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Research paper

Hyperpolypharmacy is a predictor of mortality after left ventricular assist device (LVAD) implantation

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ABSTRACT

Background: The prevalence of (hyper)polypharmacy in patients on left ventricular assist device (LVAD) support and its effect on clinical outcomeis unknown. Therefore, we aimed to determine the prevalence of (hyper)polypharmacy in LVAD patients and evaluate its association with mortality and complications.

Materials and methods: 210 patients aged ≥40 years who received a primary LVAD implantation between 2011 and 2019 were included for analysis. Polypharmacy and hyperpolypharmacy were defined as the concomitant use of 5–9 and ≥10 medications at discharge after LVAD implantation, respectively. Cause specific cox regression was used to assess the association of ≥10 medications with mortality, cardiac arrhythmia, driveline infection and major bleeding.

Results: The median age of the patients was 57.5 years, and 35.7 % were female. The average number of discharge medications was 8.8 ± 2.3 per patient. The prevalence of patients with 5–9 medications and ≥10 medications was 62.9 % and 34.8 %, respectively. The median follow-up duration was 948 days (interquartile range 874 days). The prescription of ≥10 medications was significantly associated with a higher risk of mortality (HR 2.03; 95 % CI 1.15–3.6, *p*-value 0.02) adjusted for sex, age, comorbidity and stratified for device type. The prescription of ≥10 medications was not associated with a higher risk of major bleeding, cardiac arrhythmia or driveline infection.

Conclusions: (Hyper)polypharmacy is highly prevalent in LVAD patients and is independently associated with a higher risk of mortality. Future research is needed to assess the efficacy of individual risk-benefit profiling of (cardiovascular) medication to ensure appropriate polypharmacy and to decrease negative health outcomes.

1. Introduction

Heart failure (HF) is a chronic and progressive clinical syndrome affecting at least 26 million people worldwide and its prevalence continues to increase [1]. Treatment options include lifestyle changes, pharmacological treatment, device therapy, coronary revascularisation and cardiac rehabilitation according to HF severity. In case of therapy-resistant symptomatic end-stage HF, there may be an indication for heart transplantation or mechanical support with a Left Ventricular Assist Device (LVAD) [2]. Due to the progressive nature of HF and current donor heart scarcity, patients on the heart transplant waiting list often need LVAD implantation to maintain adequate cardiac output (bridge to transplantation). LVAD implantation is also a permanent therapy for those who do not qualify or opt for heart transplantation (destination therapy). The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial has shown that LVAD destination therapy leads to a higher survival rate and quality of life in patients ineligible for transplantation [3]. Current survival at one, two and three years after LVAD implantation in the Netherlands is 83 %, 76 % and 70 %, respectively [4]. Despite these promising results, major adverse events are common after LVAD implantation: one year after LVAD implantation 41 % of the patients have

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suffered from a major infection (a clinical infection treated by antimicrobial agents), 21 % from gastro-intestinal bleeding and 13 % from stroke [5].

HF patients have a higher prevalence of co-morbidities when compared to patients of similar age without HF [6]. This is especially the case of patients for LVAD destination therapy, not eligible for heart transplantation due to advanced age, non-cardiac comorbidities or frailty [7]. The pharmacological treatment of these cardiac and non-cardiac comorbidities in patients with end stage HF generates a high prevalence of polypharmacy (17 to 99 %) [8], usually defined as the concomitant use of ≥5 regularly prescribed medications, and even of hyperpolypharmacy (26 % to 74 %) [9,10], which is defined as the use of at least 10 different medications. Although sometimes unavoidable in order to comply with guidelines, (hyper)polypharmacy should not be considered harmless. In patients with HF, polypharmacy is associated with a higher risk of overtreatment, undertreatment, medication errors, poor adherence, adverse drug-reactions and drug-drug interactions [11–13]. Kennel et al. showed that hyperpolypharmacy in patients with HF is independently associated with an increased rate of ambulatory contacts and hospital admissions [9].

No studies are available on the prevalence of polypharmacy and hyperpolypharmacy in patients on LVAD support and the association with adverse outcomes after LVAD implantation. The aim of our study was to determine the prevalence of polypharmacy (5–9 medications) and hyperpolypharmacy (≥10 medications) in patients after primary LVAD implantation and to evaluate the association of hyperpolypharmacy with overall mortality and complications while on LVAD support.

2. Methods

2.1. Study design, setting and population

We conducted a retrospective cohort study at the University Medical Centre Utrecht, a tertiary hospital in the Netherlands. All consecutive patients who underwent primary LVAD implantation between 01 and 01-2011 and 31-12-2019 were included if they were 40 years or older at implantation and survived the index admission. Data on mortality and complications were collected until 1-1-21, so each patient was followed for at least one year. We included patients 40 years of age or older, because a medication review is part of a comprehensive geriatric assessment (CGA) and we assume that a CGA in patients younger than 40 years will provide relatively few clinically relevant findings, since a CGA focuses on problems that occur particularly in older age (including impaired cognition, decreased functionality, limited social network). Patients who died during the index admission, i.e. the admission in which the LVAD was implanted, were not included in this study as no discharge medication was available for these patients. For these patients, it was not possible to use the medication list that was in use at the time of death to determine whether they were taking ≥10 medications because it often involved intercurrent medications (antibiotics, strong analgesics, inotropics), and this biased the presence of the prescription of ≥10 medications.

The local medical ethics committee gave approval for a waiver to obtain informed consent (reference number WAG/mb/20/013298) given the anonymity of data collection and the non-interventional nature of the study.

2.2. Data collection

Data were collected on patient characteristics (age at implantation, sex, body mass index), aetiology of cardiomyopathy, device type and Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile before primary implantation. The INTERMACS classification comprises 7 severity profiles corresponding to New York Heart Association class III and IV, with INTERMACS 7 corresponding to advanced New York Heart Association class III heart failure and INTERMACS 1 representing the situation of critical cardiogenic shock [14]. Data were also collected on mortality and the occurrence of complications [15].

The medical history, both cardiac and non-cardiac, was obtained from the discharge letter of the index admission. Chronic conditions and acute somatic problems from which a patient had not yet recovered during admission were documented using the 2016 version of the tenth edition of the International Classification of Diseases [16]. This data was then used to determine the Charlson Comorbidity Index (CCI) score [17]. The CCI scores the presence of certain comorbidities, with a maximum score of 33, and predicts the 10-year survival in patients with multiple comorbidities. Originally, age is included in the calculation of 10-year survival using the CCI. However, because we already included age as a variable in the cox proportional hazards models, we calculated the CCI for each patient without assigning points to age.

Discharge medication was also collected from the discharge letter of the index admission. Medications were grouped to present medication use in a convenient way and to perform analyses of associations between specific medication groups and outcomes. The internationally widely and long-used Anatomical Therapeutic Chemical (ATC) classification system was used for this purpose [18]. In the ATC classification system, the active substances are classified at five levels. We chose to use discharge medication to determine medication use because it better reflects the overall medical situation after LVAD implantation than admission medication, where some of the patients are not yet on cardiac medication or medication for other co-morbidities. The following medication was excluded from data collection: medication prescribed as needed, medication administered by cutaneous (skin cream) or ophthalmic routes (eye drops), medication without an existing ATC code and over-the-counter vitamins. Medication use was divided into 0–4 medications (no polypharmacy), 5–9 medications (polypharmacy) and ≥ 10 medications (hyperpolypharmacy).

2.3. Primary and secondary endpoints

The primary endpoint of the study was death or urgent heart transplantation (HTx). We chose to combine these two outcomes under the assumption that without receiving the heart transplantation (urgent recipient) the patient would die in the very short term. Urgent heart transplantation was defined as heart transplantation for which the patient received a priority status on the waiting list (national 1A, national 1B, or international HU). The secondary outcomes were defined using the adverse event definitions formulated by INTERMACS that occurred in at least 50 patients after discharge: cardiac arrhythmia, driveline infection and major bleeding [15].

2.4. Statistical analysis

Baseline variables are expressed as numbers and percentages for categorical variables, and mean and standard deviations (SD) or median and inter quartile ranges (IQR) for continuous variables. Differences in baseline variables and prevalence of mortality and complications between patients with 0–9 medications and ≥10 medications were determined by the Fisher's exact test for categorical variables, and independent *t*-tests or Mann-Whitney *U* test for continuous variables.

Kaplan-Meier analysis was performed, categorized in patients with 0–9 medications and ≥10 medications. Cox proportional hazards models were applied, to assess the association of the prescription ≥10 medications with our primary outcome. Patients on ongoing support at the end of follow-up and patients that received a non-urgent heart transplantation were censored. Hazard Ratios (HR) and 95 % Confidence Intervals (95 % CI) were calculated. In addition, the HRs were stratified for device type and adjusted for age at implantation, sex, comorbidities (by means of the CCI score), to examine whether the prescription ≥10 medications merely reflects the presence of comorbidities or an

independent factor. As a sensitivity analysis, an additional cox model was used with the number of medications as a continuous variable. In addition, in another cox model tertiles of the number of medications were used as a variable to study the association with the primary outcome. Because most of the deceases had a neurologic (stroke) or cardiac cause, an additional cox analysis was performed to examine the association of medications to prevent stroke and cardiac medication, with the primary outcome. Medications to prevent stroke concerned the medication groups antihypertensives (ATC groups C07-C09), antithrombotics (B01) and lipid-lowering agents (C10). Cardiac medications involved the ATC groups B01, C01, C03, C07, C08, C09, C10. Another sensitivity analysis was performed, similar to the primary multivariate cox regression analysis. However, now patients were also censored for urgent heart transplantation, as this was usually done in literature. The proportional hazard assumption was met in all cox models. The predictor variables age, sex, CCI, device type and the prescription ≥10 medications were tested for multicollinearity by inspection of correlation coefficients and variance inflation factor (VIF) values, and there was no indication of multicollinearity. To determine whether the effect of ≥10 medications on mortality was modified by age, a cox model with the interaction between age and the prescription ≥10 medications was performed.

To evaluate the association between the prescription ≥10 medications and the secondary outcomes, cause-specific cox models were used, censoring for competing outcomes (death, heart transplantation, explanation). In case of recurrent adverse events, the first event was used for analysis. HR's were stratified for device type and adjusted for age, sex and CCI. For all tests, a *p*-value ≤0.05 was considered statistically significant. All analyses were performed using R version 3.6.3.

3. Results

3.1. Patient inclusion and baseline characteristics

A total of 232 consecutive patients aged 40 years and older underwent primary LVAD implantation between January 2011 and January 2020. For 22 patients (9 %) discharge medication was not available due to postoperative in-hospital mortality. These patients were excluded from the study. In total, 210 patients were included in the study. Baseline characteristics are presented in Table 1.

The median age was 57.5 years at the time of LVAD implantation and 35.7 % were female. The number of comorbidities and the CCI score was significantly higher in the group of patients with ≥10 medications than in the group of patients with 0–9 medications (number of comorbidities 6.3 ± 2.4 versus 5.0 ± 1.8, CCI score 2.0 ± 0.9 versus 1.7 ± 0.8).

3.2. Prevalence of polypharmacy and hyperpolypharmacy

The average number of discharge medications was 8.8 ± 2.3. Five patients (2.4 %) used 0–4 medications (no polypharmacy), with a mean number of 3.6 medications per patient. The majority (132 patients, 62.9 %) used 5–9 medications (polypharmacy), with a mean of 7.6 prescriptions per patient. A total of 73 patients (34.8 %) used ≥10 medications (hyperpolypharmacy), with on average 11.3 medications per patient. Fig. 1 shows the distribution of the number of medications per patient, ranging from 3 to 15. Since only 5 patients met the criterion for no polypharmacy (0–4 medications), this group was combined with patients with 5–9 medications and compared to patients with ≥10 medications.

Of the total of 1839 prescribed medications, 1001 (54.4 %) were cardiovascular medications. Most frequently prescribed were antithrombotics (vitamin K antagonists and acetylsalicylic acid are routine medications for patients with an LVAD), diuretics, agents acting on the renin-angiotensin system and antiarrhythmic medications (predominantly amiodarone). (Supplementary Table S1) Most commonly used non-cardiovascular medications were medications for acid related disorders (in particular proton pump inhibitors), analgesics (predominantly paracetamol), and mineral supplements (mainly potassium chloride). Finally, sildenafil was commonly used. Sildenafil falls under urological agents according to the ATC classification system, but the patients in this study used it to lower pulmonary pressure (right ventricle afterload reduction).

Supplementary Fig. S1 presents the difference in medication use between patients who survived during the follow-up period and those who died or underwent urgent HTx. Antithrombotics, medication for acid related disorders and diuretics were the most commonly used medication groups. There were no differences between both patient groups.

Table 1
Baseline characteristics of patients with 0–9 medications and ≥10 medications.

Demographics		All patients (*n* = 210)	0–9 medications (*n* = 137)	≥10 medications (*n* = 73)	P-value
Sex number (%) -Female		75 (35.7)	51 (37.2)	24 (32.9)	0.64
Age at implantation (years) median [IQR]		57.5 [11]	57.0 [13]	58 [10]	0.44
Body mass index (kg/m^2) median [IQR]		24.2 [6]	23.7 [6]	25.2 [5]	0.04
Comorbidities mean ± SD					
- Total number		5.5 ± 2.1	5.0 ± 1.8	6.3 ± 2.4	<0.001
- Charlson Comorbidity Index[a]		1.8 ± 0.8	1.7 ± 0.8	2.0 ± 0.9	0.002
Number of discharge medications mean ± SD		8.8 ± 2.3	7.4 ± 1.4	11.3 ± 1.6	<0.001
Ischemic cardiomyopathy number (%)		66 (31.4)	43 (31.4)	23 (31.5)	1.00
Dilated cardiomyopathy number (%)		129 (61.4)	87 (63.5)	42 (57.5)	0.49
Device type number (%)	HeartMate II	70 (33.3)	48 (35.0)	22 (30.1)	0.57
	HeartWare	75 (35,7)	49 (35.8)	26 (35.6)	1.00
	HeartMate 3	65 (31.0)	40 (29.2)	25 (34.2)	0.55
INTERMACS profile number (%)	Temporary support	37 (17.6)	28 (20.4)	9 (12.3)	0.20
	1	7 (3.3)	2 (1.5)	5 (6.8)	0.10
	2	61 (29.0)	38 (27.7)	23 (31.5)	0.68
	3	71 (33.8)	46 (33.6)	25 (34.2)	1.00
	4	32 (15.2)	22 (16.1)	10 (13.7)	0.80
	5	2 (1.0)	1 (0.7)	1 (1.4)	1.00
	6	0 (0)	0 (0)	0 (0)	1.00
	7	0 (0)	0 (0)	0 (0)	1.00

IQR: interquartile range, SD: standard deviation.
[a] Points for age not included.

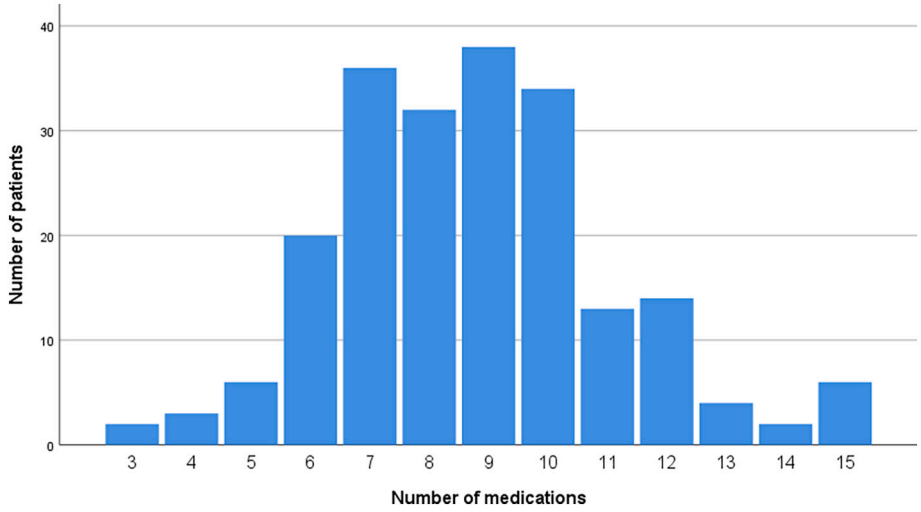

Fig. 1. Distribution of the numbers of discharge medication of the LVAD patients.

3.3. Mortality and complications

The median follow-up duration was 948 days (interquartile range 874 days). Fig. 2 shows the survival (time to death or urgent HTx, as a proxy of mortality) of patients with 0–9 medications and ≥10 medications. Patients with ≥10 medications had a significantly lower survival compared to patients 0–9 medications (crude HR 1.76; 95 % CI 1.03–2.98, *p*-value 0.04) (Table 2). This association remained significant after adjusting for age, sex, CCI and stratified for device type (adjusted HR 2.03; 95 % CI 1.15–3.6, *p*-value 0.02). A total of 56 patients (27 %) died after a median of 828 days following LVAD implantation. Table 3 lists the causes of death. A total of 56 patients received a heart transplant after a median of 1029 days, of which 32 % (n = 18) were urgent transplants. The adjusted hazard ratio was 1.23 (95 % CI 1.09–1.38, p-value 0.001) for the number of medications as a continuous variable in the multivariate cox proportional hazards model of the primary outcome (mortality or urgent HTx).

The tertiles for the number of medications were determined. The first tertile concerned 3–8 medications, the second tertile 8–10 medications and the third tertile 10–15 medications. Compared with the first tertile,

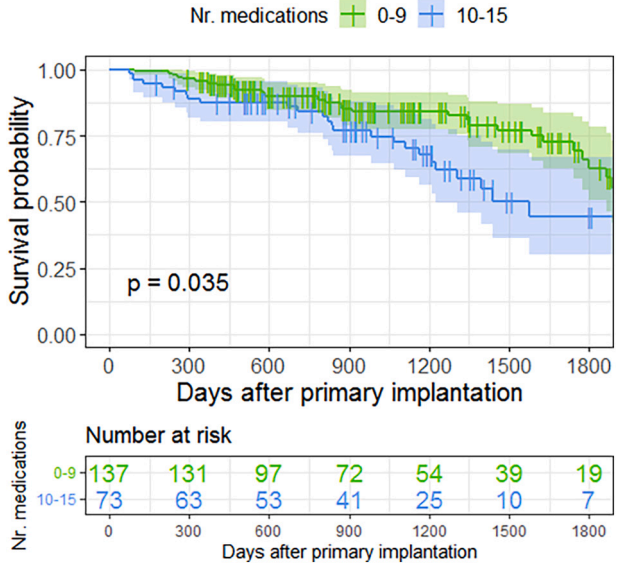

Fig. 2. Survival (time to death or urgent heart transplantation) of patients with 0–9 medications and ≥10 medications.

Table 2
The association between the prescription of ≥10 medications and survival (mortality and urgent heart transplantation).

Variables added to the cox proportional hazards models	Univariate model			Multivariate model[a]		
	HR	95 % CI	P-value	HR	95 % CI	P-value
≥10 medications	1.76	1.03–2.98	0.04	2.03	1.15–3.62	0.02
Age				1.04	0.99–1.08	0.04
Sex				0.92	0.53–1.62	0.78
Charlson Comorbidity Index				0.96	0.69–1.35	0.83

CI: confidence interval, HR: hazard ratio.
[a] Stratified for device type.

Table 3
Number and causes of death.

Cause of death	All = 56 n (%)
Device malfunction	3 (5.4)
Infection	7 (12.5)
Multi-organ failure	7 (12.5)
Neurological	18 (32.1)
Right ventricle failure	7 (12.5)
Other	14 (25)

the use of 8–10 medications did not significantly increase the risk of the combined outcome of mortality and urgent HTx (HR adjusted for age, sex, CCI and stratified for device type 1.79; 95 % CI 0.84–3.81, *p*-value 0.13), but the use of 10–15 medications did (adjusted HR 2.96; 95 % CI 1.40–6.26, p-value <0.01). Fig. 3 displays the survival for the three different tertiles. Supplementary Tables S2 and S3 show the association of the use of medications to prevent stroke and cardiac medications, respectively, with survival.

The sensitivity analysis with additional censoring for urgent heart transplantation also showed a significantly higher mortality (urgent HTx not included) for patients with ≥10 medications (adjusted HR 1.77; 95 % CI 1.07–2.95, *p*-value 0.03). An additional analysis was performed to assess whether the effect of ≥10 medications was modified by age at the time of implantation. The interaction term for age - ≥10 medications was not statistically significant when entered into the multivariate model (p-value 0.43), i.e. the association between ≥10 medications and mortality was not different for persons younger and older than 60 years.

The prescription of ≥10 medications was not associated with any of

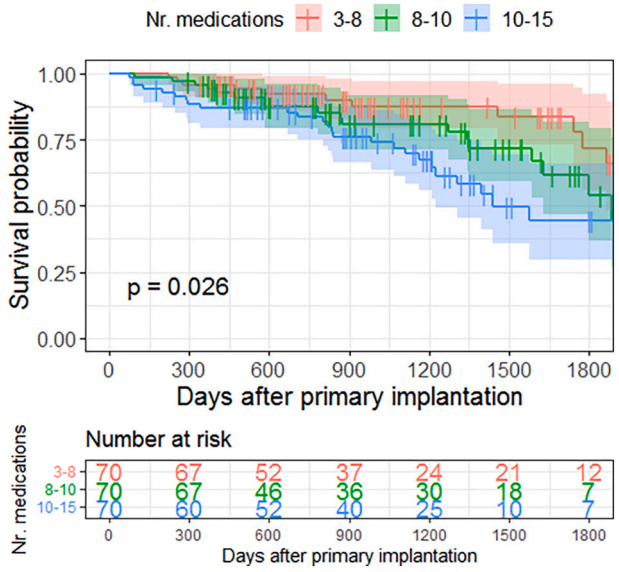

Fig. 3. Survival (time to death or urgent heart transplantation) of patients with 3–8 medications, 8–10 medications and 10–15 medications (tertiles).

the adverse events as listed in Table 4.

4. Discussion

This study showed that the prescription of 5–9 medications (polypharmacy) is highly prevalent (62.9 %) in patients after LVAD implantation. The prescription of ≥10 medications (hyperpolypharmacy) was also common (34.8 %) with on average 11.3 medications per patient. Hyperpolypharmacy was independently associated with the risk of mortality, but not with the risk of complications (major bleeding, cardiac arrhythmia or driveline infection). Supplementary Fig. S1 and Supplementary Table S2 and S3 indicate that not the type but the number of medications are associated with survival.

The prevalence and the association of (hyper)polypharmacy with outcomes in patients with an LVAD has not been investigated before. However, several previous studies addressed polypharmacy in patients with HF. A recent systematic review on the identification of a standard definition and the prevalence of polypharmacy in patients with HF, concluded that there is no standard definition of polypharmacy in HF literature and the prevalence ranged from 17.2 % to 99 % [8]. In four studies where a definition of ≥10 medications was used, the prevalence of hyperpolypharmacy varied from 26 to 74 % [9,10,19,20]. Extrapolating these findings to our study, however, is of limited value due to heterogeneity of the study populations, particularly concerning the severity of HF. Where LVAD patients have severe, end-stage HF during admission for an LVAD implantation, the overall HF population has a broad case-mix ranging from mild HF to end-stage HF. A number of medications are used routinely in every patient who receives an LVAD. In our tertiary centre, patients are prescribed at least a vitamin K antagonist, an antiplatelet drug and a proton pump inhibitor after LVAD. Blood pressure is also strictly regulated (mean arterial pressure < 80 mmHg) to reduce the risk of stroke and other complications.

The evidence on the association of polypharmacy with mortality in the general HF population is conflicting. Again, comparison with the results of the current study is hampered by the heterogeneity of the study populations. Sunaga et al. evaluated the relationship between various clinical factors and mortality in patients with HF [20]. They found that patients who were taking <6 medications on admission experienced a significantly lower all-cause 2 year-mortality than patients taking ≥6 medications (10.0 % vs. 25.0 %, $P = 0.045$). However, the study by Sunaga et al. concerned the number of medications before admission and this study determined the number of medications on discharge from hospital, with the study of Sunaga et al. not taking into account medication changes during admission. Wu et al. examined the association between the use of 10–14 medications and several adverse outcomes in patients with HF with preserved ejection fraction (HFpEF). Contrary to the finding in this study and the study of Senaga et al., Wu et al. found that the prescription of 10–14 medications was associated with a reduced risk of all-cause mortality (HR 0.61; 95 % CI 0.39–0.96, $P = 0.031$), and an increased risk of HF hospitalisation (HR 2.83; 95 % CI 1.37–5.86, $P = 0.01$) and all-cause hospitalisation (HR 1.81; 95 % CI 1.29–2.53, $P = 0.001$) [19]. However, Wu et al. included relatively stable patients with HF, whereas the study of Sunaga and our study included patients with unstable or advanced/end stage HF.

4.1. Strengths and limitations

This study was the first to examine the prevalence of the prescription of 5–9 medications (polypharmacy) and ≥10 medications (hyperpolypharmacy) and its association with adverse outcomes in a large sample of patients after primary LVAD implantation. The risk of selection bias is very small, because an existing prospective database was used for patient selection, in which data of all consecutive LVAD patients was registered. Data on the occurrence of a selection of complications were collected, using the definition of the international INTERMACS registry, making the results internationally interpretable.

This study has some limitations. The medical history and discharge medication were extracted from the discharge letter. There is a chance that these letters contained incomplete or incorrect information due to human error. Second, due to the retrospective collection of medication data, we could not take into account medication adherence, correct use or changes in medication after hospital discharge. Third, the incidence of many adverse events was very low, and therefore was not included for analysis in the current study, as there was not enough power here to demonstrate a significant association.

Finally, although this study showed that there is a significant association between the prescription of ≥10 medications and mortality, it cannot be determined whether there is a causal relationship. Despite adjustment for age, sex, device type and comorbidities, it is still possible that hyperpolypharmacy reflects the presence of frailty. Several observational studies demonstrated a significant association between an increased number of medications and frailty (possibly bidirectional) and frailty is a known risk factor for mortality in patients with HF [21,22]. Because there is no agreement on the definition of frailty and the way it should be assessed in (end stage) heart failure, hyperpolypharmacy as a proxy of frailty would in that case simplify prognostication of patients post LVAD.

Table 4
Cause specific cox regression: association of the prescription of ≥10 medications with complications.

Complication type	Number of patients (after index discharge) n (%)	Crude			Adjusted for age, sex, CCI, stratified for device type		
		HR	95 % CI	P-value	HR	95 % CI	*P*-value
Cardiac arrhythmia	98 (47)	0.80	0.53–1.25	0.35	0.76	0.48–1.20	0.24
Driveline infection	65 (31)	0.82	0.49–1.40	0.47	0.99	0.57–1.71	0.96
Major bleeding	74 (35)	1.26	0.78–2.02	0.34	1.29	0.78–2.15	0.31

CI: confidence interval, CCI: Charlson Comorbidity Index (without points for age), HR: hazard ratio.

4.2. Clinical implications and future research

Over the last few years, awareness of polypharmacy in patients with HF has been growing. The fact that this study showed that the prescription of ≥10 medications was associated with mortality, independent of the presence of comorbidities, demonstrates the importance of adequately addressing hyperpolypharmacy. However there is a lack of clarity on how best to manage polypharmacy [23–25]. Thereby, it is important to realise that polypharmacy in a number of patients with heart failure cannot be prevented and is indicated if current guidelines are followed. The common ground for addressing (hyper)polypharmacy seems to be a multidisciplinary individual approach, where a risk-benefit profile of (cardiovascular) medication should be determined and inappropriate polypharmacy should be identified and prevented. In our study, more non-cardiovascular medications were used in the hyperpolypharmacy group (reflecting the presence of more comorbidities) than in the group with 0–9 medications, which are possible targets for a medication review. A medication review leads to improved medication appropriateness, reduced polypharmacy and reduced adverse drug reactions [26], however, there is little evidence for an effect on clinical outcomes [27,28]. Future research should confirm the association between hyperpolypharmacy and mortality, adjust for the presence of frailty, assess the appropriateness of the hyperpolypharmacy and study the effect of optimising polypharmacy in a randomized controlled trial. It is recommended to collect the medication data prospectively. The completeness of the medication list, medication adherence and the correct use of medication should be verified. For longer follow-up periods, information on changes in medication use should also be collected.

5. Conclusion

This study showed that polypharmacy is highly prevalent in patients with primary LVAD implantation. Hyperpolypharmacy also occurred frequently, and was independently associated with mortality. Future research is warranted to confirm this association and to assess the efficacy of individual risk-benefit profiling of (cardiovascular) medication to ensure appropriate polypharmacy and to decrease negative health outcomes.

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CRediT authorship contribution statement

Lauren Dautzenberg: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization. **Lieke Numan:** Methodology, Software, Validation, Formal analysis, Writing – original draft, Visualization. **Wilma Knol:** Conceptualization, Methodology, Writing – review & editing. **Monica Gianoli:** Writing – review & editing. **Manon G. van der Meer:** Writing – review & editing. **Anne-Marie Troost-Oppelaar:** Writing – review & editing. **Aline F. Westendorp:** Investigation, Writing – review & editing. **Marielle H. Emmelot-Vonk:** Conceptualization, Methodology, Writing – review & editing. **Linda W. van Laake:** Conceptualization, Methodology, Writing – review & editing. **Huiberdina L. Koek:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of competing interest

LD, LN, WK, MG, ATO, AFW, MHEV and HLK declare that they have no conflict of interest. The UMCU, which employs LWvL and MGvdM, received consultancy fees from Abbott, Medtronic, Vifor, Novarti and Boehringer Ingelheim.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2022.100233.

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