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Advanced Heart Failure Treatment Options Among the Elderly

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Abstract The aging human population has emerged as a critically important factor in health care, not only due to the unique physiologic and pathologic processes associated with aging but also because of the evolution of medical and surgical therapies that have increased quality and quantity of life. Heart failure is a disease found most commonly among older populations in whom it is associated with high morbidity and mortality. Heart failure disproportionately affects the elderly, and it stands to reason that the most terminal stage, known as advanced heart failure (AHF), is more common among the elderly. Despite limited data, treatment options for AHF patients, including heart transplantation and left ventricular assist device (LVAD) therapy, have demonstrated improved quality and quantity of life. Similarly, a well-structured palliative care program may offer symptom relief and social support without the need for high-risk surgical options. Furthermore, as the therapeutic window (risk/benefit ratio) is narrower among elderly patients, the potential for positive outcomes from AHF options must be carefully evaluated together with patient-specific risks in the context of palliative care discussions. Therefore, the decision to leverage these options must be balanced with not only age, but also frailty, comorbidities, and cognition, functional, social and nutritional status to determine the right candidates for each therapy. This review strives to inform providers on the relevant considerations when leveraging AHF options among elderly patients. We conclude by providing a personalized model for care developed at a large tertiary care hospital that has performed more than 1,600 AHF procedures (870 heart transplants, 745 LVADs). (*J Patient Cent Res Rev.* 2016;3:199-206.)

Keywords aging; advanced heart failure; heart transplant; frailty; left ventricular assist device

Due to improvements in the management of acute and chronic diseases and the concept of preventive medical care, the present-day human population is living longer than any prior generation. The number of people worldwide who are 60 years or older is expected to double by 2050 (to 2.4 billion).[1] In the United States alone, there will be 83 million.[2] Particularly relevant to this review, the elderly (defined as age > 70) are the fastest growing age group in the world and projected to triple by 2050. Since the majority of health care resources and ultimate expenditures are among populations with chronic diseases (cardiovascular diseases, cancer and neurodegenerative diseases), and these conditions are most prevalent among aging populations, all societies must address the concerns of health and aging.

As cardiovascular diseases disproportionately afflict the elderly, it is not surprising that the incidence, prevalence, morbidity and mortality for heart failure (HF) is highest in this age group.[3] Within the next two decades, the incidence of HF is expected to rise to 700,000 cases annually; this translates to a 46% rise in prevalence. After age 80, the lifetime risk of HF is one in five, and once diagnosed, the prognosis is much worse for both men and women compared with younger cohorts.[4] The number of hospitalizations for HF has

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consistently increased over the last 30 years, with half of readmissions related to HF-associated comorbidities, polypharmacy and disabilities (which are all more evident among elderly cohorts).[5] The U.S. Centers for Medicare & Medicaid Services estimates HF costs at $70 billion by 2030, with 50%–74% attributed to hospitalization or long-term institutional care.[4]

Medical and device therapies have evolved to reduce morbidity and mortality of HF predominantly by decreasing disease progression. Despite these advances, HF remains a progressive disease that culminates in greater functional limitation, more hospitalization and eventual death. Various definitions have been used to characterize advanced heart failure (AHF); in general, they encompass three domains — severe functional limitations, recurrent hospitalizations and refractory symptoms — each independently associated with high short-term mortality (based on risk models).[6] Approximately 3%–6% of all patients with chronic HF have AHF, and in the United States, there are an estimated 200,000 adults with AHF, most over 70 years old.[6-9] Elderly AHF patients experience multiple hospitalizations over short periods of time and require escalating therapies, with higher mortality compared with younger cohorts.[4,10]

Traditional options advocated for patients with AHF include heart transplantation (HT), left ventricular assist device (LVAD) therapy and/or palliative care. The rational allocation of heart replacement options (HT or LVAD) among elderly patients requires an understanding of risk and benefit in the context of clinical care, disease trajectory and, particularly, noncardiac comorbidities (renal insufficiency, chronic lung disease, neuromuscular or cognitive disorders, nutrition and psychosocial isolation, etc.), including frailty. Any novel therapeutic interventions must be balanced with expected risks and benefits that may have a narrower therapeutic window among older patients. The discussion may turn from a question of "*Can* we perform the intervention?" to rather "*Should* we perform the intervention?" Therefore, objective means and decision tools must be developed to assist providers and patients in answering these questions.

Heart Transplantation

HT is believed to be the gold standard for patients with AHF. The International Society of Heart & Lung Transplantation (ISHLT) registry published data demonstrating that in any calendar year there has never been more than 4,700 heart transplants performed worldwide, clearly not meeting the aforementioned rising demand for AHF treatment. The lack of acceptable organs for donation, as well as societal norms and clinical practices, have established a general upper age limit for HT at approximately 65–70 years. It had been accepted that advanced age adversely affects long-term survival rates in HT recipients.[11-15] However, approximately 1%–3% of all transplants are still performed in patients at least 70 years old, and several case series have demonstrated similar intermediate outcomes (at 1 and 3 years) between older (age > 70) and younger HT recipients. These patients are obviously highly selected and account for less than 5% of the total cohorts evaluated.[16-20]

Extending these observations, Daneshvar et al. found no statistical difference in survival in patients over 70 compared to a younger cohort up to 10 years after HT.[21] Blanche et al. demonstrated that using select older donors for select older recipients was safe and may offer a unique strategy for organs that may be declined for younger recipients,[16] while others have advocated marginal donor hearts as acceptable options for elderly patients.[22] Select patients over age 70 who have undergone HT had lower incidences of allograft rejection, possibly as a result of natural immunosenescence associated with aging, thus making them better long-term candidates for transplant.[23] Furthermore, another study[24] observed that elderly patients experienced greater satisfaction with quality of life (QOL) posttransplant and expressed less stress and depression after transplant than younger patients. The same study also found that elderly patients were more compliant with follow-up medical programs and treatments than younger patients.[24]

In contrast to such reports, the most recently published 2015 ISHLT registry data (for approximately 100,000 HT recipients since 1982) documented that survival (by Kaplan-Meier analysis) among the 818 patients aged greater than 70 years was inferior to younger patients.[25] While this observation lost significance when the same analysis was restricted to patients in the most recent transplant analysis era (2009–2013), a multivariable investigation still found that recipient and donor age significantly impacted 1- and 5-year post-HT survival.[25] Therefore, recent ISHLT guidelines only advocate HT

in select patients over age 70 in the absence of other comorbidities known to impact short- and intermediate-term outcomes, including chronic kidney, liver or lung disease.[26] Despite data supporting HT among select elderly patients, a recent analysis of the United Network for Organ Sharing (a U.S. registry) found only 1.3% of total transplants were performed in recipients more than 70 years old.[23] Furthermore, since transplant volume appears to have a high impact on post-HT outcomes,[27,28] we would advocate transplantation in elderly patients be preferentially considered in higher-volume centers.

Evident from these data, HT will never meet the increasing demand for heart replacement options, particularly among elderly patients.[22,29] As a result, alternatives to HT for providing cardiac support, such as LVAD therapy, have been established and are growing in popularity.

Left Ventricular Assist Device Therapy

Concerns regarding clinical outcomes and the societal rationing of HT to younger recipients, compounded by the dramatic, unmet and increasing demand for heart replacement therapy in elderly AHF patients, has spurred the development of durable LVAD therapy. While initially implemented as a strategy to support patients as a bridge to transplantation, modern continuous-flow LVAD therapies are now often used as destination therapy. These LVADs offer the realistic promise of a relatively long-term (1–5 years) form of cardiac support to those who are either ineligible or do not wish to pursue HT.

Compared with medical therapies, AHF populations supported with LVAD technologies have twice the survival rate, better physical functional capacity and improved QOL metrics.[30,31] In 2010, the HeartMate II LVAD (Thoratec Corp., Pleasanton, CA) was approved by the U.S. Food and Drug Administration as destination therapy for its promise of durability and reduced complications. In previous pivotal trials of LVAD technologies, the most common indication for destination therapy was age, and subsequent trials or registries have dramatically increased the use of LVAD among elderly patients. Compared with prior iterations of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS),[29,32] current data show a significant rise in both the number of patients receiving LVAD therapy and an upward shift in those over age 60 (32% prior to 2010 and 49% in 2014).[32] While overall data indicates that age displays a moderate decrement in survival for those over age 65 (hazard ratio: 1.36, P<0.0001),[33] this registry data is incomplete and may have selection biases for reporting outcomes. Besides age, one must also take into consideration that, compared to younger patients, older cohorts have more comorbidities and do not have the option of HT, all of which may generate further bias to registry data.

Several studies have evaluated the application of LVAD technology in the elderly. Adamson et al.[34] described a single-center experience using HeartMate II in 30 patients over age 70 (mean 76 ± 3.9 years). Comparing this cohort with a younger cohort (mean 56.7 ± 14.3 years), older age was associated with nearly identical hospital length of stay, 1- and 2-year survival, and major complications (bleeding, infection, arrhythmia, renal failure, right heart failure and stroke). Authors also highlighted center experience and the rigorous evaluation by a dedicated multidisciplinary health care team to assess and optimize neurologic, nutritional, psychosocial and renal function as factors for successful outcomes.[34] Using the largest all-payer database in the United States, Kilic et al.[35] observed comparable mortality, with no independent impact of age on inpatient mortality, when comparing elderly patients (age > 70, n=1,472) to a younger group (age 60–69, n=2,787) supported with continuous-flow LVAD. Somewhat contradictory data was published by Atluri et al.,[36] who examined the INTERMACS national registry from 2006 to 2012 and similarly dichotomized patient groups into age > 70 (n=590) and age < 70 (n=4,439). They found that despite higher INTERMACS profiles (indicating less severe illness at time of enrollment), comparable heart bypass time and comparable length of stay, 2-year survival was lower in the older cohort (63% vs 71%, P<0.001). In a multivariable Cox proportional hazard analysis, age was an independent predictor of mortality (hazard ratio: 1.45 [95% confidence interval: 1.13–1.85], P=0.003). In this analysis, the older group was statistically more likely to experience a stroke (2.3% vs 0.9%, P=0.01) or gastrointestinal bleeding (19.8% vs 13.4%, P<0.001), but had much lower incidence of driveline-associated infection (5.7% vs 12.6%, P<0.001). Finally, Grady et al. examined the impact of age (n=493 > 70 years, n=977 < 70 years) among patients enrolled in INTERMACS and found that despite a higher self-reported QOL prior to LVAD implant compared to

younger cohorts, older adults demonstrated equivalent gains in QOL metrics 1 year after implantation.[37] While lower QOL score and rehospitalization after LVAD were important variables in subsequent QOL scores, age did not influence this metric.

Combining these data, the landscape for using LVAD technologies appears promising for older individuals with AHF. The best results seem to be among older patients evaluated by programs with a high level of clinical experience (by volume and outcomes) that utilize a dedicated multidisciplinary team and select patients with fewer comorbidities or more factors that optimize patient outcome. Anticipated survival is comparable to younger cohorts, and QOL gains are sustained.

Although the use of LVAD as destination therapy for older patients with AHF is promising and increasing, there are an increasing number of elderly patients with AHF who are not candidates for HT or an LVAD or who do not wish to pursue either of these surgical options. The objective of these patients' care should focus on how to improve QOL through palliative care.

Palliative Care

In the past, palliative care was considered as an adjunctive HF treatment that should be initiated only when other standard HF treatment options proved unsuccessful. Now, more and more providers and health advisory organizations have begun to realize the importance of early use of palliative care in the management of AHF. Accordingly, most major cardiovascular medical societies have issued guidelines recommending the incorporation of prognostic stratification and a palliative care evaluation (with discussion on goals of care) for treatment of patients with HF.[38] Despite these recommendations and the creation of a recognized palliative care subspecialty, the discussion tool and subsequent services have been underutilized.[39] One study revealed that only 6% of patients hospitalized for HF received palliative care consultation in spite of the fact that nearly 60% of patients studied were at elevated risk of mortality.[40] These findings are consistent with others who have examined palliative care consultation among HF and noncancer medical populations.[41,42]

Palliative care must be integrated in the assessment and evaluation of elderly patients with AHF. In many cases, LVAD or HT is not medically or surgically viable for these patients, and some patients who understand their prognosis still choose not to pursue these options. At this point, a goals-of-care discussion should focus on managing physical symptoms and the psychological well-being of both the patient and family. This discussion is often initiated by the AHF cardiologist or physician most familiar with the patient's care and illness trajectory. Frequently, a palliative care specialist is incorporated to assist in the mobilization of resources and further define specific goals toward the end of life in the context of the patient's psychosocial support and spiritual belief systems. Treatment goals are often framed in the context of patient autonomy, dignity and choice of physical location (home or facility). While age is often an important factor for palliative care referral, only after a thorough evaluation of all reasonable options in line with patient preference should end-of-life therapy be initiated.[39]

Frailty and Advanced Heart Failure Therapy Options

Frailty, particularly physical frailty, is a condition often recognized by the provider but difficult to quantify; however, it is often one of the most important factors influencing the answer to the question "Should we pursue AHF surgical options?" The traditional definition of frailty encompasses "a medical syndrome with multiple causes and contributors characterized by diminished strength, endurance, and physiologic function that increases an individual's vulnerability for developing increased dependency and/or death."[43] Frailty may not be a disease but a natural result of aging.[44] The physical definition of frailty is more often observed in both the elderly and HF populations than among the general population.[45] In the Cardiovascular Health Study,[46] almost one in four adults between age 65 and 84 were frail, and the prevalence of frailty increased with age — reaching 44% in adults 85 years or older.[47] However, frailty also may be induced and/or exacerbated by the burden of cardiac disease and is associated with negative outcomes.[48] When examined in the context of coronary artery disease, acute coronary syndromes and percutaneous coronary intervention, frailty has been extensively demonstrated to be a prognostic indicator of adverse cardiac events, rehospitalization and all-cause mortality.[48-53] Frailty itself in the elderly HF population is an independent predictor of emergency department visits, hospitalizations and mortality.[54,55] There is a close link between frailty and comorbidities, polypharmacy and malnutrition. Compounding the challenges of frailty

among the elderly is cognitive impairment, ranging on a spectrum of depression to fixed neurologic sequelae from prior stroke and/or dementia (e.g. Alzheimer's).

Since frailty appears to disproportionately affect the elderly and has a greater influence on quality and quantity of life, rational treatment options deliberated for elderly patients with AHF must include its consideration. Frail individuals have limited reserve for recovery from even transient major physiologic insults such as major surgery, prolonged intubation or intensive care time, hypoxia, hypotension or metabolic derangements. Therefore, not only will the frail patient be at greater risk from AHF treatment interventions, but he or she also will have reduced functional benefits with higher long-term adverse outcomes. Hence, incumbent on an AHF treatment program is deciphering which component of physical or cognitive frailty is associated with the HF phenotype and which is intrinsically related to the patient, as the former would be treatable with AHF therapy options while the latter may actually be made worse.

Frailty (cognitive or physical) is often much more worrisome in patients receiving LVAD as destination therapy, as this intervention is not easily rationed to younger cohorts in whom frailty is less of a concern. Neurocognitive dysfunction can negatively impact overall well-being and QOL, and has been demonstrated to pose a psychosocial burden on LVAD patients and caregivers.[56] A retrospective study of INTERMACS conducted by Fendler et al. found that the risk of cognitive decline in the first year following LVAD implantation was greater with advanced age, particularly in patients more than 70 years old.[57] The study further noted that the levels of cognitive decline after LVAD were greater than levels seen in normal aging populations.[57] Indeed, another retrospective study[58] examined outcomes in LVAD patients undergoing destination therapy at Mayo Clinic and found frailty was associated with a threefold higher risk of mortality within 24 months postimplant.[58] However, Flint et al. cautioned that the predictive value of frailty in LVAD patients is complicated by the fact that the underlying cardiac disease contributing to a patient's frailty may itself be reversed as a result of LVAD therapy.[48] Accordingly, recent studies have challenged the traditional notion that age is a predictor of mortality and adverse outcomes in patients who receive LVAD as destination therapy[34,59] and have suggested frailty may be a superior metric in preoperative assessment.

Personalized Care Model for AHF Therapy in the Elderly

As previously stated, the incidence, prevalence, morbidity, mortality and economic burden of HF disproportionately affects those over age 70. With improved treatment of acute cardiovascular diseases and the aging worldwide population, an epidemic of HF is anticipated over the next three decades. Unfortunately, more elderly people with HF will ultimately translate to a higher number of elderly people with AHF. Current viable strategies for AHF include HT, LVAD and palliative care, recognizing the latter should be part of the decision tree for either of the first two options.

Over the last three decades, our institution has performed more than 1,600 AHF surgical procedures (870 HT and 745 LVAD), with outcomes exceeding national benchmark standards. As advocated by many peer-reviewed publications,[27,28,60] center size, experience and outcomes data should be factors when leveraging AHF therapy options among nontraditional populations of patients, including the elderly. Along with many other large national programs,[33] we have seen an increased use of continuous-flow LVAD therapy as both bridge to transplantation and destination therapy strategies as well as the general aging of the patient population served with these options. Our program's relative age limit for HT is 70 years, and our percentage of transplants in this age group mirrors national and international trends (less than 3%);[23] notably, our institution has not performed HT in a patient age 75 or older in more than a decade. Within the last three years, roughly half of all LVADs implanted at our program (n=152) have been for a destination therapy indication, which calls for a multidisciplinary approach to patient evaluation, selection, data collection and reporting, and patient management. We employ several measures in the evaluation of an LVAD candidate in the context of assessing frailty. These include nutritional parameters (10% unintentional weight loss, albumin and prealbumin), physical assessment (hand grip, seated-to-rise time) and cognitive assessment (psychologic and palliative). By developing and consistently employing a multidisciplinary approach for all destination therapy patients, we have shortened the time of evaluation and decision (to a median of 12 days), reduced hospital length of stay (to a median of 14 days post-LVAD surgery) and improved clinical metrics and patient outcomes including in-hospital, 6- and 24-month survival (94%, 84% and 68%, respectively).

Central to the evaluation of a destination therapy patient is an early referral for evaluation and caregiver engagement. In addition to a team comprised of experienced AHF-certified medical and surgical cardiovascular specialists, all destination therapy patients are evaluated by program-dedicated social workers, pharmacists, psychologists, palliative care specialists, nutritionists, financial coordinators, biomedical engineers and nursing coordinators. Each professional is expected to obtain precise information and provide detailed education pertinent to his or her discipline. Each discipline is charged with candidly presenting that information during a weekly patient selection conference in the context of written programmatic guidelines. The goal of this process is to provide patients and families with equitable evaluation and education regarding AHF options and to define real and potential challenges to successful patient outcomes.

If patients are accepted for AHF treatment (most commonly LVAD as destination therapy) and elect to pursue this option, then appropriate education of both patient and caregivers is continued. Once patients have undergone destination therapy LVAD for AHF, we deploy the same multidisciplinary team to care for them as they transition from intensive care to telemetry step-down and eventually home. Once home, patients are seen weekly in outpatient clinic for 4 weeks, during which time a team comprised of an AHF provider, AHF registered nurse, dedicated HF pharmacist and a biomedical engineer optimizes medications, anticoagulation, education and LVAD parameters, taking into account patient symptoms. Postdischarge care also includes education of emergency medical services proximal to patient home location, structured cardiac rehabilitation, measurement of QOL metrics and monthly or quarterly clinic visits for ongoing medical care. Once stable, patients without arrhythmia are allowed to drive personal vehicles and return to full activities such as travel, home care, sports and recreation. Since our program mandates palliative care consultation for all patients eligible for destination therapy LVAD, we are able to seamlessly maintain continuity of care once patients transition to a terminal phase of illness while supported with LVAD therapy.

In our experience, if the patient is not frail (cognitively or physically), has reasonable renal function (chronic kidney disease stage 3 or less) and a stable supportive psychosocial situation as determined by the multidisciplinary team, then he or she would have the best chance to benefit from placement of an LVAD. Whether a comprehensive cost analysis of destination therapy LVAD will prove to reduce intermediate-term costs remains to be seen; it is anticipated that as complication rates and recurrent hospitalizations among LVAD patients continue to fall and patient selection improves, we may be able to curb health care expenditures among elderly patients with AHF.

Conclusions

The current paradigm for AHF options among elderly patients favors a broader application of LVAD as destination therapy. While these technologies have evolved from large pulsatile pumps with limited durability to smaller, more durable devices, several challenges need to be addressed in future device designs. These challenges include LVAD-associated gastrointestinal bleeding, stroke and driveline-associated infections. The promise of novel magnetically levitated pump designs, fewer moving parts with larger gaps for blood to channel and fully implantable systems with transcutaneous charging may help solve many of these concerns. Regardless of anticipated advancements, the central question should always remain: "For whom should these technologies be applied?" We advocate the development of robust multidisciplinary teams charged with meticulously evaluating patients with AHF and judiciously applying technologies for those who are most likely to gain benefit.

Patient-Friendly Recap

- Advanced heart failure, the most severe stage of heart failure, is more common among elderly patients.
- The authors reviewed the reported success rates of heart transplantation and LVAD therapy in this population as well as palliative care alternatives.
- They concluded that choice of clinical action must take into account patient-specific risks, namely, the physical and mental conditions often associated with aging.
- Additionally, an established personalized model of care for treating older patients with advanced heart failure is described in detail.

Conflicts of interest

None.

References

1. United Nations, Department of Economic and Social Affairs, Population Division. *World Population Ageing, 2015*. New York, NY: United Nations, 2015.
2. Ortman JM, Velkoff VA, Hogan H. *An Aging Nation: The Older Population in the United States*. Current Population Reports: P25-1140. Washington, DC: U.S. Census Bureau, 2014.
3. Goldwater DS, Pinney SP. Frailty in advanced heart failure: a consequence of aging or a separate entity? *Clin Med Insights Cardiol.* 2015;9(Suppl 2):39-46. CrossRef
4. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics – 2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28-292. CrossRef
5. Azad N, Lemay G. Management of chronic heart failure in the older population. *J Geriatr Cardiol.* 2014;11:329-37. CrossRef
6. Abouezzeddine OF, Redfield MM. Who has advanced heart failure? Definition and epidemiology. *Congest Heart Fail.* 2011;17:160-8. CrossRef
7. Martinelli MV, Bösch C, Signorell J, Mohacsi P. [Advanced heart failure – treatment options beyond medical management]. *Ther Umsch.* 2011;68:715-23. CrossRef
8. Nohria A, Lewis E, Stevenson LW. Medical management of advanced heart failure. *JAMA.* 2002;287:628-40. CrossRef
9. Lund LH, Matthews J, Aaronson K. Patient selection for left ventricular assist devices. *Eur J Heart Fail.* 2010;12:434-43. CrossRef
10. National Heart, Lung, and Blood Institute. *Morbidity & Mortality: 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases*. Bethesda, MD: National Institutes of Health, 2012.
11. Costanzo MR, Naftel DC, Pritzker MR, et al. Heart transplant coronary artery disease detected by coronary angiography: a multiinstitutional study of preoperative donor and recipient risk factors. Cardiac Transplant Research Database. *J Heart Lung Transplant.* 1998;17:744-53.
12. Tjang YS, van der Heijden GJ, Tenderich G, Körfer R, Grobbee DE. Impact of recipient's age on heart transplantation outcome. *Ann Thorac Surg.* 2008;85:2051-5. CrossRef
13. Bourge RC, Naftel DC, Costanzo-Nordin MR, et al. Pretransplantation risk factors for death after heart transplantation: a multiinstitutional study. The Transplant Cardiologists Research Database Group. *J Heart Lung Transplant.* 1993;12:549-62.
14. Borkon AM, Muehlebach GF, Jones PG, et al. An analysis of the effect of age on survival after heart transplant. *J Heart Lung Transplant.* 1999;18:668-74. CrossRef
15. Heroux AL, Costanzo-Nordin MR, O'Sullivan JE, et al. Heart transplantation as a treatment option for end-stage heart disease in patients older than 65 years of age. *J Heart Lung Transplant.* 1993;12:573-8; discussion 578-9.
16. Blanche C, Blanche DA, Kearney B, et al. Heart transplantation in patients seventy years of age and older: a comparative analysis of outcome. *J Thorac Cardiovasc Surg.* 2001;121:532-41. CrossRef
17. McCarthy JF, McCarthy PM, Massad MG, et al. Risk factors for death after heart transplantation: does a single-center experience correlate with multicenter registries? *Ann Thorac Surg.* 1998;65:1574-8. CrossRef
18. Hosenpud JD, Pantely GA, Norman DJ, Cobanoglu AM, Hovaguimian H, Starr A. A critical analysis of morbidity and mortality as it relates to recipient age following cardiac transplantation. *Clin Transplant.* 1990;4:51-4.
19. Morgan JA, John R, Weinberg AD, et al. Long-term results of cardiac transplantation in patients 65 years of age and older: a comparative analysis. *Ann Thorac Surg.* 2003;76:1982-7. CrossRef
20. Weiss ES, Nwakanma LU, Patel ND, Yuh DD. Outcomes in patients older than 60 years of age undergoing orthotopic heart transplantation: an analysis of the UNOS database. *J Heart Lung Transplant.* 2008;27:184-91. CrossRef
21. Daneshvar D, Czer LS, Phan A, et al. Heart transplantation in patients aged 70 years and older: a two-decade experience. *Transplant Proc.* 2011;43:3851-6. CrossRef
22. Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates--2006. *J Heart Lung Transplant.* 2006;25:1024-42. CrossRef
23. Lund LH, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report – 2013; focus theme: age. *J Heart Lung Transplant.* 2013;32:951-64. CrossRef
24. Shamaskin AM, Rybarczyk BD, Wang E, et al. Older patients (age 65+) report better quality of life, psychological adjustment, and adherence than younger patients 5 years after heart transplant: a multisite study. *J Heart Lung Transplant.* 2012;31:478-84. CrossRef
25. Lund LH, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-Second Official Adult Heart Transplantation Report – 2015; focus theme: early graft failure. *J Heart Lung Transplant.* 2015;34:1244-54. CrossRef
26. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant.* 2016;35:1-23. CrossRef
27. Russo MJ, Iribarne A, Easterwood R, et al. Post-heart transplant survival is inferior at low-volume centers across all risk strata. *Circulation.* 2010;122:S85-91. CrossRef
28. Arnaoutakis GJ, George TJ, Allen JG, et al. Institutional volume and the effect of recipient risk on short-term mortality after orthotopic heart transplant. *J Thorac Cardiovasc Surg.* 2012;143:157-67, 167e1. CrossRef
29. Kirklin JK, Naftel DC, Kormos RL, et al. Third INTERMACS Annual Report: the evolution of destination therapy in the United States. *J Heart Lung Transplant.* 2011;30:115-23. CrossRef
30. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med.* 2001;345:1435-43. CrossRef
31. Lietz K, Miller LW. Improved survival of patients with end-stage heart failure listed for heart transplantation: analysis of organ procurement and transplantation network/U.S. United Network of Organ Sharing data, 1990 to 2005. *J Am Coll Cardiol.* 2007;50:1282-90. CrossRef

32. The Data Collection and Analysis Center; University of Alabama at Birmingham. Interagency Registry for Mechanically Assisted Circulatory Support: quarterly statistical report, 2014 2nd quarter (dated Sept. 22, 2014). http://www.uab.edu/medicine/intermacs/images/Federal_Quarterly_Report/Federal_Partners_Report_2014_Q2.pdf. Accessed July 12, 2016.
33. Kirklin JK, Naftel DC, Pagani FD, et al. Sixth INTERMACS annual report: a 10,000-patient database. *J Heart Lung Transplant.* 2014;33:555-64. CrossRef
34. Adamson RM, Stahovich M, Chillcott S, et al. Clinical strategies and outcomes in advanced heart failure patients older than 70 years of age receiving the HeartMate II left ventricular assist device: a community hospital experience. *J Am Coll Cardiol.* 2011;57:2487-95. CrossRef
35. Kilic A, Conte JV, Baumgartner WA, Russell SD, Merlo CA, Shah AS. Does recipient age impact functional outcomes of orthotopic heart transplantation? *Ann Thorac Surg.* 2014;97:1636-42. CrossRef
36. Atluri P, Goldstone AB, Kobrin DM, et al. Ventricular assist device implant in the elderly is associated with increased, but respectable risk: a multi-institutional study. *Ann Thorac Surg.* 2013;96:141-7. CrossRef
37. Grady KL, Wissman S, Naftel DC, et al. Age and gender differences and factors related to change in health-related quality of life from before to 6 months after left ventricular assist device implantation: findings from Interagency Registry for Mechanically Assisted Circulatory Support. *J Heart Lung Transplant.* 2016;35:777-88. CrossRef
38. Whellan DJ, Goodlin SJ, Dickinson MG, et al. End-of-life care in patients with heart failure. *J Card Fail.* 2014;20:121-34. CrossRef
39. LeMond L, Camacho SA, Goodlin SJ. Palliative care and decision making in advanced heart failure. *Curr Treat Options Cardiovasc Med.* 2015;17:359. CrossRef
40. Greener DT, Quill T, Amir O, Szydlowski J, Gramling RE. Palliative care referral among patients hospitalized with advanced heart failure. *J Palliat Med.* 2014;17:1115-20. CrossRef
41. Johnson MJ, Houghton T. Palliative care for patients with heart failure: description of a service. *Palliat Med.* 2006;20:211-4. CrossRef
42. Holloway RG, Ladwig S, Robb J, Kelly A, Nielsen E, Quill TE. Palliative care consultations in hospitalized stroke patients. *J Palliat Med.* 2010;13:407-12. CrossRef
43. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc.* 2013;14:392-7. CrossRef
44. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. *J Am Geriatr Soc.* 2012;60:1487-92. CrossRef
45. Uchmanowicz I, Łoboz-Rudnicka M, Szeląg P, Jankowska-Polańska B, Łoboz-Grudzień K. Frailty in heart failure. *Curr Heart Fail Rep.* 2014;11:266-73. CrossRef
46. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol.* 1991;1:263-76. CrossRef
47. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001;56:M146-56. CrossRef
48. Flint KM, Matlock DD, Lindenfeld J, Allen LA. Frailty and the selection of patients for destination therapy left ventricular assist device. *Circ Heart Fail.* 2012;5:286-93. CrossRef
49. Purser JL, Kuchibhatla MN, Fillenbaum GG, Harding T, Peterson ED, Alexander KP. Identifying frailty in hospitalized older adults with significant coronary artery disease. *J Am Geriatr Soc.* 2006;54:1674-81. CrossRef
50. Boxer R, Kleppinger A, Ahmad A, Annis K, Hager D, Kenny A. The 6-minute walk is associated with frailty and predicts mortality in older adults with heart failure. *Congest Heart Fail.* 2010;16:208-13. CrossRef
51. Singh M, Rihal CS, Lennon RJ, Spertus JA, Nair KS, Roger VL. Influence of frailty and health status on outcomes in patients with coronary disease undergoing percutaneous revascularization. *Circ Cardiovasc Qual Outcomes.* 2011;4:496-502. CrossRef
52. Ekerstad N, Swahn E, Janzon M, et al. Frailty is independently associated with short-term outcomes for elderly patients with non–ST-segment elevation myocardial infarction. *Circulation.* 2011;124:2397-404. CrossRef
53. Jha SR, Hannu MK, Chang S, et al. The prevalence and prognostic significance of frailty in patients with advanced heart failure referred for heart transplantation. *Transplantation.* 2016;100:429-36. CrossRef
54. Cacciatore F, Abete P, Mazzella F, et al. Frailty predicts long-term mortality in elderly subjects with chronic heart failure. *Eur J Clin Invest.* 2005;35:723-30. CrossRef
55. Lupón J, González B, Santaeugenia S, et al. Prognostic implication of frailty and depressive symptoms in an outpatient population with heart failure. *Rev Esp Cardiol.* 2008;61:835-42. CrossRef
56. Shapiro PA, Levin HR, Oz MC. Left ventricular assist devices. Psychosocial burden and implications for heart transplant programs. *Gen Hosp Psychiatry.* 1996;18:30S-35S. CrossRef
57. Fendler TJ, Spertus JA, Gosch KL, et al. Incidence and predictors of cognitive decline in patients with left ventricular assist devices. *Circ Cardiovasc Qual Outcomes.* 2015;8:285-91. CrossRef
58. Dunlay SM, Park SJ, Joyce LD, et al. Frailty and outcomes after implantation of left ventricular assist device as destination therapy. *J Heart Lung Transplant.* 2014;33:359-65. CrossRef
59. Lushaj EB, Badami A, Osaki S, et al. Impact of age on outcomes following continuous-flow left ventricular assist device implantation. *Interact Cardiovasc Thorac Surg.* 2015;20:743-8. CrossRef
60. Laffel GL, Barnett AI, Finkelstein S, Kaye MP. The relation between experience and outcome in heart transplantation. *N Engl J Med.* 1992;327:1220-5. CrossRef