Effect of Age and Renal Function on Survival After Left Ventricular Assist Device Implantation

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Left ventricular assist devices (LVAD) are increasingly used, especially as destination therapy in in older patients. The aim of this study was to evaluate the effect of age on renal function and mortality in the first year after implantation. A retrospective multicenter cohort study was conducted, evaluating all LVAD patients implanted in the 2 participating centers (age ≥18 years). Patients were stratified according to the age groups <45, 45–54, 55–64, and ≥65 years old. Overall, 241 patients were included (mean age 52.4 ± 12.9 years, 76% males, 33% destination therapy). The mean estimated Glomerular Filtration Rate (eGFR) at 1 year was 85, 72, 69, and 49 mL/min per 1.73 m^2 in the age groups <45(n = 65, 27%), 45–54(n = 52, 22%), 55–64(n = 87, 36%), and ≥65 years (n = 37, 15%) p <0.001)), respectively. Older age and lower eGFR at baseline (p <0.01) were independent predictors of worse renal function at 1 year. The 1-year survival post-implantation was 79%,84%, 68%, and 54% for those in the age group <45, 45–54, 55–64 and ≥65 years (Log-rank p = 0.003). Older age, lower eGFR and, INTERMACS class I were independent predictors of 1-year mortality. Furthermore, older patients (age > 60 years) with an impaired renal function (eGFR <55 mL/min per 1.73 m^2) had a 5-fold increased hazard ratio for mortality during the first year after implantation (p <0.001). In conclusion, age >60 years is an independent predictor for an impaired renal function and mortality. Older age combined with reduced renal function pre-implantation had a cumulative adverse effect on survival in patients receiving a LVAD. **(Am J Cardiol 2017;120:2221–2225)**

Despite recent improvements in survival, the morbidity and mortality associated with continuous flow—left ventricular assist device (CF-LVAD) implantation remain high.[1] This is more pronounced in patients with advanced age.[2] The aim of this study was to evaluate the effect of age on mortality and renal function after CF-LVAD implantation, either as a BTT or DT, in a multicentre setting and to explore the combined effect of age and renal function on mortality during the first year after CF-LVAD implantation.

Methods

This retrospective cohort study evaluated all patients in whom a CF-LVAD was implanted between October 2004 and August 2015 in the 2 participating tertiary referral centres. The devices were either the HeartMate II (Thoratec corp. CA.) or HVAD (HeartWare international, Inc.) CF-LVADs. Exclusion criteria were age <18 years at the time of LVAD implantation. Data were obtained from a computerized database and electronic patient files. Patients were classified into 4 groups according to their age in years (younger than 45 (<45), 45 through 54 (45–54), 55 through 64 (55–64) and 65 or greater (≥65)) at time of CF-LVAD implantation. Patients were followed up to 1 year after CF-LVAD implantation. This study was approved by the institutional review boards of the Erasmus MC, University Medical Center, Rotterdam, the Netherlands and the Johns Hopkins Hospital, Baltimore, Maryland, USA.

The primary study endpoints were all-cause mortality and renal function (defined as estimated glomerular filtration rate (eGFR)) in the first year after CF-LVAD implantation. Secondary endpoints included the need for renal replacement therapy (RRT), and improvement of renal function at 1-month post-implantation. For the evaluation of renal function after CF-LVAD implantation, serum creatinine concentrations were collected at baseline, and at 1, 3, 6, 9 and 12 months of follow-up, respectively. The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula.[3] Deaths were defined as "cardiac" when a definitive cause of death related to a cardiovascular event could be identified and as "non-cardiac" when the cause of death did not relate to the cardiovascular system. When the cause of death was unknown deaths were classified as "indeterminate". Patients

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were grouped in the RRT-group if they required RRT during the first year after CF-LVAD implantation and were treated with either continuous veno-venous hemofiltration (CVVH), or intermittent haemodialysis. During the time that patients required RRT, their eGFR was set at zero. Patients were evaluated for renal improvement after CF-LVAD implantation, which was defined as an improvement in eGFR of ≥20% at 1 month after implantation compared with baseline.

Continuous parameters were expressed as median and interquartile range or mean and standard deviation and compared by Student's t-test, ANOVA or Kruskal-Wallis test. Categorical parameters were expressed as number and percentage and compared by Chi2 test, Fisher's exact test or Linear-by-Linear Association. Kaplan-Meier curves stratified by groups were constructed for the evaluation of mortality the first year after implantation. Patients were censored at the time of HTX or LVAD explantation. Differences pooled over strata were compared by log-rank test. A multivariable Cox proportional hazards analysis was performed for identification of parameters associated with mortality and a general linear model analysis was performed for the association with eGFR 1 year after implantation. Variables were included in the model with $p < 0.10$ in the univariate analysis. Both analyses were performed in a backward stepwise manner, excluding variables with $p > 0.05$. Time-dependent receiver-operating curves (ROC) were calculated to determine discriminatory power of age and renal function. Using the maximal value of the Youden index, an optimal cut-off point for age and renal function was identified. A two-tailed p-value of <0.05 was considered statistically significant. Analyses were performed using statistical software SPSS, version 20.0 for Mac (SPSS Inc., an IBM company, Chicago, IL) and GraphPad Prism version 5.0a for Mac (GraphPad Software, La Jolla, CA).

Results

Overall, 241 patients underwent CF-LVAD implantation (mean age 52.4 ± 12.9 years, 76% male). Stratified by age, there were 65 (27%), 52 (22%), 87 (36%) and 37 (15%) patients in the age groups <45, 45–54, 55–64, ≥65. The baseline characteristics stratified by age group are reported in Table 1. Older patients were more likely to be Caucasian ($p = 0.001$), male ($p = 0.01$), treated as DT, and suffered more from ischemic cardiomyopathy as the primary cause of HF ($p < 0.001$). Furthermore, older patients more often had higher CKD stages at baseline ($p = 0.001$) and had more hypertension ($p = 0.002$). Younger patients required more often Intra-Aortic Balloon Pump (IABP) support pre-implantation ($p = 0.013$). In addition, patients aged <45 years required more often RVAD therapy ($p = 0.004$) post-implantation (Table 1).

Thirty patients (12%) died within 30 days post-implantation. Stratified by age the 30-day mortality rate was 5%, 8%, 15%, and 27% for those in the age groups <45, 45–54, 55–64 and ≥65 years ($p = 0.006$), respectively. During the first year after CF-LVAD implantation 65 patients (27%) died. The most frequent cause of death was non-cardiac (58.5%) followed by cardiac (38.5%). In 2 (3.1%) patients the cause of death was undetermined. The actuarial 1-year mortality was 21%, 16%, 32% and 46%, for those in the age groups <45, 45–54, 55–64 and ≥65 years (Log-rank $p = 0.001$, Figure 1), respectively. The HTX rate did not differ between the groups ($p = 0.51$). Factors associated with 3-months mortality are reported in the Supplementary Appendix Table 1. Univariate analysis for the relationship with mortality at 1 year identified an association with age, INTERMACS class, eGFR, and the need for IABP at baseline. After multivariate analysis, older age, lower eGFR and, INTERMACS class I at baseline, remained associated with 1-year mortality (Table 2A).

The course of renal function (eGFR) stratified by age group during the first year after transplantation is presented in Figure 2. Mean eGFR at baseline for the whole group was 60 ± 25 mL/min per 1.73 m^2 and stratified by the age groups <45, 45–54, 55–64, and ≥65 years this was 72, 58, 57, and 49 mL/min per 1.73 m^2 ($p < 0.001$), respectively. There was a significant difference in mean eGFR between the age groups over all time points during the first year post-implantation ($p < 0.001$). Of the 142 patients supported by a CF-LVAD at 1 year, 2 patients had missing laboratory values and according to their age groups <45, 45–54, 55–64 and >65 years, there were 38 (58%), 37 (71%), 51 (59%) and 14 (38%) patients alive and on CF-LVAD support, with a mean eGFR of 85, 72, 69, and 49 mL/min per 1.73 m^2 ($p < 0.001$) at 1 year, respectively. Within the different age groups, the mean eGFR improved significantly at 1 year with 12, 14, and 13 mL/min per 1.73 m^2, compared to baseline in patients aged <45 ($p < 0.008$), 45–54 ($p < 0.004$), and 55–64 years ($p < 0.004$), respectively. However, there was no significant difference in mean eGFR at 1 year compared to baseline in patients aged 65 years or older ($p = 0.73$). Univariate analysis for the relationship with eGFR at 1 year identified an association with age, Ischemic cardiomyopathy as primary cardiac disease, and eGFR at baseline. As presented in Table 2B, factors independently associated with a lower eGFR at 1 year after CF-LVAD implantation were lower eGFR at baseline and older age.

To assess the effect of age and renal function on mortality, we stratified patients into fo4ur groups based on cut-off points determined through their respective Youden index. This resulted in age 60 years and eGFR 55 mL/min per 1.73 m^2 as optimal cut-off points. Time to event analysis showed that the 1-year survival was 86%, and 69% for younger patients (age < 60 years) with eGFR ≥55 and <55 mL/min per 1.73 m^2. In addition this was 71% and 48% for older patients (age ≥60 years) with eGFR ≥55 and <55 mL/min per 1.73 m^2 (log-rank $p < 0.001$, Figure 3), respectively. Furthermore, older patients (age > 60 years) with an impaired renal function (eGFR <55 mL/min per 1.73 m^2) had a 5-fold increased hazard ratio for mortality during the first year after implantation ($p < 0.001$).

Discussion

As patients with advanced are more frequently referred for CF-LVAD implantation due to ineligibility for HTX, age-related factors related to prognosis and outcome become more important. We determined that older age adversely affects renal function as well as survival 1-year post-implantation. In addition, older patients are less likely to experience an improvement in renal function following CF-LVAD implantation. Furthermore, due to the cumulative adverse effect on survival of older age and reduced renal function, these factors