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The Importance of Worsening Heart Failure in Ambulatory Patients

Definition, Characteristics, and Effects of Amino-Terminal Pro-B-Type Natriuretic Peptide Guided Therapy

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ABSTRACT

OBJECTIVES The goal of this study was to define and assess the significance of worsening heart failure (WHF) in patients with chronic ambulatory heart failure with reduced ejection fraction (HFrEF).

BACKGROUND WHF has been identified as a potentially relevant clinical event in patients with acute heart failure (HF) and is increasingly used as an endpoint in clinical trials. No standardized definition of WHF exists. It remains uncertain how WHF relates to risk for other HF events or how treatment may affect WHF.

METHODS A total of 151 symptomatic patients with chronic HFrEF were randomized to standard of care HF management or a goal to lower N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations ≤1,000 pg/ml in addition to standard of care. WHF was prospectively defined as: 1) new or progressive symptoms and/or signs of decompensated HF; and 2) unplanned intensification of diuretic therapy.

RESULTS Over a mean follow-up of 10 months, 45 subjects developed WHF. At baseline, patients developing incident WHF had higher ejection fraction (31% vs. 25%; $p = 0.03$), were more likely to have jugular venous distension and edema ($p < 0.02$), were less likely to receive angiotensin-converting enzyme inhibitors or received these agents at lower doses ($p < 0.04$), and also received higher loop diuretic doses ($p < 0.001$). Occurrence of WHF was strongly associated with subsequent HF hospitalization/cardiovascular death (hazard ratio, landmark analysis: 18.8; 95% confidence interval: 5.7 to 62.5; $p < 0.001$). NT-proBNP-guided care reduced the incidence of WHF in adjusted analyses (hazard ratio: 0.52; $p = 0.06$) and improved event-free survival (log-rank test $p = 0.04$).

CONCLUSIONS In chronic HFrEF, WHF was associated with substantial risk for morbidity and mortality. NT-proBNP-guided care reduced risk for WHF. (J Am Coll Cardiol HF 2016;4:749–55) © 2016 by the American College of Cardiology Foundation.

Heart failure (HF) is a heterogeneous clinical diagnosis, encompassing a variety of underlying pathophysiologic processes. Diagnosis and treatment of HF have improved (1), although patients affected by the diagnosis nonetheless experience considerable morbidity and mortality. Risk for death after HF hospitalization rises considerably, as high as 35% by 1 year (2), and this risk essentially doubles with each subsequent hospitalization (3). Accordingly, a better understanding of the risk factors for adverse outcomes is needed.

Part of the challenge in the care of patients with HF is the fact that the diagnosis is a heterogeneous clinical entity, whose manifestations and outcomes remain

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

CI = confidence interval

CV = cardiovascular

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

hsTnT = highly sensitive troponin T

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

sST2 = soluble ST2

WHF = worsening heart failure

difficult to predict. This challenge is particularly germane in the present era of HF care, in which increased focus on optimization of chronic HF care and simultaneous prevention of HF hospitalization represents a major effort. Emerging tools for identifying impending risk for HF events include implantable hemodynamic monitoring, as well as serial measurement of prognostic biomarkers (4,5); however, clinical history and physical examination remain highly valuable for such prognostication. In this manner, recent attention has focused on the phenomenon of worsening heart failure (WHF), which may signal HF deterioration and unfavorable prognosis (6). WHF is increasingly being used as an accepted inclusion criterion (7) and endpoint in clinical trials (8) as an indirect predictor of HF outcomes such as hospitalization or death.

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Despite growing use of WHF to include subjects in trials or as an endpoint, most studies have generally relied on clinician judgment to define the presence or absence of WHF, leading to substantial subjectivity; to our knowledge, no standardized definition of WHF has been accepted. Furthermore, the importance of WHF in the ambulatory population with heart failure and reduced ejection fraction (HFrEF) remains poorly defined, as much of the data regarding WHF have focused on those with hospitalized HF. Finally, treatment strategies that might favorably influence incidence of WHF are not defined.

In the PROTECT (Pro-BNP Outpatient Tailored Chronic HF Therapy) study, WHF was strictly and prospectively defined, and it was used as an endpoint for the trial (9). This approach provides an opportunity to examine protocol-defined WHF in a contemporary cohort of patients with HFrEF. The hypothesis of the present study was that WHF would be associated with significant subsequent adverse outcomes and that HF management guided by N-terminal pro-B-type natriuretic peptide (NT-proBNP) would reduce WHF.

METHODS

All study procedures were approved by the local institutional review board. Informed consent was obtained from participants.

PROTECT STUDY DESIGN. The design and results of the PROTECT study have been published previously (5,9). PROTECT was a prospective, randomized, single-center trial of 151 patients with New York Heart Association functional class II to IV systolic HF (left ventricular ejection fraction [LVEF] ≤40%). In brief, patients were eligible if they were >21 years of age and had experienced a decompensated HF event within 6 months before enrollment. Patients were excluded if they had severe renal disease, inoperable aortic valvular heart disease, life expectancy <1 year due to causes other than HF, cardiac transplantation or revascularization indicated or expected within 6 months, severe pulmonary disease, or coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft) within the previous 3 months.

After enrollment, patients were randomized to receive either standard HF management (with a goal of minimizing HF symptoms and achieving maximal dosages of therapies with proven mortality benefit in HF) or standard HF management plus treatment adjustments to reduce NT-proBNP concentrations ≤1,000 pg/ml. To achieve this goal, patients received up-titration of guideline-directed medical therapy according to clinical judgement (both arms) with or without supplemental testing for NT-proBNP; in the context of a therapy change, repeated office visits were made within 4 weeks. At entry to the study, patients underwent a 2-dimensional echocardiogram (10), which was repeated in study completers at a mean of 10 months from enrollment; both the technician performing the echocardiogram as well as the staff member interpreting the study were blinded to study arm or NT-proBNP values.

The primary endpoint of the PROTECT study was total cardiovascular (CV) events (including WHF) over a 1-year period.

PROTOCOL DEFINITION OF WHF. Online Table 1 details the PROTECT protocol definition of WHF, which was defined as: 1) new or progressive symptoms/signs of decompensated HF (including significant weight gain, worsening dyspnea or fatigue, newly elevated jugular venous pressure, new cardiac S3 gallop rhythm, the development of pulmonary rales, hepatic congestion, cool extremities, or lower extremity edema); and 2) unplanned intensification of oral or intravenous decongestive therapy with loop diuretic agents or the addition of a thiazide diuretic agent to loop diuresis.

STATISTICAL ANALYSES. Baseline patient characteristics were assessed and analyzed as a function of the presence or absence of subsequent incident WHF after enrollment. These factors included demographic characteristics, background medical history, physical examination at baseline, and drug therapy at baseline. As before, we expressed dosages