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Survey of the Use of Organic Nitrates for the Treatment of Chronic Congestive Heart Failure in the United States

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A survey of members of the Heart Failure Society of America revealed that despite their lack of approval by the United States Food and Drug Administration, nitrates are widely used in patients with chronic congestive heart failure (CHF). Most members reported using nitrates in patients with ischemic (90%) and nonischemic (81%) causes of chronic CHF, especially those with symptomatic CHF (43% reported using nitrates in >50% of their patients with ischemic and 25% with nonischemic causes). Ninety-six percent reported using nitrates to reduce symptoms, 74% for hemodynamic improvement, 65% for better exercise tolerance, and only 14% for left ventricular reversed remodeling. Nitrates were always combined with hydralazine in 25% of patients and occasionally combined with hydralazine in 67%. ©2004 by Excerpta Medica Inc.

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Organic nitrates were the first oral vasodilatory agents to be evaluated for the treatment of patients with chronic congestive heart failure (CHF).^{1,2} Early studies demonstrated beneficial hemodynamic effects,^{3,4} reduction of symptoms, better exercise tolerance,^{1,2} and, in combination with hydralazine, a superior effect on survival compared with placebo.² Despite these data and because of a lack of larger scale studies, the use of nitrates for the treatment of patients

with CHF has not been approved by the United States Food and Drug Administration. Despite this lack of approval, information from recent clinical trials have consistently suggested the widespread use of nitrates in the treatment of patients with CHF.^{3–5} The purpose of the present study was to evaluate the attitudes of physician members of the Heart Failure Society of America regarding the use of nitrates in the management of chronic CHF in the United States.

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We obtained information about the use of nitrates in chronic CHF in the United States by sending questionnaires to 1,348 members of the Heart Failure Society of America with addresses in the United States. Responses were collected over the next 3 months (from March to May 2001). A database was created using Excel software (Microsoft Corporation, Redmond, Washington). Data were analyzed using Excel applications. The results were expressed as percentages of total responses. Responses were received from 308 members, of whom 91% indicated that they were using nitrates for the treatment of patients with CHF (Figure 1). Most respondents reported using nitrates to treat patients with CHF with ischemic and nonischemic causes (90% and 81%, respectively), although more respondents indicated the use of nitrates in ≥50% of their patients with ischemic compared with nonischemic causes (43% vs 25%; Figure 2). Nitrates were used more often in patients with moderate to severe symptoms (New York Heart Association [NYHA] classes III and IV) compared with those with either no or only mild symptoms (NYHA classes I and II) (Figure 3). Ninety-six percent of respondents reported using nitrates for the reduction of symptoms, 74% for hemodynamic improvement, and 65% for improved exercise tolerance. Only 14% reported the use of nitrates for reverse remodeling of the left ventricle (Figure 4).

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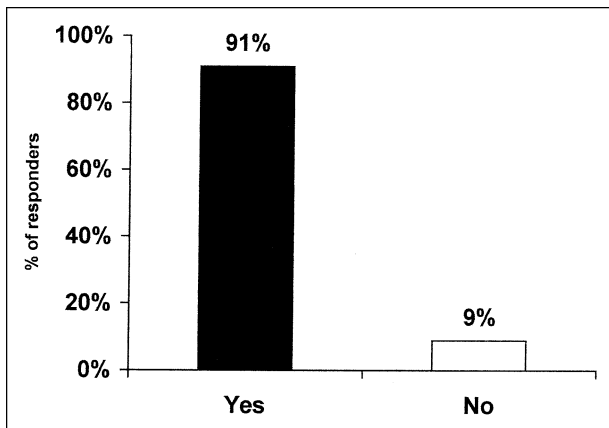


FIGURE 1. Response to the question on the use of nitrates in the treatment of patients with chronic CHF.

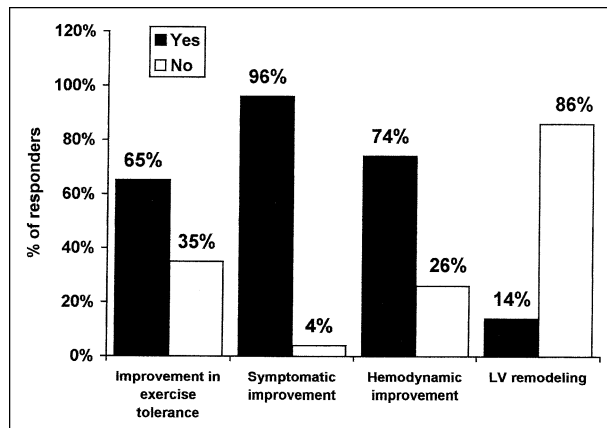


FIGURE 4. Response to the question regarding the reasons for the use of nitrates in patients with chronic CHF. LV = left ventricular.

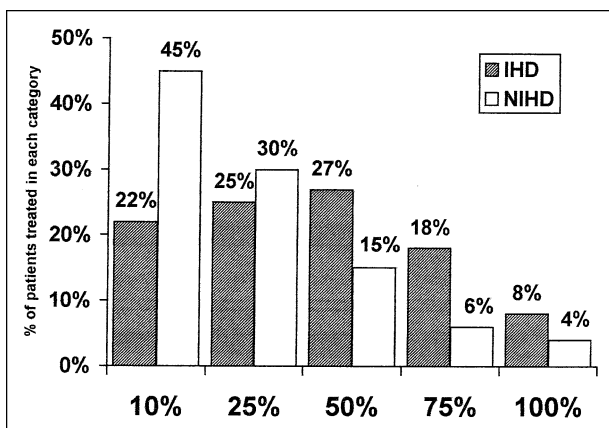


FIGURE 2. Response to the question on the percentage of patients treated with nitrates. IHD = ischemic heart disease; NIHD = nonischemic heart disease.

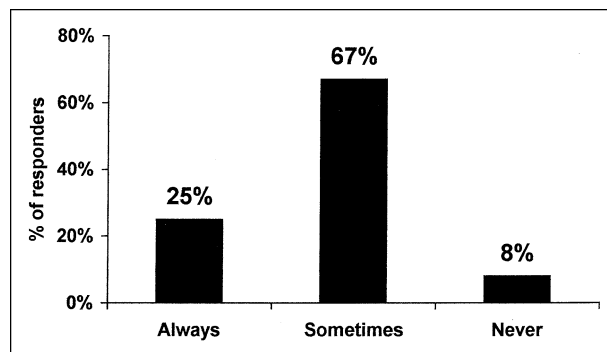


FIGURE 5. Response to the question regarding the concomitant use of hydralazine with nitrates in the treatment of patients with chronic CHF.

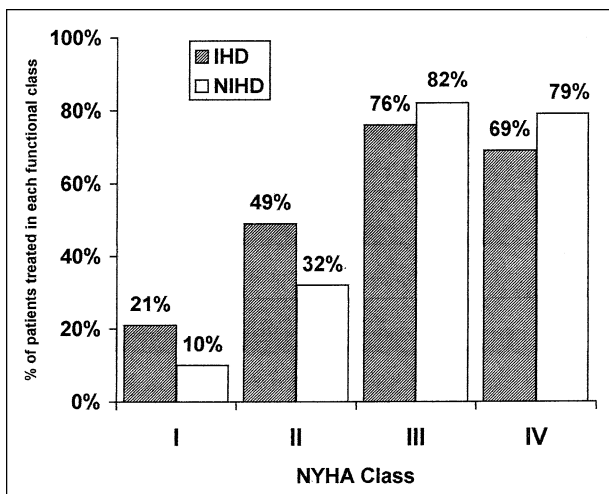


FIGURE 3. Response to the question on the use of nitrates in patients with ischemic and nonischemic causes in the different NYHA functional classes. Abbreviations as in Figure 2.

Most respondents reported the use of isosorbide mononitrate and isosorbide dinitrate (63% and 54%, respectively) for the treatment of patients with CHF. The doses of isosorbide mononitrate were 60 (73%),

30 (30%), 120 (24%), 180 (4%), and 240 mg (6%) and were used by most respondents (87%) on a daily basis. The most common doses for isosorbide dinitrate were 20 (57%) and 40 mg (45%), followed by 10 (18%) and 80 to 120 mg (6%). Most respondents used isosorbide dinitrate 3 times daily (86%), and the rest used it 4 times daily.

The administration of nitrates was always combined with hydralazine by only 25% of the respondents, whereas 67% reported the occasional use of these drugs in combination, and 8% never used hydralazine (Figure 5). The most frequent doses for hydralazine were 25, 50, and 75 mg (30%, 46%, and 20%, respectively), and 2/3 of respondents used hydralazine 3 times daily dosing, whereas 1/3 used the drug 4 times daily.

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The results of this study reflect the opinions of ≥ 300 physicians interested in CHF and show that despite the lack of approval by the United States Food and Drug Administration and the development of new therapeutic modalities, nitrates are frequently used in the treatment of patients with CHF. Although our study may be influenced by a bias toward the use of nitrates by the respondents, the results confirm information obtained from recent clinical trials.³⁻⁵ Ninety percent of respondents to the survey reported that they

were using organic nitrates in the treatment of patients with CHF, especially those with moderate and severe symptoms (NYHA classes III and IV). This therapy was used in patients with CHF of ischemic as well as nonischemic causes, with a somewhat greater prevalence in patients with ischemic cardiomyopathy, most likely because of the proved effect of nitrates in the treatment of myocardial ischemia.⁶

The selected reasons for the use of nitrates for the treatment of patients with CHF were hemodynamic improvement, a reduction in symptoms, and improved exercise capacity. This clinical impression is supported by results of numerous clinical studies. The use of oral isosorbide dinitrate was reported to result in favorable hemodynamic effects at rest^{7,8} and during dynamic and isometric exercise.^{9,10} Multiple studies have demonstrated a favorable effect of nitrates alone on exercise tolerance,^{1,11} and a recent study demonstrated a significant and sustained effect of intermittent large-dose transdermal nitroglycerin on maximal treadmill exercise time in patients with chronic CHF (NYHA classes II to IV) already treated with angiotensin-converting enzyme inhibitors.¹² Further evidence for the improvement in exercise tolerance with nitrate therapy was provided by the results of the Vasodilator Heart Failure Trial (V-HeFT), which showed a small but significant improvement in maximal oxygen consumption in patients treated with isosorbide dinitrate and hydralazine that was superior to that attributable to enalapril.¹³

Only a few respondents were of the opinion that nitrates might result in a favorable effect on left ventricular remodeling. However, previous studies have demonstrated a favorable effect of nitrates on left ventricular size and systolic function. A recent study by Elkayam et al¹² showed a statistically significant reduction in left ventricular end-diastolic and end-systolic dimensions, measured echocardiographically, in a group of patients with CHF who were receiving large doses of intermittent transdermal nitroglycerin added to standard heart failure therapy for 3 months. In addition, data from the V-HeFT¹⁴ showed significant improvement in the left ventricular ejection fraction with a combination therapy of isosorbide dinitrates and hydralazine, which was superior to the effect of the angiotensin-converting enzyme inhibitor enalapril. This improvement of the ejection fraction was associated with a favorable effect on long-term survival.

The present study demonstrates the equal use of isosorbide mononitrate and isosorbide dinitrate for the treatment of patients with CHF in the United States. Oral isosorbide dinitrate was the nitrate preparation used in the V-HeFT^{13,14} and has been the most frequently investigated drug in other studies.^{1,7,8,11} The clinical use of isosorbide mononitrate, which has not been evaluated in clinical trials, is probably due to theoretical advantages, including superior bioavailability and longer and more persistent hemodynamic effects.¹⁵ The most common dose used by the participants in our survey was isosorbide dinitrate 20 mg 3 times daily or isosorbide mononitrate 60 mg once

daily. Isosorbide dinitrate 40 mg 4 times daily was the regimen used in the V-HeFT.^{13,14} However, because of reduced vascular responsiveness to nitrates, larger doses are usually required to achieve a significant hemodynamic effect.¹⁶ In addition, substantial early tolerance was demonstrated with every 6-hour administration of the drug, which was prevented with a 12-hour nitrate washout interval.¹⁷

Only 25% of the respondents to our survey reported the use of organic nitrates always in combination with hydralazine. The concomitant use of these 2 drugs was initially based on the hemodynamic goal of a combined reduction in left ventricular pre- and afterload. The use of this drug combination in the V-HeFT resulted in improvement in the left ventricular ejection fraction, exercise tolerance, and survival, and may be preferred.^{13,14} In addition, more recent studies have demonstrated, through in vitro experiments and in vivo animal models of heart failure as well as in patients with heart failure, a favorable interaction between hydralazine and nitrates, with the augmentation of the effect of nitrates and the prevention of nitrate tolerance.¹⁸ Although these findings may provide strong support for the concomitant use of hydralazine in patients with CHF who are treated with organic nitrates, there is also clinical evidence showing the beneficial effects of nitrates when used without hydralazine, either alone or in addition to angiotensin-converting enzyme inhibitors.^{12,19}

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Circulating Tenascin-C Levels in Patients With Idiopathic Dilated Cardiomyopathy

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Circulating serum tenascin-C (an extracellular matrix glycoprotein) levels in patients with idiopathic dilated cardiomyopathy (IDC) were measured. Serum tenascin-C levels were increased in proportion to the severity of left ventricular dysfunction in patients with IDC. The associations of serum tenascin-C levels with serum troponin T and procollagen type III aminoterminal peptide levels suggest that increased levels of serum tenascin-C indicate ongoing replacement fibrosis after myocardial damage in IDC. ©2004 by Excerpta Medica Inc.

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Tamura et al¹ examined biopsy specimens of hearts obtained from 8 patients with idiopathic dilated cardiomyopathy (IDC). They found that tenascin-C, an extracellular matrix glycoprotein, is distributed in the enlarged perimysium and endomysium near replacement fibrotic lesions close to necrotizing myocytes and in the peripheral portion of the replacement fibrotic lesions. They concluded that tenascin-C plays an important role in the initiation of replacement fibrosis in patients with IDC. The present study examined circulating levels of tenascin-C in patients with IDC to clarify its relevance to IDC.

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A total of 31 patients (26 men and 5 women; mean age 63 ± 17 years) with IDC were entered into this study. Two patients were in New York Heart Association (NYHA) functional class I, 12 in class II, 13 in class III, and 4 in class IV. The diagnosis of IDC was based on patient history, physical examination, electrocardiography, chest x-ray, echocardiography, and cardiac catheterization, including coronary arteriography, left ventriculography, and endomyocardial biopsy. No patients had significant coronary artery stenosis. Exclusion criteria were other lung or heart

TABLE 1 Patient Characteristics (n = 31)

Characteristic	Value
Age (yrs)	63 ± 17
Men	26 (84%)
Smokers	23 (74%)
Systemic hypertension	11 (35%)
Diabetes mellitus	7 (23%)
Low-density lipoprotein cholesterol level >140 mg/dl	14 (45%)
NYHA functional class	
I	2 (6%)
II	12 (39%)
III	13 (42%)
IV	4 (13%)
Medication	
Angiotensin-converting enzyme inhibitors	6 (19%)
Angiotensin II receptor antagonists	15 (48%)
Calcium channel antagonists	5 (16%)
β blockers	17 (55%)
Furosemide	28 (90%)
Spirolactone	23 (74%)
Digitalis	8 (26%)
Pimobendan	8 (26%)
Nitrates	11 (35%)
Statins	6 (19%)
Left ventricular end-diastolic diameter (mm)	60 ± 10
Left ventricular end-systolic diameter (mm)	48 ± 12
Left ventricular ejection fraction (%)	38 ± 10

Data are presented as means ± SDs or numbers (%).

diseases, including secondary IDC, infectious or inflammatory diseases, collagen diseases, malignancy, impaired liver or kidney function (serum creatinine >1.2 mg/dl), and having had severe trauma or undergone surgical procedures ≤3 months before the study. We also examined 20 age- and gender-matched controls (17 men and 3 women; mean age 60 ± 10 years). They did not have chest x-ray, electrocardiographic, or echocardiographic abnormalities. The study protocol was approved by the ethics committee at our institution, and informed consent was obtained from all patients before participation in the study. Echocardiography was performed by standard techniques using an ultrasound system (model SSD-5500, Aloka Co., Ltd., Tokyo, Japan). Left ventricular end-diastolic and end-systolic diameters were measured from

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