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Invited Review

Heart failure: a hemodynamic disorder complicated by maladaptive proliferative responses

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Abstract

Heart failure has traditionally been viewed as a hemodynamic syndrome characterized by fluid retention, high venous pressure, and low cardiac output. Over the past decade, however, it has become clear that because of deterioration and progressive dilatation (remodeling) of the diseased heart, this is also a rapidly fatal syndrome. The importance of prognosis came to be appreciated when clinical trials showed that therapy which initially improves such functional abnormalities, as high venous pressure and low cardiac output, often fail to improve survival, and that some drugs which improve hemodynamics worsen long-term prognosis. The latter is true for most vasodilators which, in spite of alleviating the adverse short-term consequences of high afterload, shorten survival. Notable exceptions are ACE inhibitors, whose vasodilator effects do not explain their ability to prolong survival; instead, these drugs slow both deterioration and remodeling of the failing heart. Inotropic agents, while providing immediate relief of symptoms, generally shorten long-term survival, whereas β-blockers slow deterioration and remodeling, and reduce mortality. Aldosterone antagonists exert beneficial effects on prognosis that are not easily explained by their diuretic effects, but instead can be explained by their ability to inhibit signaling pathways that stimulate maladaptive hypertrophy, remodeling, apoptosis and other deleterious responses that cause deterioration of the failing heart. These and other findings demonstrate that heart failure is more than a hemodynamic disorder; these patients suffer from maladaptive proliferative responses that cause cardiac cell death and progressive dilatation that play a key role in determining the poor prognosis in this syndrome.

Keywords: heart failure - diuretics - ACE inhibitors - remodeling - vasodilators - positive inotropic agents - hypertrophy - overload

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Introduction

Throughout most of the 20th Century, heart failure was viewed as a hemodynamic disorder in which impaired pump performance led to increased pulmonary and systemic venous pressures, fluid retention, and low cardiac output. The goals of therapy defined by this view are to lower venous pressure with diuretics, increase myocardial contractility using inotropic agents, and unload the failing heart by administering vasodilators. Observational data and a number of short-term studies confirmed that all of these drugs led to the expected hemodynamic improvement, and so appeared to support this hemodynamic view. However, randomized clinical trials beginning in the 1980s demonstrated that therapy which improves hemodynamics is not always of long-term benefit, and in many cases shortens survival. Conversely, drugs that initially worsen symptoms can improve prognosis (Table I). These and other counterintuitive findings are now so numerous that it is no longer possible to view heart failure simply as a hemodynamic disorder [1].

It is surprising that the poor prognosis in heart failure was generally overlooked until the 1980s, when the results of long-term trials made it apparent that the average life-expectancy in most symptomatic patients was less than 5 years. This observation stimulated efforts to determine the causes of this terrible prognosis, which in turn caused the major features of this syndrome to be reexamined. The result has been the realization that long-term changes in the structure and composition of the heart play a key role in determining survival in these patients.

Therapy that initially improves hemodynamics can worsen prognosis

Diuretics

Evidence that "correcting" the hemodynamic abnormalities in patients with heart failure could have deleterious as well as beneficial effects was known for decades. The mercurial diuretics introduced in the 1920s, although of limited potency, could cause volume depletion so severe as to initiate renal and hepatic failure (the "hepato-renal syndrome"). This complication became much more common with development of powerful loop diuretics, but did not challenge the view that heart failure is a hemodynamic disorder because of the well-known ability of volume depletion to decrease end-diastolic pressure and so, according to Starling's Law of the Heart, reduce cardiac output.

Vasodilators

The first important challenge to the hemodynamic view of heart failure came when vasodilator therapy was introduced to counteract the vasoconstrictor response which has significant adverse effect in heart failure [2]. Even though it was well understood that an excessive dose of any vasodilator could cause severe hypotension, there was no reason to believe that doses which produced a moderate hemodynamic effect would fail to improve prognosis. As expected, short-term clinical studies confirmed that, as a class, vasodilators increase cardiac output and improve energetics by unloading the failing left ven-

Table I Some unexpected findings in heart failure trials

I. Direct-acting vasodilators temporarily improve hemodynamic function and symptoms, but most shorten survival

II. Inotropic drugs improve short-term hemodynamic function and symptoms but generally worsen long-term prognosis

III. β-Adrenergic receptor blockers initially worsen both the hemodynamic manifestations of heart failure and symptoms, but subsequently improve function and reduce mortality

Table II Short-term and long-term responses to vasodilators.

Class of vasodilator	Short-term response	Long term response
Converting enzyme inhibitors	++	++
AT_1 receptor blockers	++	++
Nitrates + hydralazine	++	+
Long-acting L-type Ca channel blockers	++	0
α-adrenergic blockers	++	–
Short-acting L-type calcium channel blockers	++	– –
Minoxidil	++	– – –
Prostacyclin	++	– – –
Ibopamine	++	– – –
Moxonidine	++	– – –
Flosequinan	++	– – –
Phosphodiesterase inhibitors	++	– – –

Key: ++ significant benefit; + minor benefit; 0 safe, no benefit or harm; – some harm; – – significant harm; – – – deadly

tricle. For this reason it came as a surprise when most direct-acting arteriolar dilators were found not to improve long-term prognosis [3–5]. Even more unexpected was that many direct-acting arteriolar dilators, including α-adrenergic blockers, short-acting L-type calcium channel blockers, minoxidil, prostacyclin, ibopamine, moxonidine, flosequinan, and phosphodiesterase inhibitors, shorten survival [3, 6–8], whereas converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and a drug combination that includes isosorbide dinitrate have a survival benefit [9–11] (Table II).

As discussed below, the adverse effects of most direct-acting arteriolar vasodilators arise because, even though they unload the damaged left ventricle, the lowered blood pressure causes the release of neurohumoral mediators like norepinephrine, angiotensin II, and endothelin which can activate deleterious proliferative responses.

Positive inotropic agents

Clinical trials using drugs that increase myocardial contractility present the strongest challenge to the view that heart failure is not simply a hemodynamic disorder. Cardiac glycosides, whose value in this syndrome had been known since 1785, were shown in 1958 to increase myocardial contractility [12]. In addition to improving hemodynamics, digitalis slows atrioventricular conduction which alleviates the deleterious hemodynamic effects of rapid atrial fibrillation. The latter probably accounts for most of the benefits of this drug that were seen at a time when most heart failure was caused by rheumatic heart disease, which is often accompanied by this tachyarrhythmia. Because the toxicity of the cardiac glycosides, along with their weak inotropic effect, limits the usefulness of these drugs in treating end-stage heart failure in patients with sinus

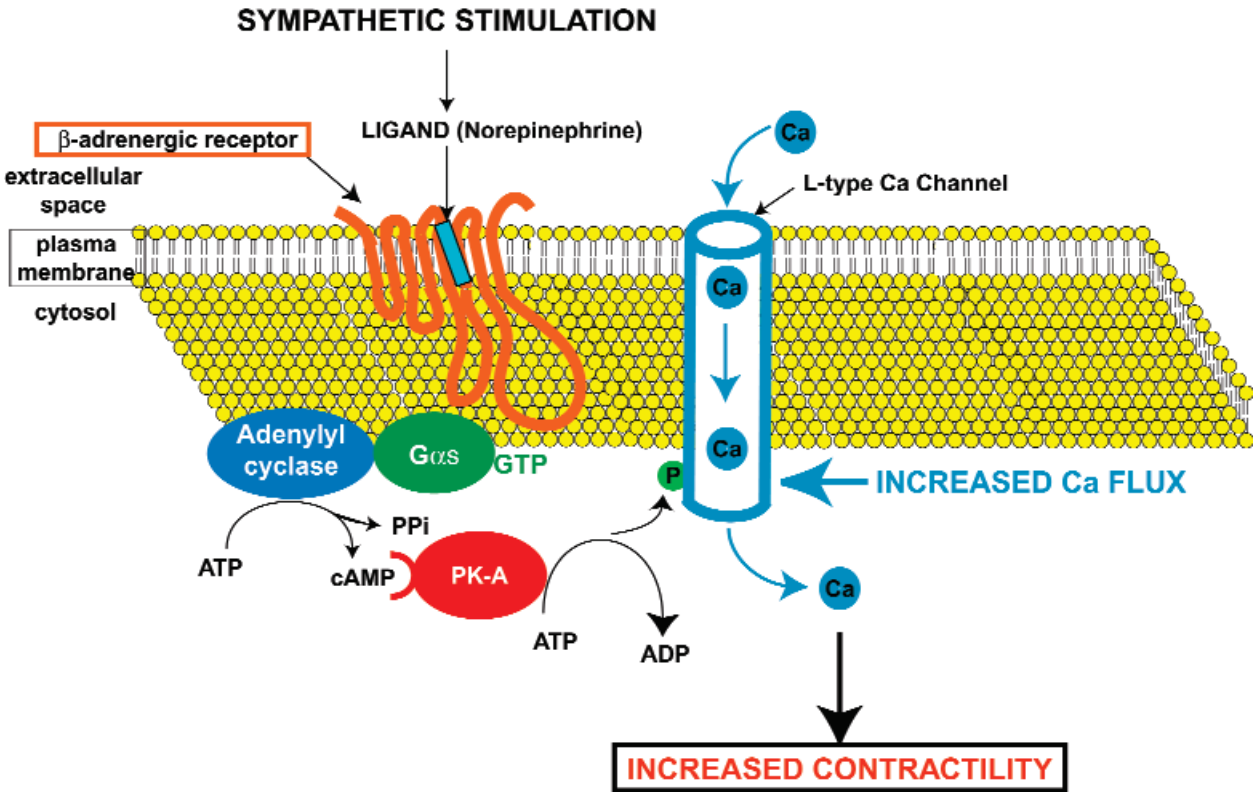

Fig. 1 Functional signaling resulting from sympathetic stimulation. The ligand, in this case the catecholamine norepinephrine, binds to the β-adrenergic receptor causing the latter to activate $G_{\alpha s}$, the α-subunit of a heterotrimeric G-protein; activation occurs when G_{α} binds to GTP. The activated G-protein then activates the enzyme adenylyl cyclase, which forms cyclic AMP from ATP. The second messenger binds to and activates a cyclic AMP-dependent protein kinase (PKA) which phosphorylates several cellular proteins. Shown is the L-type calcium channel that, when phosphorylated, has an increased probability of being in its open state. This change in a pre-existing structure (the calcium channel) increases calcium flux into the cytosol and so increases contractility.

rhythm, a search began to identify more powerful inotropic agents.

Development of inotropic drugs was stimulated in the 1950s when the ability of β-adrenergic agonists to increase myocardial contractility was recognized to improve survival in cardiogenic shock [13]. Prolonged use of β-adrenergic agonists in chronic heart failure, however, was precluded by their short half-life and need for intravenous administration. An apparent breakthrough came in the 1980s when the bipyridines, a new class of inotropic agents that included amrinone and milrinone [14–15], were found to be phosphodiesterase inhibitors whose effects, like those of β-adrenergic agonists, are mediated by increased cellular levels of cyclic AMP. As expected, these drugs led to short-term improvement, but in spite of the obvious hemodynamic term benefit, intense controversy developed regarding the long-term value of administering these drugs in chronic heart failure [16]. Cautions were raised because increased levels of cyclic AMP, a second messenger known to have deleterious energetic and arrhythmogenic effects, could worsen long-term prognosis in patients with heart failure [17]. Support for the view that these drugs adversely effect survival initially came from observational data [18], but this approach to therapy continued to be advocated until randomized trials confirmed that inotropic agents, in spite of causing an initial hemodynamic improvement, shorten long-term survival [19–26]. Further evidence that alleviating the hemodynamic abnormalities in heart failure is not always of long-term value was provided by a large clinical trial which demonstrated that cardiac glycosides fail to prolong long-term survival in heart failure patients [27].

Drugs that inhibit the neurohumoral response often improve prognosis

Clues regarding the importance of non-hemodynamic abnormalities in heart failure emerged in the early 1980s, when the neurohumoral response to low cardiac output was found to have a major adverse effect on long-term survival [28]. As pointed out in a landmark paper by Peter Harris, the neurohumoral response compensates for short-term hemodynamic challenges like exercise and hemorrhage, but has harmful effects when the response is sustained [29]. Beneficial hemodynamic effects of this response include systemic arteriolar vasoconstriction which maintains arterial pressure by increasing afterload, and expansion of extracellular volume and venoconstriction which help restore cardiac output when decreased preload reduces the work of the heart (Starling's Law). Cardiac stimulation - another element of the neurohumoral response - also maintains cardiac output by accelerating heart rate, increasing contractility, and facilitating relaxation [30]; when

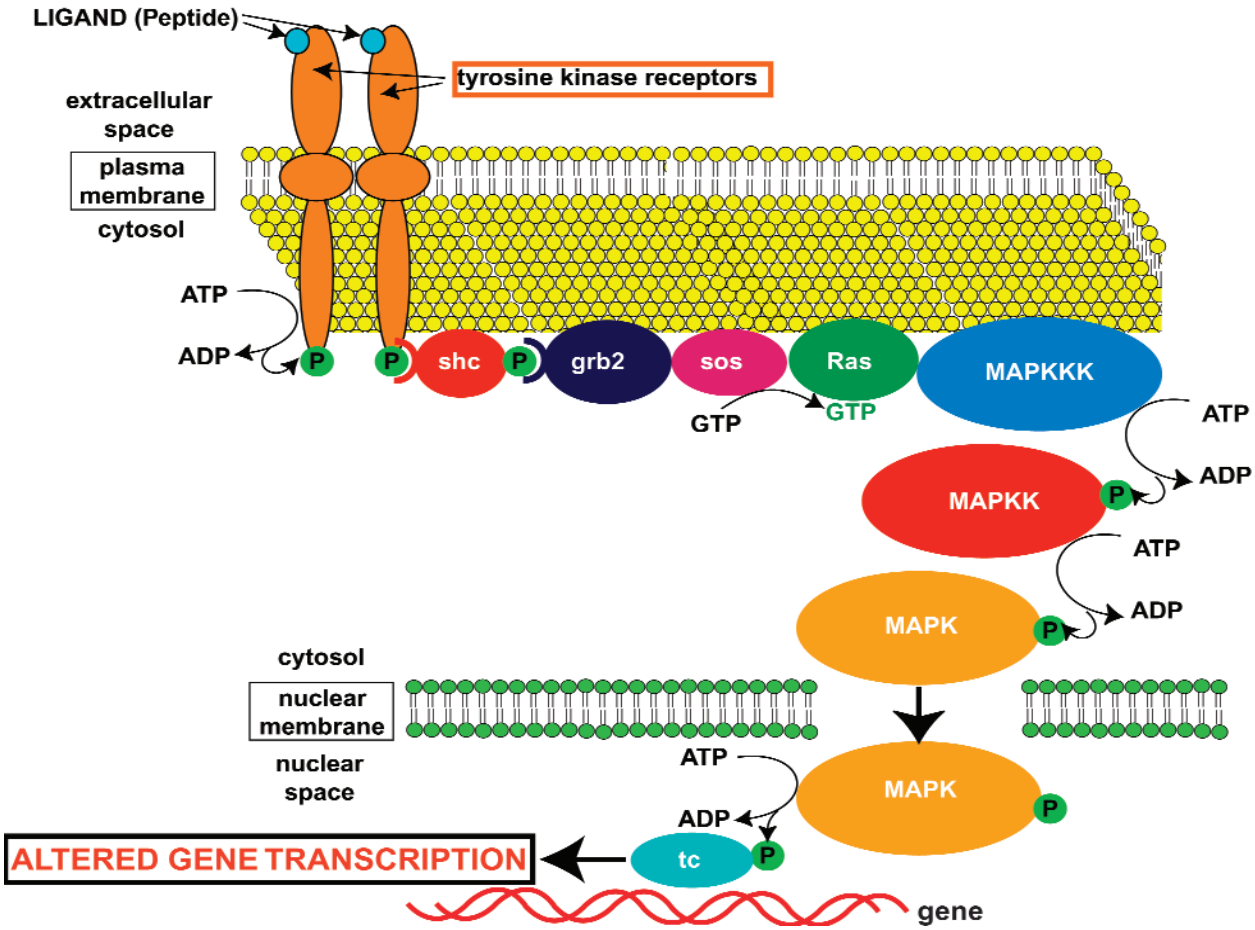

Fig. 2 Proliferative signaling by an enzyme-linked receptor. Binding of a ligand, such as a peptide growth factor, causes the receptor to form an aggregate which activates their latent tyrosine kinase activity. Autophosphorylation creates a "docking site" on the receptor that binds, and then phosphorylates the adaptor protein Shc. This creates another docking site on Shc, which adds Grb2 to a multi-protein aggregate that is assembled along the inner surface of the plasma membrane. This aggregate provides a platform that activates Sos, a guanine nucleotide-exchange factor that then activates Ras, which is similar to G_{α} shown in Fig. 1. The latter occurs when Ras-bound GDP is exchanged for GTP. The activated Ras-GTP complex then stimulates Raf-1, a MAP kinase kinase kinase (MAPKKK) that phosphorylates and activates the MAP kinase kinase (MAPKK) MEK-1, which then phosphorylates the MAP kinase (MAPK) ERK-2. Translocation of the latter to the nucleus allows the activated MAP kinase to phosphorylate nuclear transcription factors (tc) that interacts with specific DNA sequences. (Modified from Katz AM (2000). Heart Failure. Pathophysiology, Molecular Biology, and Clinical Management. Lippincott/Williams & Wilkins, Philadelphia.)

sustained in heart failure, however, this response becomes maladaptive. Some of the deleterious effects are hemodynamic, for example, when increased afterload reduces cardiac output and increases cardiac energy expenditure, and when increased preload causes systemic and pulmonary venous congestion. Sustained β-adrenergic stimulation also increases cardiac energy expenditure, which is especially harmful to the failing heart [1], and has pro-arrhythmic effects [17]. Also important is that norepinephrine, like most neurohumoral mediators, activates maladaptive proliferative responses (see below). The latter effects of β-adrenergic stimulation of the heart may explain why direct-acting vasodilators, which by lowering blood pressure increase sympathetic outflow via the baroreceptor reflex, worsen long-term prognosis in patients with heart failure [31].

The ability of spironolactone, initially used in heart failure because of its diuretic effect, to prolong survival [32] represents another unanticipated finding that is not readily explained when this syndrome is viewed primarily as a hemodynamic disorder. The long-term benefit of this drug is not likely to be due to its potassium-sparing diuretic effect. Instead, the aldosterone antagonist appears to improve prognosis by inhibiting proliferative responses such as upregulation of the synthesis of plasma membrane calcium channels in cardiac myocytes [33] and increased production of extracellular matrix proteins [34].

Perhaps the most convincing evidence advance that heart failure is much more than a hemodynamic syndrome comes from clinical trials which show that β-adrenergic blockers, in spite of causing initial worsening of hemodynamics, improve prognosis [35–38]. This counterintuitive effect reflects the ability of these neurohumoral inhibitors to slow, and often reverse temporarily, the progressive dilatation of the failing heart (see below). Prolonged survival and other benefits of β-blocker therapy show that inhibition of maladaptive proliferative signaling is more important clinically than the hemodynamic worsening caused by their negative inotropic effect.

Functional and proliferative signaling

The results of long-term survival trials in heart failure highlight the importance of proliferative, as well as functional abnormalities in this syndrome. *Functional (hemodynamic) responses* are short-term changes in cardiac performance, vascular tone and salt and water excretion that are brought about by altered behavior of existing structures within the heart, blood vessels and kidneys (Fig. 1). These are the most obvious mechanisms by which the cardiovascular system is influenced by the neurohumoral response and by disease. *Proliferative* (*transcriptional*) *responses* represent a very different type of biological response that modifies the size, shape and molecular composition of the heart and other organs. These structural changes, which occur when altered gene transcription modifies protein synthesis and other structural responses (Fig. 2), play a key role in determining long-term prognosis in patients with heart failure. Proliferative responses, like functional responses, can have both beneficial and deleterious consequences.

Hypertrophy and other architectural changes in the failing heart

The clinical importance of changes in the size and shape of diseased hearts was well known to the great clinical investigators of the 19th century, who routinely carried out autopsy examinations that revealed architectural changes in the hearts of patients who died of heart failure [40–41]. By the beginning of the 19th century, eccentric hypertrophy (dilatation) was recognized as carrying a poor prognosis because of its tendency to progress. Concentric hypertrophy of the heart was initially viewed as an adaptive response that protects patients from the adverse effects of dilatation, but by the end of the 19th century it had become clear that concentric hypertrophy, like dilatation, is associated with progression and early death [41].

The focus on the architecture of diseased hearts ended when Starling described his "Law of the Heart" in the second decade of the 20th century. Because this Law states that increased end-diastolic volume increases the ability of the heart to do work, it initially seemed to contradict the accepted view that dilatation (eccentric hypertrophy) of the failing heart is deleterious [42]. The apparent contradiction is readily explained because *acute* dilatation (Starling's Law) is an adaptive functional response whereas *chronic* dilatation (eccentric hypertrophy) in diseased hearts is a maladaptive proliferative response [1]. The emphasis on functional (hemodynamic) abnormalities became even stronger after World War II, when the

introduction of cardiac catheterization and advances in cardiac surgery incorporated hemodynamic physiology into clinical cardiology. Interest in the architectural changes caused by heart disease faded still further into the background with the growing prevalence of coronary artery disease and emphasis on restoring blood flow to the ischemic myocardium.

Attention was again drawn to the maladaptive features of cardiac hypertrophy in the 1960s when Meerson demonstrated in experimental animals that overload-induced hypertrophy has both short-term adaptive and long-term maladaptive consequences [43]. Another key observation, made possible when the applicability of the Law of Laplace to the heart was rediscovered in the 1950s [44–45], was that hypertrophy initially normalizes wall stress in patients with valvular heart disease [46–48]. The clinical importance of these architectural changes was highlighted in the 1980s when the adverse effect of progressive ventricular dilatation was rediscovered in both experimental animals and patients [49–60]. Redirection of attention from hemodynamics to the biology of the diseased heart was stimulated further when the clinical trials described above yielded results that could not be explained according to the view that heart failure is simply a hemodynamic abnormality.

The cardiomyopathy of overload

The hypertrophic response of the chronically overloaded heart, although it initially normalizes wall stress, has many deleterious consequences. The most important of the latter is shortened cardiac myocyte survival, which initiates a vicious cycle where myocardial cell death increases the load on surviving myocytes, which intensifies the proliferative stimuli that lead to cardiac hypertrophy, which causes more cell death (for review see ref. 1). Progressive dilatation (remodeling), another response of failing hearts to proliferative signaling, is due in part to cardiac myocyte elongation that occurs when sarcomeres are added in series. Remodeling establishes yet another vicious cycle, where increased cavity size increases the tension that must be developed by individual myocytes (the Law of Laplace), which provides additional stimuli for hypertrophy, which leads to further dilatation. In this way, overload-induced hypertrophy initiates progressive deleterious changes in the failing heart that can be viewed as a "cardiomyopathy of overload" [39].

Inhibition of progressive dilatation (remodeling)

Among the most important clinical effects of neurohumoral blockers in patients with heart failure is their ability to inhibit remodeling. This has been seen in experimental models and clinical trials which show that the progressive dilatation of the failing heart can be slowed, and in some cases reversed temporarily, by ACE inhibitors [63–75], β-blockers [73, 76–80], and the combination of these drugs, interfering with functional and proliferative signaling [81–83]. These studies illustrate one way that neurohumoral blockade can modify proliferative responses that contribute to the cardiomyopathy of overload.

Conclusions

The functional (hemodynamic) abnormalities in patients with heart failure fail to explain either the poor prognosis or the long-term term responses to therapy in these patients. According to the hemodynamic view, outcome should be improved by vasodilators and positive inotropic agents, potassium-sparing diuretics would not be expected to have an important effect on survival, and the negative inotropic effects of β-blockers should worsen prognosis. When heart failure is considered as a proliferative disorder of heart muscle, however, all of these findings make sense because direct-acting vasodilators and inotropes activate growth responses that can worsen the cardiomyopathy of overload, whereas β-blockers, ACE inhibitors and aldosterone antagonists block proliferative signaling pathways that shorten survival. The goals of therapy for heart failure should therefore include not only short-term functional improvement, but also slowing of the proliferative responses that cause progressive ventricular dilatation (remodeling) and hastening cardiac cell death. Although the latter goal is now achieved clinically using neurohumoral blockers like ACE inhibitors and b-blockers, new understanding of the signal transduction pathways responsible for maladaptive hypertrophy promises to identify additional means to slow progression and delay death in these patients.

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