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Self-reported adverse drug events and the role of illness perception and medication beliefs in ambulatory heart failure patients: A cross-sectional survey

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ABSTRACT

Background: Identifying patients with heart failure (HF) who are at risk of experiencing symptomatic adverse drug events (ADEs) is important for improving patient care and quality of life. Several demographic and clinical variables have been identified as potential risk factors for ADEs but limited knowledge is available on the impact of HF patients' beliefs and perceptions on their experience of ADEs.

Objective: The purpose of the study was to identify the relationship between HF patients' illness perception and medication beliefs and self-reported ADEs.

Design: A cross-sectional survey was performed between November 2008 and March 2009.

Settings: One university medical centre, two regional hospitals and 20 general practitioners in the Netherlands participated in the study.

Participants: 495 patients with HF were included.

Methods: Patients completed the validated Revised Illness Perception Questionnaire (IPQ-R) and the Beliefs about Medication Questionnaire (BMQ) which collected data on their illness perception and medication beliefs. In addition, data on ADEs as experienced in the previous four weeks were collected through an open-ended question and a symptom checklist. Multivariate logistic regression was performed to identify factors associated with these ADEs.

Results: In total, 332 (67%) patients had experienced ADEs in the previous four weeks, of whom 28% reported dry mouth, 27% dizziness and 19% itchiness as the most prevalent. In the adjusted multivariate analysis, disease-related symptoms (illness identity) (OR for 1–5 symptoms 3.57; 95% CI 2.22–5.75, OR for >5 symptoms 7.37; 95% CI 3.44–15.8), and general beliefs about medication overuse (OR 1.07; 95% CI 1.01–1.13) were independently associated with experiencing ADEs, whereas none of the demographic or clinical factors were significant.

Conclusions: HF patients who perceive a high number of disease symptoms and have negative medication beliefs are at higher risk of experiencing self-reported ADEs. We suggest that future studies and interventions to improve ADE management should focus on negative medication beliefs and assisting patients in differentiating disease symptoms from ADEs.

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What is already known about the topic?

- Patients with HF experience a number of ADEs, such as dizziness and nausea, which add to the disease burden and affect patients' medication adherence and quality of life.
- Although older age, multimorbidity and polypharmacy are potential risk factors for ADEs as documented in medical records, demographic and clinical factors seem to have a limited ability to predict self-reported ADEs experienced by HF patients.

What this paper adds

- After controlling for demographic and clinical factors, the reporting of more disease-related symptoms and stronger general beliefs about medication overuse are associated with experiencing ADEs.
- Future studies and interventions to improve ADE management in HF should focus on negative medication beliefs and assisting patients to differentiate ADEs from disease symptoms.

1. Introduction

Heart failure (HF) is a life-threatening health condition affecting approximately 15 million people in Europe and 5 million people in the United States, with a prevalence ranging from 2% to 20% in patients aged over 65 (Dickstein et al., 2008; American Heart Association, 2009). The disease management of HF is complex, often consisting of lifestyle modification and lifelong therapy with multiple medications. Alongside a reduction in mortality and morbidity, medications can also cause adverse drug events (ADEs), especially in elderly HF patients due to age-associated changes in pharmacokinetics and pharmacodynamics (Routledge et al., 2004; Shi et al., 2008). The proportion of HF patients reporting ADEs varies from 10%, assessed in randomized clinical trials (Kostis et al., 1994; Lakhdar et al., 2008), to 17%, found in an observational study (De Smedt et al., 2009). The size of this problem and its potential impact on actual medication use indicates the relevance of finding better ways to manage ADEs, not only from a clinical perspective but also from the patient's perspective.

In daily life, HF patients balance the need for prescribed medication against any perceived ADE, which may lead to non-adherence or permanent discontinuation of use of cardiac medications (Garavalia et al., 2009; van der Wal and Jaarsma, 2008; van der Wal et al., 2010). This suboptimal drug use is associated with an increase in unplanned hospital admissions due to HF decompensation, and with increased mortality and morbidity rates, accompanied by additional health-care costs (Michalsen et al., 1998; Gehi et al., 2007; Ho et al., 2008; Hope et al., 2004). Medication adherence rates in HF range from 75% to 99% (Muzzarelli et al., 2010; van der Wal et al., 2006), depending on the method used to assess it (e.g. self-reported questionnaires, pill counts, electronic monitoring and serum drug concentration) and the definition of non-adherence (e.g. cut-off value of adherent behaviour versus

poor adherent behaviour). In addition to being a precipitating factor leading to non-adherence, ADEs as perceived by patients also contribute significantly to the disease burden and a decline in patients' quality of life (Pattenden et al., 2007; Welstand et al., 2009). Thus, from both a clinical and patient perspective there is a need to prevent and detect patient-perceived ADEs at an early stage of routine care, which may lead to enhanced medication safety and wellbeing among HF patients.

Management of ADEs in HF patients appears suboptimal. Recent data has indicated that the likelihood of medication being changed after patients report ADEs is rather low, at around 38% (De Smedt et al., 2010). The failure to respond to medication-related symptoms may lead to unnecessary harm caused by ADEs, which could have been prevented or ameliorated if adequate action had been taken (Forster et al., 2005; Gandhi et al., 2003). Polypharmacy, multimorbidity, ageing and the involvement of multiple health-care providers are factors contributing to the complexity of ADE management in HF patients. Nurses and nurse practitioners are increasingly involved in the supervision of drug use and drug treatment changes in HF patients (Blue and McMurray, 2005). Therefore they have an important role in patient education about possible ADEs, ADE identification and consequently the management of ADEs.

Health-care providers and researchers have a growing interest in reducing the occurrence of ADEs and improving their management in routine care. It has been suggested that identifying patients who are at higher risk is crucial to improving patient care and outcomes (Tangiisuran et al., 2009). Higher age, the number of comorbidities and number of medications have been shown to be risk factors for ADEs in various populations (Field et al., 2004; Green et al., 2007; van den Bemt et al., 2000). These studies investigated risk factors for ADEs that were documented and/or verified by medical-record review or computer-generated signals. It is recognized that self-reported ADEs are of additional value as they incorporate patient experiences and may be more important for daily health status than clinician assessments of ADEs (Hanlon et al., 2001; Basch et al., 2009). A few studies have attempted to identify factors associated with self-reported ADEs, demonstrating that demographic and clinical variables such as age and comorbidities have a low ability to predict the risk of self-reported ADEs in HF patients and elderly patients in general (De Smedt et al., 2009; Shiyanbola and Farris, 2010). Other factors such as patients' beliefs about medication and illness can be expected to play a role in how patients perceive and deal with possible ADEs. Optimistic attitudes regarding drugs and fewer concerns about medication were found to be associated with less experience and reporting of ADEs in a general patient population (Shiyanbola and Farris, 2010; Oladimeji et al., 2008; Rief et al., 2006). The importance of illness perception has been demonstrated with respect to various outcomes, such as quality of life (Lane et al., 2009; Stafford et al., 2009), depression (Stafford et al., 2009) and treatment adherence (Molloy et al., 2009). However, thus far the role of illness and medication beliefs in the susceptibility of HF patients to perceive ADEs is not

known. A better understanding of who perceives ADEs may be achieved by identifying such patient-related factors. This can assist health-care professionals in the complex process of ADE management. If the type or number of medications is not the main risk factor for ADEs as experienced by HF patients, interventions other than medication modification need to be considered.

2. Purpose

The aim of this study is to assess the influence of illness perception and medication beliefs on self-reported ADEs experienced by HF patients.

3. Methods

3.1. Study design

A cross-sectional survey was conducted between November 2008 and March 2009. The study protocol and procedures were presented for approval to the Medical Ethics Committee at the University Medical Center of Groningen. Due to the nature of the study (survey and medical-record review), the ethics committee concluded that no official ethical approval was required to perform the study. The investigation also conforms to the principles outlined in the *Declaration of Helsinki* (1997).

3.2. Setting, patients and procedure

All ambulatory HF patients were recruited from one university hospital (urban area), two regional hospitals (rural areas) and 20 general practitioners (urban and rural areas) located in different parts of the Netherlands. The inclusion of institutions was based on geographical representation, including both urban and rural areas, the availability of an HF clinic and a willingness to collaborate.

All HF patients from outpatient HF clinics were eligible if they had a documented diagnosis of HF in their medical chart. All HF patients from the 20 general practitioners were identified by the International Classification of Primary Care code for heart failure (K77) found in their medical record and were included if their general practitioner confirmed this diagnosis. The exclusion criteria were living in a nursing home, being hospitalized, not being fluent in Dutch, or having a terminal disease or cognitive disorder.

An information letter was sent to all eligible patients by the researchers explaining the purpose of the study and requesting their participation. Permission to send a questionnaire and conduct a review of their medical record was also asked of the patient. A reminder was sent to those patients who had not responded one month after the first letter. After signing the informed consent, patients were asked to indicate on the same form whether they had experienced an adverse event of their medication in the previous four weeks.

3.3. ADE assessment

The outcome measure was any ADE experienced by patients in the previous four weeks. This short time frame

was chosen to reduce the risk of recall bias in light of the rather mild ADEs. Information on perceived ADEs was collected using a mixed method, combining an open-ended question and a symptom checklist. Various studies suggest that the mixed method is a preferred way of eliciting ADEs, as patients do not report all ADEs in response to a single open question (Sheftell et al., 2004; Wallander et al., 1991).

On the informed consent form patients were asked first to answer the following question: 'Have you experienced an adverse event with your medication in the past four weeks?' (Yes/No) If Yes, patients were then asked through an open-ended question to list the ADEs they had experienced in the previous four weeks. After receiving this information and the signed informed consent, a structured questionnaire with a checklist including 28 symptoms was sent to the patients. Patients could complete the questionnaire themselves or – on a patient's request – with the assistance of a data collector who was not a member of the research team.

The symptom checklist is presented in Fig. 1. The inclusion of symptoms in this list was partly based on a previous study which not only assessed common symptomatic ADEs in HF patients (De Smedt et al., 2009) and commonly perceived symptoms in HF were also included. Patients were first asked whether they had experienced each of the symptoms in the previous four weeks, and second, whether they attributed the symptom to an adverse event of their medication and/or to HF. The definition of ADEs experienced by HF patients used in this study includes all ADEs reported on the open-ended question plus the symptoms reported on the checklist that were exclusively considered by the patient to be an adverse event of their medication.

3.4. Measures

Illness perception: Illness perception was measured using the Revised Illness Perception Questionnaire (IPQ-R) (Moss-Morris et al., 2002). The IPQ-R is a valid and reliable measure of illness perception in chronic diseases such as cardiac disease, including patients with myocardial infarction (Moss-Morris et al., 2002). The first domain of the IPQ-R is the illness identity scale, which consists of the symptom checklist mentioned above. The score of this scale was the sum of all symptoms exclusively attributed by patients to their HF, according to the concept of illness identity (Moss-Morris et al., 2002), ranging from 0 to 28. The other seven domains of the IPQ-R included in the questionnaire were: chronic timeline (e.g. 'My HF is rather permanent than temporary'), cyclical timeline (e.g. 'The symptoms of my HF change a great deal from day to day'), consequences (e.g. 'My HF has major consequences for my life'), personal control (e.g. 'There is a lot which I can do to control my symptoms'), treatment control (e.g. 'My treatment can control my HF'), illness understanding (e.g. 'The symptoms of my HF are puzzling to me') and emotional representations (e.g. 'My HF makes me feel afraid'). Each subscale consisted of 4–6 items and a score was calculated for each of these subscales, where a higher score represented greater endorsement of the specific construct. We checked the internal reliability of the seven

Symptoms	Did you experience this symptom in the previous 4 weeks		This symptom is due to my heart failure	This symptom is an adverse event of my medication
	No	Yes		
1. Nausea	☐	☐	☐	☐
2. Dizziness	☐	☐	☐	☐
3. Gout	☐	☐	☐	☐
4. Dyspnoea	☐	☐	☐	☐
5. Swollen ankels	☐	☐	☐	☐
6. Vomiting	☐	☐	☐	☐
7. Diarrhea	☐	☐	☐	☐
8. Dry cough	☐	☐	☐	☐
9. Cough	☐	☐	☐	☐
10. Erectile dysfunction	☐	☐	☐	☐
11. Libido loss	☐	☐	☐	☐
12. Fatigue	☐	☐	☐	☐
13. Sleeping problems	☐	☐	☐	☐
14. Cold extremities	☐	☐	☐	☐
15. Headache	☐	☐	☐	☐
16. Stomach problems	☐	☐	☐	☐
17. Painful joints	☐	☐	☐	☐
18. Decrease in bodyweight	☐	☐	☐	☐
19. Increase in bodyweight	☐	☐	☐	☐
20. Fluid retention	☐	☐	☐	☐
21. Loss of appetite	☐	☐	☐	☐
22. Painful breasts	☐	☐	☐	☐
23. Dry mouth	☐	☐	☐	☐
24. Blurred vision	☐	☐	☐	☐
25. Hair loss	☐	☐	☐	☐
26. Skin rash	☐	☐	☐	☐
27. Itchiness	☐	☐	☐	☐
28. Constipation	☐	☐	☐	☐

Fig. 1. Symptom checklist.

domains using Cronbach's alpha. With the exception of both control subscales (personal and treatment), all Cronbach's alpha coefficients exceeded 0.70. Other studies have also found alpha coefficients for the personal (0.69) and treatment control scales (0.59) to be low (Aalto et al., 2005; Molloy et al., 2009). The response scale for all items consisted of a 5-point Likert scale ranging from 1 ('strongly disagree') to 5 ('strongly agree'). For the multivariate analysis, the IPQ-R subscales were categorized in 3 classes (L = low, M = medium, H = high). Scale-categorization was defined as: 4–8 (L), 9–15 (M), 16–20 (H); 5–11 (L), 12–18 (M), 19–25 (H); 6–13 (L), 14–22 (M), and 23–30 (H). Illness identity was categorized in 0 (L), 1–5 (M), and >5 (H) symptoms.

Medication beliefs: Medication beliefs were assessed using the Beliefs about Medication Questionnaire (BMQ) (Horne et al., 1999). The BMQ is a validated and reliable questionnaire that includes 18 items assessing patients' views on HF medication-related concerns ($\alpha = 0.73$) and on the necessity of their HF medication ($\alpha = 0.83$), as well as

their views on general medication overuse ($\alpha = 0.67$) and medication-related harm ($\alpha = 0.57$). The response scale for all items is a 5-point Likert scale ranging from strongly disagree (1) to strongly agree (5). For the multivariate analysis, subscales were categorized in 3 classes (L = low, M = medium, H = high). Scale-categorization for BMQ subscales included: 4–8 (L), 9–15 (M), 16–20 (H); 5–11 (L), 12–18 (M), and 19–25 (H).

Demographic and clinical variables: Data on age, gender, living situation (living alone or not) and educational level (no education, primary school, secondary school, higher education/university) were collected by self-reported questionnaire. Data on all medication currently used (name of the drug, dosage and frequency) was also collected by the questionnaire. The following data were collected by medical-record review: aetiology and duration of HF (years), left ventricular ejection fraction (LVEF) (%), N-terminal pro-'Brain Natriuretic Peptide' (NT-pro-BNP) (pg/ml) and comorbidities, which are prevalent in HF patients.

3.5. Statistical analysis

Descriptive analysis of demographic, clinical and psychosocial variables was undertaken using the mean and the standard deviation for normally distributed continuous variables or the median with interquartile ranges (IQR) in the case of data skewness. Summary statistics were calculated for all participants together and for the two subgroups separately, defined as patients who experienced an ADE and patients who did not. Differences were tested using a Chi² test for categorical variables and independent *t*-tests for continuous variables or Mann–Whitney *U* and Welch *U* tests in case of skewed distributions or unequal variances (Fagerland and Sandvik, 2009). Bonferroni post hoc test was used to correct for multiple testing. To assess whether patients from general practitioners differed from patients from HF outpatient clinics regarding the reported ADEs and both illness and medication beliefs, we tested for differences using Chi² tests, *t*-tests or Mann–Whitney *U* tests. A multivariate logistic regression was performed to evaluate the factors independently associated with experiencing ADEs. We used a stepwise selection procedure, including first those variables with a *p*-value of 0.20 or less in the univariate analysis for a forward model selection. Next, variables with a *p*-value of 0.20 or less in the forward selection regression model were included in the unadjusted multivariate model. The final model was adjusted for confounders, which were expected to be associated with experiencing ADEs and correlated with at least one of the subscales of illness perception (IPQ-R) or medication beliefs (BMQ). These were age, recent hospitalization, treated by a cardiologist (as proxy for more complicated cases), use of potassium-sparing diuretics, and use of anticoagulants. Missing values for these confounders were lower than 10%, and they were therefore imputed using multiple imputation by chained equations (van Buuren et al., 1999). We conducted an additional multilevel analysis to test for cluster effects at practice organization level, i.e. general practice or hospital outpatient clinic. The results are presented using odds ratios, with a 95% confidence interval (CI). Descriptive and comparative analyses were conducted using SPSS 16.0 software (SPSS, Inc., Chicago, IL, USA.), whereas all regression analyses and multiple imputations were conducted using Stata 11 (StataCorp LP, College Station, TX, USA).

4. Results

Of the 960 HF patients who were invited to participate in the study, 495 (response rate: 53%) patients agreed and signed the informed consent form. Of these 495 patients, 114 (23%) were recruited through their general practitioner and the remaining 381 (77%) through HF outpatient clinics. The mean age of the study sample was 71 years (SD, 12 years) (Table 1). The majority were male (60%), did not live alone (63%) and had a secondary school level of education (58%). The median LVEF was 35% (IQR, 26–45) and on average the patients took 7 (IQR, 5–9) different types of drugs a day.

Of the 495 patients, 67% (*n* = 332) had experienced an ADE in the previous four weeks. Of these, 81 (24%) reported an ADE on the open-ended question and symptom checklist, while the remaining 251 (76%) only reported an ADE on the symptom checklist. A total number of 1341 ADEs (4.0 per patient) were reported, of which 164 ADEs were noted in response to the open-ended question while the remaining 1177 ADEs were reported via the symptom checklist. Of all patients experiencing an ADE, 28% reported dry mouth, 27% dizziness and 19% itchiness as the most prevalent. Patients who experienced an ADE were somewhat younger (*p* = 0.023), used more medications (*p* = 0.001), more often took anticoagulants (*p* = 0.013) and potassium-sparing diuretics (*p* = 0.010) and were more likely to have been hospitalized in the previous year (*p* = 0.024) compared to patients who did not experience an ADE (Table 1).

When comparing HF patients treated by their general practitioner with those treated at HF outpatient clinics, the proportion of patients experiencing ADEs was not significantly different (65% and 68% respectively, *p* = 0.632).

4.1. Perceived symptoms attributed to HF (illness identity) or to medication (ADEs)

The total group of 495 patients reported 1486 symptoms (3.0 per patient) on the checklist which they attributed solely to their illness, and another 1177 symptoms (2.4 per patient) which they attributed solely to their medication (Fig. 2). Those who experienced an ADE reported significantly more symptoms (9.8 per patient) compared to patients with no ADE (5.7 per patient), and consequently attributed more symptoms to their illness (3.6 symptoms per patient versus 1.7 symptoms per patient) (both *p* < 0.001). This previous measure reflects the patient's illness identity. In addition, the patients reported 1393 symptoms that they did not attribute to either their illness or their medication, and this was higher for the patients without an ADE than for those patients who experienced an ADE (4.0 per patient versus 2.2 per patient, *p* < 0.001). Finally, 122 symptoms were attributed by patients experiencing ADEs to both the illness and the medication (Fig. 2).

4.2. Illness perception and medication beliefs

Patients who experienced an ADE reported significantly more of the following disease-related symptoms in comparison to patients without an ADE (for all *p*-value < 0.002): dyspnoea, fatigue, cold extremities, fluid retention, swollen ankles, and cough (Table 2).

In general, patients with an ADE had more negative beliefs about their illness and medication than patients without an ADE. They perceived their illness as more unstable, perceived more consequences for their daily life, and suffered more emotional distress (for all, *p* < 0.005). They also had more concerns about their medication, and had a greater belief in medication overuse (for both, *p* < 0.005).

When comparing HF patients treated by their general practitioner with those treated at HF outpatient clinics, the latter perceived more consequences of their HF (*p* = 0.008)

Table 1

Demographic and clinical characteristics of all patients and of patients with and without perceived ADEs.

Characteristic	Total (n = 495)	ADE perceived (n = 332)	No ADE perceived (n = 163)	p-Value
Demographics				
Age (years)	71 ± 12	70 ± 12	73 ± 13	0.023
Female	198 (40)	125 (38)	73 (45)	0.128
Education	275 (58)	190 (60)	85 (55)	0.243
No education/primary school	100 (21)	67 (21)	33 (21)	0.689
Secondary school	277 (59)	182 (58)	95 (61)	
Higher education/university	95 (20)	67 (21)	28 (18)	
Living alone	175 (37)	112 (35)	63 (39)	0.361
Receiving care at home	194 (41)	123 (39)	71 (46)	0.146
Clinical characteristics				
Duration of heart failure (years)*	3 (2–5)	3 (2–5)	3 (2–5)	0.648 [†]
LVEF (%)*	35 (26–45)	35 (26–46)	35 (25–46)	0.628 [†]
NT-proBNP (pg/ml)*	1054 (411–2352)	1093 (380–2341)	998 (508–2352)	0.987 [†]
Ischemic etiology of HF	249 (51)	177 (54)	72 (45)	0.051
Comorbidities				
Peripheral vascular disorders	104 (21)	71 (22)	33 (21)	0.770
Respiratory disorders (COPD/asthma)	136 (28)	93 (28)	43 (27)	0.703
Diabetes type II	112 (23)	75 (23)	37 (23)	0.977
Renal disorders	79 (16)	52 (16)	27 (17)	0.796
Depression (diagnosis)	41 (8)	31 (10)	10 (6)	0.218
Total number of prescribed medications	7.6 (0.2)	7.9 (0.2)	6.8 (0.3)	0.001 [#]
Heart failure medication				
ACE-inhibitors	302 (61)	206 (62)	96 (59)	0.499
Angiotensin receptor blockers	124 (25)	80 (24)	44 (27)	0.484
Beta-blockers	404 (82)	274 (83)	130 (80)	0.454
Diuretics				
Loop diuretics	345 (70)	239 (72)	106 (65)	0.113
Potassium-sparing diuretics	179 (36)	133 (40)	46 (28)	0.010
Cardiac glycosides	50 (10)	33 (10)	17 (10)	0.865
Other medication				
Calcium channel blockers	74 (15)	55 (17)	19 (12)	0.150
Nitrates	97 (20)	65 (20)	32 (20)	0.989
Lipid-lowering agents	234 (47)	160 (48)	74 (45)	0.558
Antiplatelet agents	163 (33)	108 (33)	55 (24)	0.787
Anticoagulants	270 (55)	194 (58)	76 (47)	0.013
Antiarrhythmic agents	52 (11)	39 (12)	13 (8)	0.198
Received care in the previous year				
Under treatment of a cardiologist	451 (92)	305 (93)	146 (90)	0.192
Under treatment of a outpatient HF clinic	381 (77)	258 (78)	123 (75)	0.875
Hospitalization	211 (44)	153 (47)	58 (36)	0.024

ADE, adverse drug event; LVEF, left ventricular ejection fraction; NT-pro BNP, N-terminal pro B-type natriuretic peptide; HF, heart failure; COPD, chronic obstructive pulmonary disease; ACE-inhibitors, angiotensin converting enzyme inhibitors.

* Continuous variable is presented as median value (25–75th percentiles).

[†] Using non-parametric Mann–Whitney *U* test.

[#] Using Welch *U* test.

but believed less in medication overuse than patients of general practitioners ($p = 0.004$).

4.3. Multivariate model

Based on the univariate selection, HF identity, timeline cyclical, consequences, emotional representation, medication necessity, medication concerns, general medication harm and overuse were included in the forward model selection (Table 3). Of these, illness identity, consequences, personal control, medication concerns and overuse were selected for the multivariate model. Looking at the unadjusted model, experiencing an ADE was significantly related to the reporting of more disease-related symptoms (strong illness identity) (OR for 1–5 symptoms 3.64 [95% CI 2.29–5.79]; OR for >5 symptoms 6.69 [95% CI 3.17–14.10]) and stronger beliefs regarding general medication overuse (OR 1.82 [95% CI 1.12–2.94]). After adjusting the model for

confounders, both factors were still independently associated with experiencing ADEs (Table 3). The demographic and clinical variables used for adjustment were not significant independent risk factors with respect to experiencing ADEs in the multivariate model (age OR 0.99 [95% CI 0.97–1.01], anticoagulants OR 1.24 [95% CI 0.79–1.94], potassium-sparing diuretics OR 1.44 [95% CI 0.91–2.29], hospitalization in the previous year OR 1.27 [95% CI 0.81–1.98], treated by cardiologist OR 0.93 [95% CI 0.43–2.01]). In the multilevel model, no evidence was found for clustering at practice organization level.

5. Discussion

The major finding of this study is that general illness and medication beliefs were associated with self-reported ADEs, which were commonly experienced in this HF patient population. After adjusting for demographic and

Fig. 2. Symptoms reported by patients and attributed to HF and/or to drugs. Note: The sum of symptoms solely attributed to HF is the illness identity. Normal range 0–28.

Table 2

Identity subscale of the IPQ-R including 28 common symptoms of heart failure.

This complaint is due to my heart failure	Total group (n = 495) n (%)	Experienced ADE (n = 332) n (%)	Experienced no ADE (n = 163) n (%)	p-Value
Dyspnoea	242 (49)	192 (58)	50 (31)	0.000*
Fatigue	227 (46)	177 (53)	50 (31)	0.000*
Cold extremities	164 (33)	126 (38)	38 (23)	0.001*
Fluid retention	130 (26)	110 (33)	20 (12)	0.000*
Swollen ankles	109 (22)	88 (27)	21 (13)	0.001*
Dry cough	71 (14)	56 (17)	15 (9)	0.022
Sleeping problems	70 (14)	56 (17)	14 (9)	0.013
Dizziness	61 (12)	50 (15)	11 (7)	0.008
Cough	49 (10)	43 (13)	6 (4)	0.001*
Increase in bodyweight	42 (9)	36 (11)	6 (4)	0.007
Dry mouth	40 (8)	28 (8)	12 (7)	0.681
Painful joints	35 (7)	29 (9)	6 (4)	0.039
Libido loss	32 (7)	27 (8)	5 (3)	0.031
Headache	32 (7)	27 (8)	5 (3)	0.031
Nausea	30 (6)	27 (8)	3 (2)	0.006
Erectile dysfunction	28 (6)	24 (7)	4 (3)	0.031
Loss of appetite	24 (5)	21 (6)	3 (2)	0.029
Blurred vision	23 (5)	21 (6)	2 (1)	0.011
Gout	16 (3)	14 (4)	2 (1)	0.077
Decrease in bodyweight	13 (3)	11 (3)	2 (1)	0.173
Painful breasts	12 (2)	11 (3)	1 (0.5)	0.066
Stomach problems	7 (1)	6 (2)	1 (0.5)	0.290
Diarrhea	7 (1)	6 (2)	1 (0.5)	0.290
Vomiting	7 (1)	7 (2)	0	0.062
Itchiness	7 (1)	4 (1)	3 (2)	0.573
Constipation	4 (1)	3 (1)	1 (0.5)	0.735
Skin rash	2 (0.5)	1 (0.5)	1 (0.5)	0.607
Hair loss	2 (0.5)	1 (0.5)	1 (0.5)	0.607
Total	1486	1202	284	

ADE, adverse drug event; HF, heart failure.

* Variables with a significance difference after applying the Bonferroni post hoc test $p < 0.05/28$ variables $p < 0.002$.

Table 3

Association of illness and medication beliefs and perceiving an ADE (0 = no ADE perceived, 1 = ADE perceived).

Factors		Univariate	Multivariate unadjusted (<i>n</i> = 485)		<i>p</i> -Value	Multivariate adjusted ^a (<i>n</i> = 485)		<i>p</i> -Value
		<i>p</i> -Value	Odds ratio	95% CI		Odds ratio	95% CI	
IPQ-R	Identity HF 1–5	<0.001	3.64	2.29–5.79	<0.0001	3.50	2.18–5.63	<0.0001
	Identity HF >5	<0.001	6.69	3.17–14.10	<0.0001	6.88	3.22–14.68	<0.0001
	Timeline chronic M	0.656	–			–		
	Timeline chronic H	0.538	–			–		
	Timeline cyclical	<0.001	–			–		
	Consequences	<0.001	1.04	1.00–1.09	0.035	1.02	0.98–1.06	0.264
	Personal control M	0.091	0.52	0.24–1.11	0.090	0.53	0.25–1.13	0.099
	Personal control H	0.254	0.52	0.24–1.16	0.111	0.51	0.23–1.14	0.100
	Treatment control M	0.369	–			–		
	Treatment control H	0.537	–			–		
	Illness coherence M	0.838	–			–		
	Illness coherence H	0.863	–			–		
	Emotional repres. M	0.039	–			–		
	Emotional repres. H	0.008	–			–		
BMQ	Necessity M	0.350	–			–		
	Necessity H	0.094	–			–		
	Concerns M	0.018	1.22	0.76–1.98	0.409	1.25	0.77–2.04	0.361
	Concerns H	0.047	1.46	0.67–3.17	0.340	1.49	0.68–3.29	0.320
	Harm M	0.061	–			–		
	Harm H	0.383	–			–		
	Overuse	0.001	1.82	1.12–2.94	0.015	1.07	1.01–1.13	0.022
			Goodness-of-fit statistics: area under ROC curve 0.747; Hosmer–Lemeshow Chi ² , <i>p</i> = 0.44			Goodness-of-fit statistics: area under ROC curve 0.749; Hosmer–Lemeshow Chi ² , <i>p</i> > 0.47 (imputed models)		

ADE, adverse drug event; IPQ-R, Illness Perception Questionnaire Revised; BMQ, Beliefs about Medication Questionnaire; HF, heart failure; M, medium score; H, high score.

^a Multivariate model adjusted for age, potassium sparing diuretics, anticoagulants, treated by a cardiologist, hospitalization in previous year.

clinical characteristics, the reporting of more disease-related symptoms and stronger general beliefs about medication overuse were associated with experiencing ADEs. In the final model, demographic and clinical characteristics were not independent risk factors for self-reported ADEs.

Patients who experienced more symptoms that were attributed to their HF (illness identity) were also more likely to experience an ADE. The importance of illness identity as a predictor of different outcomes in cardiac disease has already been described in other studies (Aalto et al., 2006; Lane et al., 2009; French et al., 2006). Our study, however, is the first to find a relationship between illness identity and the experience of ADEs. Several reasons might be given to explain this relationship. First, it is possible that patients who suffer from severe HF experience more disease-related symptoms. Increased symptoms may indicate the need to intensify drug treatment, which in turn may lead to an increased likelihood of drug-related symptoms (Gandhi et al., 2003). However, in this study, both the medications used and LVEF and NT-pro-BNP (both markers of disease severity) were not found to independently predict ADE experiences, which challenge this assumption. Moreover, we adjusted for differences in specific medication use in the final multivariate model. Taking into account the results of a previous study which also found no association between medication burden, disease severity and the experience of ADEs, we presume that the type of medication and disease severity do not play a major role as explanatory factors (De Smedt et al.,

2009). Second, patients' lack of knowledge and their inability to differentiate disease and drug-related symptoms might be a factor underlying the relationship between an illness identity and experiencing ADEs. Earlier studies have shown that HF patients have difficulties in differentiating disease and drug-related symptoms (Rogers et al., 2002). From our study results, it seems that this problem was much more apparent in the group of patients who did not report any ADEs, as the number of unattributed symptoms was much higher in this group compared to the group who did experience an ADE. This indicates that the group of patients who do not report ADEs may not have been able to clearly distinguish drug-related symptoms from HF symptoms. Nurse practitioners could play an important role in educating patients about possible ADEs and helping them in differentiating ADEs from disease symptoms (Roberts and Epstein, 2009). We did not assess the underlying rationale of patients who did not attribute the perceived symptom to HF or their medication. It is possible that patients perceived other factors such as age or comorbid diseases as causes. Elderly patients in general tend to consider observed symptoms as unavoidable aspects of ageing rather than as disease or drug-related (Lampela et al., 2007). A third and final explanation of the relationship between a strong illness identity and experiencing ADEs could be that some patients are more prone to perceive both somatic symptoms and ADEs (somatic sensitivity). Personality characteristics such as neuroticism, which is the tendency to experience negative, distressing emotions, and type D personality have been

shown to be associated with self-reported somatic symptoms (Rosmalen et al., 2007; Smith et al., 2008).

Patients who had more concerns regarding their medication and believed that medication in general is overused were more likely to experience ADEs. This is in line with an earlier study that found an association between patients' medication concerns and their reporting of ADEs to their physicians (Oladimeji et al., 2008). It was suggested that patients' beliefs about medication might also be important with respect to how symptoms are interpreted and attributed to drugs, which is supported by our results and a recent study among elderly patients (Shiyanbola and Farris, 2010). Patients who have stronger negative beliefs may be more aware of unpleasant reactions and be more prejudiced towards their medication. Patients' concerns about medication may drive them to attribute their symptoms to medication and may be a sign of their ADE tolerance level (Oladimeji et al., 2009). Our study suggests that general negative beliefs are a stronger risk factor than specific concerns about the medication which is used. This emphasizes the relevance of health-care providers checking patients' interpretations of symptoms, especially in those patients who have negative medication beliefs.

Demographic and clinical variables were not independent risk factors with respect to experiencing ADEs. This is in accordance with previous studies which examined risk factors associated with self-reported ADEs among general older populations (De Smedt et al., 2009; Hanlon et al., 1997; Oladimeji et al., 2008; Shiyanbola and Farris, 2010). However, studies using other methods to identify ADEs, such as medical-record review, clinical notes and computer-generated signals, found a number of risk factors for ADEs in the elderly, such as the number of comorbidities and scheduled medications (Field et al., 2004; Green et al., 2007; van den Bemt et al., 2000). This suggests that demographic and clinical variables are more relevant for predicting the risk of clinically assessed ADEs, while other factors such as medication beliefs and patients' susceptibility to perceive symptoms may be more relevant for predicting the risk of subjective ADEs. This highlights the complex task of health-care providers to elicit, identify and manage ADEs. Patients' perceptions are important not only in helping to identify possible ADEs, but also in managing them. A patient-tailored approach where nurse practitioners and doctors proactively communicate with their patients about possible ADEs might be valuable.

To our knowledge, this is the first study to examine the role of illness perception and medication beliefs in experiencing ADEs in a population of HF patients. Some limitations need to be addressed. This study relies on self-reported data collected by a questionnaire using an open-ended question combined with a symptom checklist to identify ADEs experienced by patients. We did not link the reported ADEs to actual drugs. No formal ADE causality assessment was carried out because the study focused on the perception of patients. Because of the cross-sectional design, no judgement about causality can be made. Another potential limitation of this study is its generalizability due to the risk of participation bias. We were not

able to compare responders and non-responders to the survey. Our study sample includes ambulatory patients from outpatient clinics and general practices. Regarding age and gender, this sample was largely comparable to another Dutch outpatient clinic population screened around 2002–2005 (mean age of 71 years in both study populations; proportion of female patients 40% versus 38%) (Jaarsma et al., 2008). In comparison with a primary care study population, the mean age was lower in our population (71 years versus 76 years), and the proportion of female patients less (40% versus 47%) (Bosch et al., 2010). There are some differences regarding treatment, which may in part be due to changes in prescribing practices over recent years. The proportion of patients treated with diuretics, angiotensin-converting enzyme inhibitors (ACE-I) and beta-blockers was higher in comparison to the primary care study population screened in 2005–2006. In comparison with the outpatient clinic study population, patients in our study sample were prescribed more beta-blockers and fewer ACE-I. Such differences in age, gender and treatment can lead to differences in the number of ADEs experienced. One can only speculate as to how this may affect the observed associations between beliefs and the experience of ADEs. We have found no literature supporting the notion that such associations are likely to be affected by age or gender.

6. Conclusion

In conclusion, this study indicates that HF patients who experience a high number of disease-related symptoms and have stronger general beliefs about medication overuse are at a higher risk of experiencing self-reported ADEs. Because of the high prevalence of such ADEs in this group of patients there is a need for adequate management. Future studies should focus on the role of personality characteristics as well as on the mechanisms underlying the observed associations. Nursing interventions could focus on providing patients with tailored information on possible ADEs, assisting them in differentiating disease symptoms from ADEs, and detecting negative medication beliefs.

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References

- Aalto, A.M., Aro, A.R., Weinman, J., Heijmans, M., Manderbacka, K., Elovainio, M., 2006. Sociodemographic, disease status, and illness perceptions predictors of global self-ratings of health and quality of life among those with coronary heart disease—one year follow-up study. *Quality of Life Research* 15 (8), 1307–1322.
- Aalto, A.M., Heijmans, M., Weinman, J., Aro, A.R., 2005. Illness perceptions in coronary heart disease. Sociodemographic, illness-related, and psychosocial correlates. *Journal of Psychosomatic Research* 58 (5), 393–402.
- American Heart Association, 2009. Heart Disease and Stroke Statistics, 2009 Update. American Heart Association, Dallas, TX.

- Basch, E., Jia, X., Heller, G., Barz, A., Sit, L., Fruscione, M., Appawu, M., Iasonos, A., Atkinson, T., Goldfarb, S., Culklin, A., Kris, M.G., Schrag, D., 2009. Adverse symptom event reporting by patients versus clinicians: relationships with clinical outcomes. *Journal of the National Cancer Institute* 101 (23), 1624–1632.
- Blue, L., McMurray, J., 2005. How much responsibility should heart failure nurses take? *European Journal of Heart Failure* 7 (3), 351–361.
- Bosch, M., Wensing, M., Bakx, J.C., van der, W.T., Hoes, A.W., Grol, R.P., 2010. Current treatment of chronic heart failure in primary care; still room for improvement. *Journal of Evaluation in Clinical Practice* 16 (3), 644–650.
- De Smedt, R.H., Denig, P., Haaijer-Ruskamp, F.M., Jaarsma, T., 2009. Perceived medication adverse effects and coping strategies reported by chronic heart failure patients. *International Journal of Clinical Practice* 63 (2), 233–242.
- De Smedt, R.H.E., Jaarsma, T., Haaijer-Ruskamp, F.M., Denig, P., 2010. The impact of perceived adverse effects on medication changes in heart failure patients. *Journal of Cardiac Failure* 16 (2) 135–141.e2.
- Dickstein, K., Cohen-Solal, A., Filippatos, G., McMurray, J.J., Ponikowski, P., Poole-Wilson, P.A., Stromberg, A., van Veldhuisen, D.J., Atar, D., Hoes, A.W., Keren, A., Mebazaa, A., Nieminen, M., Priori, S.G., Swedberg, K., Vahanian, A., Camm, J., De, C.R., Dean, V., Dickstein, K., Filippatos, G., Funck-Brentano, C., Hellemans, I., Kristensen, S.D., McGregor, K., Sechtem, U., Silber, S., Tendera, M., Widimsky, P., Zamorano, J.L., Tendera, M., Auricchio, A., Bax, J., Bohm, M., Corra, U., della, B.P., Elliott, P.M., Follath, F., Gheorghiade, M., Hasin, Y., Hemborg, A., Jaarsma, T., Komajda, M., Kornowski, R., Piepoli, M., Prendergast, B., Tavazzi, L., Vachiery, J.L., Verheugt, F.W., Zamorano, J.L., Zannad, F., 2008. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *European Journal of Heart Failure* 10 (10), 933–989.
- Fagerland, M.W., Sandvik, L., 2009. Performance of five two-sample location tests for skewed distributions with unequal variances. *Contemporary Clinical Trials* 30 (5), 490–496.
- Field, T.S., Gurwitz, J.H., Harrold, L.R., Rothschild, J., DeBellis, K.R., Seger, A.C., Auger, J.C., Garber, L.A., Cadoret, C., Fish, L.S., Garber, L.D., Kelleher, M., Bates, D.W., 2004. Risk factors for adverse drug events among older adults in the ambulatory setting. *Journal of American Geriatric Society* 52 (8), 1349–1354.
- Forster, A.J., Murff, H.J., Peterson, J.F., Gandhi, T.K., Bates, D.W., 2005. Adverse drug events occurring following hospital discharge. *Journal of General Internal Medicine* 20 (4), 317–323.
- French, D.P., Cooper, A., Weinman, J., 2006. Illness perceptions predict attendance at cardiac rehabilitation following acute myocardial infarction: a systematic review with meta-analysis. *Journal of Psychosomatic Research* 61 (6), 757–767.
- Gandhi, T.K., Weingart, S.N., Borus, J., Seger, A.C., Peterson, J., Burdick, E., Seger, D.L., Shu, K., Federico, F., Leape, L.L., Bates, D.W., 2003. Adverse drug events in ambulatory care. *New England Journal of Medicine* 348 (16), 1556–1564.
- Garavalia, L., Garavalia, B., Spertus, J.A., Decker, C., 2009. Exploring patients' reasons for discontinuance of heart medications. *Journal of Cardiovascular Nursing* 24 (5), 371–379.
- Gehi, A.K., Ali, S., Na, B., Whooley, M.A., 2007. Self-reported medication adherence and cardiovascular events in patients with stable coronary heart disease: the heart and soul study. *Archives of Internal Medicine* 167 (16), 1798–1803.
- Green, J.L., Hawley, J.N., Rask, K.J., 2007. Is the number of prescribing physicians an independent risk factor for adverse drug events in an elderly outpatient population? *American Journal of Geriatric Pharmacotherapy* 5 (1), 31–39.
- Hanlon, J.T., Maher, R.L., Lindblad, C.I., Ruby, C.M., Twersky, J., Cohen, H.J., Schmader, K.E., 2001. Comparison of methods for detecting potential adverse drug events in frail elderly inpatients and outpatients. *American Journal of Health-System Pharmacy* 58 (17), 1622–1626.
- Hanlon, J.T., Schmader, K.E., Koronkowski, M.J., Weinberger, M., Landsman, P.B., Samsa, G.P., Lewis, I.K., 1997. Adverse drug events in high risk older outpatients. *Journal of American Geriatric Society* 45 (8), 945–948.
- Ho, P.M., Magid, D.J., Shetterly, S.M., Olson, K.L., Maddox, T.M., Peterson, P.N., Masoudi, F.A., Rumsfeld, J.S., 2008. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. *American Heart Journal* 155 (4), 772–779.
- Hope, C.J., Wu, J., Tu, W., Young, J., Murray, M.D., 2004. Association of medication adherence, knowledge, and skills with emergency department visits by adults 50 years or older with congestive heart failure. *American Journal of Health-System Pharmacy* 61 (19), 2043–2049.
- Horne, R., Weinman, J., Hankins, M., 1999. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. *Psychology and Health* 14 (1), 1–24.
- Jaarsma, T., van der Wal, M.H., Lesman-Leegte, I., Luttik, M.L., Hogenhuis, J., Veeger, N.J., Sanderma, R., Hoes, A.W., van Gilst, W.H., Lok, D.J., Dunselman, P.H., Tijssen, J.G., Hillege, H.L., van Veldhuisen, D.J., 2008. Effect of moderate or intensive disease management program on outcome in patients with heart failure: Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH). *Archives of Internal Medicine* 168 (3), 316–324.
- Kostis, J.B., Shelton, B.J., Yusuf, S., Weiss, M.B., Capone, R.J., Pepine, C.J., Gosselin, G., Delahaye, F., Probstfield, J.L., Cahill, L., 1994. Tolerability of enalapril initiation by patients with left ventricular dysfunction: results of the medication challenge phase of the Studies of Left Ventricular Dysfunction. *American Heart Journal* 128 (2), 358–364.
- Lakhdar, R., Al-Mallah, M.H., Lanfear, D.E., 2008. Safety and tolerability of angiotensin-converting enzyme inhibitor versus the combination of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker in patients with left ventricular dysfunction: a systematic review and meta-analysis of randomized controlled trials. *Journal of Cardiac Failure* 14 (3), 181–188.
- Lampela, P., Hartikainen, S., Sulkava, R., Huupponen, R., 2007. Adverse drug effects in elderly people—a disparity between clinical examination and adverse effects self-reported by the patient. *European Journal of Clinical Pharmacology* 63 (5), 509–515.
- Lane, D.A., Langman, C.M., Lip, G.Y., Nouwen, A., 2009. Illness perceptions, affective response, and health-related quality of life in patients with atrial fibrillation. *Journal of Psychosomatic Research* 66 (3), 203–210.
- Michalsen, A., König, G., Thimme, W., 1998. Preventable causative factors leading to hospital admission with decompensated heart failure. *Heart* 80 (5), 437–441.
- Molloy, G.J., Gao, C., Johnston, D.W., Johnston, M., Witham, M.D., Struthers, A.D., McMurdo, M.E., 2009. Adherence to angiotensin-converting-enzyme inhibitors and illness beliefs in older heart failure patients. *European Journal of Heart Failure* 11 (7), 715–720.
- Moss-Morris, R., Weinman, J., Petrie, K.J., Horne, R., Cameron, L.D., Buick, D., 2002. The revised Illness Perception Questionnaire (IPQ-R). *Psychology and Health* 17 (1), 1–16.
- Muzzarelli, S., Brunner-La Rocca, H., Pfister, O., Foglia, P., Moschovitis, G., Mombelli, G., Stricker, H., 2010. Adherence to medical regime in patients with heart failure. *European Journal of Heart Failure* 12 (4), 389–396.
- Oladimeji, O., Farris, K.B., Urmie, J.G., Doucette, W.R., 2008. Risk factors for self-reported adverse drug events among Medicare enrollees. *Annals of Pharmacotherapy* 42 (1), 53–61.
- Oladimeji, O., Farris, K.B., Urmie, J.G., Doucette, W.R., 2009. Symptomatology, attribution to medicines, and symptom reporting among Medicare enrollees. *Research in Social Administrative Pharmacy* 5 (3), 225–233.
- Pattenden, J.F., Roberts, H., Lewin, R.J., 2007. Living with heart failure; patient and carer perspectives. *European Journal of Cardiovascular Nursing* 6 (4), 273–279.
- Rief, W., Avorn, J., Barsky, A.J., 2006. Medication-attributed adverse effects in placebo groups: implications for assessment of adverse effects. *Archives of Internal Medicine* 166 (2), 155–160.
- Roberts, M.E., Epstein, B.J., 2009. Optimizing management of hypertension with combination therapy: considerations for the nurse practitioner. *Journal of Cardiovascular Nursing* 24 (5), 380–389.
- Rogers, A., Addington-Hall, J.M., McCoy, A.S., Edmonds, P.M., Abery, A.J., Coats, A.J., Gibbs, J.S., 2002. A qualitative study of chronic heart failure patients' understanding of their symptoms and drug therapy. *European Journal of Heart Failure* 4 (3), 283–287.
- Rosmalen, J.G., Neeleman, J., Gans, R.O., de Jonge, J.P., 2007. The association between neuroticism and self-reported common somatic symptoms in a population cohort. *Journal of Psychosomatic Research* 62 (3), 305–311.
- Routledge, P.A., O'Mahony, M.S., Woodhouse, K.W., 2004. Adverse drug reactions in elderly patients. *British Journal of Clinical Pharmacology* 57 (2), 121–126.
- Sheftell, F.D., Feleppa, M., Tepper, S.J., Rapoport, A.M., Ciannella, L., Bigal, M.E., 2004. Assessment of adverse events associated with triptans—methods of assessment influence the results. *Headache* 44 (10), 978–982.
- Shi, S., Morike, K., Klotz, U., 2008. The clinical implications of ageing for rational drug therapy. *European Journal of Clinical Pharmacology* 64 (2), 183–199.
- Shiyanbola, O.O., Farris, K.B., 2010. Concerns and beliefs about medicines and inappropriate medications: an internet-based survey on risk

- factors for self-reported adverse drug events among older adults. *American Journal of Geriatric Pharmacotherapy* 8 (3), 245–257.
- Smith, O.R., Pedersen, S.S., Van Domburg, R.T., Denollet, J., 2008. Symptoms of fatigue and depression in ischemic heart disease are driven by personality characteristics rather than disease stage: a comparison of CAD and CHF patients. *European Journal of Cardiovascular Prevention and Rehabilitation* 15 (5), 583–588.
- Stafford, L., Berk, M., Jackson, H.J., 2009. Are illness perceptions about coronary artery disease predictive of depression and quality of life outcomes? *Journal of Psychosomatic Research* 66 (3), 211–220.
- Tangiisuran, B., Wright, J., Van der, C.T., Rajkumar, C., 2009. Adverse drug reactions in elderly: challenges in identification and improving preventative strategies. *Age and Ageing* 38, 358–359.
- van Buuren, S., Boshuizen, H.C., Knook, D.L., 1999. Multiple imputation of missing blood pressure covariates in survival analysis. *Statistics in Medicine* 18 (6), 681–694.
- van den Bemt, P.M., Egberts, A.C., Lenderink, A.W., Verzijl, J.M., Simons, K.A., van der Pol, W.S., Leufkens, H.G., 2000. Risk factors for the development of adverse drug events in hospitalized patients. *Pharmacy World & Science* 22 (2), 62–66.
- van der Wal, M.H., Jaarsma, T., Moser, D.K., Veeger, N.J., van Gilst, W.H., van Veldhuisen, D.J., 2006. Compliance in heart failure patients: the importance of knowledge and beliefs. *European Heart Journal* 27 (4), 434–440.
- van der Wal, M.H., Jaarsma, T., 2008. Adherence in heart failure in the elderly: problem and possible solutions. *International Journal of Cardiology* 125 (2), 203–208.
- van der Wal, M.H., Jaarsma, T., Moser, D.K., van Gilst, W.H., van Veldhuisen, D.J., 2010. Qualitative examination of compliance in heart failure patients in The Netherlands. *Heart & Lung* 39 (2), 121–130.
- Wallander, M.A., Dimenas, E., Svardsudd, K., Wiklund, I., 1991. Evaluation of three methods of symptom reporting in a clinical trial of felodipine. *European Journal of Clinical Pharmacology* 41 (3), 187–196.
- Welstand, J., Carson, A., Rutherford, P., 2009. Living with heart failure: an integrative review. *International Journal of Nursing Studies* 46 (10), 1374–1385.
- World Medical Association Declaration of Helsinki, 1997. Recommendations guiding physicians in biomedical research involving human subjects. *Journal of the American Medical Association* 277 (11), 925–926.