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ORIGINAL RESEARCH ARTICLE

Economic impact of heart failure with preserved ejection fraction: insights from the ALDO-DHF trial

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Abstract

Aims Although heart failure (HF) with preserved ejection fraction (HFpEF) is a leading cause for hospitalization, its overall costs remain unclear.
Therefore, we assessed the health care-related costs of ambulatory HFpEF patients and the effect of spironolactone.
Methods and results The aldosterone receptor blockade in diastolic HF trial is a multicentre, prospective, randomized, double-blind, placebo-controlled trial conducted between March 2007 and April 2011 at 10 sites in Germany and Austria that included 422 ambulatory patients [mean age: 67 years (standard deviation: 8); 52% women]. All subjects suffered from chronic New York Heart Association (NYHA) class II or III HF and preserved left ventricular ejection fraction of 50% or greater. They also showed evidence of diastolic dysfunction.
Patients were randomly assigned to receive 25 mg of spironolactone once daily (n = 213) or matching placebo (n = 209) with 12 months of follow-up. We used a single-patient approach to explore the resulting general cost structure and included medication, number of general practitioner and cardiologist visits, and hospitalization in both acute and rehabilitative care facilities. The average annual costs per patient in this cohort came up to €1, 118 (±2,475), and the median costs were €332. We confirmed that the main cost factor was hospitalization and spironolactone did not affect the overall costs. We identified higher HF functional class (NYHA), male patients with low haemoglobin level, with high oxygen uptake (VO_2max) and coronary artery disease, hyperlipidaemia, and atrial fibrillation as independent predictors for higher costs.
Conclusions In this relatively young, oligosymptomatic, and with regard to the protocol without major comorbidities patient cohort, the overall costs are lower than expected compared with the HFrEF population. Further investigation is needed to investigate the impact of, for example, comorbidities and their effect over a longer period of time. Simultaneously, this analysis suggests that prevention of comorbidities are necessary to reduce costs in the health care system.

Keywords Heart failure; Heart failure with preserved ejection fraction; Economic costs; Economics

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Introduction

Patients suffering from heart failure (HF) account for nearly 1–2% of the adult population in developed countries, rising up to ≥10% among people above 70 years of age with increasing prevalence due to demographic changes.[1–4] HF patients are mainly categorized into HF with reduced (HFrEF) and preserved ejection fraction (HFpEF) due to different underlying aetiologies, demographics, comorbidities, and response to therapies.[5,6] The prevalence of both entities and their prognoses is comparable.[7] Despite remarkable progress in HF research, we still miss a specific treatment for HFpEF, at the moment the guidelines focus on optimizing the comorbidities.

However, the economic burden of HF treatment increases with its prevalence. Cardiovascular diseases are estimated to cost about $130 billion in Europe annually with HF as a major matter of expense.[8] HF cost estimates in the USA amount to $39.2 billion in direct costs,[9] which do not include the impact on the economic reduction in work force nor the informal care these patients receive. A key portion of HF direct costs is caused by hospitalization, while ~5% of all hospital admissions in Western countries are due to HF.[10–12] Projected total medical costs in 2030 will rise up $53.1 billion, and nearly 80% of these projected expenses are attributed to increased hospitalizations.[13–15] All these details are mainly based on databases from national registries and insurance companies.[16] These databases underestimate the costs of HF patients systematically because of differently attributed diagnoses for hospitalization due to common comorbidities of HF patients. In particular, HFpEF patients are inadequately represented because of various comorbidities and a systematic neglect due to the absence of direct treatment options.[17] Based on the recommended guideline treatment for HFrEF patients, monitoring HFrEF costs is easier on a non-individual-based approach in registries.

The aldosterone receptor blockade in diastolic HF (aldo-DHF) study was a randomized, controlled trial investigating the effects of chronic aldosterone receptor blockade in 422 outpatient stable HFpEF patients during a 12-month follow-up period.[18] Its co-primary endpoints were E/e' and peakVO_2.

Thus, in this analysis, we aim to (i) analyse the structure of the costs and to (ii) assess the direct health costs for this stable outpatient HFpEF population. Ultimately, we aim to (iii) evaluate the effect of spironolactone on the overall direct costs and the cost distribution and to (iv) identify predictors for higher costs in subjects based on these findings.

Methods

Study design and setting

The aldo-DHF trial was a multicentre, randomized, placebo-controlled, double-blind study within the framework of the German Competence Network Heart Failure (KNHI) between 2007 and 2012.[19] The study design and the primary results of the aldo-DHF trial have been previously published.[18,20] Briefly, eligible patients were enrolled and randomized to spironolactone 25 mg once daily or matching placebo. The diagnosis of HFpEF was based mainly on the Paulus criteria [symptomatic HF, left ventricular ejection fraction (LVEF) $\geq$ 50% at rest and echocardiographic signs of diastolic dysfunction (tissue doppler-derived E/e' $>$ 15 or E/e' $>$ 8 in combination with the presence of either elevated N terminal pro brain natriuretic peptide or brain natriuretic peptide or atrial fibrillation)].[21] Ultimately, symptomatic patients with New York Heart Association class II or III, LVEF $\geq$ 50% at rest, echocardiographic evidence of grade $\geq$ I diastolic dysfunction or present atrial fibrillation, and peak $VO_2 \leq$ 25 mL/kg/min were eligible for participation.[20] Major exclusion criteria included prior documented LVEF $\leq$ 40%, significant coronary artery disease, myocardial infarction or coronary artery bypass graft surgery within 3 months, definite or probable pulmonary disease [vital capacity $<$ 80% or forced expiratory volume in 1 s $<$ 80% of reference values on spirometry], body mass index $\geq$ 36 kg/m, or serum creatinine $>$ 1.8 mg/dL. After the baseline examination and the randomization, patients were seen at visits after 1 week and 3, 6, 9, and 12 months. Examination results, questionnaires, and changes of medication were recorded at each visit. The study protocol was reviewed and approved by the institutional review board of each participating centre, and all patients provided written informed consent prior to enrolment. Aldo-DHF was conducted in accordance with national laws, guidelines for good clinical practice, and the Declaration of Helsinki.

Subject population

We analysed the data of 422 patients. The data collection also consisted of details regarding physician visits, rehabilitation, and hospital admissions as well as the concomitant medication at the screening, the baseline, and the follow-up visits every 3 months for a year.

Endpoint

The main endpoint in focus was defined as the overall direct costs. These direct costs were based on (i) structural costs assessed by the number of general practitioner (GP) and cardiologist visits, number of HF hospitalizations, duration of cardiac rehabilitation, and duration of required nursing care as well as (ii) medication costs assessed by the number of days the medication was taken and the individual composition of medication per day.

Cost parameter assessment

We analysed the cost of illness with a bottom-up-approach[22,23] based on the details of every single patient. We considered cardiovascular medication as relevant for our analysis and therefore as distinguishable from other medication. These considered medication included beta-blocker, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, cardiac glycosides, statines, other lipid-lowering agents, antiarrhythmic agents, calcium channel

blocker, anticoagulants, nitrates, oral antidiabetic medication, and insulin and pulmonary medication. For the calculations of the costs due to the concomitant medication, we used the price for the cheapest generic in the largest available package size on the German market in the year 2011 for our calculations.

Regarding outpatient physician visits, we considered visits to GPs, specialists in internal medicine, and cardiologists as relevant for our analysis. Reliable data for costs per physician visit were only available from the year 1999.[24] Therefore, we adjusted these for inflation and set the year 2011 as the reference point of time.

The direct costs of hospitalization were assessed when the hospitalization reported at the baseline visit for the previous 12 months or any other follow-up visit was due to HF. The direct economic costs of a hospitalization emerge from both the treatment costs and the infrastructural costs of the health care provider. We used an established approach to assess these costs by including the average HF costs based on diagnosis-related group statistics from the Federal Statistical Office of Germany and added the infrastructural state funding per day multiplied by the duration of the hospital stay to assess the hospitalization costs.[24]

Statistical methods

Study cohort and subgroups are described by absolute and relative frequencies for categorical data, by mean and standard deviation (SD) for symmetric continuous variables and in addition, median and quartiles/interquartile range for skewed continuous variables.

We compared frequencies by χ^2 test and Fisher's exact test. Continuous variables were compared by *t*-tests for independent samples with Satterthwaite approximation or by Mann–Whitney *U* tests.

For the analysis of both the physician visits and the hospitalizations, we summed up the details at each visit per patient. Medication costs were calculated as a product of daily dosage, price per dosage, and number of days taken.

In searching baseline variables associated with the total direct costs, we built various regression models. After simple linear regression models with variables from *Table 1*, we built a multiple regression model and excluded irrelevant variables by backward selection with probabilities for inclusion: p_in = 0.2 and exclusion p_out = 0.05. Final models were built with the variables selected that way to get correct estimates for incidence rate ratios, which were calculated including two-sided 95% confidence intervals.

Table 1 patient characteristics I

Variable	Spironolactone *n* (%)	Placebo *n* (%)	*P value*
Female	111 (52)	110 (53)	0.9150
CAD	92 (43)	78 (37)	0.2188
Arterial hypertension	197 (92)	190 (91)	0.5565
CVD	23 (11)	22 (11)	0.9279
PAD	7 (3)	10 (5)	0.4338
Atrial fibrillation	30 (14)	36 (17)	0.3746
Chronotropic incompetence	9 (4)	16 (8)	0.1356
NYHA III	33 (15)	26 (12)	0.3659
Hyperlipidemia	130 (61)	143 (68)	0.1123
Diabetes mellitus	36 (17)	34 (16)	0.8611
sleep apnoea	29 (14)	21 (10)	0.2569
COPD	11 (5)	3 (1)	0.0535
Depression	22 (10)	25 (12)	0.5939
Paulus criteria positive	111 (52)	109 (52)	0.9934

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; PAD, peripheral artery disease; Paulus criteria, HFpEF criteria mentioned above.[21]

Results

Subject population

A total of 422 patients were randomly assigned to receive spironolactone (*n* = 213) or matching placebo (*n* = 209) with 12 months of follow-up. Patients who dropped out were analysed until their dropout. There was no relevant difference in the number of dropouts (9 vs. 13, *P* = 0.22) nor in the baseline characteristics (*Tables 1 and 2*) between both groups.

Costs per item: physician visits and hospitalizations

Because most data were collected in 2011, that year was also set as the reference point of time for all calculations.

The latest costs per outpatient physician visit given by the German physician's association were from 1999. We adjusted those values for inflation in 2011 and calculated 19.95 € per visit to the general practitioner and 71.16€ per visit to the cardiologist.

The average diagnosis-related group-based cost was 3168.03 € per hospitalization. We calculated additional 64.43 € per day in hospital for infrastructural costs. For rehabilitation, we calculated additional 121.12 € per day.

Overall direct cost

As shown in *Figure1*, the overall direct costs are the sum of the costs for outpatient physician visits, hospitalization, rehabilitation, and medication. The mean overall cost per patient was 1188€. The median cost was in contrast 332€ as a result

Table 2 Patient characteristics II

	Spironolactone					Placebo					
Variable	*N*	Mean	SD	Median	IQR	N	Mean	SD	Median	IQR	*P value*
Age [years]	213	66.9	7.7	67.0	12.0	209	66.7	7.5	68.0	11.0	0.8038
BMI [kg/m^2]	213	28.9	3.6	29.0	5.0	209	28.9	3.6	28.8	5.1	0.9644
MAP [mmHg]	213	97.6	11.4	96.3	16.0	209	98.2	12.2	98.0	14.7	0.5435
Pulse pressure [mmHg]	213	55.8	14.8	54.0	19.0	209	55.8	15.8	55.0	20.0	0.9667
HR in ECG [min^{-1}]	213	66.5	13.8	65.0	15.0	208	64.3	11.8	63.0	11.5	*0.0815*
eGFR [ml/min/1.73 m^2]	211	79.3	19.2	77.7	25.6	208	78.1	18.3	77.9	24.9	0.5095
VO_2max [ml/min/kg]	213	16.4	3.6	16.1	4.4	209	16.4	3.5	16.3	4.6	0.8731
E/e' (medial)	213	12.7	3.6	11.9	4.3	209	12.8	4.4	11.9	3.6	0.6252
log10NTproBNP	204	2.2	0.5	2.3	0.6	195	2.2	0.4	2.2	0.5	0.5052
LAVI [ml/m^2]	212	28.2	9.1	26.4	10.4	208	27.8	7.7	26.7	9.7	0.9586
LVMI [ml/m^2]	212	107.9	29.2	106.8	29.8	209	109.3	26.8	107.4	35.8	0.5347
Hb [g/dl]	213	13.8	1.2	13.8	1.5	209	13.8	1.3	13.8	1.8	0.8135
VACI	206	0.5	0.7	0.5	0.3	202	0.5	0.3	0.5	0.2	*0.0849*

Values in italic are smaller than 0.2, selection criterion before multiple regression model
BMI: body mass index; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; HR: heart rate; IQR: interquartile range; LAVI: left atrial volume indexed to body surface area; LVMI left ventricular mass indexed to body surface area; MAP :mean arterial pressure; SD: standard deviation; VACI: Ventricular-atrial Coupling Index; VO_2max: maximal oxygen uptake

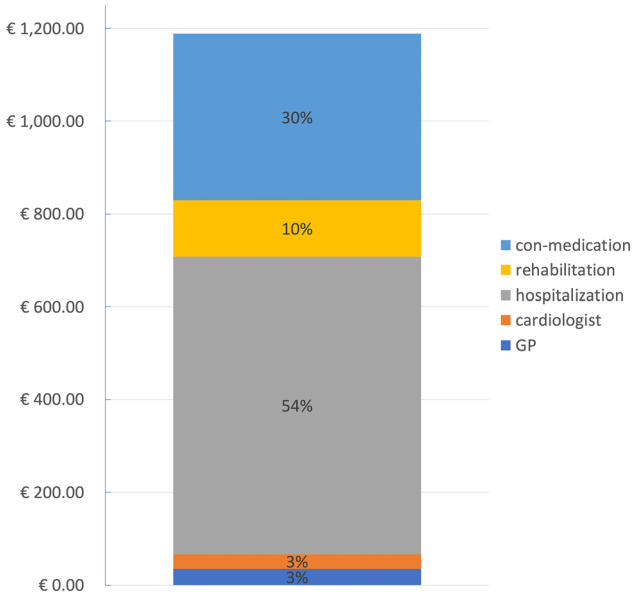
of most patients contributing to less than 1000€ per patient per year. The main component was hospitalization due to HF.

Hospitalization and rehabilitation

Because only 14.7% (62/422) of all subjects were hospitalized during the follow-up period, its contribution to the overall costs of the investigated HFpEF cohort was very limited. However, for patients who were hospitalized, hospitalization was the most expensive item. This resulted in 640.7€ [SD: ±1995.7€, median 0€ (Q_1: 0€; Q_3: 0€)] average costs for hospitalization per study subject during the 12 months of follow-up.

The same applies to patients who were admitted to rehabilitation and their costs. 5.5% (23/422) of subjects had at least one admission for rehabilitation care that generated an average cost of 122.3€ [SD: ±693.3€, median 0€ (Q_1: 0€; Q_3: 0€)] per rehabilitation treatment per patient annually.

Figure 1 Distribution of mean overall direct costs of the complete study population. Con-medication: medication taken besides study drug (spironolactone/placebo); cardiologist: outpatient visits to cardiologist; GP: outpatient visits to general practitioner; hospitalization: hospitalization due to heart failure (HF); rehabilitation: rehabilitation due to HF.



Outpatient visits

Among patients who were not hospitalized, outpatient visits, either to the cardiologist or the GP, were the most relevant cost item besides the prescribed medication.

One-third of the study population had no visit to the GP during the follow-up period. Seventy-five percent of patients had up to two visits, and one patient was outlying with 48 GP visits during the follow-up period. Thus, on average, 35.3€ [SD: ±67.9, median 20€ (Q_1: 0€; Q_3: 40€)] was spent for GP visits per patient during the follow-up period.

Visits to the cardiologist were noticeably fewer but with a similar pattern. Seventy-five percent of the study population had up to one visit to the cardiologist. The subject with the most visits to the cardiologist during the follow-up had 10 visits. In total, visits to the cardiologist added up to an average cost of 31.2€ [SD: ±68.5€, median 0€ (Q_1: 0€; Q_3: 71€)] per patient during the follow-up period.

Medication

Considering the follow-up visits at 3, 6, 9, and 12 months, about 29% of subjects on average reported altered

medication and 66.1% (279/422) reported none or one change in medication during the complete follow-up period. The con-medication taken from all participants is shown in *Table 3*.

Some of the frequently taken drugs created low median costs, like beta-blockers (17€) and statins (23€). Some of the less frequently taken drug groups generated higher median costs, like antiarrhythmic agents (1313.6 €) and antidepressants (1894.9€). Anticoagulation, which included antiplatelet therapy in our analysis, was frequently taken and contributed notably to the costs with a relatively high median cost (1109.5€). These findings resulted in median con-medication costs of 223€ per subject per year. The large distribution lead to nearly 100 subjects (one quartile) with costs less than 100 € and a quartile with costs more than 487€ per patient per year. These results are accompanied by mean costs of 358.7€ (SD: ±396.5) per patient per year.

Effect of spironolactone

The costs for outpatient visits to both the GP and the cardiologist, the hospitalizations, and rehabilitation care were not different in the two study arms. *Table 4* shows the distribution in the total patient cohort.

The medication costs between both treatment arms are not relevantly different ($P = 0.84$). Certain medication groups were different between these study arms but had no impact on the overall costs [calcium channel blockers were taken more often in the placebo group ($P = 0.01$) and loop diuretics more in the spironolactone group ($P = 0.02$)].

Table 3 Absolute and relative frequency of medication groups in both treatment arms

	Spironolactone ($n = 213$)		Placebo ($n = 209$)	
Medication group	No. (n)	Rel. (%)	No. (n)	Rel. (%)
Antiarrhythmic agents	12	6	21	10
Beta blockers	150	70	160	77
CCB	47	22	74	35
ACE inhibitors	103	48	92	44
ARBs	85	40	80	38
Loop diuretics	46	22	27	13
Other diuretics	97	46	99	47
Nitrates	23	11	18	9
Cardiac glycosides	4	2	4	2
Statins	117	55	119	57
Other cholesterol-lowering medication	19	9	15	7
Anticoagulants	132	62	119	57
Oral antidiabetic medication	30	14	20	10
Pulmonary medication	13	6	9	4
Insulins	4	2	11	5
Antidepressants	21	10	16	8

Mediation group was considered positive, when at least one drug from a medication group was reported to be part of the taken by patient at one of the study visits.
ACE: angiotensin-converting-enzyme inhibitor; anticoagulants: including antiplatelet therapy; ARBs: Angiotensin II receptor blockers; CCB: calcium channel blockers; Rel.: relative frequency.

Table 4 Comparison of the descriptive cost items without medication costs

	Total patient cohort ($n = 422$)				
Cost item	Min	Max	Med	Q_1	Q_3
GP	0	958	20	0	40
Cardiologist	0	712	0	0	71
Hospitalization	0	18,288	0	0	0
Rehabilitation	0	8,478	0	0	0

Costs in € (Euro).GP, costs of outpatient visits to the general practitioner; cardiologist, costs of outpatient visits to the cardiologist; hospitalization, costs of hospitalizations due to heart failure; rehabilitation, costs of rehabilitation care due to heart failure.

Predictors

Factors associated with impact on the costs are shown in *Table 5*. Factors like atrial fibrillation, coronary artery disease, and higher HF functional class were associated with higher costs, while higher haemoglobin levels in women predicted lower costs. Other factors, for example, age, arterial hypertension, and chronic obstructive pulmonary disease, as well as the level of diastolic dysfunction (E/e'), showed no impact on higher costs.

Discussion

In this analysis, we measure for the first time the costs of an ambulatory HFpEF cohort, which account for a median amount of 332 € per patient per year (1118€ on average). The analysis of the structure revealed hospitalization as the driving cost factor followed by medication, rehabilitation, and outpatient visits. Spironolactone did not change the overall costs or the distribution over the different items; however, it showed associations with certain compositions of the con-medication. Independent predictors for higher costs included men with lower haemoglobin values, better VO_2max, as well as the presence of coronary artery disease, hyperlipidaemia, and atrial fibrillation.

Table 5 Incidence rate ratio of relevant predictive factors for overall costs

Predictive factor	IRR	95% CI	P
Haemoglobin	0.791	0.706–0.887	<0.001
VO_2max	1.049	1.009–1.090	0.015
Female vs. male	0.619	0.464–0.824	0.001
CAD, yes vs. no	1.399	1.026–1.910	0.034
Hyperlipidaemia, yes vs. no	1.608	1.189–2.175	0.002
Atrial fibrillation, yes vs. no	2.164	1.516–3.093	<0.001
NYHA III vs. II	1.640	1.120–2.406	0.011

CAD: coronary artery disease; CI: confidence interval; IRR: incidence rate ratio; NYHA: New York Heart Association.

This analysis gained power through the bottom-up-approach, which focused on the use of resources on every level of each subject instead of referring to aggregated cohort data.

Analyses by other authors investigating HF populations and providing their use of medical resources focused mainly on a different selection of patients, for example, Biermann *et al*. investigated a pooled HF cohort with LVEF $< 50\%$.[25] In that analysis, HFrEF and HF with mid-range ejection fraction patients showed higher need for medical resources indicating higher costs. There were more often outpatient visits to both GPs as well as cardiologists than in our cohort [6.1 (±9) and 1.7 (±2.5) vs. 1.8 (±3.4) and 0.4 (±1.0) per year]. Hospital admissions due to HF were more frequent in those patients [0.8 (±1.2) vs. 0.2 (±0.6) per year]. However, even the basic characteristics differed: the cohort was younger and there were more male subjects [25.2% female subjects and mean age 62.9 (± 13.6) years vs. 52% female subjects and mean age 67 (± 8) years]. Both analyses, theirs and ours, could show that higher HF functional classes were associated with higher costs.

Focusing on HFpEF populations only, similar effects could be shown, for example, by Redfield *et al*. In the RELAX trial, they investigated the effect of phosphodiesterase-5 inhibition with administration of sildenafil for 24 weeks, compared with placebo in an HFpEF cohort.[26] It did not result in significant improvement in exercise capacity or clinical status, but the data could be analysed in the same bottom-up-approach like ours and showed also a significant higher need for medical resources in both medication and hospitalization terms. Although the RELAX cohort was similar to the ALDO cohort regarding the basic baseline characteristics (mean age 69 years, 49% women), they differed in others, such as the comorbidities. In summary, comorbidities were more present in the RELAX than in the ALDO group, for example, arterial hypertension 85% vs. 92%, diabetes mellitus 43% vs. 17%, chronic obstructive pulmonary disease 19% vs. 3%, and atrial fibrillation 51% vs. 15%. Consequently, the number of con-medication was higher than in the ALDO cohort, for example, loop diuretics 77% vs. 17% or ACEi 70% vs. 46%. Even in laboratory and clinical testing, the RELAX group appeared to be sicker with median N-terminal pro brain natriuretic peptide values around 700 pg/mL vs. 158 pg/mL in the ALDO cohort. VO_2max was at 11.7 mL/min/kg vs. $>$16 mL/min/kg in the aldo-DHF data. Diastolic parameters like E/e' (16 vs. 11.8) and left atrial volume indexed to body surface area (44 mL/m^2 vs. 26 mL/m^2) were also different. This constellation indicates that patients with a higher disease burden have higher costs, represented by the fact that HF hospitalization was an inclusion criterion in RELAX but not in aldo-DHF. In contrast, only 37% of aldo-DHF patients had a hospitalization before baseline. Korves *et al*.[27] could show that hospitalization and especially the 6 months after HF hospitalization are the most costly periods of the patient journey.

Conclusively, we show that early stage HFpEF patients have lower costs and because managing the comorbidities is the main treatment approach at the moment, an early diagnosis and prevention as well as treatment of comorbidities reduces the economic costs even of an oligosymptomatic, relatively young HFpEF cohort.

In analysing the predictive factors for higher costs, the only item that we can change and improve besides optimal therapy of comorbidities is VO_2max. This underlines the idea that physical exercises could improve HFpEF population outcomes and lower the costs of their care.

Limitations to this analysis include focusing on direct costs. Indirect costs, for example, disability to work, early retirement, and commute to diagnosis or treatment, were not included. Incidental costs in an elderly population with HFpEF are negligible due to their higher age (67 ± 8 years) and the presumed retirement. Intangible costs were not observed in the study protocol.

Compared with many other studies focusing on HFpEF, our study population is relatively young. Being young and only oligosymptomatic with a relatively low rate of HF hospitalization created lower costs.

But even the number of outpatient visits was much lower than expected, especially regarding visits to the cardiologist. Regular study visits may have influenced the number of other outpatient visits to the GP or cardiologist although subjects were instructed to keep regular appointments, including those required for prescriptions for the con-medication.

Regarding the con-medication, we most likely underestimate the real costs because we always calculated for the cheapest generic per largest pack size drug of an agent. At the same time, we only calculated single medication therapies and did not include polypills, which are usually cheaper than the combination of two drugs.

We could calculate the costs of a stable, oligosymptomatic patient with HFpEF per year. Because the hospitalizations and the following patient monitoring create the highest costs, we need to find methods to reduce HF hospitalizations and processes to decrease their impact on the overall costs in future steps.

Conflict of interest

None declared.

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