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Perceived Adverse Drug Events in Heart Failure

Patients' Perception and Related Factors

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Background: Patients with heart failure (HF) often perceive adverse drug events (ADEs), affecting quality of life. For weighing the benefits and burden of medication in HF care, knowledge on patients' perception of ADEs is needed. Our aim was to assess these ADE perceptions and to identify factors related to these perceptions. **Methods:** A cross-sectional study was performed including HF patients recruited from primary care and outpatient clinics. Patients were included in the analysis if they perceived an ADE in the past 4 weeks. This information was collected using an open-ended question and a symptom checklist. Data on ADE perception were obtained using a modified version of the Revised Illness Perception Questionnaire. Demographic, clinical, and ADE characteristics were collected by self-administered questionnaire and chart review. The relations between these factors and ADE perceptions were analyzed using regression analyses. **Results:** In total, 261 HF patients perceived an ADE and completed the questionnaire. Patients reported 814 ADEs, of which 26% of the patients reported dizziness and 24% reported dry mouth as being the most prevalent. Almost half of the patients (46%) perceived their ADE as something serious, with major consequences for their daily life (40%) and reported to be worried (36%) about the ADE. Patients perceived the ADE as a chronic problem (91%), and the majority believed more in the ability of the health care provider to control the ADE (61%) than in their own ability (46%). Demographic and clinical variables had a limited contribution to the explained variance of ADE perceptions after adjusting for ADE characteristics, such as perceived severity. **Conclusion:** Patients with HF perceive particular negative consequences and emotional distress of symptomatic ADE. Open communication between patients and providers with attention for patients ADE perceptions would be valuable during the decision process of ADE management and may result in a regimen aligned with patients' preferences and needs.

KEY WORDS: adverse effects, heart failure, perception, physician-patient relation

Reduction of mortality and morbidity is the main objective of the pharmacological management of heart failure (HF) described in recent guidelines.[1] Relieving symptoms of HF and improving quality of life are recognized as important treatment goals. Up-titration to an optimal dosage is vital and should be considered as long as no significant health problem occurs, for example, hyperkalemia or worsening renal function in case of prescribing angiotensin-converting enzyme (ACE) inhibitors.[1] Such adverse drug events (ADEs) occur in approximately 1% of HF patients, and they are considered severe and clinically relevant requiring immediate clinical intervention.[2]

Besides those severe ADEs, a considerable proportion of HF patients experience symptomatic ADEs such as dizziness and nausea.[3] This type of ADEs may

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be considered as mild and clinically inconsequential from the medical point of view. These ADEs may not have immediate consequences for dose uptitration, because they do not endanger the health in a direct way. However, the frequency of medication modification initiated by health care professionals differs greatly between the types of perceived ADEs. For example, in case of dry cough, the likelihood that medication is being changed was found to be high, greater than 80%.[4] The most common medication change was a switch from an ACE inhibitor to an angiotensin receptor blocker. When comparing this with other mild common perceived ADEs in HF such as dizziness, the initiation of medication modifications was much lower (<40%). However, patients may have a different perspective on these ADEs as they form an additional barrier to medication adherence[5,6] and causing substantial discomfort and worries affecting the overall quality of life.[7,8] In routine care, it is important as a health care provider to weigh the benefits and burden of medication in a patient-tailored approach.[9] Therefore, it is relevant to know patients' individual perceptions of the severity and impact of ADEs.

As a guidance to outline HF patients' perception of ADEs, we used the Common Sense Model of self-regulation of Leventhal and colleagues.[10,11] In this model, there are 2 processes active in an individual who faces a health threat to make sense of it: the cognitive interpretation of the threat and the emotional representations. Both types of perceptions will give guidance to patients' coping behavior. This model is often adopted to outline the perceptions of patients of various chronic diseases, such as cardiac diseases.[12–14] In recent years, the utility of the model has been widely investigated using the Illness Perception Questionnaire.[15] This questionnaire contains 5 domains and was extended with 2 more domains and renamed in the Revised Illness Perception Questionnaire (IPQ-R).[16] Recently, the Common Sense Model is also applied to outline patients' perception of ADEs in HIV patients, because as an illness, ADEs can also be perceived as a health threat.[17]

We aimed to describe both cognitive and emotional perceptions of reported ADEs by HF patients using the Common Sense Model of self-regulation. Second, we aimed to identify the factors (demographics and clinical factors) that influence these ADE perceptions after adjusting for the characteristics of the ADE.

Methods

Design, Setting, and Participants

A cross-sectional study was performed including ambulatory HF patients who were recruited between November 2008 and March 2009 from 20 general practitioners, 1 university hospital and 2 regional hospitals in different parts of the Netherlands. Patients with HF from primary care were identified using the International Classification of Primary Care code of HF (K77), which is afterwards verified by each general practitioner. Patients from outpatient HF clinics were eligible if they had a documented diagnosis of HF.

Patients were excluded if they were younger than 18 years, lived in a nursing home, participated in a clinical study, or had a terminal disease or cognitive disorder.

All eligible patients received written information about the study and an informed consent form. A reminder was sent to those patients who did not respond after 1 month of the first mailing. The study was approved by the local Medical Ethical Committee, conforming to the principles outlined in the Declaration of Helsinki.

In total, 959 patients with HF were found eligible and were invited during the study period, of which 495 patients (52%) signed informed consent. For the present study, only patients who perceived an ADE in the past 4 weeks were included in the analysis. Information on perceived ADE was based on self-reported data (see following section).

Perceived ADE

Data on perceived ADEs were collected using a mixed method: an open-ended question and a symptom checklist. A slight preference has been mentioned for the mixed method to elicit perceived ADEs, as patients do not report all ADEs in response to a single open question.[18] Patients could report an ADE by answering the following open-ended question asked in the information letter: "Did you experience an adverse event of your medication in the past 4 weeks?" (yes/no). If patients answered yes, they were asked to list the perceived ADE. Patients had also the possibility to report an ADE on a symptom checklist provided in the self-administered questionnaire. The checklist consisted of 28 symptoms and was constructed to collect data on symptoms that HF patients could have perceived in the past 4 weeks. Subsequently, patients were asked whether they attribute the perceived symptom to their HF or to their medication (ADE). The selection of the symptoms was based on a previous study investigating perceived symptomatic ADEs in HF patients.[3] For the present study, only those patients who reported a symptom on the checklist that they solely endorsed as ADE and patients who reported an ADE on the open-ended question were receiving additional questions about their ADE perception.

Perception of ADE

Data on patients' perception of experienced ADE were collected by a modified version of the IPQ-R.[16] When patients reported more than 1 ADE, this questionnaire was completed for the most "relevant" or "important" ADE indicated by the patient. We replaced

"my illness" of the original IPQ-R into "my ADE" and excluded 1 item ("the symptoms of my condition are puzzling to me") because of difficult transformation to the ADE context. We performed an Explorative Principal Component Analysis using varimax rotation method with Kaizer normalization. The final model explained 57% of the total variance, and the original IPQ-R structure was replicated except that the items of the original "consequences" and "emotional representation" subscales loaded on 1 factor, which we renamed in "consequences and emotions." The 6 subscales were the following, which showed all good reliability using Cronbach α coefficients: timeline chronic ($\alpha = .86$), timeline cyclical ($\alpha = .77$), personal control ($\alpha = .80$), treatment control ($\alpha = .82$), ADE understanding ($\alpha = .78$), and consequences and emotions ($\alpha = .89$). Higher scores on these subscales imply that the ADE is perceived as chronic and unstable over time, controllable both by patient himself/herself and treatment (health care providers), and well understood, and have serious consequences and cause emotional distress. All items were rated on a 5-point Likert scale ranging from (1) strongly disagree to (5) strongly agree. To facilitate comparison between the subscales, mean subscales scores were calculated by dividing the total subscale score by the number of items in the subscale, resulting in a range of 1 to 5.

Characteristics of ADE and Demographic and Clinical Data

Perceived severity of the ADE, indicated by the patient as most relevant, was assessed using a visual analog scale ranging from 0 (lowest perceived severity) to 10 (highest perceived severity). Perceived duration (in months) of the ADE, patients' knowledge of the causal drug, and whether the ADE had led to the following situations: hospitalization, consultation with a health care provider, and modification of drug treatment, were collected by means of the self-reported questionnaire. Data on sociodemographics, current medication use, and characteristics of received health care (care at home, hospitalization in the previous year, treated by a cardiologist, treated at an outpatient HF clinic) were also collected by the questionnaire. The following clinical characteristics were obtained by chart review: etiology of HF, duration of HF, severity of HF (measured by the left ventricular ejection fraction [LVEF] and N-terminal pro–brain-type natriuretic peptide [NT-proBNP]) and diseases which are commonly comorbid with HF.

Data Analysis

Descriptive statistics were used to describe the study population, the characteristics of the reported ADE, and the 6 subscales of the modified IPQ-R. In case of data skewness, the median and interquartile ranges (IQRs) were calculated, and otherwise, mean values with the SDs were presented. The percentage of patients scoring greater than scale midpoint was calculated for each of the subscales. This percentage indicates the proportion of patients who hold a strong view about the particular phenomenon measured.[19] Although the aim of this study was not to compare the 2 methods of eliciting ADEs (open-ended question vs symptom checklist), we controlled for differences between the 2 methods by adding a variable representing them in the analysis. We also performed subanalyses and report the data separately whenever we consider them relevant or informative. Finally, a hierarchical multivariate regression analysis was performed to examine the role of demographic and clinical variables in explaining variation of the different perceptions of ADE after controlling for ADE characteristics. The variables NT-proBNP and LVEF were excluded from the predictor list because of a high number of missing data. Missing values of the remaining predictors ranged from 1% to 10% per variable and were therefore imputed using the expectation-maximization algorithm.[20] After checking the assumptions of normality, homoscedasticity, and linearity, models were built for all 6 subscales of the IPQ-R as outcome variables. To control for the characteristics of ADE (knowledge of the ADE cause, duration and severity of ADE, and the method of questioning [open-ended question vs symptom checklist]), these variables were entered into block 1 of the regression analyses. The second block included the demographic characteristics, and the third block consisted of the clinical characteristics. Finally, the received care features were entered. To assess the differences in explained variance between the blocks, change in adjusted R^2 (ΔR^2) and the overall explained adjusted R^2 were calculated. $P < 0.05$ was considered as significant for all calculations. All data were analyzed using SPSS 16.0 software (SPSS, Inc, Chicago, Illinois).

Results

Of the 495 HF patients who signed informed consent, 332 (67%) patients reported at least 1 ADE that they experienced in the past 4 weeks. Eighty-one patients (24%) reported an ADE on the open question and the remaining (n = 251, 76%) only on the symptom checklist. Of these 332 patients, 261 (78%) completed the questionnaire and constituted the population of the present study.

The mean age of the present study population was 70 (SD, 12) years (range, 18–98 years), and 38% was female. Median LVEF was 35% (IQR, 25%–48%), and 55% had a documented ischemic etiology of HF. Patients were taking 7 different medications (IQR, 5–10 medications) per day, and the majority was on

standard HF medications, with 61% of the patients having been prescribed an ACE inhibitor, 25% an angiotensin receptor blocker, and 84% a β-blocker (Table 1). Patients who reported an ADE on the open-ended question were significantly younger (mean age, 67 [SD, 13] years vs 71 [SD, 11] years; $P = .022$), used more β-blockers (91% vs 81%; $P = .035$), and used less potassium-sparing diuretics (30% vs 42%; $P = .036$) compared with patients who reported an ADE only on the symptom checklist.

The total group of 261 patients reported a total of 814 ADEs (3 per patient), of which 26% of the patients reported dizziness, 24% dry mouth, and 21% itches as most frequent (Table 2). Patients reported 42 other

TABLE 1 Demographic and Clinical Characteristics of the Study Population (n = 261)

	n (%)
Demographics	
Age, mean (SD), y	70 (12)
Female sex	98 (38)
Education (≥12 y)	156 (63)
Living alone	85 (34)
Receiving care at home	93 (37)
Clinical characteristics	
Duration of HF, years median (P_{25}, P_{75})	3 (2, 5)
LVEF, median % (P_{25}, P_{75})[a]	35 (25, 48)
NT-proBNP, pg/mL median (P_{25}, P_{75})[a]	1119 (444, 2356)
Ischemic etiology of HF	142 (55)
Comorbidities	
Peripheral vascular disorders	52 (20)
Respiratory disorders (COPD/asthma)	73 (28)
Diabetes	55 (21)
Renal disorders	37 (14)
Depression (diagnosis)	22 (9)
No. of all used medications, median (P_{25}, P_{75})	7 (5, 10)
HF medication	
Angiotensin-converting enzyme inhibitors	158 (61)
Angiotensin receptor blockers	65 (25)
β-Blockers	220 (84)
Diuretics	
Loop diuretics	191 (73)
Potassium-sparing diuretics	102 (39)
Cardiac glycosides	22 (8)
Other medication	
Calcium-channel blockers	45 (17)
Nitrates	47 (18)
Lipid-lowering agents	124 (48)
Antiplatelet agents	83 (32)
Anticoagulants	159 (61)
Antiarrhythmic agents	31 (12)
Received care in the previous year	
Treated by a cardiologist	242 (94)
Treated at an outpatient HF clinic	207 (79)
Hospitalization	122 (48)

LVEF, left ventricular ejection fraction; NT-pro BNP, N-terminal pro–brain-type natriuretic peptide; HF, heart failure; COPD, chronic obstructive pulmonary disease.
[a]Missing values n = 157 for LVEF and n = 264 for NT-proBNP.

TABLE 2 All Reported Adverse Drug Events and for the 2 Methods of Eliciting Adverse Drug Events

	Total (n = 261)	Open Question (n = 81)	Checklist (n = 180)
	n (%)	n (%)	n (%)
Dizziness[a]	67 (26)	18 (22)	49 (27)
Dry mouth[a]	63 (24)	3 (4)	60 (33)
Itches[a]	54 (21)	15 (19)	39 (22)
Erectile dysfunction[a]	42 (16)	2 (3)	40 (22)
Dry cough[a]	41 (16)	4 (5)	37 (21)
Libido loss[a]	38 (15)	2 (3)	36 (20)
Cold extremities[a]	39 (15)	5 (6)	34 (19)
Blurred vision/vision problems[a]	37 (14)	5 (6)	32 (18)
Fatigue[a]	33 (13)	8 (10)	25 (14)
Painful joints[a]	32 (12)	8 (10)	24 (13)
Nausea[a]	28 (11)	4 (5)	24 (13)
Cough[a]	28 (11)	4 (5)	24 (13)
Sleeping problems[a]	26 (10)	4 (5)	22 (12)
Skin rash[a]	26 (10)	5 (6)	21 (12)
Other gastrointestinal problems	24 (9)	9 (11)	15 (8)
Constipation[a]	22 (8)	3 (4)	19 (11)
Diarrhea[a]	22 (8)	4 (5)	18 (10)
Gout[a]	18 (7)	2 (3)	16 (9)
Fluid retention[a]	18 (7)	3 (4)	15 (8)
Headache[a]	17 (7)	7 (9)	10 (6)
Hair loss[a]	16 (6)	3 (4)	13 (7)
Increase of body weight[a]	14 (5)		14 (8)
Dyspnea[a]	13 (5)	3 (4)	8 (4)
Loss in appetite[a]	12 (4)		12 (7)
Swollen ankles[a]	8 (3)		8 (4)
Vomiting[a]	7 (3)		7 (4)
Shortness of breath[a]	6 (2)	6 (7)	
Painful breasts[a]	6 (2)		6 (3)
Decrease in body weight[a]	4 (1)		4 (2)
Other skin problems	4 (1)	4 (5)	
Bleeding problems	4 (1)	4 (5)	
Thyroid problems	3 (1)	3 (4)	
Concentration problems	2 (1)	2 (3)	
Other complaints	42 (16)	24 (30)	18 (10)
Total	814	164	650

[a]These symptoms were included in the 28-symptom checklist.

complaints besides those listed, with the most frequent being myalgia and balance disorders. The most frequent reported ADEs on the open-ended question were dizziness (22%), itches (19%), and other gastrointestinal problems (11%). Of the ADEs that were indicated by the patients as most relevant, gout, erectile dysfunction, and libido loss were rated by the patients as most severe (Figure 1). Of the 81 patients who reported an ADE on the open-ended question, 64% reported a marked (≥7) severity of the ADE, whereas this was 38% of the patients who reported an ADE on the checklist.

Most patients reported that they consulted the health care professional (63%), 31% of the patients had a medication change, and 5% reported to have been
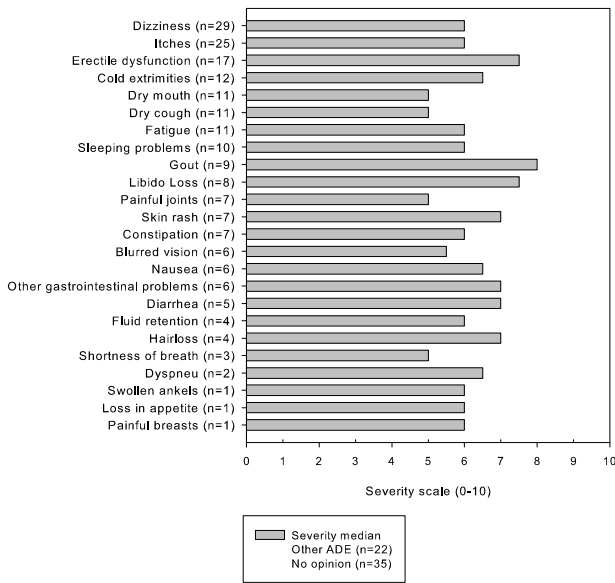
FIGURE 1. *Perceived ADE indicated by patients as most relevant (n = 261) and their scored severity.*

hospitalized because of the ADE, with dizziness, bleedings, and gout as most often mentioned by patients (Table 3). Nearly 70% of the patients reported to know the drug that was causing the ADE, of which 65% of the patients believed it was due to an HF medication. Commonly reported non-HF medications as cause of the ADE were antiarrhythmic and lipid-lowering drugs. As can be seen from Table 3, patients who reported an ADE on the open-ended question perceived the ADE as more severe and experienced more consequences of the ADE such as hospitalization.

Perceptions of ADE

In total, 46% of the patients perceived their ADE as something serious, with much effect (45%) and major consequences on their daily life (40%) (Table 4). Patients reported to be afraid (32%) and worried (36%) because of the ADE. Almost all patients (91%)

had a strong perception that their ADE is a chronic problem. Patients had a stronger belief in the ability of the health care provider to control the ADE than in their own ability to do so, with a mean score for the treatment control subscale of 3.0 versus 2.5 for the personal control subscale (paired-samples *t* test, *P* < .0001). Patients believed especially in the actions of the health care provider to prevent (43%), alleviate (44%), or control (43%) the ADE. Two-thirds of the patients (66%) perceived a clear understanding of their ADE. Figure 2 presents the comparison between the 2 methods of eliciting ADEs and the patients' ADE perceptions. Patients who reported an ADE on the open-ended question perceived the ADE as a more cyclical problem and perceived more consequences and emotional distress due to the ADE than patients who reported the ADE only on the checklist.

Determinants of ADE Perceptions

Of the 4 blocks entered, ADE characteristics explained mainly the variances of the different ADE perceptions, which ranged from 3% for timeline cyclical and treatment control to 32% for consequences and emotions (Table 5). Demographic variables explained only 2% of the variance in treatment control, and another 4% in understanding. When the blocks of clinical characteristics and features of received care were entered, no differences emerged among the 6 perceptions. Inspection of the individual *β* coefficients of significant predictors showed that the severity of ADEs was the strongest predictor of ADE perceptions (Table 6). Higher perceived severity is associated with a lower understanding, a stronger belief in the control abilities of health care providers, a stronger perception of a chronic timeline of the ADE and a higher perceived emotional distress and consequences. The ADEs reported on the open-ended question were more strongly perceived as unstable over time (cyclical timeline), with

TABLE 3	Perceived Adverse Drug Event Characteristics[a]			
	All Patients	**Open Question**	**Checklist**	
	n = 261	**n = 81**	**n = 180**	***P***
Duration				.618
<6 mo	67 (29)	22 (31)	45 (28)	
>6 mo	166 (71)	49 (69)	117 (72)	
Overall severity,[b] mean (SD)	6.0 (2.9)	6.8 (2.1)	5.6 (2.5)	.000
Consequences				
Hospitalization	14 (5)	8 (10)	6 (3)	.030
Consultation with a health care professional	165 (63)	68 (84)	97 (54)	.000
Modification of medication therapy	81 (31)	34 (42)	47 (26)	.010
Patient with the knowledge of the causal drug	173 (69)	63 (81)	110 (64)	.006

[a]Absolute number and percentages are presented unless mentioned otherwise.
[b]Severity was measured on a visual analog scale ranging from 0 to 10.

| TABLE 4	Modified Revised Illness Perception Questionnaire for the Total Study Sample (n = 261)	
		n (%)[a]
Consequences and emotions		
1 This ADE makes me feel afraid		82 (32)
2 When I think about my ADE, I get upset		42 (16)
3 This ADE makes me feel angry		57 (22)
4 Having this ADE makes me feel anxious		59 (23)
5 I get depressed when I think about this ADE		65 (25)
6 This ADE does worry me		93 (36)
7 This ADE has major consequences for my life		105 (40)
8 This ADE causes difficulties for those who are close to me		77 (30)
9 This ADE is a serious something		121 (46)
10 This ADE does have much effect on my life[b]		118 (45)
11 This ADE has serious financial consequences		32 (12)
12 This ADE strongly affects the way others see me		62 (24)
Subscale mean (1–5) (SD)[c]		2.4 (1.0)
Percentage scoring above scale midpoint		40
Timeline chronic		
13 This ADE will last for a long time		186 (72)
14 I expect to have this ADE for the rest of my life		160 (62)
15 This ADE is likely to be permanent rather than temporary		182 (71)
16 This ADE will not improve in time[b]		132 (52)
17 This ADE will not last for a short time[b]		161 (62)
18 This ADE will not pass quickly[b]		183 (70)
Subscale mean (1–5) (SD)[c]		3.9 (1.0)
Percentage scoring above scale midpoint		91
Personal control		
19 What I do can determine whether my ADE gets better or worse		78 (30)
20 The course of this ADE depends on me		51 (20)
21 There is a lot that I can do to control this ADE		79 (21)
22 I have the power to influence this ADE		68 (26)
23 What I do will affect my ADE[b]		94 (36)
24 My actions will have effect on this ADE[b]		82 (32)
Subscale mean (1–5) (SD)[c]		2.5 (1.0)
Percentage scoring above scale midpoint		46
Treatment control		
25 The actions of the doctor or nurse will be effective in alleviating my ADE		116 (44)
26 The actions of the doctor and/or nurse can control this ADE		111 (43)
27 The negative effects of this ADE can be prevented by the actions of the doctor or nurse		105 (40)
28 There is much that can be done to alleviate this ADE[b]		62 (24)
29 There is something that can help my ADE[b]		99 (38)
Subscale mean (1–5) (SD)[c]		3.0 (1.1)
Percentage scoring above scale midpoint		61
Understanding		
30 I have a clear picture of this ADE		158 (61)
31 This ADE is not a mystery to me[b]		130 (50)
32 This ADE does make sense to me[b]		92 (35)
33 I do understand my ADE[b]		104 (40)
Subscale mean (1–5) (SD)[c]		3.2 (1.2)
Percentage scoring above scale midpoint		66
Timeline cyclical		
34 I go through cycles in which my ADE gets better and worse		120 (46)
35 This ADE is very unpredictable		118 (46)
36 This ADE changes a great deal from moment to moment		101 (39)
37 This ADE comes and goes in cycles		99 (38)
Subscale mean (1–5) (SD)[c]		2.9 (1.2)
Percentage scoring above scale-midpoint		59

[a]Percentage of the patients who scored above item midpoint; agree or strongly agree with the item.
[b]This item was in the questionnaire reversed formulated, but transferred in the table to improve understanding.
[c]Five-point Likert scale: (1) strongly disagree, (2) disagree, (3) neither disagree or agree, (4) agree, (5) strongly agree.

stronger consequences and emotional distress as the ADEs reported on the symptom checklist. Furthermore, younger patients believed stronger in their personal ability to control the ADE and perceived a better understanding of their ADE than the older participants. Finally, male patients believed stronger in the abilities of
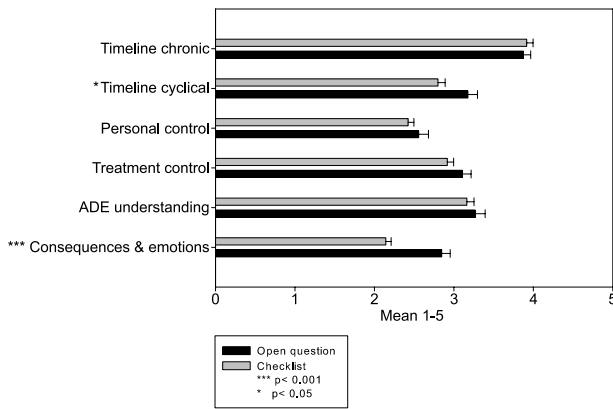
FIGURE 2. *Comparison of ADE perceptions between patients who reported an ADE on the open-ended question and the checklist.*

the health care providers to control or alleviate the ADE than female patients.

Discussion

Heart failure patients receive a range of different medications and have the potential to experience many symptomatic ADEs. We reported a detailed analysis on how HF patients perceived their reported ADEs. Our results show the importance of outlining patients' perception of experienced ADE when evaluating pharmacotherapy in HF patients. One of 2 patients perceived at least 1 ADE, of which dizziness, itches, and erectile dysfunction are reported frequently and perceived as moderately severe. Dizziness can be of particular concern of HF patients who may fear that medications make them feel more ill with consequences for their quality of life.[8] Patients reported to experience major consequences affecting their daily life accompanied with emotional distress. These results significantly contribute to the existing data that, although this type of frequently perceived ADEs does not endanger the health of the patients severely, patients are struggling with ADE alongside the symptoms of their HF, which adds to the disease burden.[21] The impact of these ADE on patients' well-being is not always recognized and acknowledged in clinical practice. Physicians mainly report serious ADEs,[22] suggesting that they are more focused on those ADEs that they judge as clinically relevant, necessitating treatment modification.[23,24] Modification of medication prescribed by physicians in case of mild ADEs, even after multiple reporting, is shown to be relatively low (only in 38% of the cases).[4] Our results suggest that the meaning of a "significant health problem" as a justification of discontinuation or uptitration as mentioned in the European guidelines of HF treatment[1] may be put into a broader perspective including the more mild ADEs, with patients' tolerance as cutoff. There is still a low level of dialogue about

TABLE 5 Summary of the Results of the Hierarchical Multivariate Regression Analyses of the Variances of the 6 Subscales of the Modified Revised Illness Perception Questionnaire

	Timeline Chronic			Timeline Cyclical			Personal Control			Treatment Control			ADE Understanding			Consequences and Emotions		
	F	Adj R²	ΔR²	F	Adj R²	ΔR²	F	Adj R²	ΔR²	F	Adj R²	ΔR²	F	Adj R²	ΔR²	F	Adj R²	ΔR²
Block 1																		
ADE characteristics	13.2	0.16a	0.16a	3.2	0.03b	0.03b	0.4	−0.01	−0.01	2.8	0.03b	0.03b	2.4	0.02	0.02	31.0	0.32a	0.32a
Block 2																		
Demographics	8.1	0.16a	0.00	2.2	0.03b	0.00	0.8	0.00	0.01	2.8	0.05c	0.02b	3.4	0.06c	0.04c	17.9	0.32a	0.00
Block 3																		
Clinical characteristics	5.8	0.16a	0.00	2.0	0.04b	0.01	1.1	0.01	0.01	2.1	0.04b	−0.01	2.4	0.05c	−0.01	12.6	0.31a	−0.01
Block 4																		
Received care features	4.1	0.15a	−0.01	1.7	0.04	0.00	0.9	−0.01	−0.02	1.8	0.04	0.00	2.1	0.06b	0.01	8.9	0.31a	0.00

Abbreviations: ADE, adverse drug event.; Adj, adjusted.
a $P < .001$.
b $P < .05$.
c $P < .01$.

TABLE 6 Final Hierarchical Regression Model (When All Blocks Are Entered)[a]

	Timeline Chronic		Timeline Cyclical		Personal Control		Treatment Control		Understanding		Consequences and Emotions	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Block 1: ADE characteristics												
Knowledge of the cause of ADE	−.08	−2.61 to 0.52	−.03	−1.63 to 1.00	.02	−1.47 to 1.95	.10	−0.36 to 2.53	.11	−0.16 to 2.42	−.05	−3.92 to 1.56
Duration of ADE	.37	**3.50 to 6.71**	−.11	−2.52 to 0.18	−.04	−2.24 to 1.26	−.11	−2.79 to 0.17	−.02	−1.56 to 1.08	.04	−1.76 to 3.89
Severity of ADE	.12	**0.01–0.59**	−.10	−0.45 to 0.05	.00	−0.32 to 0.32	.13	**0.01–0.55**	−.14	**−0.51 to −0.03**	.47	**1.71–2.74**
Open-ended vs symptom checklist	.05	−0.98 to 2.19	−.15	**−2.87 to −0.18**	−.04	−2.29 to 1.20	−.04	−1.94 to 0.99	−.03	−1.60 to 1.03	−.22	**−8.38 to −2.77**
Block 2: Demographics												
Age	−.11	−0.12 to 0.01	−.09	−0.09 to 0.02	−.15	**−0.14 to −0.01**	.00	−0.06 to 0.06	−.21	**−0.13 to −0.03**	−.07	−0.18 to 0.04
Sex	−.01	−1.79 to 1.45	.06	−0.81 to 1.90	.05	−1.20 to 2.32	.19	**0.50–3.48**	−.01	−1.42 to 1.24	−.04	−3.75 to 1.93
Education (≥12 y)	.03	−1.30 to 2.21	.02	−1.19 to 1.75	−.07	−3.01 to 0.81	−.11	−3.01 to 0.22	.01	−1.38 to 1.50	.01	−2.77 to 3.37
Block 3: Clinical characteristics												
Length of disease	.05	−0.14 to 0.33	.02	−0.17 to 0.23	−.04	−0.34 to 0.18	.00	−0.22 to 0.21	.03	−0.15 to 0.23	.02	−0.34 to 0.49
No. of medications	.05	−0.12 to 0.31	.11	−0.03 to 0.33	−.01	−0.25 to 0.21	−.07	−0.30 to 0.09	.05	−0.11 to 0.24	.05	−0.21 to 0.53
Ischemic cause of HF	−.04	−1.96 to 0.98	.03	−0.92 to 1.54	.11	−0.02 to 0.39	−.04	−1.72 to 0.98	−.05	−1.64 to 0.77	.00	−2.47 to 2.66
Block 4: Received care features												
Care at home	−.05	−2.29 to 1.09	.01	−1.30 to 1.54	.05	−1.18 to 2.51	.04	−1.12 to 2.00	−.05	−1.84 to 0.94	−.00	−3.06 to 2.88
Hospitalized previous year	.00	−1.53 to 1.54	.07	−0.64 to 1.93	.02	−1.42 to 1.92	.05	−0.90 to 1.91	−.10	−2.19 to 0.32	.02	−2.23 to 3.14
Under treatment of cardiologist	−.00	−3.28 to 3.10	.09	−0.84 to 4.51	.01	−3.33 to 3.62	.05	−1.75 to 4.12	.07	−1.25 to 3.98	.04	−3.64 to 7.51
Under treatment of HF clinic	−.01	−1.86 to 1.50	−.01	−1.52 to 1.29	.04	−1.30 to 2.37	.07	−0.72 to 2.37	−.06	−1.95 to 0.82	−.01	−3.28 to 2.61

Abbreviations: ADE, adverse drug event; β, standardized regression coefficient; CI, confidence interval; HF, heart failure.
[a]Text in bold indicates significant results ($P < .05$).

medication use between patients and physicians during medical encounters,[25] because not all physicians consider ADE as a concern related to clinical practice.[26] Nurse practitioners are increasingly involved in drug titration and treatment algorithms and may have therefore an important role in the identification and management of potential ADEs.[27] Shared decision making is often advocated as an ideal model for treatment decision making in routine care, but it requests both parties (health care provider and patient) to be involved.[28] This may put a question mark to the current debate on the implementation of telemonitoring in modern HF management programs.[29]

Our study emphasizes the importance of the role of health care providers in ADE management. Patients believed more in the ability of the physicians and nurses to control, prevent, or alleviate the ADE than in their own ability to do so. This is in contrast on how cardiac patients perceive their illness.[12,30] Although patients believed stronger in the abilities of the health care providers to control the ADE, it should be noted that around 40% of the patients did not. Patients are not always aware of the importance of discussing perceived ADEs with providers. The failure to discuss ADEs may result in patients experiencing ameliorable ADEs, of which the duration or severity could have been reduced when action would have been undertaken in an earlier stage.[31,32]

The present study highlights the complexity of effective ADE communication. Only 31% of the patients perceiving an ADE actually did report the ADE on the open-ended question, which is lower compared with previous studies.[3,33] As in line with the expectations, patients who reported an ADE on the open-ended question perceived the ADE as more severe and experienced higher consequences and emotional distress because of the ADE. However, still a considerable number of patients (38%) who rated high the perceived severity of the ADE (≥ 7) reported the ADE only on the checklist. This may indicate that a single open-ended question may not be sufficient to detect or identify truly perceived ADEs in practice. Therefore, nurses and doctors need to proactively communicate with patients about potential ADEs but in particular about the importance for patients to report ADEs back to their providers once perceived. Although elimination of all unpleasant ADEs might be impossible, when patients share their experiences with providers, prescribing would become more aligned with specific patients' needs and may reflect their preferences.

In this study, demographic, clinical, and received care characteristics showed only few and low associations with ADE perceptions after adjusting for the characteristics of the ADE itself. Only age and sex significantly explained some variance of the control subscales and the subscale of perceived ADE understanding. Elderly patients believed less in personal control and perceived a lower understanding of their ADE than younger patients, and male patients believed more in the ability of health care providers to control or manage the ADE than women. This latter finding is in line with a previous study among cardiac patients, showing that men perceived greater treatment effects than women.[12] As one would expect, perceived ADE severity was most related with negative perceptions such as less understanding and more severe consequences and emotions.

Findings of this study have implications for both research and clinical practice. Framing of the ADE perceptions using the Common Sense Model may appear an important source for designing interventions to improve ADE management. For example, increasing patient–health care provider interaction and hereby focusing on presence of ADE and perceived severity may increase patients' comprehension and diminish medication-related emotional distress and negative consequences. Moreover, giving more education and information to elderly HF patients may increase their ADE comprehension and finally increases their sense of personal control. Further research is warranted to detect other factors explaining the variance of negative and positive ADE perceptions, such as medication beliefs. Second, how these ADE perceptions on their turn are associated with coping strategies and other outcomes such as quality of life need to be investigated.

The strengths of this study are the inclusion of HF patients invited from both primary and secondary care, the mixed method of open questioning and checklist for identifying perceived ADE,[34] and the use of a well-established theory model, the Common Sense Model, for measuring the perception of ADE. However, the cross-sectional design, the reliance on self-reported data, the exclusion of potential important disease severity parameters (LVEF and NT-proBNP) from the hierarchic multivariate analyses, and the lack of comparison between responders and nonresponders need to be addressed as limitations of our study. However, concerning the nonresponse, the characteristics of our study population are largely comparable to those of a large national study on HF.[35] Because we were interested in rather mild symptomatic ADEs, a longer time window than the previous 4 weeks would have been more sensitive to potential recall bias. No causal assessment between perceived ADEs and medication was performed. Consequently, there is an existing likelihood that the reported ADEs are incorrectly attributed by the patient to their drugs. For example, symptoms might have been rather a consequence of the disease itself or of undertreatment because only 86% of the patients received a renin-angiotensin-aldosterone system inhibitors. However, the relevance of this study lies in patients' own perception that they have an ADE because this perception guides their coping efforts

> ### What's New and Important
>
> - Symptomatic ADEs such as dizziness and dry mouth are commonly perceived by ambulatory HF patients.
> - Nearly 1 of 3 patients perceived the ADE as something serious with major consequences on their daily life accompanied with emotional distress such as worries.
> - Demographic and clinical characteristics are limited associated with different ADE perceptions after adjusting for ADE characteristics, such as perceived severity.
> - Elderly patients believed less in personal control and perceived a lower understanding of their ADE than younger patients, and male patients believed more in the ability of health care providers to control or manage the ADE than women.
> - Patient-health care provider interaction needs to be stimulated regarding the presence of possible ADE and related negative perceptions. Patients' perception may be valuable to include in the decision process of ADE management.

despite the true (unknown) origin of the adverse event.[36] Finally, we included only ambulatory HF patients and thus have no information on the generalizability of the results to HF patients admitted to the hospital or living in a nursing home.

We conclude from this study that ADEs in ambulant HF patients are often perceived as moderately severe, accompanied with major consequences for daily life and with emotional distress. Our data suggest that proactive communication between patients and providers should be stimulated where patients can share their perceptions of ADE. This information can be valuable in the providers' judgment on how to manage ADE—preventing, ameliorating, or accepting—and on how to change the drug regimen that reflect patients' preferences.

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Effects of a cardiovascular risk reduction intervention with psychobehavioral strategies for Korean adults with type 2 diabetes and metabolic syndrome: ERRATUM

In the article that appeared on page 117 of volume 26, issue 2, a few words were misspelled in the text. There are three instances of the word Koran found in the text on pages 119 and 126. In all of these instances, the word should appear as Korean. Also, the heading Hypotheses on page 119 should appear as Hypothesis.