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Triage of Patients With Moderate to Severe Heart Failure

Who Should Be Referred to a Heart Failure Center?

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Objectives The purpose of this study was to evaluate simple criteria for referral of patients from the general practitioner to a heart failure (HF) center.

Background In advanced HF, the criteria for heart transplantation, left ventricular assist device, and palliative care are well known among HF specialists, but criteria for referral to an advanced HF center have not been developed for generalists.

Methods We assessed observed and expected all-cause mortality in 10,062 patients with New York Heart Association (NYHA) functional class III to IV HF and ejection fraction <40% registered in the Swedish Heart Failure Registry between 2000 and 2013. Next, 5 pre-specified universally available risk factors were assessed as potential triggers for referral, using multivariable Cox regression: systolic blood pressure ≤90 mm Hg; creatinine ≥160 μmol/l; hemoglobin ≤120 g/l; no renin-angiotensin system antagonist; and no beta-blocker.

Results In NYHA functional class III to IV and age groups ≤65 years, 66 to 80 years, and >80 years, there were 2,247, 4,632, and 3,183 patients, with 1-year observed versus expected survivals of 90% versus 99%, 79% versus 97%, and 61% versus 89%, respectively. In the age ≤80 years group, the presence of 1, 2, or 3 to 5 of these risk factors conferred an independent hazard ratio for all-cause mortality of 1.40, 2.30, and 4.07, and a 1-year survival of 79%, 60%, and 39%, respectively ($p < 0.001$).

Conclusions In patients ≤80 years of age with NYHA functional class III to IV HF and ejection fraction <40%, mortality is predominantly related to HF or its comorbidities. Potential heart transplantation/left ventricular assist device candidacy is suggested by ≥1 risk factor and potential palliative care by multiple universally available risk factors. These patients may benefit from referral to an advanced HF center. (J Am Coll Cardiol 2014;63:661–71)

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Heart failure (HF) affects 2% of the Western population (1–4) and is associated with poor quality of life and high mortality. Pharmacologic therapy, cardiac resynchronization therapy (CRT), and implantable cardioverter-defibrillators (ICDs) have improved prognosis in HF with reduced ejection fraction (EF) but have also increased the number of patients living with advanced HF. Improved survival after acute coronary syndromes and aging of the population are further contributing to an increased prevalence of HF. Thus, there is an unmet and growing need for advanced HF therapy (1–3).

Heart transplantation (HTx) and left ventricular assist devices (LVADs) improve quality of life and survival in advanced HF (4–6). LVADs are used mainly as bridge to transplantation (BTT), but with donor organ shortage and improving outcomes with continuous flow devices, they are increasingly being used as permanent therapy, or destination therapy (DT) (7). Palliative care improves quality of

Abbreviations and Acronyms

BTT = bridge to transplant
CI = confidence interval
DT = destination therapy
CRT = cardiac resynchronization therapy
EF = ejection fraction
HF = heart failure
HR = hazard ratio
HTx = heart transplantation
ICD = implantable cardioverter-defibrillator
LVAD = left ventricular assist device
NYHA = New York Heart Association
RAS = renin-angiotensin system

life and is indicated in refractory HF, especially if HTx and LVAD are ruled out (2,8).

However, patients with advanced HF are believed to be underserved by these treatments (1,3,5,6,8,9). Reasons may include HF care performed by generalists with lack of awareness of prognosis and indications for advanced treatment, and inadequate or delayed referral to advanced HF centers, which are best suited to perform triage to different interventions. Indeed, although there are well-established criteria for HF specialists performing in particular HTx and LVAD selection, there are no tools or criteria for generalists to determine who to refer for evaluation.

Therefore, the aims were: first, to assess the contemporary observed and expected survival in an unselected population with New York Heart Association (NYHA) functional class III to IV HF and reduced EF; and second, to test the hypothesis that simple universally available variables can independently predict prognosis and can be used as triggers for referral to advanced HF centers. Because NYHA functional class II versus III is a subjective distinction and many clinicians base referrals on symptoms alone, we also assessed the triggers separately in NYHA functional class II.

Methods

Study protocol. The Swedish Heart Failure Registry has been previously described (10). The inclusion criterium is clinician-judged HF. Eighty variables are recorded at discharge from hospital or outpatient visit and entered into a Web-based database managed by the Uppsala Clinical Research Center (Uppsala, Sweden). The database is run against the Swedish death registry monthly. (The protocol, registration form, and annual report are available at www.rikssvikt.se.) Establishment of the registry and analysis of data was approved by a multisite ethics committee and conforms to the Declaration of Helsinki. Individual patient consent is not required, but patients are informed of entry into national registries and are allowed to opt out.

Between May 11, 2000, and June 5, 2013, there were 85,291 registrations from 68 of approximately 75 hospitals and 102 of approximately 1,000 primary care outpatient clinics in Sweden. Of these, there were 10,062 first registrations with NYHA functional class III to IV and EF <40% and 9,463 first registrations with NYHA functional class II and EF <40%. The main analysis was NYHA functional class III to IV and included baseline characteristics, observed and expected all-cause mortality, and risk factors for all-cause mortality. The separate analysis was NYHA functional class II and included baseline characteristics and risk factors for all-cause mortality (Fig. 1).

Statistical analysis. Statistical analysis was performed in R version 2.15.3 (R Foundation for Statistical Computing, Vienna, Austria). The level of significance was set to 5%, and all reported p values and confidence intervals (CIs) are 2-sided.

Baseline characteristics. Forty-six clinically-relevant baseline variables were included for analysis (Table 1) and were compared among 3 age groups: ≤65 years, 66 to 80 years, and >80 years. The age cut-offs were based on general European practice: HTx considered mainly for age ≤65 years, DT-LVAD for patients in their 70s, and for carefully selected patients, up to age 80 years; and palliation for age >80 years or for younger patients with contraindications to HTx or LVAD.

Observed and expected all-cause mortality. Observed mortality for the overall study population and the 3 age groups was charted with the Kaplan-Meier method together with the expected mortality (Fig. 2). The expected mortality is for the study population if it had the same mortality probability as the general Swedish population matched to the sex, age, and year of observation of the study population (11). The mortality probabilities for the Swedish population were obtained from the Human Mortality database (http://www.mortality.org). The difference between observed and expected yields the "excess" mortality, which can be interpreted as the mortality related to HF itself and/or to associated comorbidities.

Risk factors for all-cause mortality. Because patients with advanced HF and age >80 years are generally not candidates for HTx or LVAD and are generally agreed to be suitable for palliation, they were excluded from the following risk factor analysis (Fig. 1).

Five simple and universally available variables, and cut-offs for continuous variables, were prospectively selected as potential independent risk factors for all-cause mortality based on previous studies (12–15) and as potential triggers for referral to an HF center (Table 2): systolic blood pressure ≤90 mm Hg (a criterion for cardiogenic shock); creatinine ≥160 μmol/l (which represents considerable end-organ impairment but generally not yet a contraindication to HTx or LVAD [15]); hemoglobin ≤120 g/l (a marker of the cardiorenal syndrome and progressive HF [15]); and absent renin-angiotensin system antagonist or beta-blocker treatment (12,15). We cannot show that absent drug therapy is due to intolerance, and certainly every effort should be made to utilize these medications. However, whether the lack of drug therapy is because of true intolerance or is a reflection of the generalist's perception of patient frailty or unease about follow-up and monitoring, both of these reasons warrant referral to an advanced HF center for optimization.