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Coping with adverse drug events in patients with heart failure: Exploring the role of medication beliefs and perceptions

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Coping with adverse drug events in patients with heart failure: Exploring the role of medication beliefs and perceptions

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This study describes coping strategies that patients with heart failure (HF) use to manage adverse drug events (ADEs). The included coping strategies were social support seeking, information seeking, non-adherence and taking alleviating medication. The role of beliefs about medication and ADE perceptions in explaining these coping strategies was assessed using the Self-Regulation Model. We performed a cross-sectional study including 250 HF patients who experienced an ADE. Patients completed validated questionnaires assessing their coping strategies, ADE perceptions and medication beliefs. Social support (60%) and information seeking (32%) were the most commonly used strategies to cope with ADEs. Non-adherence was reported by 7% of the patients. Multivariate linear regression analysis showed that demographics, clinical factors and medication beliefs explained only a small amount of the variance in coping strategies, whereas ADE perceptions explained a substantial amount of variance. Path analysis showed that patients' perceptions about the timeline, consequences and controllability of ADEs by the health care provider were directly related to their coping behaviour. The effect of patients' medication beliefs on their coping strategies was consistent with mediation through their ADE perceptions. Our results support the value of the Self-Regulation Model in understanding patients' coping behaviour with regard to ADEs.

Keywords: adverse drug events; coping; perception; medication beliefs

Introduction

Heart failure (HF) is a progressive lifelong condition affecting over 15 million people in Europe. It is a condition in which the heart does not have the ability to provide the body's organs and tissues with enough blood needed for proper functioning.

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The most common symptoms are oedema, shortness of breath and fatigue. Disease management often includes lifestyle modifications and lifelong pharmacological treatment requiring an active role of the patient. Pharmacological treatment is the cornerstone of HF management and often consists of multiple drugs. Medications may relieve symptoms and reduce morbidity and mortality, but can also cause adverse drug events (ADEs). Previously, we reported that 17% of patients with HF experience symptomatic ADEs, such as nausea and dizziness (De Smedt, Denig, Haaijer-Ruskamp, & Jaarsma, 2009). These events may cause patients with HF substantial discomfort and anxiety, increase their disease burden and decrease their quality of life (Gandhi et al., 2000; Pattenden, Roberts, & Lewin, 2007). Patients' reactions to ADEs may include discussing the event with a health care provider, stop taking the medication temporarily or permanently or taking additional medication to alleviate the adverse symptom (De Smedt et al., 2009). However, there is still a lack of a clear understanding how patients try to cope with a perceived ADE and which factors may affect their coping strategies.

The aim of this study was to describe how patients with HF cope with ADEs and the way their perceptions of these events and beliefs about medication influence their coping behaviour. This information may enable patients and health care providers to improve the way they manage ADEs. We used the conceptualisation and measurement of coping developed by Johnson and Neilands (2007) in their study of how patients infected with the human immunodeficiency virus cope with ADEs (Johnson & Neilands, 2007). They developed a measurement instrument which is based on the Stress and Coping Theory (Lazarus & Folkman, 1984) and consists of five coping subscales. The subscales represent positive emotion-focused coping (positive reappraisal, benefit-reminding, humour and distraction), social support seeking (seeking social (emotional) support from family and relatives in response to the ADE), non-adherence (reducing the medication dose or stop taking the medication), information seeking (actively seeking out information about the ADE and the cause) and taking medication to alleviate ADEs (the use of other medication to reduce the distress of the ADE). The subscales represent specific coping actions and responses (behavioural approach) that patients may actually conduct to deal with specific ADEs. Maes, Leventhal, and de Ridder (1996) have argued that for a better understanding of the coping process it is important to evaluate concrete rather than general coping strategies in reaction to a particular source of stress, such as a specific perceived ADE of a given duration and severity (Maes et al., 1996).

We expect that coping with ADEs can be better understood if more is known about the role of patients' perceptions of the ADE that they experience. To study these perceptions, we used the theory of Self-Regulation by Leventhal and Diefenbach (1992) as a framework (Leventhal & Diefenbach, 1992). This theory describes patients' coping behaviour as a common sense reaction to their cognitive and emotional perceptions and interpretations of a specific threat, such as an illness or an experienced ADE. The model is multi-dimensional with five dimensions and includes: symptom labelling (*identity*); perceived time course (*timeline*); causal factors (*cause*); potential ways of curing or controlling the threat (*control/cure*); and physical, social and economic consequences (*consequences*). Patients' perceptions of their diseases have shown to be an important determinant of medication non-adherence (Molloy et al., 2009) but little is known about the role of their perceptions of ADEs. We know from previous studies that the Self-Regulation Model, which emphasises the importance of symptom interpretation for coping behaviour, can also

be useful for describing how patients understand perceived medication adverse events (DeWitt & Sorofman, 1999; Johnson & Folkman, 2004). Patients also use the five cognitive elements as described for illness perception to describe a prototype of an ADE (DeWitt & Sorofman, 1999). This does not mean that the way patients cope with the symptoms of a chronic illness is the same as the way they cope with ADEs. There are fundamental differences between the two concepts. The interpretation of the cause is clearly different, since the drug is seen as the causal factor for an ADE. Therefore, ADEs may be viewed as more controllable by the patient, as they have the power to eliminate the burden by reducing the dosage or stop taking the drug. In contrast, it is more difficult and less straightforward to influence the cause of chronic illness. Hence, it is likely that coping with ADEs is a different challenge to that of coping with the symptoms of a condition (Johnson & Neilands, 2007).

We expect that medication beliefs play a role in how patients perceive and cope with ADEs. Medication beliefs significantly add to the explanation of non-adherence among patients with asthma beyond what was explained by their perceptions of illness (Horne & Weinman, 2002). The influence of illness perception on non-adherence was largely mediated by the medication beliefs. Medication beliefs have also shown to be relevant for medication adherence among patients with HF (George & Shalansky, 2007). However, we do not know what role medication beliefs play in patients' specific ways of coping with ADEs, and to what extent these medication beliefs interact with their ADE perceptions. Patients' medication concerns have been shown to be related with self-reported ADEs (Oladimeji, Farris, Urmie, & Doucette, 2008). We expect that patients who have concerns about their medication and have negative beliefs towards medication in general are more likely to perceive and report ADEs because they are more likely to attribute perceived symptoms to their medication. Moreover, we expect that patients with negative feelings about medication will also have more pronounced negative perceptions of ADEs.

In this study, we describe the coping strategies that patients with HF use to manage perceived ADEs. We also assess the relationship between patients' perceptions of ADEs and their medication beliefs to their coping strategies. We formulated two hypotheses:

- (1) Patients' perceptions of ADEs will explain the use of different coping strategies beyond the effects of demographics, clinical characteristics, care received and the characteristics of the ADEs.
- (2) Stronger concerns about negative drug effects will be associated with more labelling of ADEs and with perceiving more consequences and emotional reactions of the ADEs, which thus may mediate their relationship with coping.

Methods

Design

We used a cross-sectional design to study coping strategies and possible determinants of coping behaviour in patients with HF who had recently experienced an ADE. Data were collected between November 2008 and March 2009 using patient-administered questionnaires. The study protocol and procedure were approved by the Medical Ethics Committee of the University Medical Centre Groningen, the Netherlands.

Participants and procedures

Patients with HF were recruited from 20 primary and 3 secondary care centres in the Netherlands in order to have a sample reflecting the population of patients with HF living in the Dutch community. Patients from primary care were included if they had a documented diagnosis of HF (International Classification Primary Care code K77) in their electronic medical record which was subsequently confirmed by their general practitioner. Patients from the outpatient HF clinics were included if they had a documented diagnosis of HF in their medical chart at the clinic. Patients were excluded when they were younger than 18 years, hospitalised, participated in a clinical trial, lived in a nursing home or had a terminal disease or cognitive disorder.

An information letter was sent by the research group to all eligible patients explaining the purpose of the study, asking them to participate in the study and give informed consent. A second letter was sent to patients who did not reply within 1 month. After receiving patients' written informed consent, a self-administered questionnaire was sent out. Patients could ask for help to fill in the questionnaire. The assistance was provided by someone outside the research and health care provider group. Patients who experienced an ADE in the past 4 weeks were included in this study (see next section).

ADEs experienced by patients

Data on ADEs perceived by the patients were collected using a combination of an open-ended question and a symptom checklist. This method is suggested as being a better way of obtaining data on perceived ADEs than a single open-ended question (Sheftell et al., 2004; Wallander, Dimenas, Svardsudd, & Wiklund, 1991). Patients were asked whether they had experienced one or more 'side effects' (lay term of ADEs) related to their medication during the previous 4 weeks. A 4-week time frame was chosen to reduce recall bias, especially for mild events. If the answer was yes, patients were asked to list the experienced ADE. A checklist of 28 symptoms was provided which was on a previous study on perceived ADEs (De Smedt et al., 2009). Patients were asked whether they experienced any of the symptoms in the previous 4 weeks, and whether they attributed it as a 'side effect' of their medication or as a symptom of HF. Symptoms reported exclusively as side effects were included as perceived ADEs. Patients who reported an ADE on the open-ended question or the symptom checklist received additional questions on their coping behaviour and their perception of ADEs. When patients reported more than one ADE, the questionnaire was completed for the most 'relevant' ADE as indicated by the patient. They were also asked to record general characteristics of the ADE, i.e. the duration of the ADE, the severity of the ADE using a visual analogue scale (VAS) ranging from 0 (lowest perceived severity) to 10 (highest perceived severity), and the drug they believed to cause the event (knowledge of the ADE).

Demographic and clinical variables

Data on socio-demographic variables, the type of care received in the previous year and the number of medications used were collected by means of the patient questionnaire. Data on the aetiology, duration and severity of HF were obtained

from patients' medical records. The severity of HF was expressed using the left ventricular ejection fraction.

Questionnaires on coping, perception of ADEs and medication beliefs

Development of the coping with ADEs questionnaire

Coping strategies were assessed using a revised version of the Side Effect Coping Questionnaire (SECOPE) (Johnson & Neilands, 2007). The original SECOPE consists of five subscales: positive emotion-focused coping, social support seeking, non-adherence, information seeking and taking medication to alleviate the ADE. All items are rated on a five-point Likert type scale: *never, rarely, sometimes, often* and *very often*. All original items were included in the initial version of the revised questionnaire. Based on a pilot study of cognitive interviews with seven patients, the following two items were added: 'I accept the side effect and take the medication as prescribed' and 'I ask my doctor to prescribe another medication'. Although the first item consists of two elements, patients during the cognitive interviews emphasised that agreeing with this statement implied that they took their medication and thereby accepted the ADE. These changes resulted in a total number of 21 items.

Development of the ADE Perception Questionnaire

The developed ADE Perception Questionnaire (APQ) was based on the Revised Illness Perception Questionnaire (IPQ-R) (Moss-Morris et al., 2002). The IPQ-R is a valid and reliable questionnaire which has been used to describe patients' perceptions of several chronic diseases (Chilcot, Wellsted, & Farrington, 2010; Gould, Brown, & Bramwell, 2010). The IPQ-R was modified by changing the term 'my illness' with 'the side effect' which is the lay term for an ADE. The term 'treatment' of the 'treatment control' subscale was substituted with 'actions of the doctor or nurse' and we renamed the subscale 'provider control'. Furthermore, we excluded the domain cause (personal ideas about the cause of the condition) since an ADE already implies that medication is seen as the underlying cause. The 'ADE identity' subscale was expressed as the absolute number of symptoms that the patients endorsed as ADEs on the checklist of 28 symptoms in the patient-administered questionnaire (mentioned in the previous sections). This scale was continuous, ranging from 0 to 28. The other seven domains are measured on subscales, consisting of four to six items, assessing the patients' perceptions about chronic timeline (e.g. 'My ADE will last for a long time'), cyclical timeline (e.g. 'My ADE come and go in cycles'), consequences (e.g. 'My ADE has major consequences on my life'), emotional representation (e.g. 'My ADE makes me feel afraid'), personal control (e.g. 'I have the power to influence my ADE'), provider control (e.g. 'Healthcare providers can control my ADE') and ADE understanding (e.g. 'I have a clear picture or understanding of my ADE'). The item 'The symptoms of my condition are puzzling to me' was excluded since we could not transfer it to a meaningful item for the ADE understanding subscale, resulting in 37 items in the seven subscales. The items were all rated on the original five-point Likert type scale: *strongly disagree, disagree, neither agree nor disagree, agree* and *strongly agree*. A higher score on the subscales represents a greater endorsement of the specific construct.

Medication beliefs

This was measured using the Beliefs about Medication Questionnaire (BMQ; Horne, Weinman, & Hankins, 1999). This validated questionnaire consists of 18 items assessing personal beliefs on medication-related concerns, the necessity of prescribing, general beliefs on medication overuse and related harm. The response scale is a five-point Likert type scale, ranging from *strongly disagree* to *strongly agree*.

Statistical analysis

To assess the construct validity of the modified SECOPE (21 items) and of the APQ (37 items), we conducted exploratory principal component analysis (PCA) using the varimax rotation method with Kaiser normalisation. The internal consistencies of the subscales of the instruments were analysed using Cronbach's alpha. Items which loaded more than 0.4 on a factor were assigned to that factor for the subsequent analyses. Cross-loadings, defined as items loading with more than 0.4 on more than one factor, were explored.

Descriptive statistics are used to describe the patient sample and the patients' scores on the subscales of the questionnaires. Two scores were calculated for each subscale of the SECOPE, the APQ and the BMQ. First, mean scores were computed by averaging across scale items, yielding a possible range of scores for each subscale from one to five. These scores were used in all further models. Second, we assessed percentages of patients scoring above the midpoint of each subscale to reflect overall endorsement of the items per subscale.

Linear regression models were constructed to assess how patients' perceptions of ADEs and medication beliefs contributed to the explained variance of each of the four coping strategies, controlling for the socio-demographic and clinical characteristics, received care, and general characteristics of the ADE. The left ventricular ejection fraction was excluded from the analysis because it had a large number of missing values. Missing data of the remaining predictors were less than 10% per variable and therefore imputed using the expectation-maximization algorithm (Schafer, 1997).

Finally, a structural equation model (SEM) was built to explore the underlying structure of relationships between beliefs about medication, perceptions of ADEs, the characteristics of the ADEs and coping strategies. We used AMOS Version 18.0 for our SEM modelling and used maximum likelihood estimation (SPSS Inc., Chicago, IL, USA). The SEM was constructed to examine direct and indirect or mediated effects of the included variables on the coping strategies. First, we assessed the direct effects of ADE perceptions on coping strategies based on our hypothesis and on the results of the multivariate linear regression analysis. To examine our second hypothesis, we added negative medication beliefs to the direct effects model. We explored Pearson's correlations among variables for other possible direct or indirect associations. Based on this, we added other relevant variables to the model. The fit of the models were specified by the root mean square error of approximation (RMSEA) as a non-centrality based fit index, the standardised root mean square residual (SRMR) as an absolute fit index, the comparative fit index (CFI) and the parsimony normed fit index (PNFI). Generally, an RMSEA greater than 0.10, an SRMR greater than 0.08 and a CFI less than 0.85 indicate poor model fit, whereas an RMSEA and an SRMR less than 0.05 and a CFI greater than 0.95 indicate a

good fit (Hu & Bentler, 1999; Kline, 2005). There is no commonly agreed upon cutoff value for an acceptable model using the PNFI.

Results

Patient characteristics and reported ADE

In total, 960 patients with HF were invited to participate in the main study. Of these patients, 495 (53%) agreed and gave informed consent, including less than 20% of patients who responded to the second information letter. The demographic and clinical characteristics of these patients are presented in Table 1. These are largely comparable with those found in a study of 1023 patients with HF in the Netherlands (Jaarsma et al., 2008). We had no data on the characteristics of the non-responders.

Of the 495 patients who responded, 332 (67%) had experienced at least one ADE in the previous 4 weeks. This group represented our population and was sent the full questionnaire. A total of 71 (21%) patients did not return this and another 11 patients (3%) were excluded because of missing data on the coping questionnaire. Hence, our results are based on the responses of 250 patients. The 82 patients who dropped out were significantly less educated (education ≥ 12 years; 50% versus 66%, $p = 0.010$) and were slightly older (mean age: 72 versus 70 years, $p = 0.051$) than the

Table 1. Demographic and clinical data of the study sample ($n = 250$).

Characteristics	Study sample
<i>Demographics</i>	
Mean age in years ($\pm$ SD)	69.6 $\pm$ 11.9
Female	91 (36.4%)
Level of education (12 missing)	
No education/primary school	43 (17.2%)
Secondary school	141 (56.4%)
Higher education/university	54 (21.6%)
Living alone (12 missing)	81 (32.4%)
<i>Clinical characteristics</i>	
Median duration of HF in years (IQR) (6 missing)	3.0 (2.0–5.7)
Left ventricular ejection fraction <45–50% (70 missing)	153 (61.2%)
Ischemic aetiology of HF (3 missing)	137 (54.8%)
Median number of all used medication (IQR)	7.0 (5.0–9.3)
<i>Treatment in the previous year</i>	
Treated by a cardiologist (2 missing)	234 (93.6%)
Treated at an outpatient HF clinic (3 missing)	170 (68.0%)
Hospitalisation (4 missing)	118 (47.2%)
Receiving care at home (8 missing)	88 (35.2%)
<i>Characteristics of the ADE</i>	
Mean severity (rated on a 0–10 VAS) ($\pm$ SD)	6.0 $\pm$ 2.5
Duration of the ADE (25 missing)	
< 6 months	62 (24.8%)
> 6 months	163 (65.2%)

Notes: IQR, inter-quartile range; ADE, adverse drug event.

Means are calculated on all available data, percentages are calculated out of the total of 250 patients.

250 patients who were included in the study. No significant differences between the two groups were found with regard to gender ($\chi^2 = 1.17$, $p = 0.278$) and number of experienced ADEs ($t = -1.10$, $p = 0.274$).

The 250 patients had perceived a total of 765 ADEs (three per patient) in the previous 4 weeks. The events with the highest prevalence were dizziness (26%), a dry mouth (24%) and itching (20%). Patients rated on average the severity of the perceived ADE a six on a VAS from 0 to 10 (Table 1). The majority of patients (72%) perceived the ADE over more than 6 months.

The modified SECOPE Questionnaire

All 21 items of the modified SECOPE were entered in an exploratory PCA (Table S1). This resulted in a model which explained 62.5% of the total variance. The 'positive emotion-focused coping' subscale, however, showed a low reliability coefficient (Cronbach's $\alpha = 0.47$), and also a low contribution to the overall explained variance. Since it also had been assigned a low relevance by patients in the pilot study, we decided to exclude this subscale from the subsequent analyses. All other subscales had a good level of internal reliability, i.e. social support seeking ($\alpha = 0.81$), information seeking ($\alpha = 0.77$), non-adherence ($\alpha = 0.89$) and taking additional medication ($\alpha = 0.76$). We observed no clear cross-loadings. However, the two items on medication requests loaded strongly on the 'information-seeking' subscale instead of on the 'taking additional medication' subscale, and were therefore included in the 'information-seeking' subscale for the subsequent analyses. The exploratory analysis thus resulted in a 16-item questionnaire including four subscales. The final model explained 54.0% of the total variance.

The APQ

All 37 items were initially entered in an exploratory PCA. This resulted in a seven-factor model which explained 60.6% of the total variance. However, just one item ('This ADE has serious financial consequences') loaded on the seventh factor, which had an eigenvalue of 1.38 and explained only 3.7% of the total variance. Based on these findings and after investigating the Scree plot, we decided to repeat the analysis with a six-factor solution. The total explained variance of this model was 56.9%. Five of the six factors corresponded with five subscales of the original IPQ-R, whereas the 12 items of the original 'consequences' and 'emotional representation' subscales all loaded on one factor (all loadings > 0.4). This factor had the greatest eigenvalue of 6.60 and explained 17.8% of the total variance. We rephrased this domain into 'consequences and emotions'. No clear cross-loadings were seen for any of the 37 items, indicating a strong match between the items and the six factors. Further analysis showed good internal reliability of the six subscales with Cronbach's α ranging from 0.77 for the 'cyclical timeline' subscale to 0.89 for the 'consequences and emotions' subscale.

Beliefs about Medication Questionnaire

The reliability coefficients of the four subscales ranged from 0.57 for the 'general harm' subscale until 0.83 for the 'medication necessity' subscale.

Reported coping strategies

The number of patients who reported to use specific coping behaviour at least 'sometimes' are summarised in Table 2. A total of 149 (60%) patients scored above the midpoint on the 'social support-seeking' subscale, 102 (41%) patients on the 'information-seeking' subscale, 34 (14%) patients on the 'taking additional medication' subscale and 17 (7%) patients on the 'non-adherence' subscale. Furthermore, 64 (26%) patients did not score above the subscale midpoint on any coping strategy, 96 (38%) scored above the subscale midpoint on a single strategy, 68 (27%) on two strategies and 18 (7%) on three strategies. Of the 18 patients, who scored above the subscale midpoint on three coping strategies, 14 (78%) scored as such on 'social support seeking', 'information seeking' and 'taking additional medication'.

Perception of ADE and medication beliefs

Most patients perceived their ADE as a chronic problem, with 90% scoring above scale midpoint (Table 3). A total of 101 (40%) patients perceived negative consequences and emotional distress, such as anxiety and feeling depressed, because of the ADE. Among the patients, there was more belief in the ability of their health care provider to control ADEs than in their own power to do so, as 152 (61%) patients scored above midpoint on the 'provider control subscale' and 116 (46%) patients scored above midpoint on the 'personal control' subscale. While 239 (96%) patients felt that their medication was necessary, 100 (40%) patients had particular concerns about their own medication. A total of 160 (64%) patients believed that medication in general is being overused, and 110 (44%) patients felt that medication in general is harmful.

ADE perceptions and coping strategy

The determinants of the four coping strategies using linear regression analysis are given in Table 4. Patients' perceptions of ADEs contributed significantly to variations in the use of social support-seeking, information-seeking and non-adherence coping strategies. Patients who experienced a higher number of ADEs (ADE identity), who perceived more negative consequences and emotional distress of the ADE, and who had beliefs about the controllability of the ADE by the health care providers (provider control), were more likely to seek information (overall explained variance 27%). Furthermore, higher scores on ADE identity and provider control were also associated with more social support seeking (overall explained variance 8%). Patients who perceived the ADE as temporary were more likely to display non-adherence than those who believed that the ADE is chronic or that it will come and go over time (overall explained variance 18%). There were no significant relationships between any of the patients' perceptions of ADEs and the likelihood that they used additional medication to alleviate the ADE. The linear regression analyses demonstrated that medication beliefs had no significant direct associations with any of the four coping strategies.

Table 2. The patients' responses to individual items on the SECOPE questionnaire ($n = 250$).

Items	Number of patients who reported using each type of coping behaviour (sometimes, often, very often)	
Social support-seeking subscale		
I share my feelings and thoughts with others	167 (66.8%)	
I get support from other people	175 (70.0%)	
I talk to my family, friends and loved ones about the problem	168 (67.2%)	
I let others know what I am going through	109 (43.8%)	
Subscale mean, $\pm$ SD		2.7 $\pm$ 0.9
Patients with more than 10 points (midpoint of the scale)		149 (59.6%)
Information-seeking subscale		
I talk to my doctor or health care provider about the problem	123 (49.3%)	
I try to get information about the medication or ADE	136 (54.9%)	
I try to find out as much as I can about what is causing the ADE	132 (53.1%)	
I request medication from my doctor or HF nurse to alleviate the ADE	99 (39.9%)	
I ask my doctor to prescribe another medication	72 (29.0%)	
Subscale mean, $\pm$ SD		2.3 $\pm$ 0.9
Patients with more than 13 points (midpoint of the scale)		102 (40.8%)
Non-adherence subscale		
I reduce the dose of the medication that is causing the ADE	23 (9.3%)	
I take less of the medication to see if the ADE is not so bad	19 (7.6%)	
I take a break from the medication	21 (8.5%)	
I decide that the medication is not worth the ADE and stop taking it	15 (6.1%)	
I accept the ADE and take the medication as prescribed ^a	230 (92.2%)	
Subscale mean, $\pm$ SD		1.3 $\pm$ 0.7
Patients with more than 13 points (midpoint of the scale)		17 (6.8%)
Taking additional medications subscale		
I take another medication to deal with the ADE (i.e. pain medication)	33 (13.3%)	
I take a medication that will make the ADE feel better or go away	72 (28.9%)	
Subscale mean, $\pm$ SD		1.6 $\pm$ 1.0
Patients with more than 5 points (midpoint of the scale)		34 (13.6%)

Note: ^aReversed items and added to the SeCOPE. Scores on the SeCOPE; 1 = never, 2 = rarely, 3 = sometimes, 4 = often and 5 = very often.

Table 3. Patients' perceptions of ADEs (modified IPQ-R) and their medication beliefs (BMQ) ($n = 250$).

Questionnaire and subscales		Mean	SD	Patients' scoring above the midpoint of the scale
Modified IPQ-R	ADE Identity	4.2	3.2	NA
	Chronic timeline	3.9	1.0	226 (90.4%)
	Timeline cyclical	2.9	1.2	148 (59.2%)
	Consequences and emotions	2.4	1.0	101 (40.4%)
	Personal control	2.5	1.0	116 (46.4%)
	Provider control	3.0	1.1	152 (60.8%)
	Understanding of ADE	3.2	1.2	167 (66.8%)
BMQ	Medication necessity	4.3	0.8	239 (95.6%)
	Medication concerns	2.4	1.0	100 (40.0%)
	General overuse	2.9	0.9	160 (64.0%)
	General harm	2.5	0.9	110 (44.0%)

Notes: NA, not applicable. Scores on the BMQ and IPQ-R are: 1 = totally disagree, 2 = disagree, 3 = neither agree or disagree, 4 = agree and 5 = totally agree.

Medication beliefs and ADE perceptions

Effects of medication beliefs and perceptions of ADEs on coping strategies were investigated using structural equation modelling. After investigating the direct effects between ADE perceptions and coping strategies, negative medication beliefs were added to the model to evaluate mediating effects through ADE perceptions. Other relevant factors, including perceived severity and duration of ADE, were also entered based on their associations with ADE perceptions and coping strategies (Table S2). The final model, presented in Figure 1, can be specified as a close fit model (RMSEA = 0.058; SRMR = 0.081; CFI = 0.872; and PNFI = 0.598). This model demonstrates that patients' strategies for coping with ADEs are associated with most of the ADE perceptions as described in the Self-Regulation Model. As was hypothesised, the patients' beliefs about medication were indirectly related to the coping strategies suggesting mediation through patients' perceptions of ADEs. The 'medication concerns' and 'medication harm' subscales accounted for 13% of the variance of the 'ADE identity' scale. The 'severity of the ADE' and 'medication concerns' subscale accounted for 40% of the variance in the 'consequences and emotions' subscale. Patients' beliefs on medication overuse did not play a significant role in the model. As in the linear regression analysis, it was found that patients' perceptions of 'ADE identity', 'consequences and emotions' and 'provider control' were related to information-seeking and social support-seeking behaviour, whereas 'timeline perceptions' but also 'consequences and emotions' were found to be related to non-adherence.

An important observation was that some of the coping strategies were also related to each other. Patients who sought social support were also more likely to seek information, and patients those sought information were also more likely to take additional medication to alleviate the ADE.

Table 4. The determinants of the four coping strategies using linear regression analysis.

	Social support seeking			Information seeking			Non-adherence			Taking additional medication		
	β	SE	P	β	SE	P	β	SE	P	β	SE	P
Socio-demographics												
Age	-0.04	0.02	0.604	0.01	0.03	0.858	0.04	0.02	0.595	0.14	0.01	0.075
Gender (0 = female)	-0.10	0.53	0.180	-0.04	0.68	0.482	0.03	0.50	0.671	-0.11	0.31	0.136
Educational level	0.03	0.48	0.632	0.12	0.63	0.049	-0.01	0.46	0.936	-0.04	0.28	0.585
Clinical variables												
Duration of HF	-0.09	0.07	0.192	-0.09	0.10	0.122	-0.06	0.07	0.331	-0.01	0.04	0.910
Total number of drugs	-0.08	0.08	0.246	0.09	0.10	0.168	0.10	0.07	0.152	-0.01	0.05	0.950
Ischemic HF	-0.01	0.47	0.891	0.02	0.61	0.775	-0.02	0.45	0.812	-0.02	0.28	0.730
Received care at home	0.20	0.55	0.007	0.04	0.72	0.544	0.06	0.53	0.379	-0.03	0.33	0.701
Hospitalised	0.01	0.50	0.876	0.05	0.64	0.465	0.02	0.47	0.801	0.00	0.29	0.985
Treated at outpatient clinic	0.03	0.54	0.717	0.10	0.70	0.102	0.08	0.51	0.233	-0.01	0.32	0.921
Treated by a cardiologist	-0.03	1.07	0.668	-0.01	1.38	0.963	-0.13	1.01	0.048	0.07	0.63	0.305
ADE characteristics												
Duration of ADE	-0.08	0.56	0.244	-0.05	0.73	0.459	-0.14	0.54	0.037	-0.03	0.33	0.719
Knowledge of ADE	-0.08	0.49	0.204	0.09	0.64	0.115	0.11	0.47	0.071	-0.02	0.29	0.758
Severity of ADE	0.08	0.11	0.291	0.09	0.14	0.226	0.06	0.11	0.420	0.07	0.07	0.413
Medication beliefs												
Medication necessity	-0.00	0.06	0.959	-0.12	0.08	0.068	-0.07	0.06	0.287	0.03	0.04	0.698
Medication concerns	0.12	0.05	0.124	0.07	0.07	0.307	0.05	0.05	0.542	0.06	0.03	0.459
General harm	-0.05	0.08	0.537	-0.06	0.11	0.426	-0.03	0.08	0.721	-0.04	0.05	0.678
General overuse	-0.04	0.07	0.608	0.06	0.10	0.390	-0.02	0.07	0.789	0.07	0.04	0.368
ADE perceptions												
ADE identity	0.16	0.07	0.025	0.15	0.10	0.015	0.07	0.07	0.304	0.12	0.04	0.103
Timeline chronic	0.02	0.05	0.840	-0.06	0.06	0.402	-0.31	0.04	0.000	0.08	0.03	0.356
Timeline cyclical	0.13	0.05	0.076	0.06	0.07	0.353	-0.17	0.05	0.015	0.07	0.03	0.332
Consequences and emotions	-0.05	0.03	0.577	0.21	0.03	0.007	0.13	0.03	0.104	0.05	0.02	0.560
Personal control	0.04	0.04	0.614	-0.09	0.05	0.180	0.08	0.04	0.264	0.04	0.02	0.076
Provider control	0.15	0.05	0.044	0.29	0.06	0.000	0.03	0.05	0.703	0.14	0.03	0.521
ADE understanding	0.12	0.06	0.107	0.07	0.07	0.283	-0.05	0.05	0.477	0.05	0.03	0.550
	Adjusted $R^2=0.08$, $F=1.87$, $p < 0.01$			Adjusted $R^2=0.27$, $F=4.73$, $p < 0.001$			Adjusted $R^2=0.18$, $F=3.17$, $p < 0.001$			Adjusted $R^2=0.02$, $F=1.19$, ns		

Note: ADE, adverse drug event; β , standardized regression coefficient; SE, standard error of β .

Figure 1. SEM of the reported strategies for coping with perceived ADEs.

Note: The terms e1–e8 represent unobserved variables that could have an effect on the endogenous variable.

Discussion

The most commonly used strategies of patients with HF to cope with ADEs were social support seeking and information seeking. Few patients reported to reduce the dose or to stop taking the medication because of the ADE. In accordance with our hypothesis, patients' perceptions of ADEs were related to their coping strategies. Our study supports the relevance of the Self-Regulation Model for understanding how HF patients perceive, interpret and deal with adverse events. Medication beliefs show no direct association with coping behaviour but their effect on coping appears to be mediated through the patients' perceptions of ADEs. As in other studies, demographic and clinical factors did not play a large role in explaining the variance of the different coping strategies (Horne & Weinman, 1999, 2002).

Social support seeking was the most commonly reported strategy for coping with ADEs in our sample but the patients' perceptions of ADEs were only weakly associated with their tendency to seek social support. The way patients perceive an ADE does not seem to be relevant for employing this coping strategy, suggesting that this is a more non-specific coping reaction. A recent review on coping in HF patients suggested that women tend to use more emotion-focused strategies to cope with their condition, such as seeking social support (Allman, Berry, & Nasir, 2009). Our findings suggest that this is not the case in the context of coping with ADEs. Patients who sought social support were more likely to seek information. Both strategies imply active seeking behaviour and social support has been associated with an increase of the development of effective coping skills (Pierce & Sarason, 1996).

As in a previous study, seeking information was the second most often used strategy to deal with ADEs (De Smedt et al., 2009). Half of the patients reported trying to find information about the ADE and the medication that may be causing it. Earlier research has suggested that patients can be categorised into two groups according to their information-seeking behaviour, i.e. monitors who actively seek information and blunters who try to avoid information (Miller, 1987). It was found that cancer patients who display the monitor coping style are more distressed, have more concerns and experience higher numbers of treatment adverse events (Miller, 1995). This profile of information seekers fits with our results. Patients who perceived a larger number of ADEs (ADE identity scale) and stronger consequences and experienced more emotional distress were more likely to seek information. In addition, patients who think that health care providers can do something about the ADE are more likely to seek information. Patients, who do not have this belief, are thus less likely to discuss the ADE with their caregiver. This finding is relevant for improving the management of ADEs, since up to 65% of commonly perceived events can be alleviated by adjusting the dose or changing the treatment (Gandhi et al., 2003; Weingart et al., 2005). It is therefore important that health care providers take an active role and explain to patients the relevance of reporting ADEs that they experience. Our results also show that patients with a lower level of education are less likely than those with a higher level of education to seek information, suggesting that patients with a lower level of education may benefit from extra attention in this area.

Only a minority of patients with HF counteracted the perceived ADE by taking additional medication in order to reduce the event. This may not be surprising given the nature of the most frequent reported ADEs, i.e. dizziness, dry mouth and cold extremities. These ADEs are not easily resolved by taking additional drugs. As can be concluded from our results, patients were more likely to take additional medication when they perceived a large number of ADEs and when they were seeking information. This finding supports the previous assumption that the decision to take additional medication may be less driven by patients' beliefs about medication or perceptions of the ADE but more by other factors such as the availability and knowledge of options for alleviating the ADE.

Few patients choose to reduce the dosage or stop taking their medication and thus become non-adherent. In most cases, this strategy would be considered suboptimal. Perceived ADEs are reported as a frequent reason of patients with HF to stop taking their medication temporarily or permanently (van der Wal & Jaarsma, 2008; van der Wal, Jaarsma, & van Veldhuisen, 2005). Patients who believed that

ADEs would only be present for a short period of time were more likely to deal with them by becoming non-adherent. Patients, who viewed their ADE as chronic or fluctuating over time may have found other ways to cope with those events and learned to live with them. This is confirmed by our findings that the majority of patients reported that they accepted the ADE and took their medication as prescribed. Previous studies have showed conflicting results regarding the relation between patients' medication beliefs and non-adherence (Horne & Weinman, 1999, 2002; Maguire, Hughes, & McElnay, 2008; Ross, Walker, & McLeod, 2004). Most of these studies only investigated the direct relationships between medication beliefs and non-adherence, whereas we included the pathway through patients' perceptions of ADEs. Our results suggest that studies that do not take indirect relationship between medication beliefs and coping behaviour into account may fail to capture the whole complexity of coping.

When interpreting our findings, some limitations should be considered. First, as we used a cross-sectional design, we could only consider associations and cannot make judgements on causal relationships. The SEM explores the underlying structure of relationships which conveys causal assumptions but should not be interpreted as validated causal conclusions. Although the fit indices of our model do not achieve the recommended levels of a good fit, they indicate a close fit, and the model is considered helpful to expand the general framework of coping with health threats to coping with ADEs. Second, our results are based on data reported by patients, and they may have given socially desirable answers. In particular, adherence to medication may have been overestimated by patients. Studies using more objective measurements, such as medication event monitoring system or serum levels of certain drugs, often show higher non-adherence levels than patient-reported non-adherence (Molloy et al., 2009; Wu, Moser, Chung, & Lennie, 2008). Nonetheless, our findings give insight into the psychological antecedents of this behaviour. Finally, the results may have been affected by selection bias and non-response. We were not able to compare responders with non-responders of the survey. The findings described in our study are specific to ambulant patients with HF where we included both patients from outpatient clinics and primary care practices. Our study population was comparable with regard to age and gender to another Dutch outpatient population (mean age of 70 versus 71 years; percentage of female patients 36% versus 38%) (Jaarsma et al., 2008). In comparison to a sample from primary care practices, our study population was younger (70 versus 76 years) and included less females (36% versus 47%) (Bosch et al., 2010). Although we offered assistance of an independent data collector to help patients to complete the questionnaire, some patients dropped out. These patients had on average a lower level of education and were slightly older than the patients who completed the whole questionnaire but they did not differ regarding numbers of perceived ADEs. It is not clear how this selection in patient population regarding age or level of education might affect the observed association between beliefs, perceptions and coping. We did not find any clear associations between demographic characteristics and coping strategies.

Our findings have several implications for clinical practice and future research. It appears that most patients with HF found ways of dealing with perceived ADEs, since only 7% reported reacting to these events by becoming non-adherent. However, more information is needed on the timeline and clinical consequences of this type of coping behaviour since patients tend to use this strategy if they think that

the ADE is temporary. We do not know to what extent the ADEs were linked to medication that patients may have used for longer periods. Furthermore, the explained variance of the regression models was rather low. Other variables need to be investigated, such as the contribution of personality features including level of anxiety, neuroticism and type D personality which all have been shown related to self-reported ADEs (Cocco, 2009; Gandhi et al., 2000; Silvestri et al., 2003). The reliance of patients on health care providers to manage their ADEs implies that providers need to probe for such events and inform patients of possibilities to alleviate perceived ADEs. Recent studies have shown that health providers may underestimate the frequency and burden of mild ADEs, and that not all health care providers consider these events as a concern for clinical practice (Jarernsiripornkul, Kakaew, Loalukkana, & Krska, 2009). Future research assessing how coping strategies are related to outcomes such as quality of life may be valuable.

In summary, our study shows that patients' perceptions of the consequences and timeline of ADEs can partly explain the use of coping strategies. The perception that an ADE has major consequences for the patients' daily life and that it can be controllable by the health care provider play a role in the patients' information-seeking behaviour. Perceptions of ADEs as being temporary and of having more consequences are a factor for non-adherence to medication. Negative medication beliefs do not appear to have a direct influence on coping behaviour.

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