Usefulness of *Isosorbide Dinitrate* and *Hydralazine* as Add-on Therapy in Patients Discharged for Advanced Decompensated Heart Failure

Wilfried Mullens, MD[a], Zuheir Abrahams, MD, PhD[b], Gary S. Francis, MD[c], George Sokos, DO[d], Randall C. Starling, MD, MPH[b], James B. Young, MD[b], David O. Taylor, MD[b], and W.H. Wilson Tang, MD[b,*]

Data supporting the use of oral isosorbide dinitrate and/or hydralazine (I/H) as add-on therapy to standard neurohormonal antagonists in advanced decompensated heart failure (ADHF) are limited, especially in the non–African-American population. Our objective was to determine if addition of I/H to standard neurohormonal blockade in patients discharged from the hospital with ADHF is associated with improved hemodynamic profiles and improved clinical outcomes. We reviewed consecutive patients with ADHF admitted from 2003 to 2006 with a cardiac index ≤2.2 L/min/m^2 admitted for intensive medical therapy. Patients discharged with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers (control group) were compared with those receiving angiotensin-converting enzyme inhibitors/angiotensin receptor blockers plus I/H (I/H group). The control (n = 97) and I/H (n = 142) groups had similar demographic characteristics, baseline blood pressure, and renal function. Patients in the I/H group had a significantly higher estimated systemic vascular resistance (1,660 vs 1,452 dynes/cm^5, p <0.001) and a lower cardiac index (1.7 vs 1.9 L/min/m^2, p <0.001) on admission. The I/H group achieved a similar decrease in intracardiac filling pressures and discharge blood pressures as controls, but had greater improvement in cardiac index and systemic vascular resistance. Use of I/H was associated with a lower rate of all-cause mortality (34% vs 41%, odds ratio 0.65, 95% confidence interval 0.43 to 0.99, p = 0.04) and all-cause mortality/heart failure rehospitalization (70% vs 85%, odds ratio 0.72, 95% confidence interval 0.54 to 0.97, p = 0.03), irrespective of race. In conclusion, the addition of I/H to neurohormonal blockade is associated with a more favorable hemodynamic profile and long-term clinical outcomes in patients discharged with low-output ADHF regardless of race. **(Am J Cardiol 2009;103: 1113–1119)**

Although isosorbide dinitrate and hydralazine (I/H) were considered 1 of the earliest "evidence-based" treatment strategies for systolic heart failure (HF) based on the cardiocirculatory model of HF,[1,2] its current use is eclipsed by the large volume of evidence supporting the use of neurohormonal antagonists. Recently, the African-American Heart Failure Trial demonstrated a significant decrease in adverse clinical outcomes in response to therapy with a fixed-dose formulation of I/H on top of neurohormonal blockade in ambulatory African-American patients who were highly symptomatic and had significant cardiac impairment and remodeling.[3] As a result, the latest clinical guidelines advocate the use of a combination of I/H as "a reasonable option" as part of the treatment strategy for patients with stable but advanced systolic HF who remain symptomatic despite optimal standard therapy.[4,5] Perhaps the major benefit of neurohormonal antagonist is to delay the disease progression of HF syndrome. Hence, hemodynamic perturbations may only be delayed (rather than decreased) as the disease progresses, and at advanced stages hemodynamic effects of vasodilators may sustain the failing heart from further deterioration. Because angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) may not provide the same hemodynamic balance of preload and afterload decrease or mechanistic benefits as I/H, the primary aim of this study was to determine if addition of I/H to standard neurohormonal blockade after an episode of advanced decompensated HF (ADHF) would be associated with sustained hemodynamic improvement and better clinical outcomes in patients admitted with ADHF.

Methods

We reviewed consecutive patients ≥18 years of age with chronic (>6 months) systolic HF (New York Heart Asso-

[a]Department of Cardiology, Ziekenhuis Oost Limburg, Genk, Belgium; [b]Department of Cardiovascular Medicine, Kaufman Center for Heart Failure, Cleveland Clinic, Cleveland, Ohio; [c]Cardiovascular Diseases Division, University of Minnesota, Minneapolis, Minnesota; and [d]Gerald McGinnis Cardiovascular Institute, Allegheny General Hospital, Pittsburgh, Pennsylvania. Manuscript received October 16, 2008; revised manuscript received and accepted December 21, 2008.

Dr. Tang is supported in part by the National Institutes of Health, National Center for Research Resources, CTSA 1UL1RR024989, Cleveland, Ohio.

*Corresponding author: Tel: 216-444-2121; fax: 216-445-6165.

E-mail address: tangw@ccf.org (W.H.W. Tang).

0002-9149/09/$ – see front matter © 2009 Elsevier Inc.
doi:10.1016/j.amjcard.2008.12.028

ciation class III to IV) who underwent intensive medical therapy guided by pulmonary artery catheter at the Cleveland Clinic (Cleveland, Ohio) in a dedicated HF intensive care unit from January 1, 2003, to December 31, 2006. From this cohort, we narrowed our study population to include only patients discharged from the hospital after therapy. Subjects who met the additional inclusion criteria at the time of admission were enrolled in the study: (1) impaired left ventricular systolic function as defined by a left ventricular ejection fraction <30% measured by the Simpson method within 2 months before admission; (2) impaired cardiac output, defined by a cardiac index ≤2.2 L/min/m^2; and (3) evidence of congestion as determined by a pulmonary capillary wedge pressure >18 mm Hg and/or central venous pressure >8 mm Hg. Exclusion criteria included (1) those with congenital heart disease, (2) recipients of a heart transplant, and (3) those with a mean arterial pressure <65 mm Hg. Institutional review board approval of this research project and informed consent were obtained for hospitalization, treatment, and all standard invasive procedures and documented in the medical records, according to protocol and Cleveland Clinic policy.

Systemic blood pressure was generally measured noninvasively by an automatic cuff sphygmomanometer and central hemodynamic parameters were derived from pulmonary artery catheter measurements every 15 minutes (except for cardiac index, which was calculated at 4-hour intervals). Complete hemodynamic information was collected in all subjects before starting intensive medical therapy and again before removing the pulmonary artery catheter. Central venous pressure and pulmonary capillary wedge pressure were assessed at end-expiration with a balloon-tipped catheter at steady state with the subject in a supine position. Cardiac index was determined by calculation using the Fick equation through sampling of a mixed central venous blood gas taken in the pulmonary artery while assuming standard metabolic rates. Estimated systemic vascular resistance (SVR) was calculated according to the formula 80 × (mean arterial pressure − right atrial pressure)/cardiac output.

The pharmacologic approach and hemodynamic goals of intravenous therapy for ADHF have been described previously.[6,7] Briefly, optimal hemodynamic response was defined as a decrease in pulmonary capillary wedge pressure to ≤18 mm Hg, a decrease in central venous pressure to ≤8 mm Hg, and an improvement in cardiac index to ≥2.2 L/min/m^2 while mean arterial pressure was maintained at >65 to 70 mm Hg and/or systolic blood pressure at >85 mm Hg. To achieve the hemodynamic goals, most patients were treated with parental vasodilators or inotropic agents with or without intravenous loop diuretic therapy. Oral drug regimens including ACE inhibitor or ARB, β blockers, and spironolactone were continued at their admitting doses as tolerated (except in the case of intravenous dobutamine or vasodilator administration, when β blockers or I/H would be stopped, respectively). The duration of infusions of intravenous agents in the intensive care unit was typically 24 to 48 hours.

Upon stabilization, the decision to use I/H in addition to an ACE inhibitor (or ARB) versus further up-titration of ACE inhibitor (or ARB) alone was at the discretion of the physician caring for the patient and no randomization scheme was employed. Regardless, titration of oral drugs was aimed to wean off parental therapy and based on maintaining a target mean arterial pressure of 65 o 70 mm Hg and/or systolic blood pressure >85 mm Hg. Titration of oral vasodilator drugs followed standard protocols established in our HF intensive care unit and was conducted by highly trained nursing staff experienced in the care of patients with advanced HF (Figure 1), but the sequence of drugs was also at the attending cardiologist's discretion. Systemic blood pressure was generally measured noninvasively by an automatic cuff sphygmomanometer every 15 minutes. If hypotension occurred during the titration protocol, the previously tolerated dose was administered without further up-titration. Once blood pressure goals were achieved and optimal hemodynamic measurements maintained, patients were discharged from the intensive care unit to a regular nursing floor (usually within 48 to 72 hours). Neurohormonal antagonists and I/H were further titrated, as tolerated, to guideline-recommended therapeutic doses if not already achieved in the HF intensive care unit. Standard HF patient education materials and counseling were given to the patient during the admission, and postdischarge follow-up visits were provided by an HF disease management clinic.

Captopril

Incremental ↑ 6.25→12.5→25→50 mg
Begin at 6.25-12.5 mg orally
After 2 hours, if initial dose tolerated, ↑ incrementally to next dose
After 2 hours, if previous dose tolerated, ↑ incrementally to next dose
After 6 hours, if previous dose tolerated, then 50 mg orally TID*

Isosorbide Dinitrate

Begin 10 mg orally
After 2 hours, if initial dose tolerated, ↑ to 20 mg
After 8 hours, if 20 mg tolerated, ↑ to 40 mg
After 8 hours, if 40 mg tolerated, ↑ to 60 mg
After 8 hours, if 60 mg tolerated, then 60 mg orally TID*

Hydralazine

Begin 25 mg orally (10 mg if systemic blood pressure low or patient in labile condition)
After 2 hours, if initial dose tolerated, ↑ to 50 mg
After 6 hours, if 50 mg tolerated, ↑ to 75 mg
After 6 hours, if 75 mg tolerated, ↑ to 100 mg
After 6 hours, if 100 mg tolerated, then 100 mg orally TID or QID*

* If previous dose is not tolerated, administer highest dose tolerated TID or QID

Figure 1. Standard oral medication protocols for the Cleveland Clinic HF intensive care unit. ACE-I = ACE inhibitor; QID = 4 times/day; TID = 3 times/day.

Our objectives were to determine if addition of I/H to an ACE inhibitor or ARB was associated with not only improved hemodynamic profiles at discharge but also improved long-term clinical outcomes. Three long-term clinical end points were analyzed and compared between patients who received an ACE inhibitor or ARB alone (control group) and those who received I/H plus an ACE inhibitor or ARB (I/H group) at discharge, namely all-cause mortality, cardiac transplantation, and first readmission for HF after index hospitalization discharge. A combined end