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Cardiac transplantation is still the method of choice in the treatment of patients with severe heart failure

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Abstract

A significant progress in the treatment of heart failure occurred during the last 20 years. These advances were associated with the introduction and subsequent widespread use of angiotensin--converting enzyme inhibitors and beta blockers, but also with progress in device therapy and cardiac surgery. Overall, prognosis in patients with severe heart failure is similar to outcomes reported in multicenter randomized clinical trials, such as CONSENSUS, CIBIS II, MERIT-HF, and COPERNICUS. In 2003–2007, a registry of patients with severe heart failure was established in Poland (POLKARD-HF) that included all patients initially considered candidates for heart transplantation (HTX). Mean duration of follow-up was 601 days (range 1-1462 days). One-year mortality (defined as death or super-urgent HTX) was 20% and differed from data presented by Stewart (2001). In addition, patient survival in the POLKARD-HF registry depending on the New York Heart Association (NYHA) class changed significantly in comparison to outcomes reported in the late 1980s. However, one-year mortality among NYHA class IV patients is still high and exceeds 50%. As reported in the POLKARD-HF registry, one--year risk of death among patient who underwent elective HTX was about 20%, and 3-year risk was about 22%, significantly different from the risk of death among medically treated patients with heart failure. These results are similar to other European data and warrant reconsideration of appropriatness of HTX in elective patients (UNOS 2 status). Undoubtedly, NYHA class IV patients are candidates for HTX and should remain under specialist care in cardiac transplantation centers, and HTX should be performed in this group when indications for this procedure become urgent (UNOS 1 and 1a status).

A specialized system of care for patients with severe heart failure should be created in Poland, particularly for patients referred for HTX. There is also an urgent need to introduce modern systems of mechanical cardiac support (left ventricular assist devices, LVAD) that would allow precise determination of indications and contraindications to HTX and create opportunities for long-term treatment. (Cardiol J 2009; 16, 6: 493–499)

Key words: severe heart failure, cardiac transplantation, prognosis

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In 2001, Stewart et al. [1] noted that the 5-year survival in patients with heart failure was worse than in patients with most cancers. One-year survival with heart failure was less than 60%, and 4-year survival was about 35%, thus heart failure was dubbed "more malignant then cancer".

During the last 20 years, a significant progress in the treatment of heart failure occurred, related not only to pharmacotherapy, but also to device therapy and invasive treatment [2–6]. These advances in therapy resulted in improved prognosis and quality of life of patients with heart failure, including those with severe heart failure. In patients with the New York Heart Association (NYHA) class IV patients who participated in the CONSENSUS study, treatment with enalapril was associated with a relative reduction of the risk of death by 40% at 6 months and by 31% at one year of treatment compared to the control group [4, 6]. Another advance in pharmacotherapy of heart failure was the introduction of $beta_1$-adrenergic receptor antagonists (beta-blockers). A metaanalysis of CIBIS II, MERIT HF, and COPERNICUS studies showed a relative reduction of the risk of death by 33% in NYHA class III patients and 31% in NYHA class IV patients [5, 7, 8]. Based on these studies, it may be theoretically assumed that one-year mortality in patients with severe heart failure receiving conventional treatment (i.e. with digitalis and diuretics) would be 52%. Treatment with a angiotensin-converting enzyme (ACE) inhibitor should lower this mortality rate to 36%, and additional use of an aldosterone antagonist would result in lowering one-year mortality to 18%. Full treatment according to current guidelines should lower one-year mortality among patients with severe heart failure (NYHA class III–IV) to about 12% [9].

These estimations have been confirmed in numerous contemporary epidemiological studies. In the United States, one-year mortality among patients with severe heart failure in 1994–1997 was about 20%, and 3-year mortality was about 67%. In 1999–2001, corresponding mortality rates were 12% and 79%, respectively. The effects of treatment depend on the age of patients. Prognosis in patients aged less than 75 years is similar to that found in the above mentioned studies from the United States but it is significantly worse among patients over 75 years of age. One-year mortality among patients aged more than 75 years is about 37%, and 3-year mortality is about 60% [10–12].

Further considerations, as related to the main topic of this paper, will be restricted to patients with severe heart failure under 65 years of age. This is the population of patients primarily considered for heart transplantation (HTX).

Outcomes after HTX improved substantially with the introduction of modern immunosuppresive treatment, mainly with calcineurin inhibitors such as cyclosporine. Data from the International Society for Heart and Lung Transplantation (ISHLT) registry show that in 1993–2000, survival at 1, 3, 5, and 10 years was about 85%, 75%, 70%, and 50%, respectively [13, 14].

Potential candidates to HTX (based on [15]) are patients under 65 years of age with heart failure who fulfill the following criteria despite optimal treatment:

— NYHA class III–IV heart failure symptoms;
— episodes of hypervolemia or reduced cardiac output at rest;
— ejection fraction reduced below 30%;
— Doppler evidence of impaired left ventricular diastolic filling;
— high left ventricular end-diastolic pressure or mean pulmonary capillary wedge pressure > 19 mm Hg and mean right atrial pressure > 12 mm Hg;
— elevated level of N-terminal propeptide of the brain natriuretic peptide (NT-proBNP) (> 2000 pg/mL);
— frequent hospitalizations due to heart failure during the last 6 months, requiring administration of catecholamines;

and in whom functional studies show:

— inability to exercise (NYHA class IV);
— 6-minute walking distance of less than 300 m;
— maximal oxygen uptake (VO_2max) of less than 12–14 mL/kg/min.

Extrapolating data from the ISHLT registry in 1999–2001, approximately 850 patients in Poland should qualify for HTX during 3 years (in 2003–2005, in fact 335 patients actually qualified), including 50% of patients qualifying for an urgent transplantation (about 20% patients in Poland).

The Poltransplant criteria for an urgent HTX are as follows:

— mechanical cardiac support due to acute circulatory decompensation;
— continuous mechanical ventilation;
— severe refractory arrhythmia;
— acute heart failure within 7 days after HTX.

Poltransplant HTX qualifying criteria are more liberal than the UNOS or Eurotransplant criteria but do not account data regarding prognosis in these patients. This is an important issue due to a different system of care for patients qualifying for HTX in Poland compared to other European countries

and the United States. In Poland, patients qualifying for an urgent HTX who present to transplantation centers are usually critically ill. In these circumstances, precise determination of indications and contraindications for HTX is sometimes difficult. This is probably the main reason of worse HTX outcomes in these patients compared to the United States and Western Europe. Systems of mechanical cardiac support available in Poland that might improve diagnostic work-up and prognosis in patients qualifying for an urgent HTX may be used only for a relatively brief period (about 2–3 months) and only in hospitalized patients. A larger group (about 80% of patients in Poland) that is very heterogeneous in terms of clinical characteristics and prognosis includes patients qualifying for an elective HTX.

In 2003–2007, a registry of patients with severe heart failure initially considered as candidates for HTX (POLKARD-HF) was set up in Poland using a grant from the Polish Ministry of Health [16]. The main objective of this program was to evaluate prognosis in patients with severe heart failure prior to HTX and also after HTX in patients who eventually underwent transplantation. An additional goal was to identify risk factors for death or an urgent HTX. Results of this registry may be used to extend previous data and define more precise criteria allowing qualification for HTX. Overall, 983 patients were included in the registry in four centers performing HTX in Poland in 2003–2007 (Table 1).

Most of these patients (n = 658) qualified for HTX and during the period covered by the registry, transplantation was actually performed in 325 patients. Patients included in the registry were young (mean age 49 ± 11 years), had advanced heart failure with ejection fraction of 21.6 ± 8%, low systemic blood pressure (102 ± 15 mm Hg), and showed evidence of moderate pulmonary hypertension. Laboratory tests showed elevated levels of high-sensitivity C-reactive protein (hsCRP) (mean 3.0 mg/L, range 0.03–347.0), and NT-proBNP (mean 2294 pg/mL, range 28–46128), while mean sodium level was 136 ± 4 mEq/L. The mean duration of follow-up was 601 days (range 1–1462) (Fig. 1).

Survival of patients with severe heart failure or undergoing an urgent HTX was about 80% at one year and 67% at 3 years of follow-up, and thus was substantially higher than among patients with heart failure included in the study by Stewart et al. [1] (56% and 34%, respectively) (Fig. 2).

Analysis of outcomes in patients with heart failure depending on the NYHA functional class also showed significant improvement compared to the studies performed in the late 80s [12–14, 16, 17]. Of note, prognosis among NYHA class IV patients is still very poor, as one-year mortality in this group (defined as death or a very urgent HTX) was 50% (Table 2).

Table 1. Characteristics of patients with severe heart failure included in the POLKARD-HF registry in 2003–2007 [16].

Variable	N	Mean ± SD *Median [Min–Max]
Age (years)	983	49.38 ± 11.245
Body mass [kg]	982	77.9 ± 15.42
Height [cm]	980	172.8 ± 9.71
BMI [kg/m^2]	979	25.982 ± 4.5004
EF (%)	978	21.6 ± 8.13
LVEDD [mm]	953	71.93 ± 10.472
LVESD [mm]	905	60.30 ± 13.217
HR [bpm]	962	78.3 ± 15.80
Systolic BP [mm Hg]	975	102.6 ± 14.97
Diastolic BP [mm Hg]	975	67.0 ± 11.12
PASP [mm Hg]	629	44.9 ± 17.41
Mean PCWP [mm Hg]	695	20.8 ± 9.41
CI [L/min/m^2]	530	1.95 ± 0.854
PVR [Wood Units]	64	3.13 ± 2.392
PG [mm Hg]	654	10.61 ± 6.677
hsCRP [mg/L]*	679	3.00 [0.03–347.00]
NT-proBNP [pg/mL]*	694	2294.5 [28.0–46128.0]
VO_2max [mL/kg/l]	687	13.05 ± 4.345
HFSS	952	7.7 ± 0.98
Na [mEq/L]	973	136.4 ± 4.41

BMI — body mass index; EF — ejection fraction; LVEDD — left ventricular end-diastolic diameter; LVESD — left ventricular end-systolic diameter; HR — heart rate; BP — blood pressure; PASP — pulmonary artery systolic pressure; PCWP — pulmonary capillary wedge pressure; CI — cardiac index; PVR — pulmonary vascular resistance; PG — pulmonary gradient; hsCRP — high sensitivity C-reactive protein; NT-proBNP — N-terminal propeptide of the brain natriuretic peptide; VO_2max — maximal oxygen uptake; HFSS — Heart Failure Survival Score; Na — sodium

Based on Kaplan-Meier survival analysis, the following significant prognostic factors were identified: pulmonary artery systolic pressure, mean pulmonary capillary wedge pressure, left ventricular ejection fraction, NYHA functional class, low systemic blood pressure, hsCRP level, NT-proBNP level, body mass index, sodium level, and Heart Failure Survival Score (HFSS) proposed by Aaronson et al. (Table 3) [17, 18].

In multivariate analysis, after removal of NYHA functional class and HFSS as dependent variables, the following variables remained independent risk factors for death or a very urgent HTX: NT-proBNP level ≥ 4302 pg/mL and sodium level ≤ 135 mEq/L. Of note, HFSS calculated using the Aaronson formula, incorporating clinical, functional, and bio-

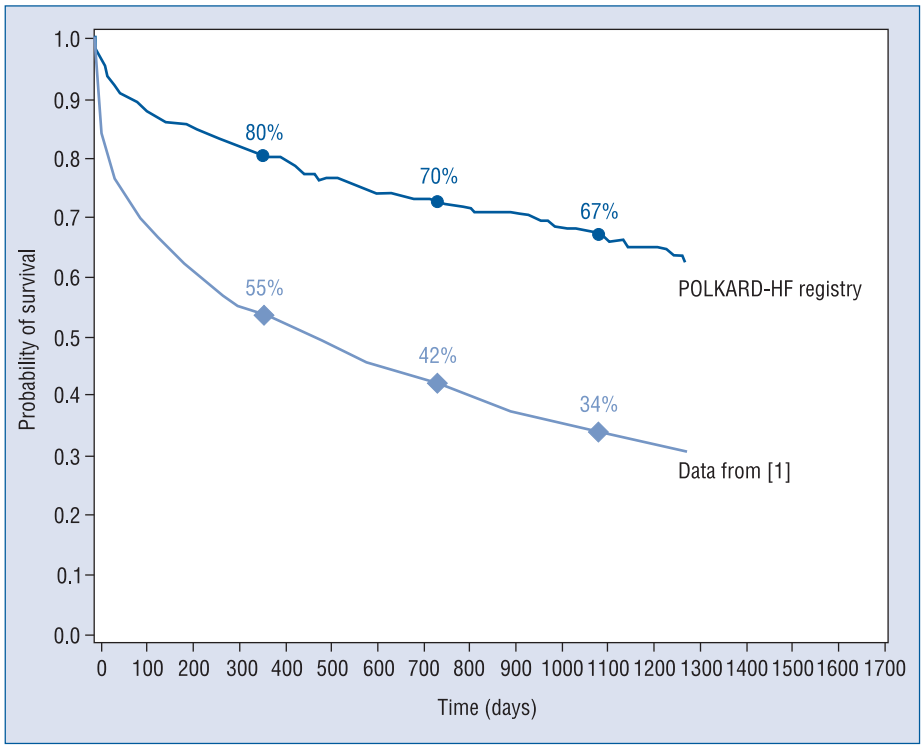

Figure 1. Probability of survival of patients with heart failure [1, 16].

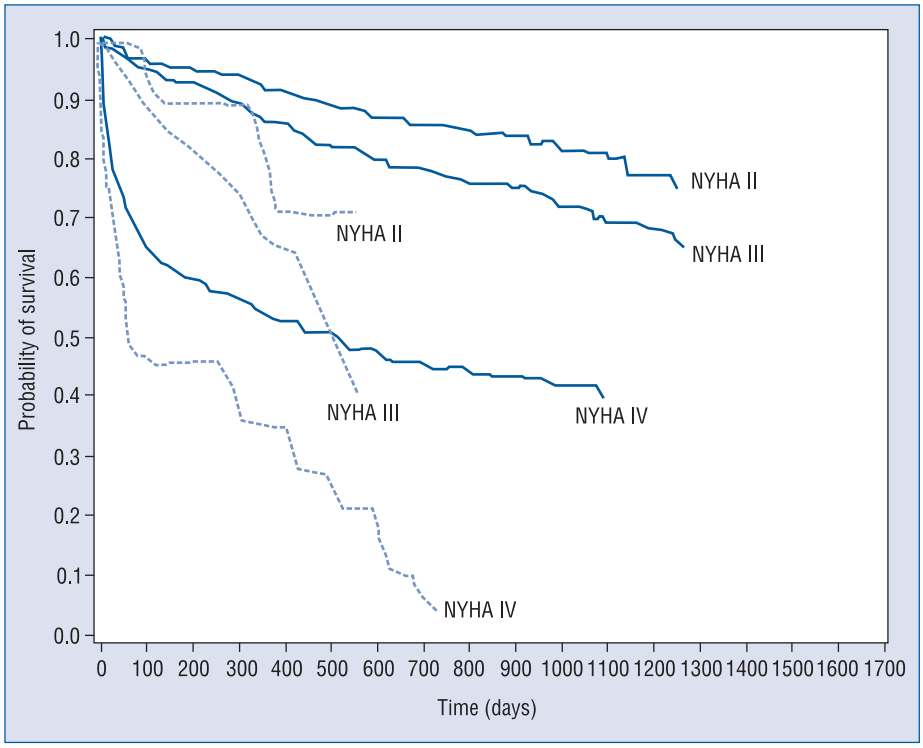

Figure 2. Probability of survival of patients with heart failure depending on the New York Heart Association (NYHA) functional class (— Kaplan-Meier curves for patients with heart failure included in the POLKARD-HF registry, ···· Kaplan-Meier curves for patients with heart failure based on data from Massie B et al. Circulation, 1987; 75: 11–19).

Table 2. Risk factors for death of an urgent heart transplantation (values are upper or lower limits of terciles determined as statistically significant in the Kaplan-Meier analysis); POLKARD-HF [16].

YES	NO
Pulmonary artery systolic pressure ≥ 50 mm Hg	Pulmonary vascular resistance
Pulmonary capillary wedge pressure ≥ 25 mm Hg	Pulmonary gradient
Left ventricular ejection fraction ≤ 17%	Cardiac index
NYHA functional class IV	VO_2max
Systolic blood pressure ≤ 90 mm Hg	Diastolic blood pressure
hsCRP 6.5 mg/L	Etiology of heart failure
NT-proBNP ≥ 4302 pg/mL	Sex
HFSS ≤ 7.19	
Sodium ≤ 135 mEq/L	
Body mass index ≤ 23.8 kg/m^2	

NYHA — New York Heart Association; hsCRP — high sensitivity C-reactive protein; NT-proBNP — N-terminal propeptide of the brain natriuretic peptide; HFSS — Heart Failure Survival Score; VO_2max — maximal oxygen uptake.

Table 3. Variables included in the Heart Failure Survival Score (HFSS) proposed by Aaronson et al. [18, 26].

Ischemic heart disease (yes = 1, no = 0)	(..... x 0.6931) = +
Intraventricular conduction distrubances (yes = 1, no = 0)	(..... x 0.6083) = +
Ejection fraction (%)	(..... x 0.0464) = +
Heart rate [bpm]	(..... x 0.0221) = +
Sodium level [mEq/L]	(..... x – 0.0470) = +
Mean arterial pressure [mm Hg]	(..... x – 0.0255) = +
Maximal oxygen uptake (VO_2max)	(..... x – 0.546) = +
	HFSS = ...

chemical parameters, is routinely evaluated in patients with heart failure and has a very high prognostic importance. Values of 5.5–7.19 are associated with a high risk of death, values of 7.2–9.09 with a moderate risk, and values of 8.1–10.49 with a low risk of death. In the POLKARD-HF registry of patients with severe heart failure, mean HFSS was 7.7 ± 0.98, and in the highest risk group (with one-year mortality of 50%) it was ≤ 7.19 [18–22].

Patients entering the registry were generally treated according to the current guidelines, with 90–100% of patients receiving beta$_1$-adrenergic receptor antagonists, ACE inhibitors and diuretics, and about 80% of patients treated with aldosterone antagonists. However, the doses used were much lower than those recommended in the current guidelines, as the doses of standard drugs, except diuretics, were only about 25% of the recommended dosage on admission (and entry into the registry), and about 50% at hospital discharge (unpublished results based on patients entered into the registry in the Institute of Cardiology).

As most patients were not initially receiving adequate treatment, final evaluation of indications for HTX was done, if possible, at 3 months after the entry into the registry, thus allowing time for treatment optimalization.

Patients scheduled for elective HTX remained under the ambulatory care until transplantation in the centers participating in the registry. Patients at higher risk of HTX, mainly with reversible (reactive) pulmonary hypertension, were evaluated every 3 months, and the remaining patients were evaluated every 6 months. Patients with heart failure who were considered potential candidates but were not scheduled for elective HTX, also remained under the ambulatory care in the centers participating in the registry.

Three-year outcomes in patients who underwent elective HTX differed from outcomes in medically treated patients, mainly due to deaths occurring in the first days or weeks after HTX (Fig. 3).

Our experience and data collected in other centers suggest that it is questionable whether HTX should be performed at all in patients scheduled for

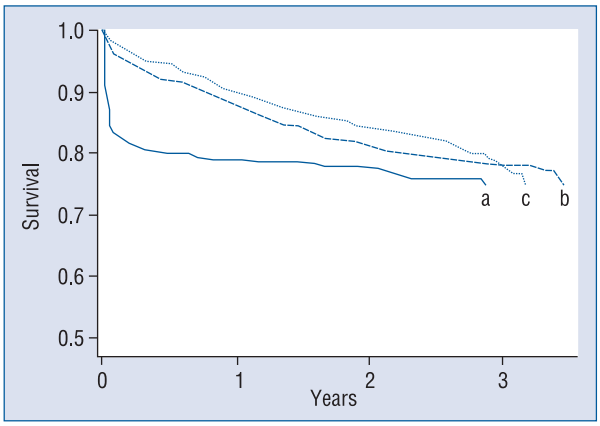

Figure 3. Prognosis in patients with severe heart failure; a — heart transplantation, elective qualification; b — drug therapy, elective qualification; c — drug therapy, no indications for heart transplantation; POLKARD-HF [16].

an elective procedure, in whom one-year mortality does not exceed 20%. Based on the data available in the literature and the results of the registry, one-year mortality in patients with severe heart failure (excluding patients with indications for an urgent HTX) is 9.7–13.5%. Thus, it seems that the potential benefit of HTX in these patients, realized after 5–10 years, does not warrant the decision to proceed with the transplantation. There is an urgent need to verify indications for HTX based not only on the patient clinical condition [11, 12, 23–26] but also using additional prognostic factors such as HFSS and NT-proBNP level [11, 18, 21, 22]. It also seems that patients scheduled for elective HTX who require recurrent hospitalizations related to cardiac decompensation and need support with inotropic drugs despite apparently optimal treatment, should be considered candidates for an urgent HTX. There is also an urgent need to establish a system of specialist care for patients with severe heart failure, preferably in centers performing HTX and able to use modern systems of mechanical cardiac support.

Conclusions

1. Modern drug therapy as recommended in the current guidelines has resulted in significantly improved outcomes in patients with severe heart failure.
2. Cardiac transplantation is still the method of choice in the treatment of patients with severe heart failure qualifying for an urgent HTX (NYHA class IV).
3. Patients scheduled for elective HTX in whom low HFSS value or high NT-proBNP level is demonstrated, or who require recurrent hospitalizations due to cardiac decompensation despite apparently optimal treatment, should undergo an urgent HTX.
4. Top priorities should include immediate implementation of modern systems of mechanical cardiac support and establishing highly specialized centers caring for patients with severe heart failure.

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