

Drug therapy, referred to as the "dinosaur approach," involves the use of pharmacological blockade of the compensatory systems increasing myocardial workload. Such approaches are known to prolong life in patients with heart failure. However, such therapy is limited since it will not cure the patient, the myocardium will remain damaged, since mammalian hearts are not able to significantly regenerate lost tissue. Therefore, conventional therapy may only serve to prolong the inevitable progress of heart failure. Leading on from this approach, the authors describe a novel therapy by which the patient's myocardial cells are encouraged regenerate and replace, or prevent the generation of, scar tissue, thus avoiding long-term drug therapy. Although not currently available, the rationale behind this concept is well defined in the article. Modification of the adult myocyte cell cycle is possible *in vitro*; however, we do not fully understand how an adult heart will cope with reintroduction of proliferative capacity. Moreover, control of cardiomyocyte replication will present a bigger challenge to modern biotechnology.

Although cloning of human tissue is not yet possible for ethical reasons, the concept of regenerating an immunologically compatible organ from nuclei taken from a skin biop-

sy is also discussed. The "Dolly approach," as it is termed, describes the concept of manufacturing a copy of the patient's heart around a biodegradable scaffold. Although there is no evidence to support this process it is, at least theoretically, possible, but would require an intimate knowledge of cardiomyocyte differentiation, which is currently absent. Akin to organ cloning, there is much controversy surrounding stem cell therapy. Stem cells have the innate ability to transform into any cell type given the right environmental factors. The authors are cautious to expand on the efficacy of this approach, as there have not been any large controlled studies using stem cells.

The authors suggest the use of cautious optimism when it comes to the development of these new therapies: so much more needs to be known before carefully controlled clinical trials of any of these new therapies can be undertaken.

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### 2004

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At least 10 bombs explode on four commuter trains in Madrid during the rush hour, killing 191 people and wounding more than a thousand; in the biggest expansion in its 55-year history, NATO formally admits seven new countries, from the former Iron Curtain zone; and NASA announces that its robot explorer Opportunity has detected signs that water once covered rocks in a small crater on Mars

## Do we understand who benefits from resynchronisation therapy?

O. A. Breithardt, P. Claus, G. R. Sutherland

*Eur Heart J.* 2004;25:535-536

Cardiac resynchronization therapy (CRT) is now an accepted tool in the treatment of severe left ventricular dysfunction. In this editorial, Breithardt et al explain that despite growing use of this technique, there is evidence that up to 30% of those treated fail to respond. The underlying strategy centers on reducing the contraction delay between each ventricle and/or between regions of the left ventricle. There is evidence that both these forms of delay may be important. Improved synchrony is achieved by preexcitation of the late-activated regions through the implantation of left ventricular or biventricular pacing electrodes.

The authors explain that the tools used to select the patients may be insufficiently precise to predict who will respond. In particular, it is those cardiac segments with the most delayed onset of contraction that need to be identified. The ideal tool to achieve such identification remains an area of controversy. Similarly, there is a lack of consensus as to whether intraventricular or interventricular dyssynchrony is more responsive to CRT.

The authors outline the criteria for selecting an ideal imaging technique that will determine clinically important abnormalities in the timing of onset of regional ventricular active force development. Such a technique also would need to be easy to interpret, reproducible, and cost-effective. A high sampling rate is also critical, since the intervals responsible for delay are extremely short. Currently, the technique that best fulfills these criteria is echocardiography. A fundamental question is what degree of delay is sufficient to be labelled abnormal and likely to benefit from correction. In addition, there are a number of methods for measuring this delay. Regional longitudinal systolic velocity profiles may be obtained from all ventricular segments, but do not indicate the regional contractility. The more novel techniques of strain rate and strain estimation imaging reflect contractility better, although technology does not allow their application in thin walled segments.

The cardiac event to be used as the marker to determine delay is clearly very significant. Some researchers advocate

the time-to-onset of regional systolic motion, whereas others propose the time-to-peak systolic motion, or measure time to postsystolic events. The authors conclude that the first of these options is preferable, since the presence of a plateau in the velocity profile will create possible errors in determining the exact time of peak systolic motion, and the earlier a parameter is measured within the cardiac cycle, the less prone it is to distortion introduced by alterations in loading conditions or segmental interactions.

Once having determined the presence of dyssynchrony by selecting a reliable technique and an appropriate parameter to measure, the authors highlight further important potential pitfalls relating to the underlying pathophysiology. For example, resynchronization therapy may reduce postsystolic shortening (PSS). PSS occurs in left bundle branch block due to delayed segment activation, an appropriate target for resynchronization. However, it may similarly occur in the presence of ischemia, when it is a passive phenomenon, and there will be no response to CRT.

The authors conclude that echocardiography is fundamental in the selection of patients suitable for this therapy. The first line of selection requires an abnormal QRS duration, with echocardiographic confirmation of dyssynchrony. The more precise evaluation requires the use of the modalities discussed above, but large controlled trials are required to determine which is the optimal technique.

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### 2004

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Pakistani scientist Abdul Qadeer Khan admits passing on nuclear weapon technology to other countries; new Spanish Prime Minister José Luis Rodríguez Zapatero orders the recall of all Spanish soldiers from Iraq; and North Korea's reclusive leader, Kim Jong-Il, arrives in Beijing for talks on his country's future



## Hypertrophic cardiomyopathy

P. Elliott, W. J. McKenna

*Lancet*. 2004;363:1881-1891

**H**ypertrophic cardiomyopathy (HCM) was first described in 1869. Although initial research focused on the morphology of the disorder, as evidence for an inherited pattern emerged, the focus turned to genetic studies, culminating in the first culprit gene mutation in the  $\beta$ -myosin heavy chain coding sequence.

Many further mutations in genes encoding this and other components of the contractile apparatus have since been discovered, suggesting that this is the unifying factor in the disparate group of phenotypes that constitute HCM. Detailed research into genotype-phenotype correlations has failed to demonstrate consistent associations.

HCM is uncommon in children, and although a number of conditions cause a similar pattern of disease in adults, attempts to distinguish the two should be made. The characteristic hypertrophy of the septum may also extend to other parts of the left ventricular wall, and rarely the right ventricle, but not the right ventricle alone. The histological hallmark is myocyte disarray.

One of the difficulties with the management of this condition is that there may be few symptoms, and these may be nonspecific. Similarly, the examination may be unrevealing. A bisferious pulse indicates dynamic outflow obstruction, which will be associated with a systolic flow murmur. Mitral regurgitation may also be evident, relating to the anterior movement of the mitral valve during systole.

The echocardiogram is the major diagnostic tool, and any wall segment with a thickness of more than 15 mm without an alternative explanation is diagnostic. In the nonblack patient, it is unusual for such hypertrophy to occur due to hypertension unless this is severe. Another major diagnostic conundrum is the athlete with hypertrophy, in whom it may be difficult to make a certain diagnosis, though in this group, both ventricles are usually enlarged. Dynamic obstruction may also be revealed using echocardiography. Further echocardiographic parameters are discussed, including diastolic assessment and tissue Doppler imaging.

The role of cardiac magnetic resonance imaging in clinical practice is generally similar to that of echocardiography.

Metabolic exercise testing usually reveals reduced peak oxygen consumption, while a premature lactic acidosis may be indicative of mitochondrial myopathy. Symptoms relating to outflow tract obstruction may be treated with  $\beta$ -blockers, or occasionally disopyramide or verapamil. If drug therapy is unsuccessful, septal myectomy or septal alcohol ablation may be performed. The treatment of heart failure in HCM mirrors that due to other causes and, as atrial fibrillation may cause significant deterioration in HCM, restoration of sinus rhythm is important. There is a predisposition to sudden death in HCM, thought to be due to ventricular arrhythmia in most cases. Implantable cardioverter-defibrillators may help to prevent such deaths, and should be offered to those at high risk. A major challenge exists to detect these individuals in advance of a first event. The major risk predictors include a family history of sudden cardiac death, unexplained syncope, non-sustained ventricular tachycardia on Holter monitoring, severe hypertrophy (>30 mm), and a flat blood pressure response during upright exercise.

Finally, the article discusses the need for genetic counseling and suggests that an ECG and echocardiogram should be performed in first-degree relatives of affected individuals, and that echocardiography should be repeated every 5 years, because of the possibility of late-onset disease.

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### 2004

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The Cassini spacecraft inserts into orbit around Saturn and transmits detailed photographs of the planet's complex ring system; Mike Melvil pilots "SpaceShipOne" into space, becoming the first person to do so in a privately developed aircraft; and dozens of Colombian coca farmers are killed by Marxist rebels

# Heart Failure

## *Bibliography of One Hundred Key Papers*

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