Meta-Analysis of the Effect of Preoperative Atrial Fibrillation on Outcomes After Left Ventricular Assist Device Implantation

Muhammad Shariq Usman, MBBS[a], Saba Ahmed, MBBS[a], Naser Yamani, MD[b], Tauseef Akhtar, MD[b], Nisar Asmi, MD[b], Tariq Jamal Siddiqi, MBBS[a], Safi U. Khan, MD[c], Rami Doukky, MD[b,d], and Muhammad Shahzeb Khan, MD[b,*]

The effect of preoperative atrial fibrillation (AF) on clinical outcomes after left ventricular assist device (LVAD) implantation remains uncertain. We sought to conduct a meta-analysis to assess the safety and efficacy of LVAD implantation in AF patients. Medline and Scopus were searched for studies that assessed the effect of preoperative AF on clinical outcomes in patients who underwent LVAD implantation. Outcomes of interest included all-cause mortality, thromboembolic events, and bleeding. Estimates were combined using random effects model to calculate risk ratios (RRs) with 95% confidence intervals. In this meta-analysis of 7 studies including 5,658 patients, preoperative AF was not associated with increased risk of all-cause mortality at 30 days (RR = 0.84 [0.51, 1.37]; p = 0.49; I^2 = 0%), 6 months (RR = 1.17 [0.96, 1.14]; p = 0.11; I^2 = 21%), 1 year (RR = 1.16 [0.84, 1.60]; p = 0.37; I^2 = 53%) and 2 years (RR = 1.14 [0.96, 1.36]; p = 0.12; I^2 = 23%). Preoperative AF did not increase the risk of thromboembolism (RR = 0.86 [0.38, 1.92]; p = 0.71; I^2 = 26%), pump thrombosis (RR = 1.22 [0.88, 1.68]; p = 0.23; I^2 = 49%), stroke (RR = 1.02 [0.87, 1.19]; p = 0.79; I^2 = 11%), or major bleeding (RR = 0.86 [0.38, 1.92]; p = 0.71; I^2 = 26%) after LVAD implantation. However, AF was associated with significantly increased risk of gastro-intestinal bleeding in patients receiving LVADs (RR = 1.27 [1.05, 1.55]; p = 0.014; I^2 = 0%). In conclusion, this meta-analysis reports a significantly increased risk of gastrointestinal (GI) bleeding in LVADs recipients having concomitant AF. However, AF had no significant effect on all-cause mortality, stroke, or thromboembolic events in these patients. Further well-conducted studies are needed to validate these results. **(Am J Cardiol 2019;124:158−162)**

The use of left ventricular assist devices (LVAD) in the treatment of end-stage heart failure (HF) has increased over the past decade with more than 2,000 devices being implanted annually in the United States.[1] LVADs have become the preferred therapy in patients with advanced HF as a bridge to cardiac transplantation or as a destination therapy in terminal cardiac dysfunction.[2,3] Both atrial fibrillation (AF) and HF often coexist and foster each other. According to a recent report by American Heart Association (AHA), AF is prevalent in >50% of patients suffering from advanced HF with reduced ejection fraction. Since patients with AF are at a higher risk for adverse outcomes after coronary artery bypass grafting,[4] extrapolating this evidence to LVAD patients, it has been hypothesized that AF is associated with worse outcomes post LVAD implantation. This aspect can potentially increase the morbidity and generate futile consumption of resources.[5] However, studies based on this hypothesis have yielded conflicting results, expanding from generating adverse outcomes to neutral results in patients with AF. To address this inconsistency, we decided to pool the data and systematically evaluate the safety and efficacy of LVAD implantation in AF patients.

Methods

This systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic review and Meta-Analyses guidelines, and the AHA guidelines.[6,7]

Two independent authors (TJS and SA) performed the literature search using Scopus and MEDLINE from the inception of these databases to December 2018. No restrictions were applied on study design, language, or follow-up duration. Detailed search strategies for each database are given in the supplementary files (Table S1). Snowballing from relevant articles was also performed to ensure no pertinent articles were missed.

The predefined eligibility criteria were: (1) All cohort (whether prospective or retrospective) and randomized control trials that sought to determines the effect of preoperative AF on outcomes in HF patients who underwent LVAD implantation; and (2) studies reporting all-cause mortality and/or incidence of cardiovascular events in adult patients (≥18 years).

[a]Internal Medicine, Dow University of Health Sciences, Karachi, Pakistan; [b]Internal Medicine, John H Stroger Jr Hospital of Cook County, Chicago, Illinois; [c]Department of Internal Medicine, West Virginia University, Morgantown, West Virginia; and [d]Division of Cardiology, Rush University Medical Center, Chicago, Illinois. Manuscript received February 8, 2019; revised manuscript received and accepted March 19, 2019.

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*Corresponding author: Tel: (404) 259-3490.

E-mail address: shahzebkhan@gmail.com (M.S. Khan).

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All articles retrieved from the systematic search were exported to Endnote Reference Library (Version X8.1; Clarivate Analytics, Philadelphia, Pennsylvania) software, where duplicates were identified and removed. Two reviewers (TSJ and SA) independently screened all remaining articles based on priori inclusion/exclusion criteria. Any discrepancy was resolved by discussion, referring back to original article or third party review (MSK). Relevant articles were initially short listed on the basis of the title and abstracts, after which the full text was read to confirm relevance.

Data were abstracted on a standardized data collection and the following information was extracted: baseline characteristics of the participants, events, nonevents, sample size, point estimates, and follow-up duration. Outcomes of interests were 6-month mortality, 1-year mortality, 2-year mortality, pump thrombosis, stroke, ischemic stroke, hemorrhagic stroke, and gastrointestinal (GI) bleeding. Data extraction was carried out by 2 independent authors (TJS and SA) and data adjudication was performed by MSK. End points were defined as reported in the individual studies. Quality assessment was carried out using the Newcastle-Ottawa scale and a score of >7 out of 9 on the Newcastle-Ottawa scale are considered to have a good methodological quality and low bias.[8]

The Open MetaAnalysis software was used to perform the statistical analyses. The results from trials were presented as risk ratios (RRs) with 95% confidence intervals. Hazard ratios were treated as RRs if they did not change over time. Outcomes were combined using generic invariance random effects model. Higgins I^2 statistic was used to evaluate heterogeneity across studies and a value of $I^2 = 25\%$ to 50% was considered mild, 50% to 75% as moderate, and >75% as severe.[9] A visual inspection of the funnel plot and Egger's regression test were used to assess publication bias. To assess impact of individual study on pooled outcomes, we conducted leave-one-out sensitivity analysis for the following outcomes: 6-month mortality, 1-year mortality, 2-year mortality, stroke, GI bleeding, and pump thrombosis by Open Meta-Analyst. A p value of <0.05 was considered significant for all analyses.

Results

An initial literature search yielded 211 potentially relevant articles. After applying eligibility criteria, 7 studies were selected for the current meta- analysis. The Preferred Reporting Items for Systematic review and Meta-Analyses flow chart (Fig. 1) outlines the literature search.

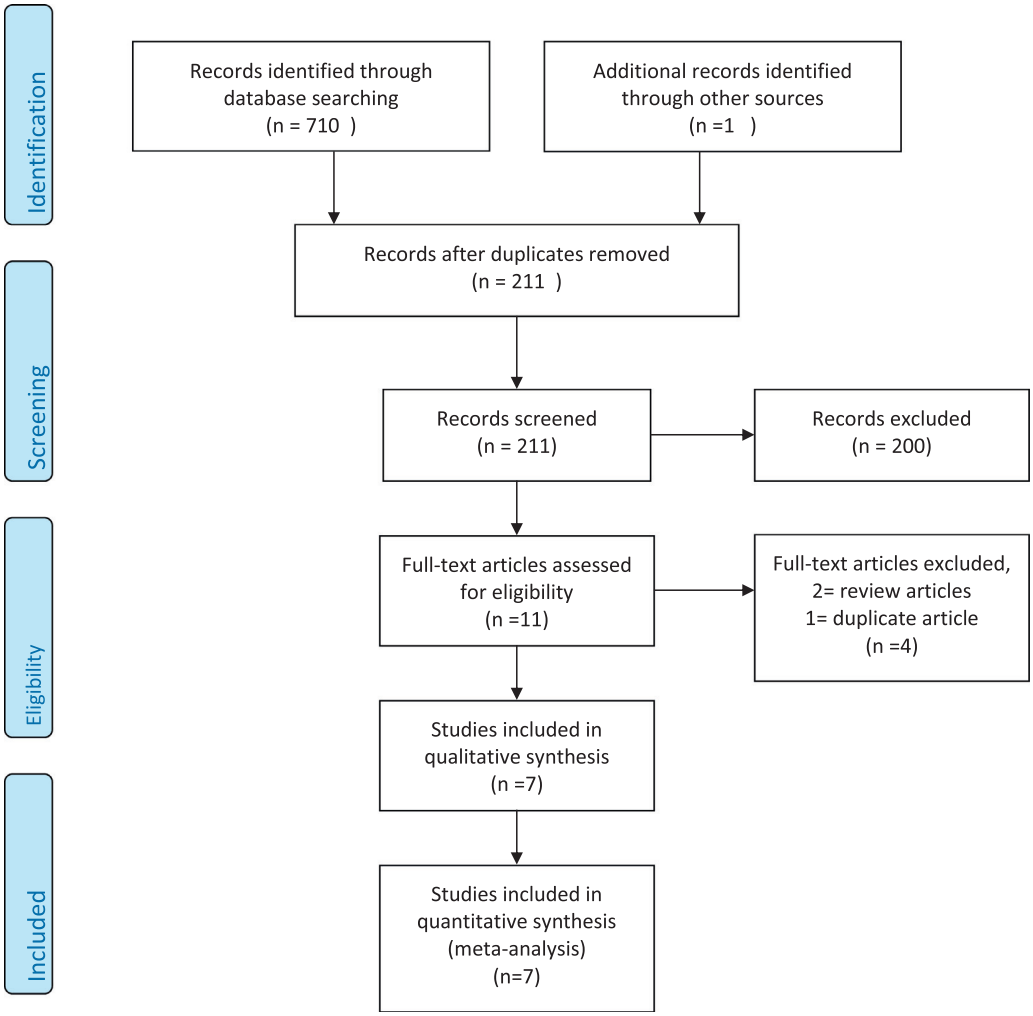

Figure 1. PRISMA chart outlining the literature search.

Table 1
Baseline characteristics of the included studies

First author, year	Sample size	Mean age (years)	Men	DM (%)	HTN (%)	Follow-up (months)
	AF/NAF	AF/NAF	AF/NAF	AF/NAF	AF/NAF	
Stulak JM, 2013.[5]	120/269	60.0	79.2%	28.0%	37.0%	10
Enriquez AD, 2014.[10]	55/51	N/A	80.0%/84.3%	52.3%/33.3%	N/A	N/A
Xuereb L, 2016.[23]	78/162	55.7/ 53.9	82.1%/71.6%	38.5%/50.6%	85.9%/84.0%	N/A
Xia Y, 2016.[15]	838/3071		82.9%/77.8%	38.5%/50.6%	85.9%/84.0%	8.5
Oezpeker C, 2017.[11]	117/205	60.0/52.5	89.7%/83.5%	14.1%/18.3%	42.7%/25.9%	24
Deshmukh A, 2017.[24]	152/179		78.9%/76.0%	25.6%/24.9%	42.7%/25.9%	11
Kurihara C, 2018.[25]	229/297	58.5/53.0	81.2%/75.6%	46.7%/42.1%	64.2%/58.2%	N/A

The 7 studies consisted of 5,658 patients who underwent LVAD implantation (AF patients = 1,424; Non-AF patients = 4,234). All studies were prospective cohort studies. The mean age across studies ranged from 53 to 60 years with the median being 56 years. The mean follow-up time was 16 months. Characteristics of the included studies are outlined in Table 1. Visual inspection of the funnel plot and Egger's regression test (p = 0.267) both suggested absence of publication bias (Figure 2). Quality assessment suggested high methodological quality for most studies (Table S2).

The summarized results of our meta-analysis are shown in Figure 3. Four studies reported mortality at 6 months (AF patients = 1,168; Non-AF patients = 3,709; Figure S1.1) and 2 years (AF patients = 544; Non-AF patients = 993; Figure S1.2). Although, 1-year mortality was provided by 5 studies (AF patients = 405; Non-AF patients = 907; Figure S1.3).

Patients who had AF underwent LVAD implantation were not associated with an increased risk of mortality at 6 months (RR = 1.17 [0.96, 1.14]; p = 0.11; I^2 = 21%), 1 year (RR = 1.16 [0.84, 1.60]; p = 0.37; I^2 = 53%), or 2 years (RR = 1.14 [0.96, 1.36]; p = 0.12; I^2 = 23%).

Pump thrombosis (Figure S1.4) was provided by 3 studies (AF patients = 1,184; Non-AF patients = 3,573). We found patients with AF before LVAD implant were not at an increased risk of pump thrombosis (RR = 1.22 [0.88, 1.68]; p = 0.23; I^2 = 49%).

Stroke (Figure S1.5) was reported by 3 studies (AF patients = 1,184; Non-AF patients = 3,573). AF in patients with LVAD implant did not increase the risk of stroke (RR = 1.02 [0.87, 1.19]; p = 0.79; I^2 = 11%). No statistical difference was seen when we analyzed patients separately for hemorrhagic stroke (RR = 0.96 [0.68, 1.35]; p = 0.83; I^2 = 0%; Figure S1.6) or ischemic stroke (RR = 1.10 [0.78, 1.56]; p = 0.57; I^2 = 0%; Figure S1.7).

Three studies (AF patients = 1,184; Non-AF patients = 3,573) reported GI bleeding (Figure S1.8). We found patients with AF before LVAD implant were at a significantly increased risk of GI bleeding (RR = 1.27 [1.05, 1.55]; p = 0.014; I^2 = 0%).

Leave-one-out sensitivity analysis revealed that the following outcomes were heavily influenced by 1 single study: 6-month mortality, GI bleeding, and pump thrombosis. The remaining outcomes were robust, and results did not differ with removal of any single study. Details of this analysis

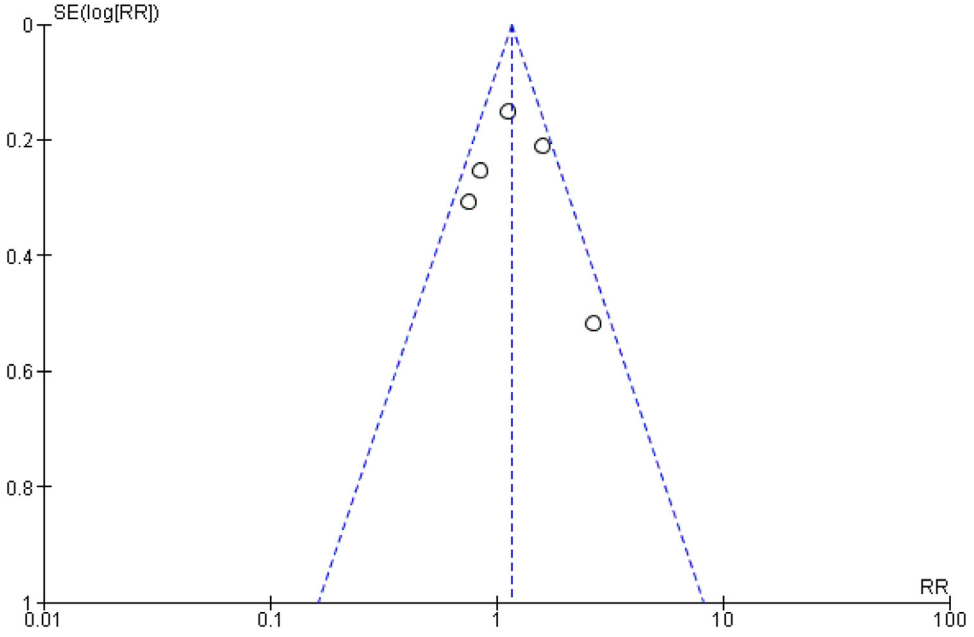

Figure 2. Funnel plot.

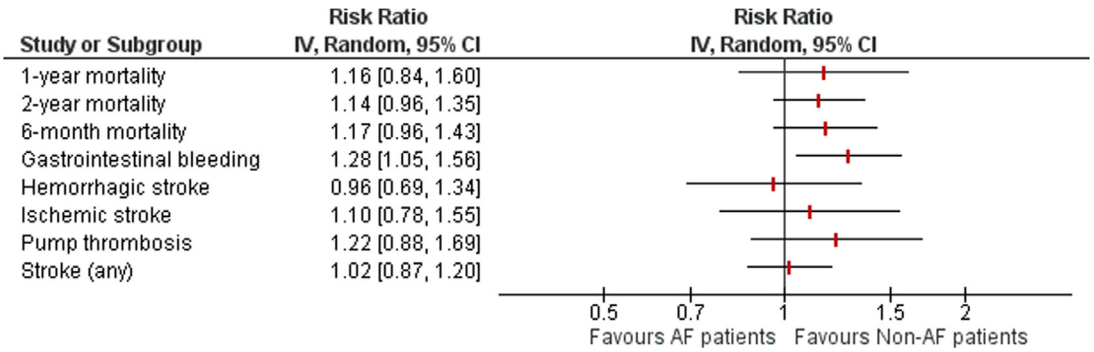

Figure 3. Summarized results of the meta-analysis.

are provided in the supplemental material (Figure S2.1 to S2.6).

Discussion

In this meta-analysis of 7 studies including 5,658 patients, preoperative AF in patients receiving LVADs was not significantly associated with increased risk of all-cause mortality. Preoperative AF did not increase the risk pump thrombosis or stroke after LVAD implantation. However, there was significantly 27% increased relative risk of gastro-intestinal bleeding in these patients.

We compare our results with former reports. A study by Oezpeker et al found significantly higher 2-year mortality rates in patients with AF while another study be Enriquez et al demonstrated increased mortality in patients with persistent AF.[10,11] In both cases, the patient population with AF was significantly older and had a significantly higher percentage of hypertension and diabetes mellitus, respectively. These differences might have contributed to worse outcomes after LVAD implantation in the aforementioned studies.

Although we did not find any significant difference in the increased incidence of major bleeding between the 2 groups, there was a significantly increased risk of GI bleeding in patients with preoperative AF. A previous study found GI to be the most common site for bleed in patients with LVAD implants.[12] The American College of Cardiology/AHA AF guidelines recommends that anticoagulation therapy should be tailored to individual patients based on the relative and absolute risk of stroke and bleeding[13] Some studies even suggest a higher INR target value for patients with AF in order to reduce TE events, which in turn potentiates the risk of bleeding.[14,15] Furthermore, the risk of GI bleeding associated with old age has been well documented in older studies.[16] Uriel et al demonstrated that the risk for bleeding post-LVAD implantation in a patient more than 60 years of age is 65%.[17] In our analysis the median age in the AF group was higher in all studies, and this could have predisposed the patients to bleeding.

The direct contact between the foreign material on LVAD and blood causes a hypercoagulable state via activation of platelets and altered coagulation profile.[18] As AF is also associated with increased blood stasis, it appears to increase the risk of thromboembolism in patients with LVAD implants. Our results are inconsistent with this theory. According to our analysis, AF is not associated with an increased risk of thromboembolism or pump thrombosis. This could be attributed to more advanced anticoagulation regime employed by different studies with some patients even self-monitoring INR which has shown to reduce thromboembolic events.[19,20] Conversely, Enriquez et al demonstrated equal thromboembolic events in both groups despite of increased anticoagulation provided to the AF group. Further research is required to fully understand the effect of altered anticoagulation on the risk of TE and bleeding in patients with AF. Furthermore, we did not find increased risk of any type of stroke even though, preoperative AF has been documented to increase the incidence of stroke in adults who underwent cardiac surgery.[21,22]

To our knowledge, this is the first meta-analysis to combine the results of the effects of preoperative AF in patients with LVAD implants. However, our study has certain limitations. The setting for the studies conducted was different, each employed their own operative and postoperative management and different regimens for prevention of adverse events. Discrepancies in baseline patient demographics and clinical characteristic may have affected the results and contributed to clinical heterogeneity. Observational studies are likely to have residual confounding, and hence meta-analysis of these studies is prone to bias as well.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.03.038.

1. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Miller MA, Baldwin JT, Young JB. Sixth INTERMACS annual report: a 10,000-patient database. *J Heart Lung Transpl* 2014;33:555–564.
2. Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, Ulisney KL, Baldwin JT, Young JB. Third INTERMACS annual report: the evolution of destination therapy in the United States. *J Heart Lung Transpl* 2011;30:115–123.
3. Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, Baldwin JT, Young JB. The fourth INTERMACS annual report: 4,000 implants and counting. *J Heart Lung Transpl* 2012;31:117–126.

4. Bramer S, van Straten AH, Soliman Hamad MA, Berreklouw E, Martens EJ, Maessen JG. The impact of preoperative atrial fibrillation on early and late mortality after coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2010;38:373–379.
5. Stulak JM, Deo S, Schirger J, Aaronson KD, Park SJ, Joyce LD, Daly RC, Pagani FD. Preoperative atrial fibrillation increases risk of thromboembolic events after left ventricular assist device implantation. *Ann Thorac Surg* 2013;96:2161–2167.
6. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
7. Rao G, Lopez-Jimenez F, Boyd J, D'Amico F, Durant NH, Hlatky MA, Howard G, Kirley K, Masi C, Powell-Wiley TM, Solomonides AE, West CP, Wessel J, American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; and Stroke Council. Methodological standards for meta-analyses and qualitative systematic reviews of cardiac prevention and treatment studies: a scientific statement from the American Heart Association. *Circulation* 2017;136:e172–e194.
8. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. (2014). Accessed March 15, 2019: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
9. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–560.
10. Enriquez AD, Calenda B, Gandhi PU, Nair AP, Anyanwu AC, Pinney SP. Clinical impact of atrial fibrillation in patients with the HeartMate II left ventricular assist device. *J Am Coll Cardiol* 2014;64:1883–1890.
11. Oezpeker C, Zittermann A, Pühler T, Ensminger S, Gummert JF, Morshuis M. Permanent atrial fibrillation and 2 year clinical outcomes in patients with a left ventricular assist device implant. *ASAIO J* 2017;63:419–424.
12. Boyle AJ, Jorde UP, Sun B, Park SJ, Milano CA, Frazier OH, Sundareswaran KS, Farrar DJ, Russell SD, HeartMate II Clinical Investigators. Pre-operative risk factors of bleeding and stroke during left ventricular assist device support: an analysis of more than 900 HeartMate II outpatients. *J Am Coll Cardiol* 2014;63:880–888.
13. Feldman D, Pamboukian SV, Teuteberg JJ, Birks E, Lietz K, Moore SA, Morgan JA, Arabia F, Bauman ME, Buchholz HW, Deng M, Dickstein ML, El-Banayosy A, Elliot T, Goldstein DJ, Grady KL, Jones K, Hryniewicz K, John R, Kaan A, Kusne S, Loebe M, Massicotte MP, Moazami N, Mohacsi P, Mooney M, Nelson T, Pagani F, Perry W, Potapov EV, Eduardo Rame J, Russell SD, Sorensen EN, Sun B, Strueber M, Mangi AA, Petty MG, Rogers J. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: executive summary. *J Heart Lung Transpl* 2013;32:157–187.
14. Boyle A. Arrhythmias in patients with ventricular assist devices. *Curr Opin Cardiol* 2012;27:13–18.
15. Xia Y, Stern D, Friedmann P, Goldstein D. Preoperative atrial fibrillation may not increase thromboembolic events in left ventricular assist device recipients on midterm follow-up. *J* Heart Lung Transpl 2016;35:906–912.
16. Morgan JA, Paone G, Nemeh HW, Henry SE, Patel R, Vavra J, Williams CT, Lanfear DE, Tita C, Brewer RJ. Gastrointestinal bleeding with the HeartMate II left ventricular assist device. *J Heart Lung Transpl* 2012;31:715–718.
17. Uriel N, Pak SW, Jorde UP, Jude B, Susen S, Vincentelli A, Ennezat PV, Cappleman S, Naka Y, Mancini D Uriel N, Pak SW, Jorde UP, Jude B, Susen S, Vincentelli A, et al. Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation. *J Am Coll Cardiol* 2010;56:1207–1213.
18. John R, Panch S, Hrabe J, Wei P, Solovey A, Joyce L, Hebbel R. Activation of endothelial and coagulation systems in left ventricular assist device recipients. *Ann Thorac Surg* 2009;88:1171–1179.
19. Oezpeker C, Zittermann A, Pühler T, Ensminger S, Gummert JF, Morshuis M. Permanent atrial fibrillation and 2 year clinical outcomes in patients with a left ventricular assist device implant. *ASAIO J* 2017;63:419–424.
20. Heneghan C, Ward A, Perera R, Bankhead C, Fuller A, Stevens R, Bradford K, Tyndel S, Alonso-Coello P, Ansell J, Beyth R. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. *Lancet* 2012;379:322–334.
21. Attaran S, Shaw M, Bond L, Pullan MD, Fabri BM. A comparison of outcome in patients with preoperative atrial fibrillation and patients in sinus rhythm. *Ann Thorac Surg* 2011;92:1391–1395.
22. Bramer S, van Straten AH, Soliman Hamad MA, Berreklouw E, Martens EJ, Maessen JG. The impact of preoperative atrial fibrillation on early and late mortality after coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2010;38:373–379.
23. Xuereb L, Go PH, Kaur B, Akrawe S, Nemeh HW, Borgi J, Williams CT, Paone G, Morgan JA. Impact of preoperative atrial fibrillation on postoperative thromboembolic events after left ventricular assist device implantation. *Ann Thorac Surg* 2016;102:1543–1549.
24. Deshmukh A, Kim G, Burke M, Anyanwu E, Jeevanandam V, Uriel N, Tung R, Ozcan C. Atrial arrhythmias and electroanatomical remodeling in patients with left ventricular assist devices. *J Am Heart Assoc* 2017;6. pii: e005340.
25. Kurihara C, Critsinelis A, Kawabori M, Sugiura T, Civitello AB, Morgan JA. Effect of preoperative atrial fibrillation on patients with chronic heart failure who undergo long-term continuous-flow LVAD implantation. *ASAIO J* 2018;64:594–600.