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Can a Left Ventricular Assist Device in Advanced Systolic Heart Failure Improve or Reverse the Frailty Phenotype?

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Abstract

Background/Objectives—Frailty, characterized by decreased physiologic reserves, is strongly associated with vulnerability to adverse outcomes. Features of frailty overlap with those of advanced heart failure (HF), making a distinction between these phenotypes difficult. We sought to determine if implantation of a left ventricular assist device (LVAD) would improve the frailty phenotype.

Design—Prospective, cohort study

Setting—Five academic medical centers.

Participants—29 frail subjects (age 70.6±5.5 years, 72.4% male)

Measurements—Frailty assessed prior to LVAD and at 1, 3 and 6 months post-LVAD and was defined as ≥3 Fried Frailty phenotype criteria. Other domains assessed included quality of life using the Kansas City Cardiomyopathy Questionnaire, mood using PHQ9, and cognitive function using trail maker B test

Results—After 6 months, 3 subjects died and 1 underwent a heart transplant; among 19 subjects with serial frailty measures, the average number of frailty criteria decreased from 3.9±0.9 at baseline to 2.8±1.4 at 6 months, p=0.003. Improvements were not observed until 3–6 months of support. However, 10 (52.6%) continued to meet ≥3 Fried criteria and all subjects met at least one at 6 months. Changes in the frailty phenotype were associated with improvement in QOL but not with changes in mood or cognition. eGFR at baseline was independently associated with improvement in frailty phenotype.

Conclusions—The frailty phenotype was improved in approximately 50% of older adults with advanced HF after 6 months of LVAD support. Strategies to enhance frailty reversal in this population are worthy of additional study.

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Keywords

Frailty; Advanced Heart Failure; Ventricular Assist Device

Frailty is a clinical syndrome[1] characterized by decreased physiologic reserves and is strongly associated with increased vulnerability to functional decline [2, 3] and complications from medical [4, 5], percutaneous [6] and surgical interventions [7], especially in older adults with cardiovascular disease [2, 3, 8]. Specifically, frailty has been associated with a greater prevalence of adverse outcomes in heart failure patients [9–11] and in those undergoing cardiac surgery [12, 13] or transcatheter aortic valve replacement [6, 14]. The measurement of the frailty phenotype employs a combination of functional capacity, strength, mobility, fatigue[1] and sometimes mood and cognition [15–17]. However, the systematic measurement of frailty has not permeated cardiovascular practice, despite its potential as a risk factor to guide selection of candidates for circulatory support[18]. Additionally, frailty is not clinically employed serially to evaluate the impact of interventions.

While no single therapeutic intervention has been shown to consistently reverse the frailty phenotype, there is a growing body of clinical evidence from the heart failure literature suggesting that placement of a left ventricular assist device (LVAD) may reverse several features of the frailty phenotype[19] such as improved muscle strength [20, 21], increased six minute walk distance[22, 23] and reduced exhaustion[24, 25]. When used as an alternative to heart transplantation, destination therapy (DT) LVADs extend and improve the lives of advanced heart failure patients [25–27], many of whom are older adults with limited cardiopulmonary reserve, who appear frail. By restoring cardiac output and adequate organ perfusion, LVADs are capable of reversing the catabolic state associated with advanced heart failure. The return to an anabolic state can result in a reversal of sarcopenia, low energy expenditure, slow gait speed, exhaustion and cardiac cachexia which are all components of the frailty phenotype.

The primary hypothesis of this study was that elective implantation of an LVAD in older adults with advanced systolic heart failure would improve or even reverse the frailty phenotype. A secondary exploratory hypothesis was that persistence of the frailty phenotype would be associated with age and other modifiers (e.g. co-morbidities, lab results, INTERMACS score, procedural factors, serious adverse events).

Methods

Study Design

We conducted a prospective, multi-center cohort pilot study at 5 academic medical centers within the Greater New York Geriatric Cardiology Consortium (www.gnygcc.org): Columbia University Medical Center, Mount Sinai Hospital, New York University Medical Center, Weil Cornell University Medical Center and Thomas Jefferson University. In this study, measurably frail older adults scheduled for a left ventricular assist device (LVAD) for standard clinical indications were evaluated to determine the whether mechanical circulatory support would impact the frailty phenotype.

Study Subjects

Older adults (age ≥ 60 years) eligible to receive an elective LVAD as destination therapy. Inclusion criteria included: frail, as defined by the presence of ≥3 frailty criteria (see below), plans for placement of elective VAD (e.g. INTERMACS profile ≥ 2) for clinical indications, and able and willing to provide informed consent. Exclusion criteria included inability to perform required assessments (e.g. non-elective VAD), prior heart transplantation, renal failure requiring dialysis or a co-morbidity other than advanced heart disease anticipated to limit survival to less than 6 months, active alcohol or substance abuse or documented noncompliance, which were determined as part of standard LVAD evaluation. All subjects enrolled reviewed and signed informed consent documents. The respective IRBs of each participating institution approved the protocol.

Protocol

Patients were screened and enrolled up to 4 weeks prior to LVAD implantation. Informed consent, complete history, physical examination and medication list were obtained prior to LVAD implantation. Pre-operative testing done to determine eligibility for the LVAD implantation was used as direct eligibility criteria for this study. Subjects completed a frailty evaluation and several questionnaires to assess QOL (Kansas City Cardiomyopathy Questionnaire)[28], mood (Physician Health Questionnaire-9, PHQ-9), energy (anergia scale)[29, 30] and cognitive function (trail maker B)[31] which was measured concordantly with frailty evaluations. Frailty was measured by the Fried criteria[1] including unintentional weight loss of > 10 pounds (i.e., not due to diuretic use, dieting or exercise) or 5% of previous body weight in last year; exhaustion, based on response to two questions including “I felt that everything I did was an effort” and “I could not get going,” with a frequency of at least 3 days per week; Physical Activity, based on the short version of the Minnesota Leisure Time Activity questionnaire, with kcals per week expended calculated using a standardized algorithm (men doing <383 kcal/week and women <270 kcal/week me frailty criteria); Gait speed, stratified by gender and height (gender-specific cutoff a medium height) with following cutoff for time to walk 15 feet criterion for frailty, men, Height ≤ 173 cm ≥7 seconds, height >173 cm ≥6 seconds, women, Height ≤ 159 cm ≥7 seconds, eight >159 cm ≥6 seconds; and grip strength, stratified by gender and body mass index (BMI) quartiles as previously published.[1] Subjects were frail if they met 3 or more of the aforementioned criteria.

Statistical Analysis

Data was entered into a secure REDCap database designed for this study. Descriptive statistics were used to characterize variables of the study participants. For the primary analysis, we used a Wilcoxon rank sum test to compare to compare the components of the frailty phenotype present at baseline to those present 6 months after LVAD implantation. Secondary exploratory analyses focused on how baseline covariates predicted an improvement in frailty scores after LVAD implantation. To identify potential baseline characteristics associated with frailty improvement, we used Wilcoxon Rank sum tests to compare to compare demographic and clinical factors between those who did and did not have improvements in frailty at six months. These factors were then evaluated for predictive

performance using multivariate logistic regression. To characterize the time course of the change in frailty during the study period, we delineated changes over time in grip strength, weight, physical activity, gait speed and exhaustion) at 1, 3 and 6 months after LVAD implant. We also used logistic regression to evaluate the impact of serious adverse events on the improvement in the frailty phenotype, treating the number of serious adverse events (SAEs) as a continuous predictor of the binary frailty outcome.

Results

The study population (Figure 1) included 50 subjects who were eligible to receive DT LVAD, of whom 42 underwent surgery and 8 declined. The 42 subjects enrolled represent 59% of subjects ≥60 years of age undergoing destination therapy LVAD at the five institutions during the ~1.5 year recruitment period. There were 29 subjects enrolled in the longitudinal analysis of frailty at 1, 3 and 6 months after LVAD placement; 13 were excluded from the longitudinal analysis because they did not meet inclusion criteria (required urgent LVAD, were not frail or had insufficient data to determine frailty status). As shown in Table 1, the subjects were typical of a population with advanced systolic heart failure: predominately male, with ischemic heart disease, an ejection fraction <20% and multiple co-morbid conditions. The cohort that underwent serial frailty assessments did not differ significantly from the other cohorts (Table 1).

Frailty measures at baseline were not correlated with HeartMate II survival score[32] (r^2=0.0899, p= 0.11). The average number of frailty criteria fulfilled by those subjects with serial frailty analysis was 3.9±0.9 at baseline and decreased to 2.8±1.4 at 6 months, p=0.003. In those subjects who had <3 frailty criteria after six months (n=9, 47.4%) compared to subjects who continued to have ≥ 3 frailty criteria, there were significant differences in gait speed (0.8±0.2 vs. 0.5±0.2 m/sec, p=0.025), handgrip strength (26.2±7.8 vs. 17.81±10.1 kg/m^2, p = 0.045), energy expenditure (396.6±159.2 vs.105.5±152.3 kcal/wk, p= 0.003), exhaustion (12.5% vs. 70%, p=0.02) and weight change in the preceding year (−0.3%±10% vs. −14.7%±14%, p = 0.033). Changes in the frailty phenotype occurred after 3 to 6 months of LVAD support (Table 2). Of note, all subjects continued to meet at least one frailty criterion at each time point.

Changes in the frailty phenotype at 6 months were associated with improvements in other measures (Table 3) of QOL, specifically with subscales of total symptoms, their frequency and burden, and the clinical and overall summary scores, but not with changes in mood or cognition. Baseline factors that were associated (p<0.1) with the improvement of the frailty phenotype (Supplementary Table 1) included INR, creatinine and eGFR. In logistic regression analysis, eGFR was the only baseline variable that was significantly associated with improvement in frailty phenotype (p = 0.029); the addition of other predictors did not significantly improve the model.

Days alive out of hospital was greater for those who had improvement in frailty than those who did not (165.2±78.6 vs. 142.7±55.9 days,) but this was not statistically significant (Supplementary Table 2). Since it is plausible that the presence, frequency and type of adverse events could affect reversal of the frailty phenotype, we recorded serious adverse

events (SAEs) during the six months post LVAD implant. A majority of the subjects (n=25, 86.2%) had at least one SAE and several subjects had multiple SAEs including infection (n=13), gastrointestinal bleeding (n=10), hypovolemia (n=7), decompensated heart failure (n=4), death (4) ventricular tachycardia (n=2), mental status changes, traumatic fall and acute kidney injury (n=1 each). The total number of SAEs and mean number of SAEs tended to be lower in those who had improvements in frailty phenotype (14 total SAEs, mean of 1.6 SAE per patient) than those who remained frail (27 total SAEs, mean of 2.7 SAEs per patient). In general, the presence of serious adverse events was associated with a lower chance of improving frailty criterion, which was not significant (estimated OR 0.56, p=0.12).

Discussion

The principle findings of this study are: (1) in older advanced HF patients who were frail prior to undergoing LVAD implantation the frailty phenotype, is improved in approximately half after 6 months of LVAD support;(2) that is took at least 3 months on LVAD support to begin to see improvement in frailty, (3) those in whom frailty improved experienced significantly greater improvement in QOL compared to those in whom frailty did not improve; and (4) baseline renal dysfunction may be associated with lower chance of improving the frailty phenotype.

The coalescence of the frailty phenotype and advanced heart failure presents a unique opportunity to assess any LVAD mediated improvement of vascular congestion and cardiac output that may potentially improve the slowness, weakness, fatigue, weight loss and physical inactivity that comprise the frailty phenotype. Indeed, Flint and colleagues[18] suggested that there may be two forms of frailty, one responsive to an LVAD placement and another not as responsive. Our data support this construct. While the current study population is small, the careful and serial assessment of the components of the frailty phenotype post-LVAD surgery demonstrates that approximately half of subjects who survive to 6 months have improvements in the frailty phenotype. The improvements in frailty components were of a small but statistically significant magnitude. When viewed in the context of individual criteria, those improvements are clinically meaningful with differences of ~0.3 m/sec, 8.4 gm/kg and >350 kcal/week increases in gait speed, handgrip strength and energy expenditures between those that did and did not improve the frailty phenotype after 6 months of LVAD support. Notably, weight change was the frailty criterion most resistant to change over time with LVAD implantation, which is in contrast to prior research showing weight gain in LVAD patients.[35] This may be related to a short observation time period (6 months as opposed to the 1 year time period used to define the frailty phenotype); weight fluctuations that occur as a result of volume overload and diuretic use or some other unmeasured confounder.

The improvement in the frailty phenotype, which is highly prevalent among older adult subjects with advanced heart failure,[33, 34] was associated with improvement in quality of life, particularly in subscales related to symptom burden and frequency which led to an improvement in the overall score. Interestingly, improvements in frailty post LVAD were not associated with significant differences in measures of mood or cognition. The absence of

any association between improvements in the frailty phenotype and mood or cognition may be related to the relatively low rates of mood disorders and cognitive dysfunction in our population. While subjects had evidence of depressive symptoms at baseline, these symptoms were mild in nature. Similarly, while trail making B tests results were prolonged, when accounting for education and age[31], the decrements in executive function were not severe. More severe cognitive dysfunction and mood disorders may be underrepresented in this cohort as these are considered relative contraindications for LVAD candidacy. In addition, a more sensitive instrument, such as the Montreal Cognitive Assessment, may have identified more mild cognitive impairment.

While the study population recruited is too small to meaningfully evaluate the impact of residual frailty on survival, length of stay during the initial implant was longer and days alive out of hospital were fewer, albeit not statistically significantly, in those who remain frail compared to those that improve the frailty phenotype. Similarly, the total and median number of serious adverse events resulting in re-hospitalizations tended to be higher in those who remain frail. It is possible that frailty that is not responsive to LVAD therapy contributed to these events or that such events impeded or delayed improvement in frailty.[36]

We hypothesized that factors including age, co-morbidities, lab parameters or INTERMACS score at baseline could be used to identify the subgroup of frail older adults with heart failure who receive a LVAD and remain frail. However, age, gender, INTERMACS score and nutritional state as evidenced by serum albumin levels did not differ significantly at baseline between those who had improvements in frailty and those who did not. Previous studies have observed a lack of association between age and the presence of the frailty phenotype in advanced HF patients.[33, 34] The present finding that age is not associated with improvement in frailty status following LVAD implantation further supports the concept that biological age is a more robust determinant of outcomes than chronological age.[37]

The only parameter that was independently associated with lack of improvement in frailty phenotype was baseline estimated glomerular filtration rate. This finding is consistent with the growing body of evidence linking renal dysfunction with the frailty phenotype[38]. Chronic kidney disease (CKD) affects 45% of persons older than 70 years of age, and is associated with changes in organ systems that have been implicated in the causal chain of frailty including muscle and bone[39], nutritional[40], inflammatory[41] and vascular[42]. CKD is an independent contributor to decline in physical and cognitive functions in older adults and can double the risk for physical impairment, cognitive dysfunction, and frailty[43]. Accordingly, concomitant renal dysfunction in advanced heart failure may be an important factor related to improvement in frailty with LVAD implantation

It is clear that improvements to the frailty phenotype take time, with observed changes seen after months of LVAD support. This is similar to the effects of beta blockers on ejection fraction in subjects with systolic heart failure, which were consistent with a biological and not pharmacologic effect [44, 45]. Such effects are consistent with the complex biological underpinnings of the frailty phenotype including inflammatory, metabolic and nutritional factors, which may be partly addressed through reversal of the HF clinical syndrome. It is possible that with longer follow-up greater improvements in frailty would have been

observed as changes in the percentage of frail and pre-frail were still improving from 3 to 6 months of LVAD support (Table 2).

While these data suggest that implantation of an LVAD and restoration of cardiac output can lead to improvement in the frailty phenotype, our findings also suggest this intervention alone will not completely reverse frailty or even improve frailty in a large portion (nearly 50%) of older, frail LVAD recipients. What then could be used to further address frailty in this population? Continuous focused attention using targeted interventions such as physical rehabilitation and nutritional supplementation appear promising. Given the known benefits of cardiac rehabilitation programs for subjects with cardiovascular disease undergoing procedures such as coronary artery bypass grafting[46], percutaneous coronary intervention[47], valve surgery either percutaneously or surgically[48], the opportunity to routinely include cardiac rehabilitation post LVAD placement is worthy of additional study as it may address the unmet need of residual frailty and poor function in these individuals. A small randomized trial [49] showed significant differences in KCCQ and leg strength in subjects receiving cardiac rehabilitation post LVAD compared to controls. Novel physical rehabilitation interventions specifically designed for older, frail HF patients in the early stages of recovery also appear promising.[50] If larger trials confirm such interventions are effective[51], then in the era of bundled payments and a focus on quality, it is conceivable that cardiac rehabilitation would become a standard intervention post LVAD implantation. The timing and structure of such an approach could conceivably be based on serial measurements of frailty.

There are multiple limitations to this multicenter pilot study including a small number of subjects enrolled which limits statistical power (potentially resulting in a Type II error) and hampers subgroup analyses. Indeed, while LVAD use is becoming more widespread [27], including among older adults [52], our inclusion criteria of an age greater than 60 years of age (which were modified down from an initial cutoff of 65 years) limited the population available for study at the five institutions. While the multicenter nature of the study facilitated recruitments, it also introduced heterogeneity. However, most programs utilize criteria for LVAD implantation specified by CMS and ISHLT.[53] The relatively short term nature of the study (e.g. 6 months) does not allow any conclusions regarding whether longer term support would provide more benefit in terms of frailty improvement or reversal. Additionally, we employed the Fried Frailty Index as the primary outcome measure, which is focused on physical function, but also included measure of cognition and mood, albeit with measures that have not been extensively validated in this population. Finally, the inability to measure frailty in all subjects at each time period despite dedicated study personnel speaks to the difficulty of incorporating conventional frailty measures in clinical practice in this population with advanced heart failure and other competing priorities. These missing data could introduce potential bias in our results, resulting in a type I error.

In conclusion, among older adults with advanced systolic heart failure and concomitant frailty, who are having an LVAD placed for standard clinical indications, improvements in the frailty phenotype are seen in ~50% of subjects after 6 months of LVAD support. Improvement in frailty measures were associated with other domains (e.g. quality of life)

and a trend toward fewer re-hospitalizations, suggesting that strategies to enhance frailty reversal in this population are worthy of additional study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. 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:M146–156. [PubMed: 11253156]
2. Boyd CM, Xue QL, Simpson CF, Guralnik JM, Fried LP. Frailty, hospitalization, and progression of disability in a cohort of disabled older women. Am J Med. 2005; 118:1225–1231. [PubMed: 16271906]
3. Fried LP, Kronmal RA, Newman AB, et al. Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. JAMA. 1998; 279:585–592. [PubMed: 9486752]
4. 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; 16:208–213. [PubMed: 20887617]
5. Morley JE, Haren MT, Rolland Y, Kim MJ. Frailty. Med Clin North Am. 2006; 90:837–847. [PubMed: 16962845]
6. Green P, Woglom AE, Genereux P, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. JACC Cardiovasc Interv. 2012; 5:974–981. [PubMed: 22995885]
7. Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a predictor of surgical outcomes in older patients. J Am Coll Surg. 2010; 210:901–908. [PubMed: 20510798]
8. Afilalo J, Karunananthan S, Eisenberg MJ, Alexander KP, Bergman H. Role of frailty in patients with cardiovascular disease. Am J Cardiol. 2009; 103:1616–1621. [PubMed: 19463525]
9. Murad K, Kitzman DW. Frailty and multiple comorbidities in the elderly patient with heart failure: implications for management. Heart Fail Rev. 2012; 17:581–588. [PubMed: 21626426]
10. Harkness K, Heckman GA, McKelvie RS. The older patient with heart failure: high risk for frailty and cognitive impairment. Expert Rev Cardiovasc Ther. 2012; 10:779–795. [PubMed: 22894633]
11. Sanchez E, Vidan MT, Serra JA, Fernandez-Aviles F, Bueno H. Prevalence of geriatric syndromes and impact on clinical and functional outcomes in older patients with acute cardiac diseases. Heart. 2011; 97:1602–1606. [PubMed: 21795299]
12. Afilalo J, Mottillo S, Eisenberg MJ, et al. Addition of frailty and disability to cardiac surgery risk scores identifies elderly patients at high risk of mortality or major morbidity. Circ Cardiovasc Qual Outcomes. 2012; 5:222–228. [PubMed: 22396586]

13. Afilalo J, Eisenberg MJ, Morin JF, et al. Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. J Am Coll Cardiol. 2010; 56:1668–1676. [PubMed: 21050978]
14. Green P, Woglom AE, Genereux P, et al. Gait speed and dependence in activities of daily living in older adults with severe aortic stenosis. Clin Cardiol. 2012; 35:307–314. [PubMed: 22331630]
15. Rodriguez-Manas L, Feart C, Mann G, et al. Searching for an Operational Definition of Frailty: A Delphi Method Based Consensus Statement. The Frailty Operative Definition-Consensus Conference Project. J Gerontol A Biol Sci Med Sci. 2012
16. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr. 2008; 8:24. [PubMed: 18826625]
17. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. J Gerontol A Biol Sci Med Sci. 2007; 62:738–743. [PubMed: 17634321]
18. 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; 5:286–293. [PubMed: 22438521]
19. Butler CR, Jugdutt BI. Mechanical circulatory support for elderly heart failure patients. Heart Fail Rev. 2012; 17:663–669. [PubMed: 22237460]
20. Dimopoulos SK, Drakos SG, Terrovitis JV, Tzanis GS, Nanas SN. Improvement in respiratory muscle dysfunction with continuous-flow left ventricular assist devices. J Heart Lung Transplant. 2010; 29:906–908. [PubMed: 20462771]
21. Chung CJ, Wu C, Jones M, et al. Reduced handgrip strength as a marker of frailty predicts clinical outcomes in patients with heart failure undergoing ventricular assist device placement. J Card Fail. 2014; 20:310–315. [PubMed: 24569037]
22. Allen JG, Weiss ES, Schaffer JM, et al. Quality of life and functional status in patients surviving 12 months after left ventricular assist device implantation. J Heart Lung Transplant. 2010; 29:278–285. [PubMed: 19837607]
23. Hasin T, Topilsky Y, Kremers WK, et al. Usefulness of the six-minute walk test after continuous axial flow left ventricular device implantation to predict survival. Am J Cardiol. 2012; 110:1322–1328. [PubMed: 22819427]
24. Fang JC. Rise of the machines--left ventricular assist devices as permanent therapy for advanced heart failure. N Engl J Med. 2009; 361:2282–2285. [PubMed: 19920052]
25. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med. 2009; 361:2241–2251. [PubMed: 19920051]
26. Estep JD, Starling RC, Horstmanshof DA, et al. Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients: Results From the ROADMAP Study. J Am Coll Cardiol. 2015; 66:1747–1761. [PubMed: 26483097]
27. Jorde UP, Kushwaha SS, Tatooles AJ, et al. Results of the destination therapy post-food and drug administration approval study with a continuous flow left ventricular assist device: a prospective study using the INTERMACS registry (Interagency Registry for Mechanically Assisted Circulatory Support). J Am Coll Cardiol. 2014; 63:1751–1757. [PubMed: 24613333]
28. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol. 2000; 35:1245–1255. [PubMed: 10758967]
29. Cheng H, Gurland BJ, Maurer MS. Self-reported lack of energy (anergia) among elders in a multiethnic community. J Gerontol A Biol Sci Med Sci. 2008; 63:707–714. [PubMed: 18693225]
30. Shaffer JA, Davidson KW, Schwartz JE, et al. Prevalence and characteristics of anergia (lack of energy) in patients with acute coronary syndrome. Am J Cardiol. 2012; 110:1213–1218. [PubMed: 22835409]
31. Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education. Arch Clin Neuropsychol. 2004; 19:203–214. [PubMed: 15010086]
32. Cowger J, Sundareswaran K, Rogers JG, et al. Predicting survival in patients receiving continuous flow left ventricular assist devices: the HeartMate II risk score. J Am Coll Cardiol. 2013; 61:313–321. [PubMed: 23265328]

33. Madan SA, Fida N, Barman P, et al. Frailty Assessment in Advanced Heart Failure. J Card Fail. 2016; 22:840–844. [PubMed: 26883168]
34. 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; 100:429–436. [PubMed: 26516676]
35. Emani S, Brewer RJ, John R, et al. Patients with low compared with high body mass index gain more weight after implantation of a continuous-flow left ventricular assist device. J Heart Lung Transplant. 2013; 32:31–35. [PubMed: 23164534]
36. Gill TM, Gahbauer EA, Han L, Allore HG. The relationship between intervening hospitalizations and transitions between frailty states. J Gerontol A Biol Sci Med Sci. 2011; 66:1238–1243. [PubMed: 21852286]
37. Blaha MJ, Hung RK, Dardari Z, et al. Age-dependent prognostic value of exercise capacity and derivation of fitness-associated biologic age. Heart. 2016; 102:431–437. [PubMed: 26732181]
38. Chowdhury R, Peel NM, Krosch M, Hubbard RE. Frailty and chronic kidney disease: A systematic review. Arch Gerontol Geriatr. 2017; 68:135–142. [PubMed: 27810661]
39. Kooman JP, van der Sande FM, Leunissen KM. Kidney disease and aging: A reciprocal relation. Exp Gerontol. 2017; 87:156–159. [PubMed: 26880178]
40. Kim JC, Kalantar-Zadeh K, Kopple JD. Frailty and protein-energy wasting in elderly patients with end stage kidney disease. J Am Soc Nephrol. 2013; 24:337–351. [PubMed: 23264684]
41. Chang SS, Weiss CO, Xue QL, Fried LP. Association between inflammatory-related disease burden and frailty: results from the Women's Health and Aging Studies (WHAS) I and II. Arch Gerontol Geriatr. 2012; 54:9–15. [PubMed: 21763008]
42. Nadruz W Jr, Kitzman D, Windham BG, et al. Cardiovascular Dysfunction and Frailty Among Older Adults in the Community: The ARIC Study. J Gerontol A Biol Sci Med Sci. 2016
43. Anand S, Johansen KL, Kurella Tamura M. Aging and chronic kidney disease: the impact on physical function and cognition. J Gerontol A Biol Sci Med Sci. 2014; 69:315–322. [PubMed: 23913934]
44. Reiken S, Wehrens XH, Vest JA, et al. Beta-blockers restore calcium release channel function and improve cardiac muscle performance in human heart failure. Circulation. 2003; 107:2459–2466. [PubMed: 12743001]
45. Maurer MS, Sackner-Bernstein JD, El-Khoury Rumbarger L, Yushak M, King DL, Burkhoff D. Mechanisms underlying improvements in ejection fraction with carvedilol in heart failure. Circ Heart Fail. 2009; 2:189–196. [PubMed: 19808339]
46. Niebauer J. Is There a Role for Cardiac Rehabilitation After Coronary Artery Bypass Grafting? Treatment After Coronary Artery Bypass Surgery Remains Incomplete Without Rehabilitation. Circulation. 2016; 133:2529–2537. [PubMed: 27297345]
47. Anderson L, Oldridge N, Thompson DR, et al. Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease: Cochrane Systematic Review and Meta-Analysis. J Am Coll Cardiol. 2016; 67:1–12. [PubMed: 26764059]
48. Pulmonary R, et al. American Association of C; American College of Cardiology F. AACVPR/ACCF/AHA 2010 Update: Performance Measures on Cardiac Rehabilitation for Referral to Cardiac Rehabilitation/Secondary Prevention Services Endorsed by the American College of Chest Physicians, the American College of Sports Medicine, the American Physical Therapy Association, the Canadian Association of Cardiac Rehabilitation, the Clinical Exercise Physiology Association, the European Association for Cardiovascular Prevention and Rehabilitation, the Inter-American Heart Foundation, the National Association of Clinical Nurse Specialists, the Preventive Cardiovascular Nurses Association, and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2010; 56:1159–1167. [PubMed: 20863958]
49. Kerrigan DJ, Williams CT, Ehrman JK, et al. Cardiac rehabilitation improves functional capacity and patient-reported health status in patients with continuous-flow left ventricular assist devices: the Rehab-VAD randomized controlled trial. JACC Heart Fail. 2014; 2:653–659. [PubMed: 25447348]

50. Reeves GR, Whellan DJ, O'Connor CM, et al. A Novel Rehabilitation Intervention for Older Patients With Acute Decompensated Heart Failure: The REHAB-HF Pilot Study. JACC Heart Fail. 2017

51. Reeves GR, Whellan DJ, Duncan P, et al. Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) trial: Design and rationale. Am Heart J. 2017; 185:130–139. [PubMed: 28267466]

52. 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; 96:141–147. [PubMed: 23731606]

53. Feldman D, Pamboukian SV, Teuteberg JJ, et al. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: executive summary. J Heart Lung Transplant. 2013; 32:157–187. [PubMed: 23352391]

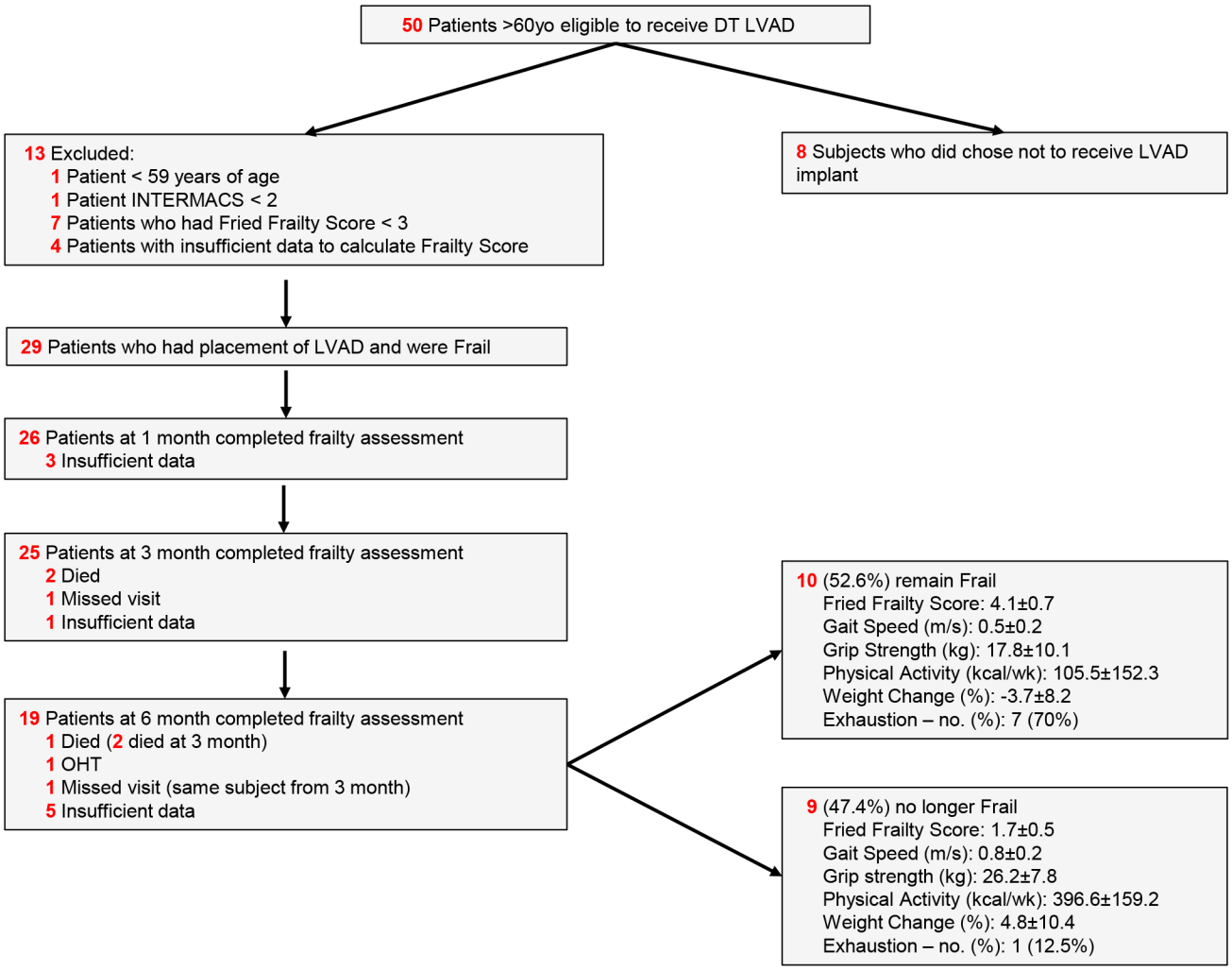

Figure 1. Study Population and Breakdown by Frailty Status after Six months

Flow chart of study population showing 50 subjects who were eligible to receive DT LVAD, of whom 42 underwent surgery and 8 declined with 29 subject enrolled in the longitudinal analysis of frailty at 1, 3 and 6 months after LVAD placement. Frailty criteria at six months after LVAD placement with weight change from baseline, prior to LVAD placement.

Table 1

Demographic and Clinical Characteristics of Subjects with LVAD Implantation who underwent Serial Assessments of Frailty (n=29) compared to other cohorts.

Parameter	Overall (n=50)	Serial Assessments (n=29)	Subjects Not Receiving LVAD (n=8)	Subjects Excluded From Serial Assessments (n=13)
Age (years)	69.5±6.2	70.6±5.5	71±5.3	66.2±7.3
Gender				
(% Male)	38 (76%)	21 (72%)	6 (75%)	11 (85%)
(% Female)	12 (24%)	8 (28%)	2 (25%)	2 (15%)
Race				
White	25 (50%)	16 (55%)	2 (25%)	7 (54%)
Black	17 (34%)	10 (34%)	3 (38%)	4 (31%)
Other	8 (16%)	3 (10%)	3 (38%)	2 (15%)
Ethnicity (% Hispanic)	7 (14%)	3 (10.3%)	2 (25%)	2 (15%)
INTERMACS (0–7)	3.1±0.7	2.9±0.5	3.4±0.8	3.2±1.1
Co-Morbidities				
Average Number	6.9±2.3	7.6±2.2	6.1±2.1	5.9±2.3
Arrhythmia	38 (76%)	24 (83%)	5 (63%)	9 (69%)
Renal Disease	36 (72%)	21 (72%)	7 (88%)	8 (62%)
Anemia	36 (72%)	22 (76%)	6 (75%)	8 (62%)
Hypertension	35 (70%)	21 (72%)	5 (63%)	9 (69%)
Hyperlipidemia	32 (64%)	20 (69%)	2 (25%)	10 (77%)
Coronary artery disease	32 (64%)	20 (69%)	5 (63%)	7 (54%)
BMI (Kg/m2)	25.2±4.3	25.4±4.8	24.5±2	25±4.3
Ejection Fraction (%)	16±4	16±4	18±5	15±4
HeartMate II Risk Score	2.29±0.94	2.28±1.04	2.78±0.81	2.06±0.73
Low Risk (<1.58)	9 (18%)	7 (24%)	0 (0%)	2 (15%)
Medium Risk (1.58–2.48)	23 (46%)	13 (45%)	2 (28.6%)	8 (62%)
High Risk (>2.48)	17 (34%)	9 (31%)	5 (71.4%)	3 (23.1%)

Table 2

Timing of changes in Frailty Score and Components after LVAD placement

Parameter	Baseline		1 Month		3 Months		6 Months	
	N	Value	N	Value	N	Value	N	Value
Frailty Score (0–5)	29	3.7±0.9	26	4±0.8	25	3±1.2	19	3.0±1.4
Frailty Grouping								
Frail – score 3–5 (%)	29	29 (100%)	26	26 (100%)	25	19 (76%)	19	10 (52.6%)
Pre-frail – score 1–2 (%)	29	0 (0%)	26	0 (0%)	25	6 (24%)	19	9 (47.4%)
Not frail – score 0 (%)	29	0 (0%)	26	0 (0%)	25	0 (0%)	19	0 (0%)
Grip strength (Kg/m^2)	28	22.4±9.5	27	18.2±8.2	23	21.9±8	23	21.5±9.5
Gait speed (m/sec)	19	0.56±0.36	20	0.64±0.19	21	0.68±0.23	16	0.65±0.22
Physical activity (Kcal)	28	69.5±109.3	25	227.7±366.6	24	222.6±260.3	20	315.2±382.1
Exhaustion	29	17 (59%)	27	16 (59%)	26	8 (31%)	22	10 (45.5%)
Weight change in last year (%)	27	−12%±11%	27	−14%±12%	24	−13%±12%	22	−7%±13%

Table 3

Changes in 6MWT, KCCQ, Trail Maker B and Anergia Score after LVAD placement in association with frailty status at 6 months

Parameter	Reduction in Frailty (n=9)		Remain Frail (n=10)		p-value
	N	Value	N	Value	
TMT part B	8	−5.4±37.2	5	−24±107.7	0.606
KCCQ					
Overall summary	8	32.5±24.9	10	4.7±30.1	0.043
Clinical summary	8	24.7±24.4	10	−2±20	0.021
Physical limitation	8	17.5±31.8	10	−8.4±24.3	0.154
Symptom stability	8	31.3±32	10	12.5±48.9	0.321
Symptom frequency	9	37.3±23.4	10	6.3±28.7	0.037
Symptom burden	8	30.2±34.5	10	2.5±22.9	0.055
Total symptom	8	31.9±24.8	10	4.4±23.1	0.037
Self-efficacy	8	3.1±5.8	10	10±17.5	0.577
Quality of life	8	39.6±29.5	10	15±54.4	0.306
Social limitation	7	43.8±34.6	9	10.9±49	0.138
PHQ-9	8	−0.3±7.1	10	−0.8±10.5	0.789
Anergia scale	8	−2.4±2.1	9	−1.1±3.1	0.379