

# Role of Neurohumoral Modulation in Congestive Heart Failure: Focus on the New Generation Calcium Channel Blockers

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## ABSTRACT

Despite improvement in the control of risk factors such as coronary artery disease and systemic hypertension, the incidence of congestive heart failure (CHF) is actually increasing. Wide use of angiotensin-converting enzyme inhibitors has influenced the survival of patients in the community but mortality in patients with advanced disease remains about 15% after one year.

It has become clear that, while neurohumoral activation is important in supporting cardiac function after the loss of myocardial tissue following infarction, such stimulation contributes to the further deterioration of the cardiac muscle and this is detrimental in patients with CHF. An increase in regional cardiac adrenergic activity has been associated with an adverse outcome in patients with CHF. The effects of certain drugs that work to dilate the arteries without activating the overall neurohumoral system, and more specifically the adrenergic nervous system, may help to explain the success of these medications in CHF. Current trials indicate second-generation calcium channel blockers such as amlodipine are well tolerated and improve the neurohumoral milieu in CHF. Accordingly, these agents may prove useful as adjunctive treatments for congestive heart failure.

**Key words:** calcium channel blockers, cardiac adrenergic activity, congestive heart failure, neurohumoral system

## RÉSUMÉ

Rôle de la modulation neurohormonale dans le traitement de l'insuffisance cardiaque congestive : plein feu sur la nouvelle génération d'inhibiteurs des canaux calciques.

Malgré les avancés dans la maîtrise des facteurs de risque comme les coronaropathies et l'hypertension, l'incidence de l'insuffisance cardiaque congestive (ICC) est actuellement à la hausse. L'usage répandu des inhibiteurs de l'enzyme de conversion de l'angiotensine a eu une influence sur la survie des patients dans la communauté, mais la mortalité chez les patients dont la maladie est avancée est toujours d'environ 15 % après un an.

Il est maintenant évident que, bien que l'activation neurohormonale joue un rôle important dans le maintien de la fonction cardiaque suite à une nécrose du tissu myocardique consécutive à un infarctus, la stimulation cardiaque soutenue

contribue à la détérioration du muscle cardiaque et qu'elle est délétère chez les patients atteints d'ICC. Un accroissement de l'activité adrénergique cardiaque locale a été associée à une issue indésirable chez les patients atteints d'ICC. Les effets de certains médicaments qui ont une activité dilatatrice sur les artères, mais non sur tout le système neurohormonal et plus particulièrement le système sympathique, pourraient expliquer le succès de ces médicaments dans le traitement de l'ICC. Les essais actuels révèlent que les inhibiteurs des canaux calciques de deuxième génération, comme l'amlodipine, sont bien tolérés et améliorent le milieu neurohormonal des patients souffrant d'ICC. Par conséquent, ces agents pourraient s'avérer utiles comme traitement adjuvant dans l'insuffisance cardiaque congestive.

**Mots clés :** activité adrénergique cardiaque, inhibiteurs des canaux calciques, insuffisance cardiaque congestive, système neurohormonal

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## INTRODUCTION

Congestive heart failure (CHF) affects about 1% of the North American population.<sup>1</sup> The two leading causes of CHF are coronary artery disease and systemic hypertension.<sup>2</sup> Despite improvement in the control of these risk factors, and despite a decrease in the incidence of coronary disease over the last 15 years, the incidence of heart failure is actually increasing.<sup>2</sup> This is due in part to the aging population. Furthermore, the costs related to this morbid condition are greater than those for the treatment of all cancers combined.<sup>1</sup>

The treatment of CHF has evolved significantly over the last decade. The most important change to the standard

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regimen, which has affected both the functional capacity and survival of patients suffering from this condition, has been the use of angiotensin-converting enzyme (ACE) inhibitors. The use of this class of agent has increased survival by about 25 to 30%.<sup>3-5</sup> Their broad use has also influenced the survival of patients in the community.<sup>6</sup> Nevertheless, mortality in patients with advanced disease remains about 15% after one year and close to 50% after five years. Statistics from the SOLVD trial indicate that nearly half of patients with symptoms of CHF and with a left ventricular (LV) ejection fraction, less than 35% treated with enalapril died or were hospitalized for decompensated CHF over the duration of the study.<sup>4</sup> In addition, the SOLVD trial also demonstrates the use of enalapril was contraindicated in 11% of patients potentially eligible to receive it.<sup>4</sup> Finally, some clinical data suggest the effect of ACE inhibition may be lost over time, and some neurohormones such as aldosterone, although initially suppressed by ACE inhibitor, may "escape" and increase over time.<sup>7</sup> Thus, these observations have justified the search for the use of alternative and/or adjunctive treatments in CHF.

The purpose of this review is to present the importance of the neurohumoral activation in CHF based on the results of some important contemporary clinical trials. The rationale for the use of adjunctive agents such as the new generation calcium channel blockers in patients with CHF is also presented.

### Neurohumoral Activation and Adverse Outcome

Myocardial injury caused by myocardial infarction (MI) or other viral, toxic, or metabolic diseases results in an early increase in vasoconstrictive hormones such as norepinephrine, renin, angiotensin, and endothelin.<sup>8,9</sup> The release of these hormones occurs early in the course of the disease before symptoms such as dyspnea and fatigue appear.<sup>8</sup> The elevation in circulating levels of these substances causes an increase in the pumping ability of the damaged myocardium and helps to sustain blood pressure by enhancing cardiac output and causing peripheral vasoconstriction. These mechanisms are important to support cardiac function after the loss of myocardial tissue. However, chronic stimulation causes myocardial damage and likely contributes to further deterioration of the cardiac muscle. In fact, increased circulating levels of norepinephrine, renin, or endothelin, as well as other surrogates of chronic neurohumoral activation such as hyponatremia, have all been significantly related to a poor outcome in patients with CHF (Figure 1).<sup>10-12</sup> In response to this chronic elevation of vasoconstrictor hormones, there is a parallel increase in vasodilatory hormones such as prostaglandin and atrial natriuretic peptides.<sup>13</sup> As with the vasoconstrictive sub-

stances, the elevation of these counteracting vasodilatory hormones has been associated with an adverse outcome in CHF patients. Interestingly, while chronic systemic activation is related to survival in CHF, an increase in regional cardiac adrenergic activity appears to be even more powerfully related to a poor outcome. In a recent study by Kaye and coworkers, the cardiac regional release of norepinephrine or norepinephrine "spillover" was a significantly better predictor of adverse outcome than systemic plasma norepinephrine levels (Figure 2).<sup>14</sup> This finding suggests that any intervention that lowers

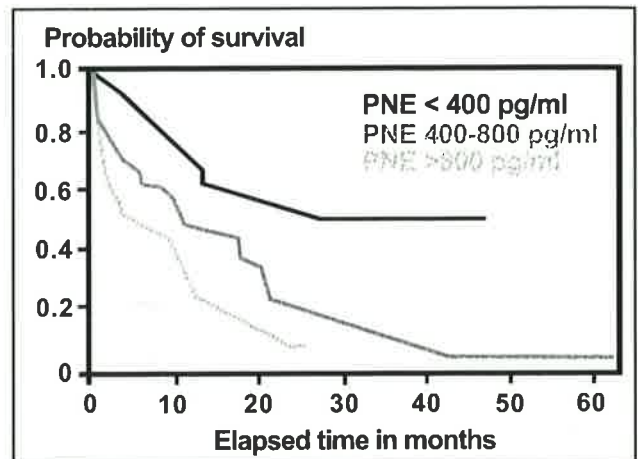


Figure 1. Life-Table Analysis of Survival, According to Tertile Based on Level of Plasma Norepinephrine (PNE) in Patients with CHF. (Source: Cohn JN et al. *N Engl J Med* 1984;311:819-23.(ref. 10)) (Reprinted with permission from the Massachusetts Medical Society, *New England Journal of Medicine* 1984;311:819-23. Copyright 1984 Massachusetts Medical Society. All rights reserved.)

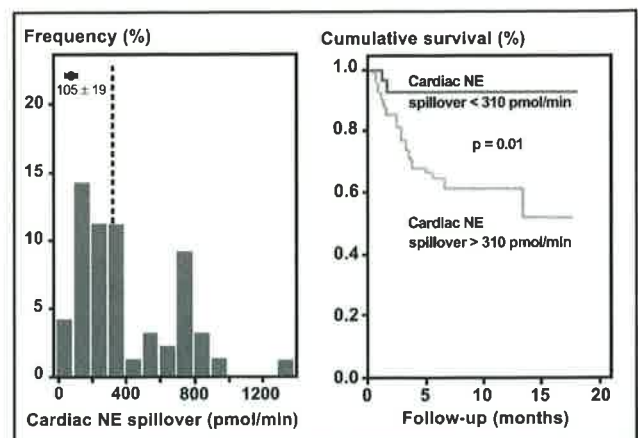


Figure 2. Prognostic Value of Cardiac Adrenergic Activity in Patients with CHF. (Right panel taken from: Kaye et al *J Am Coll Cardiol* 1995;26:1257-63. (ref. 14)).(Reprinted with permission from the American College of Cardiology (*Journal of the American College of Cardiology* 1995;26:1257-63.)

cardiac regional adrenergic drive will likely confer a significant decrease in mortality.

The beneficial effects of certain drugs on the neurohumoral milieu help to explain the success of CHF medications that work to dilate the arteries without activating the overall neurohumoral system, and more specifically the adrenergic and the renin-angiotensin-aldosterone systems (Table I).<sup>15</sup> The use of ACE inhibitors improves the neurohumoral status.<sup>16</sup> For example, enalapril improves survival and prevents the development of symptoms of CHF and clinical deterioration in patients with chronic CHF of any etiology.<sup>3,4</sup> Similarly, captopril, lisinopril, and ramipril decrease mortality when administered early after a myocardial infarction, and in the case of captopril and lisinopril, even when there is no clinical evidence of CHF.<sup>17,18,19</sup> The benefit of a vasodilator that also improves the neurohumoral status, in comparison with direct-acting agents such as hydralazine, becomes more apparent in the presence of high neurohumoral activation. In the VHeFT-II trial, in which the combination of hydralazine and nitrates was compared with enalapril, the excess mortality in the group of patients treated with hydralazine/nitrates was restricted to those with high circulating levels of norepinephrine.<sup>20</sup> In addition, the reduction in mortality related to ACE inhibition was also significantly greater in very sick patients compared to those with milder heart failure symptoms.<sup>3,4</sup>

Some other agents improve symptoms and/or survival such as  $\beta$ -blocker or digoxin without activating the neurohumoral system.  $\beta$ -adrenergic blockade of second and third generation calcium channel blockers such as metoprolol<sup>21</sup> or carvedilol<sup>22</sup> improves symptoms and ejection fraction and reduces hospitalization for heart failure. Carvedilol has also been shown to improve survival<sup>22</sup> in CHF due to ischemic or dilated cardiomyopathy. Although these agents cause little change in the systemic level of norepinephrine, they significantly decrease the transmyocardial norepinephrine balance and, thus, regional cardiac adrenergic activity.<sup>23</sup> Digoxin is an inotrope which enhances the parasympathetic tone and baroreflex responsiveness.<sup>24</sup> This agent improves functional capacity, and in the recently presented DIG trial,<sup>25</sup> despite a neutral effect on survival, reduces the risk for the deterioration and hospitalization for CHF. Finally, angiotensin-II blockers such as losartan can be used in patients intolerant to ACE inhibitors as they provide similar benefits for up to 12 weeks.<sup>26</sup> Whether an angiotensin-II blocker causes similar benefits to an ACE inhibitor in the longer term is currently being investigated.

While vasodilator and neurohumoral modulators improve survival, pharmacologic agents that activate the neurohumoral system increase mortality despite a beneficial effect on functional class and exercise tolerance. For example, chronic administration of xamoterol, a  $\beta_1$ -agonist,<sup>27</sup> and milrinone, a phosphodiesterase inhibitor,<sup>28</sup> increases mortality and activates the vasoconstrictive neurohumoral system when administered orally in patients with severe CHF (Table I). In the PROFILE study, the effect of a direct vasodilator, flosequinan, was compared to placebo in patients with moderate to severe heart failure.<sup>29</sup> Flosequinan induces a mild increase in heart rate and, thus, activates the adrenergic nervous system. Despite a functional class improvement noted early in the trial, an increased mortality was observed at one year in patients treated with flosequinan causing premature cessation of the trial. As a whole, these data indicate that even in the presence of improved pump function, activation of the neurohumoral system is associated with poor survival.

### Role for Calcium Channel Blockers

Early studies involving the use of calcium channel blockers in CHF were not promising. In fact, although short-acting nifedipine improved systemic hemodynamics when given acutely, chronic administration of this agent to patients with CHF was associated with worsening heart failure.<sup>30</sup> Similar observations were reported with diltiazem.<sup>31</sup> In that study, the chance of developing CHF in patients treated with diltiazem after an MI was directly related to the magnitude of impairment in systolic function at the time of randomization. The mechanism for this worsening in cardiac function in patients chronically treated with these agents is likely related to chronic neurohumoral activation.<sup>32</sup> In fact, potent vasodilation by these

**Table I.** Natural History and Treatment of Heart Failure as Defined by Some of the Large, Contemporary, Placebo-Controlled Trials

Trial	Study Drug	Patient Population	Mean FU (months)	RR	NA
VHeFT-1	HZ/Nt	Class II-III	27	0.64	⇒
CONSENSUS-1	Enalapril	Class IV	6	0.56	⇓
SOLVD, trt	Enalapril	CHF, EF ≤ 35%	41	0.84	⇓
SOLVD, pvt	Enalapril	Asymptomatic, EF ≤ 35%	37	0.82	⇓
SAVE	Captopril	Post-MI, EF ≤ 40%	42	0.81	⇓
Xamoterol	Xamoterol	Class III-IV	3	2.54	⇑
PROMISE	Milrinone	Class III-IV	6.1	1.27	⇑

RR = relative risk, NA = neurohumoral activation  
Adapted from Armstrong PW et al. *Circulation* 1994;88:2941-52 (ref. 15)  
trt = treatment, pvt = prevention, HZ = hydralazine, Nt = nitrate



short-acting calcium channel blockers stimulates the baroreflex responses, increasing sympathetic discharge to compensate for the negative inotropic effect of these agents on the diseased myocardium.<sup>33</sup> However, chronic neurohumoral activation, which appears to cause myocyte hypertrophy, calcium-mediated cellular damage and increased oxidative stress, eventually contributes to further deterioration of the cardiac muscle.

### Newer Calcium Channel Blockers

The new generation of calcium channel blockers has recently shown promising results in patients with CHF. Early work performed by Packer and colleagues showed that administration of amlodipine for eight weeks improves exercise time and decreases circulating levels of norepinephrine in 118 patients with class II to III symptoms treated with diuretics and digitalis and most of them (67%) with an ACE inhibitor (Table II).<sup>34</sup> This study was important because it demonstrated that further vasodilation with calcium channel blockers was safe and could lower norepinephrine levels. This finding prompted the Prospective Randomized Amlodipine Survival Evaluation in Heart Failure (PRAISE) study.<sup>35</sup> In this trial, NYHA Class III and IV patients with ejection fractions less than 30% and receiving triple background therapy of ACE inhibitors, digoxin and diuretics were randomized to receive amlodipine or placebo.<sup>17</sup> The patients treated chronically with amlodipine exhibited a trend toward survival ( $p=0.07$ ) after a median follow-up of 13.8 months. Interestingly, no significant changes in survival were observed in the group with heart failure caused by ischemic heart disease. In contrast, the patients in whom heart failure was caused by dilated cardiomyopathy exhibited a 45% reduction in mortality when treated with amlodipine ( $p=0.001$ ). In that study, amlodipine was as well tolerated as placebo, with a discontinuation rate of 16% for placebo versus 14% for the group receiving amlodipine. Peripheral and pulmonary edema occurred more often while uncontrolled hypertension and angina occurred less often in the amlodipine group. Nevertheless, despite the increase in pulmonary edema, the amlodipine treated group yielded a decrease in life-threatening arrhythmias and death, two events generally associated with the clinical progression of CHF.

The mechanisms underlying such important differences in the response of ischemic versus idiopathic dilated cardiomyopathy to amlodipine remain largely unknown. Nevertheless, significant differences exist between these two conditions. The myocardium injured by coronary artery disease has a mix of scarred areas chronically deprived of blood supply, and areas of viable but poorly functioning cardiac muscle. In addition, the quantity of remaining noninfarcted myocardium is less in ischemic cardiomyopathy and yields more

significant abnormalities with regard to the beta adrenergic neuroeffector pathways, such as less  $\beta_1$ -receptor downregulation and more uncoupling from myocardial contraction.<sup>36</sup> Consequently, ischemic cardiomyopathy might be less amenable to pharmacologic modulation than heart failure caused by idiopathic dilated cardiomyopathy. These hypotheses remain speculative and more work needs to be done to improve our understanding of the differences between these two conditions. The PRAISE-II trial is now underway and will involve only patients with dilated cardiomyopathy. Patients with severe CHF treated with triple therapy will be randomized to receive amlodipine versus placebo. Many substudies will be performed and combined with the main trial in order to better understand the effect of amlodipine on the failing myocardium.

The VHeFT-III trial was a study of felodipine in patients with mild to moderate CHF.<sup>37</sup> In this study, patients with class II-III symptoms and ejection fraction below 45% and/or a cardiothoracic ratio greater than 55% were randomized to receive felodipine versus placebo in addition to triple drug therapy. Two-hundred and twenty four (224) patients were randomized to receive felodipine and 227 patients received placebo, and were followed for three years. Similar to amlodipine, felodipine was well tolerated and had a neutral effect on survival. However, the mortality rate was very low in both the felodipine and the placebo-treated patients (about 20% at three years), and thus the study lacked the power to detect a significant effect of felodipine on survival. Despite these limitations, it is possible to conclude that felodipine is safe to use in patients with mild to moderately severe CHF.

The results from these trials have important consequences for clinical practice. It is safe to use amlodipine as an anti-ischemic agent in patients who have angina and CHF. Also, some patients with heart failure, especially when heart failure is due to or associated with systemic hypertension, may continue to exhibit systemic hypertension or may present significant mitral valvular

**Table II. Improvement in Exercise Time and Symptoms, and Decrease with Amlodipine**

	Placebo		Amlodipine	
	4 weeks	8 weeks	4 weeks	8 weeks
Change in exercise time (sec)	+12 ± 13	+22 ± 13	+30 ± 13	+62 ± 30*†
% of patients with improvement in symptoms	—	+29	—	+55%
Change in norepinephrine levels (pg/mL)	—	+30	—	-95†

\*  $p < 0.05$  (8 weeks vs. baseline)

†  $p < 0.05$  (amlodipine vs. placebo)

Adapted from Packer M. *J Am Coll Cardiol* 1991;17:274A (ref. 34)

regurgitation despite high doses of ACE inhibitor. Amlodipine and felodipine may help to provide further vasodilation without activating the neurohumoral system.

In conclusion, unlike short-acting first-generation agents, the new generation of dihydropyridine calcium channel blockers which have better vascular selectivity and improved pharmacokinetics appear to be safe when used in moderate and even severe CHF. These promising results provide the clinician with additional tools to improve symptoms and cardiac function in patients with CHF and concomitant conditions such as angina or hypertension. Currently under investigation is a group of new agents, such as mibefradil, which block L- and T-calcium channels<sup>37</sup> and a large survival trial involving patients with heart failure is currently underway (the MACH-1 study). The results from this trial and from the PRAISE-II study should provide additional valuable insight into the role of such agents in the treatment of CHF. ☐

## REFERENCES

1. Statistics Canada 84-203. Causes of mortality 1970, 1975, 1980, 1985, 1989.
2. Smith WM. Epidemiology of congestive heart failure. The Framingham study. *N Engl J Med* 1971;285:1441-6.
3. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results from the cooperative north Scandinavian enalapril survival study (CONSENSUS). *N Engl J Med* 1987;316:1429-35.
4. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. *N Engl J Med* 1991;325:293-302.
5. Pfeffer MA, Braunwald E, Moye LA, et al, for the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1992;327:669-77.
6. Stevenson WG, Stevenson LW, Middlekauff HR, et al. Improving survival for patients with advanced heart failure. A study of 737 consecutive patients. *J Am Coll Cardiol* 1995;26:1417-23.
7. Cleland JGF, Daragie HJ, Hodsman GP, et al. Captopril in heart failure: A double-blind controlled trial. *Br Heart J* 1984;52:530-5.
8. Rouleau JL, Kortas C, Bichet D, De Champlain J. Neurohumoral and hemodynamic changes in congestive heart failure: lack of correlation and evidence of compensatory mechanisms. *Am Heart J* 1988;116:746-57.
9. Stewart DJ, Cernacek P, Costello KB, Rouleau JL. Elevated endothelin-1 in heart failure and loss of normal response to postural changes. *Circulation* 1992;85:510-7.
10. Cohn JN, Levine RB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;311:819-23.
11. Dzau JV, Colucci WF, Hollenberg NK, Williams GH. Relation of the renin-angiotensin-aldosterone system to clinical state in congestive heart failure. *Circulation* 1981;63:645-51.
12. Omland T, Lie RT, Aakvaag A, et al. Plasma endothelin determination as a prognostic indicator of 1-year mortality after acute myocardial infarction. *Circulation* 1994;89:1573-9.
13. Hall C, Rouleau JL, Moye L, et al. N-terminal proatrial natriuretic factor. An independent predictor of long-term prognosis after myocardial infarction. *Circulation* 1994;89:1934-42.
14. Kaye DM, Lefkivits J, Jenning GL, et al. Adverse consequences of high sympathetic nervous activity in the failing human heart. *J Am Coll Cardiol* 1995;26:1257-63.
15. Armstrong PW, Moe GW. Medical advances in the treatment of congestive heart failure. *Circulation* 1994;88:2941-52.
16. Benedict CR, Francis GS, Shelton B, et al. Effect of long-term enalapril therapy on neurohormones in patients with left ventricular dysfunction. *Am J Cardiol* 1995;75:1151-7.
17. Latini R, Maggioni AP, Flather M, et al. ACE inhibitor use in patients with myocardial infarction. Summary of evidence from clinical trials. *Circulation* 1995;92:3132-7.
18. ISIS-4 Collaborative Group. ISIS-4: A randomized factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet* 1995;345:669-85.
19. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: Effects of lisinopril and transdermal glyceryl trinitrate singly or together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994;343:1115-22.
20. Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A, for the V-HeFT VA Cooperative Studies Group. Plasma norepinephrine, plasma renin activity and congestive heart failure. *Circulation* 1993;87:VI40-8.
21. Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. *Lancet* 1993;342:1441-6.
22. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 1996;334:1349-55.
23. Gilbert EM, Abraham WT, Olsen S, et al. Comparative hemodynamic, left ventricular functional, and anti-adrenergic effects of chronic treatment with metoprolol versus carvedilol in the failing heart. *Circulation* 1996;94: 2817-25.
24. Ferguson DW, Berg WJ, Sanders JS, Roach PJ, Kempf JS, Kienzle MG. Sympathoinhibitory responses to digitalis glycosides in heart failure patients: direct evidence from sympathetic neural recordings. *Circulation* 1989;80:65-77.
25. Garg R, Gorlin R, Smith T, Yussuf S and the Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997; 336: 525-33.
26. Crozier I, Ikram H, Awan N, et al for the Losartan Hemodynamic Study Group. Losartan in heart failure: Hemodynamic effects and tolerability. *Circulation* 1995;91:691-7.
27. The Xamoterol in Severe Heart Failure Study Group. Xamoterol in severe heart failure. *Lancet* 1990;336:1-6.
28. Packer M, Caver JR, Rodeheffer RJ, et al, for the PROMISE Study Research Group. Effect of oral milrinone in severe chronic heart failure. *N Engl J Med* 1991;325:1468-75.
29. Packer M, Rouleau J, Swedberg K, Pitt B, Fisher L, Klepper M and the PROFILE Investigators. Effects of flosequinone on survival in chronic heart failure: preliminary results of the PROFILE Study. *Circulation* 1993;88:1-301.
30. Elkayam U, Amin J, Mehra A, et al. A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with that of

- isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. *Circulation* 1990;82:1954-61.
31. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988;319:385-92.
  32. Packer M. Pathophysiological mechanisms underlying the adverse effects of calcium channel-blocking drugs in patients with chronic heart failure. *Circulation* 1989;80:59-67.
  33. Opie LH. Calcium channel antagonists in the treatment of coronary artery disease: Fundamental pharmacological properties relevant to clinical use. *Prog Cardiovasc Dis* 1996;38:273-290.
  34. Packer M, Nicol P, Khanderia BR, et al. Randomized, multicenter, double-blind, placebo-controlled evaluation of amlodipine in patients with mild-to-moderate heart failure. *J Am Coll Cardiol* 1991;17:274A.
  35. Packer M, O'Connor C, Ghali JK, et al for the Prospective randomized Amlodipine Survival Evaluation Study Group. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med* 1996;335:1107-14.
  36. Bristow MR, Anderson FL, Port JD, et al. Differences in  $\beta$ -adrenergic neuroeffector mechanisms in ischemic versus idiopathic dilated cardiomyopathy. *Circulation* 1991;84:1024-39.
  37. Cohn JN. The V-HeFT-III (Vasodilator-Heart Failure-III) trial: background and main results. Presented at the American Heart Association Annual meeting, November 1995, Anaheim, CA.
  38. Osterreider W, Holck M. In vitro pharmacologic profile of RO 40-5967, a novel Ca<sup>2+</sup> channel blocker with potent vasodilator but weak inotropic action. *J Cardiovasc Pharmacol* 1989;13:754-9.
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