Assessment of drug treatment quality in two Danish health-care centres

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INTRODUCTION: Bridging the primary and secondary sector, health-care centres aim to reduce morbidity and prevent further hospitalization in patients with chronic heart diseases. The aim of this study was to describe the quality of drug treatment in patients with chronic heart diseases in two Copenhagen health-care centres.

MATERIAL AND METHODS: Over a period of three months, 28 patients with heart failure (HF) or ischaemic heart disease (IHD) were included. The participants were interviewed and clinically examined.

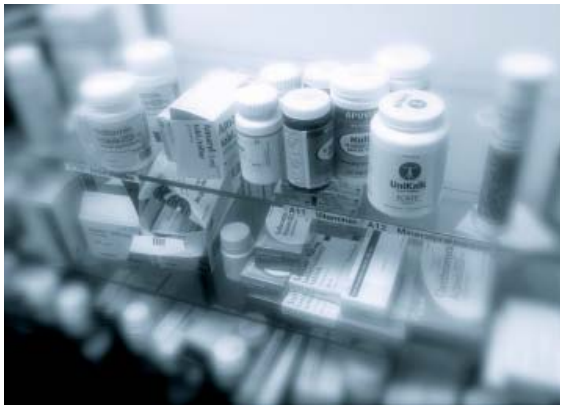
RESULTS: The patients received an average of nine drugs, and only about one third were clinically well-treated. Among IHD patients, 74% received beta blockers and 64% angiotensin converting enzyme-inhibitors (ACE-I) as indicated. All received statins and 92% acetylsalicylic acid. Among HF patients, 67% received ACE-I, 87% beta blockers and 77% diuretics as indicated. Overall, 10%, 31% and 40% of the HF patients received smaller than recommended doses of ACE-I, beta blockers, and diuretics, respectively. In 68% of the patients, 35 potential drug interactions were identified, none of which were deemed potentially harmful.

CONCLUSION: This small descriptive study indicates that patients in health-care centres might be undertreated and receive drug therapy only partly in accordance with the guidelines. However, since we had no access to medical charts, any reasons for not treating patients with a certain drug or selecting a lower than recommended dose could not be evaluated. Nevertheless, patients may benefit from closer involvement of clinicians or GPs in the multidisciplinary teams of the health-care centres.

Polypharmacy (PP) has no clear definition [1]. A common definition, however, is the concurrent use of multiple medications, i.e. from two or five drugs daily [2]. PP is often considered undesirable and it is associated with an increased risk of unwanted drug interactions and adverse drug reactions [3-4]. But defining PP simply as the number of medications taken above a certain threshold may be of limited value [1] as evidence-based guidelines often recommend concurrent use of several drugs to treat a single condition, e.g. heart failure (HF) and ischaemic heart disease (IHD) [3]. It may therefore be more useful to consider PP, not simply as a number of concurrently used drugs, but as either rational and evidence-based medicine or irrational therapy that lacks indication and effectiveness [4]. Recent studies have indicated that undertreatment with recommended pharmacotherapy is a common problem of PP [3, 5]. This is e.g. the case in patients with IHD and HF, in whom underprescribing is prevalent despite the fact that specific guidelines for the treatment of HF and IHD are available [6]. Moreover, medicine is underdosed in patients with HF and IHD and rarely up-titrated during long-term treatment [7, 8]. The Copenhagen-based Oesterbro and Noerrebro health-care centres were established in 2005 and 2007, respectively, with the purpose of providing rehabilitation and education to patients with stable chronic diseases, e.g. HF and IHD. Multidisciplinary teams are formed comprising nurses, physiotherapists and clinical dieticians. Since the establishment of the Oesterbro and Noerrebro centres, two similar centres have been formed and one is about to open in the Capital Region [9]. To the best of our knowledge, the quality of the treatment provided in the health-care centres has not been studied. The aim of this study was to describe the quality of drug treatment of patients with chronic heart diseases in health-care centres by examining the patients' clinical state and by assessing if guidelines were followed, and by analysing the prevalence of potential drug interactions.

MATERIAL AND METHODS

Study site and population: This descriptive study was approved by the Danish Data Protection Agency (J.no.



The complexity of polypharmacy.

ORIGINAL ARTICLE

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2008-41-2310) and the managers of the health-care centres. Approval by the regional ethics committee was not needed. The study was carried out in the Municipality of Copenhagen. Over a period of three months (from July 2008 to September 2008), patients with IHD or HF were included from the Oesterbro and Noerrebro health-care centres. Patients were identified from the centres' lists of heart patients who had been referred from either general practitioners or hospital physicians. Patients referred in 2007 and 2008 were eligible for inclusion. Subjects were contacted directly and/or over the telephone. Written informed consent was obtained before inclusion. Patients who could not communicate in Danish without a translator or had impaired communicative skills (aphasia or severe dementia) were excluded. In all, 45 of the 78 patients we approached were excluded due to lacking language skills. Furthermore, two refused to participate and three did not respond. The referral diagnoses of the 28 included patients were IHD (n = 25) and HF (n = 3).

Data collection: All included patients were interviewed and examined in their own homes by the same person (KE) for approximately one hour. Demographic data and relevant medical histories were recorded. The participants were asked to present their drug storage (including any prescribed drugs, over the counter (OTC) drugs and any alternative medication). Each drug name was noted and the patient was asked about dose and frequency of use. The degree of HF was estimated using the New York Heart Association (NYHA) classification [10]. Finally, a clinical examination was conducted which included recording of blood pressure, auscultation of heart and lungs and assessment of peripheral oedema. Levels of hypertension were defined according to the Danish Society of Cardiology (DSC) guidelines (normal, moderately elevated, high and isolated systolic hypertension) [11]. Peripheral oedema was significant when it presented bilaterally. Patients who had normal blood pressure and normal clinical findings were categorised as clinically well-treated.

Accordance with guidelines: Patients were categorized according to their referral diagnosis, and medicine charts were subsequently compared with the Danish guidelines (2008 edition) for treatment of IHD or HF (**Table 1**) [11]. The medicine charts of the IHD patients who had concurrent symptoms of HF, NYHA (2-4), were compared with both guidelines. Non-pharmacological treatment was not assessed. The Danish guidelines are compiled by the DSC and are considered the gold standard for treatment. Undertreatment was defined as the absence of a recommended drug and a daily dosage lower than recommended target dosages.

Prevalence of drug interactions: The prevalence of drug interactions was determined by using the Danish Interaction Database. This is a web-based tool providing information on drug interactions. The Danish Medicines Agency (DMA) [12] authorizes the database.

Statistics: Descriptive statistics were used (percentages and mean standard deviation (SD)). Association between categorical variables was analysed with Fisher's exact test. A two-tailed p value of < 0.05 was considered statistically significant. JMP 6.0 (SAS Institute Inc.) was used for the analyses.

RESULTS

68% of the study participants were men and 82% were native Danes. Their mean age was 63.4 (SD ± 8.8 years, range 46-79). Patients received an average of nine drugs (SD ± 3.5, range 4-16). A total of 24 patients with IHD had a prior event of acute coronary syndrome (ACS) and

TABLE 1

Drugs recommended by the Danish Society of Cardiology in the 2008 edition guidelines.

	Drug	Indication	Dosage
IHD patients	Salicylic acid	All patients	75 mg
	Clopidogrel	Indicated in case of salicylic acid intolerance and 1-12 months after invasive treatment with stent implantation	75 mg
	Statins	All patients	Individual dosages
	Beta blockers	Indicated in heart failure or an earlier event of myocardial infarction	Dosage not stated
	ACE-I/ARB	Indicated when the following risk factors are present: diabetes mellitus, hypertension, apoplexy, peripheral vascular disease, symptomatic heart failure or EF ≤ 0.45	Dosage not stated
HF patients	ACE-I/ARB	All patients with NYHA 1-4	Different dosages for different generics
	Diuretics	All patients with signs of fluid retention	Dosages should be kept as low as possible
	Beta blockers	All patients with symptomatic heart failure	Different dosages for different generics
	Spironolactone	All patients with NYHA 3-4	12.5-50 mg

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blockage; EF = ejection fraction; HF = heart failure; IHD = ischaemic heart disease; NYHA = New York Heart Association (functional classification of heart failure).

TABLE 2

Compliance with 2008 edition of the guidelines for patients with ischaemic heart disease and heart failure published by the Danish Society of Cardiology.

	Number of patients (%)				
	receiving the drug	treatment was indicated but not prescribed	treatment was not relevant	allergy or side effects prevented treatment	treated according to guidelines
Guidelines for IHD (n = 25)					
ASA	22	2	1[a]	0	22/24 (92)
correct dosage (75 mg)	19				19/22 (86)
Clopidogrel	7	0	18	0	7/7 (100)
correct dosage (75 mg)	7				7/7 (100)
Statins	25	0	0	0	25/25 (100)
ACE-I/ARB	14	8	3	0	14/22 (64)
Beta blockers	17	6	1	1	17/23 (74)
Guidelines for HF (n = 15)					
ACE-I/ARB	10	5	0	0	10/15 (67)
target dosage	9				9/10 (90)
Diuretics	10	3	2	0	10/13 (77)
relevant dosage	6				6/10 (60)
Beta blockers	13	2	0	0	13/15 (87)
target dosage	9				9/13 (69)
Spironolactone	3	4	8	0	3/7 (43)

ASA = acetylsalicylic acid; ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blockage; HF = heart failure
IHD = ischaemic heart disease.
a) The patient received vitamin K antagonist and clopidogrel.

12 had concurrent symptoms of HF (IHD+HF). The study population included patients recently discharged from hospital, as well as patients who had not been hospitalized for many years.

Accordance with guidelines: **Table 2** illustrates the accordance between the patients' drug treatment and the guidelines for treatment of IHD and HF. Most of the patients with IHD received acetylsalicylic acid (ASA), but three patients received higher than recommended doses. In two cases, ASA was indicated, but not given. Both patients received lifelong treatment with warfarin, which may be considered a relative contraindication to ASA due to the increased bleeding risk. Beta blockers were given to 74% and angiotensin-converting enzyme-inhibitors (ACE-I) to 64% of the IHD patients, as indicated. Six of the patients who did not receive a beta blocker (26%) had a previous event of myocardial infarction (MI). All IHD patients who did not receive ACE-I had IHD risk factors: three out of eight had diabetes mellitus, six had elevated blood pressure, two patients had a previous event of apoplexy, five patients had symptoms of peripheral vascular disease and two patients had symptoms of HF (NYHA 2).

Among the patients with symptomatic HF, two-thirds received ACE-I/angiotensin receptor blocker (ARB) as indicated, and in 90% the dosages were optimal. Though the majority (87%) of the patients were being treated with beta blockers, the dosages were lower than recommended in 31%. Diuretics were given to 77% as indicated, 60% of whom received the relevant dosages. Spironolactone was given to 43% of the patients in NYHA class 3.

Overall, ten of 28 patients were clinically well-treated (**Table 3**). Compensated clinical findings were more common in HF patients whose treatment was in accordance with guidelines ($p = 0.02$). This was, however, not the case for patients with IHD ($p = 0.43$).

Potential drug interactions: **Table 4** summarises the 35 potential drug interactions identified in 19 patients. Nine patients had no potential drug interactions. The drugs most commonly involved in potential interactions were ACE-I, vitamin K antagonist, digoxin and statins. None of the interactions were potentially harmful.

DISCUSSION

This small descriptive study indicates that undertreatment in patients with chronic heart diseases may be prevalent in health-care centres. Thus, only ten out of 28 patients were clinically well-treated with normal blood pressure and normal clinical findings, and drug treatment was only partly in accordance with guidelines in the majority of the patients.

The patients with IHD were mainly undertreated with beta blockers and ACE-I, which was given to 74% and 64%, respectively. Most IHD patients received salicylic acid, which is in line with the results from previous studies (13-14). All patients received statins.

Undertreatment with beta blockers, ACE-I and statins has been reported elsewhere. Thus, Vermeer et al

TABLE 3

Clinical findings in relation to accordance with the ischaemic heart disease and heart failure guidelines.

Patients diagnosis (n = 28)	Treatment in accordance with IHD guidelines[a]	Treatment in accordance with HF guidelines	Blood pressure[b]	Regular heartbeats	Pulmonary congestion	Peripheral oedemas	Clinically well- treated[c]
IHD (n = 13)	Partly	–	Mild	Yes	No	No	No
	Completely	–	Normal	Yes	No	Yes	No
	Completely	–	Normal	Yes	No	Yes	No
	Partly	–	Mild	Yes	No	No	No
	Completely	–	Normal	Yes	No	No	Yes
	Partly	–	Moderate	Yes	No	No	No
	Partly	–	Normal	Yes	No	No	Yes
	Partly	–	Normal	Yes	No	No	Yes
	Partly	–	Normal	Yes	No	No	Yes
	Completely	–	Normal	Yes	No	No	Yes
	Partly	–	Moderate	Yes	No	No	No
	Partly	–	Isolated systolic	Yes	No	No	No
	Partly	–	Isolated systolic	Yes	No	No	No
IHD + HF (n = 12)	Partly	Partly	Isolated systolic	Yes	No	No	No
	Completely	Partly	Normal	Yes	Yes	No	No
	Completely	Partly	Normal	Yes	No	No	Yes
	Completely	Completely	Normal	Yes	No	No	Yes
	Completely	Completely	Normal	Yes	No	No	Yes
	Completely	Partly	Mild	Yes	No	Yes	No
	Partly	Partly	Normal	Yes	No	No	Yes
	Completely	Completely	Normal	No	No	No	Yes
	Partly	Partly	Isolated systolic	Yes	Yes	No	No
	Completely	Partly	Moderate	Yes	No	Yes	No
	Completely	Partly	Isolated systolic	Yes	No	Yes	No
	Partly	Partly	Isolated systolic	Yes	No	Yes	No
HF (n = 3)	–	Partly	Normal	No	Yes	Yes	No
	–	Partly	Moderate	Yes	No	No	No
	–	Party	Normal	No	No	Yes	No

HF = heart failure; IHD = ischaemic heart disease.

a) Partly was defined as absence of a recommended drug and or a daily dosage lower than the recommended target dosages according to the guidelines.

b) Definitions and classification of blood pressure levels (mmHg) according to the Danish Society of Cardiology.
Normal: < 140 and < 90.
Grade 1 (mild hypertension): 140-159 or 90-99.
Grade 2 (moderate hypertension): 160-179 or 100-109.
Grade 3 (severe hypertension): ≥ 180 or ≥ 110.
Isolated systolic hypertension: ≥ 140 and < 90.

c) Patients with normal blood pressure and normal clinical findings.

studied patients with ACS and reported that at hospital discharge, 82%, 79% and 86% received beta blockers, ACE-I/ARB, and statins, respectively [13]. Lee et al found that 63.9%, 51.8% and 62.6% received beta blockers, ACE-I and statins, respectively, three months after an ACS event [15]. Moreover, studies have shown that ACS therapy compliance has a tendency to decline with time [7, 16].

Dosages of beta blockers and ACE-I are not stated in the Danish IHD guidelines and are therefore not covered by this study. Dosages of statins were also left out as these dosages correlate with individual cholesterol values, data to which we had no access. It is possible that undertreatment in IHD patients is underestimated because of these missing data. Gislason et al calculated dosages of beta blockers, ACE-I and statins and compared the average dosage with the dosages used in major randomized clinical trials and found that underdosing was prevalent and that dosages generally comprised 50% or less of the dosages used in randomized trials [7].

In the HF patients, ACE-I, beta blockers and diuretics were underused both in terms of the number of patients receiving these drugs and in terms of the doses given. The most commonly prescribed drug was beta blockers (87%) followed by diuretics (77%), ACE-I (67%) and spironolactone (43%). Several other studies have evaluated the medical treatment of HF. In a large Danish study including over 100,000 patients conducted from 1995 to 2004, ACE-I was the most commonly initiated

treatment (43%) followed by beta blockers (27%) and spironolactone (19%) [8]. In the present study, the consumption rates were higher than those found in the Danish study, which may indicate a higher degree of compliance with guidelines. A large European study conducted in 24 countries found that the most frequently prescribed drugs in heart failure patients were diuretics (86.9%) followed by ACE-I (61.8%), beta blockers (36.9%) and spironolactone (20.5%) [6].

De Groote et al reported similar findings [17]. In contrast to these studies, our results indicate a higher utilization rate of beta blockers. One explanation for the high rates of beta blockers is that 80% (n = 12) of the HF population were also diagnosed with IHD. Other studies have shown that HF patients with IHD are more likely to receive beta blockers than HF patients without IHD [6, 17].

In patients with HF, doses of beta blockers and diuretics were often given at doses lower than recommended. Thus, 31% and 40% received smaller dosages of beta blockers and diuretics, respectively. In contrast, 90% received correct doses of ACE-I. Low dosages may be explained by the fact that this kind of treatment was recently initiated, but in most cases it was not possible to determine whether underdosing was due to side effects or suboptimal up-titration.

Only ten out of 28 patients were considered clinically well-treated. Furthermore, there was a positive correlation between the adherence to treatment guidelines and normal clinical findings. However, this was only statistically significant in HF patients (p = 0.02). In line with this finding, Ohsaka et al found a significant correlation between adherence to HF treatment and NYHA class improvement in HF patients [18]. The relationship between clinical parameters and guideline adherence should be addressed in future studies.

Potential drug interactions were frequent, but most had no likely clinical significance. The most common drugs to be involved were cardiovascular drugs, which was also observed by Bjerrum et al [19]. Since the risk of potential drug interactions increases with an increasing number of drugs [20], it is important that physicians pay extra attention to patients receiving multiple drugs in general and patients receiving cardiovascular drugs in particular.

This study has some important limitations. Firstly, 45 of 78 patients did not speak Danish and were therefore excluded. Poor communication skills can affect patients' understanding of and compliance with medicine intake, and our results might therefore be underestimated. Secondly, since the study is small and was performed in only two health-care centres, the applicability to other systems is unknown. Thirdly, for patients with IHD + HF, the HF diagnosis was not validated by medical charts. The NYHA classification 2-4 was therefore used as a proxy for HF. Furthermore, the reasons for not treating patients with a certain drug or selecting at a lower than recommended dose could not be evaluated because we had no access to medical charts. Also, the risk of intraobservatory error cannot be excluded as the same person conducted all examinations. However, we limited the risk by using the same procedure and equip-

TABLE 4

Potential drug interactions among 28 patients with chronic heart diseases.

Drug 1	Drug 2	Number of patients	Interaction	Clinical implication
ACE-I	Salicylates	12	Reduced antihypertensive effect of ACE-I	Small dosage (< 100 mg) of salicylates can be used with ACE-I
	Oral antidiabetics/insulin	9	Risk of hypoglycaemia	Control of blood sugar levels at beginning and end of treatment
	Potassium	1	Risk of hyperkalaemia	Control of electrolytes
Vitamin K antagonist	Loop diuretics	3	Risk of lowering effect of vitamin K antagonist	Frequent monitoring of INR
	Paracetamol	2	Risk of enhancing the effect of vitamin K antagonist	Theoretical risk with large doses of paracetamol
	Statins	2	Risk of high INR and rhabdomyolysis	Theoretical risk Frequent control of INR
Digoxin	Beta blockers	1	Increased effect of digoxin	Consider reducing dosage of digoxin
	Loop diuretics	1	Increased sensitivity of digoxin	Consider reducing dosage of digoxin
	Potassium-sparing diuretics	1	Increased plasma concentration of digoxin	Consider reducing dosage of digoxin
Statin	Diltiazem	1	Risk of rhabdomyolysis and myopathy	Consider reducing dosage of statin
	Carbamazepin	1	Risk of reduced effect of statin	Increase dosage of statin or shift to rosuvastatin
Beta blockers	Beta-2 agonists	1	Risk of bronchospasms in asthmatic patients	Inform the patient

ACE-I = angiotensin-converting enzyme inhibitor; INR = international normalized ratio.

ment in every clinical examination. Finally, we used the Danish Interaction Database as a reference. This database is developed by the DMA where independent physicians systematically evaluate and review the quality of published literature. However, data have not been compared with a reference database.

Despite its shortcomings, this descriptive study indicates that the drug treatment of chronic heart patients in the studied health-care centres leaves room for improvement. Given that approximately two thirds of the patients were not clinically well-treated, these rehabilitation patients may benefit from frequent clinical monitoring and adjustment of the drug therapy, e.g. by closer involvement of clinicians or GPs in the multidisciplinary teams of the health-care centres.

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