Adverse cardiovascular effects of drugs in patients with heart failure

Pharmaco-epidemiological studies on ibopamine and NSAIDs

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Cardiovasculaire bijwerkingen van geneesmiddelen bij patiënten met hartfalen

Farmaco-epidemiologische studies betreffende NSAIDs en ibopamine

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Overige leden: Prof.dr. P.A. de Graeff
Prof.dr. H.G.M. Leufkens
Dr. B.H.Ch. Stricker (tevens copromotor)
Prof. J.H.P. Wilson

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Chapter 1

Introduction

Heart failure is one of the most common cardiovascular disorders in western countries (1, 2). Because (congestive) heart failure is a chronic, incapacitating disease with a poor prognosis and a substantial public health impact, the attention paid to this disorder in research and both scientific as well as popular publications is fully justified. In addition, the incidence and prevalence of heart failure tend to increase, in particular because of ageing of the population and increased survival after acute myocardial infarction.

Heart failure is characterized by periods of exacerbating signs and symptoms. Identifying precipitating factors for relapsing heart failure may contribute to optimal heart failure management. Only few studies have addressed the issue of precipitating factors for relapsing heart failure (9, 10). Relapses of heart failure are associated with substantial morbidity and health care expenditures due to hospital readmissions. In chapter **2.1**, potentially precipitating factors of relapsing heart failure are discussed.

Several classes of drugs have been associated with drug-induced heart failure. Drugs may either induce the first occurrence of heart failure or may precipitate relapsing heart failure. Chapter **2.2** discusses several classes of drugs that may play a role in drug-induced heart failure.

Awareness of precipitating factors for a first occurrence or a relapse of heart failure may contribute to optimal treatment and care of heart failure patients. In chapter **2.3**, we reviewed hospital discharge letters for the presence of a description of potentially precipitating factors. Moreover, we studied medication compliance in patients who were readmitted to hospital because of relapsing heart failure.

NSAIDs have been associated with the occurrence of heart failure in a number of reports (11-15). Chapter **3.1** presents a review of the adverse cardiovascular effects of non-steroidal anti-inflammatory drugs in patients with heart failure.

Over the years, the Drug Safety Unit of the Inspectorate for Health Care in The Netherlands has received a number of case reports on NSAID-associated heart failure and fluid retention(16). This case-series is described in chapter **3.2**.

In Chapter **3.3**, we studied the association between left ventricular fractional shortening and current use of NSAIDs in participants of the Rotterdam Study who underwent echocardiography at study baseline. The aim of this study was to assess a potential effect of current use of NSAIDs on left ventricular systolic function.

We separately studied the association between use of NSAIDs and the occurrence of heart failure in patients with either incident or prevalent heart failure. These

studies are described in chapter **3.4** and **3.5**, respectively. To study the effect on *incident* heart failure, data were used from the Rotterdam Study, a prospective population-based cohort study (17). To study the effect of NSAIDs in patients with *prevalent* heart failure, defined as patients with a history of one hospital admission for heart failure, we used data from the PHARMO record linkage database (18).

Because of the significance of heart failure in terms of morbidity and mortality, several cardiovascular drugs have been developed and introduced on the market for its treatment, with varying success. Particularly, positive inotropic agents have shown to be associated with increased mortality risk (3-5). Unfortunately, this also applied to ibopamine, an oral dopaminergic agent registered in The Netherlands in 1991 for the treatment of mild, moderate, and severe heart failure. The PRIME-II trial, carried out in patients with NYHA III and IV heart failure and published in August 1995, demonstrated an increased mortality risk in patients treated with ibopamine compared to placebo (6). Patients with mild heart failure were not included in this trial. To assess the effects of ibopamine in heart failure patients under everyday circumstances for all registered indications, including mild heart failure (NYHA II), we initiated a nationwide cohort-study among heart failure patients who had been prescribed ibopamine (7) (chapter **4.1**). In addition, the sudden change of an indication of a drug to a strict contraindication offered a unique opportunity to study quantitatively the impact of "confounding by contraindication" in an epidemiological study. This study is described in chapter **4.2**.

Apart from its effect on morbidity and health care expenditures, relapsing heart failure may have a significant impact on quality of life. Chapter **4.3** discusses quality of life in heart failure, focussing on the problem of heart failure treatments which may improve quality of life but which also have shown to be associated with shortened survival (8).

Chapter **5** evaluates the various aspects of heart failure treatment and how treatment may further be improved in the near future. Finally, the general discussion in chapter **6** discusses the results from the perspective of drug safety and recent and future developments in heart failure treatment.

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Chapter 2

Precipitating factors for heart failure

Prevention of relapses in patients with congestive heart failure: the role of precipitating factors

ABSTRACT

Relapse of congestive heart failure (CHF) frequently occurs and has serious consequences in terms of morbidity, mortality and health care expenditure. Many studies have investigated the aetiologic and prognostic factors of CHF, but there are only limited data on the role of precipitating factors that trigger relapse of CHF. Knowledge of potential precipitating factors may help to optimise treatment and provide guidance for patients with CHF. The literature was reviewed to identify factors that may influence haemodynamic homeostasis in CHF. Precipitating factors that may offer opportunities for preventing relapse of CHF were selected. Potential precipitating factors are discussed in relation to the pathophysiology of CHF: alcohol, smoking, psychological stress, uncontrolled hypertension, cardiac arrhythmias, myocardial ischemia, poor treatment compliance, and inappropriate medical treatment.

Poor treatment compliance in particular is frequently encountered in patients with CHF. Furthermore, studies on medical treatment under everyday circumstances indicate that some aspects of the management of CHF can be improved.

In conclusion, the identification of precipitating factors for relapses of CHF may strongly contribute to optimal treatment. Improvement of treatment compliance and optimalisation of medical treatment may offer important possibilities to clinicians to reduce the number of relapses in patients with CHF.

INTRODUCTION

There is increasing interest in congestive heart failure (CHF) from both clinicians and researchers. The prevalence of CHF continues to increase despite advances in the treatment of various risk factors for this disease, such as hypertension and coronary artery disease (1, 2). According to a recently published simulation model, a further shift from acute to more chronic cardiovascular disease, including CHF, is expected in the near future (3). This increase in the prevalence of CHF is the result of several medical and demographic developments: an aging population, decreasing mortality of patients with acute myocardial infarction, and improved treatment of patients with angina pectoris and hypertension (4, 5). In addition, survival in patients with CHF has improved since the introduction of angiotensin-converting-enzyme-inhibitors (ACE-inhibitors) (6, 7). Epidemiological studies also indicate a substantial age-adjusted increase in hospitalisation rates for CHF over the last twenty years in western countries (1, 8).

CHF is clinically characterised by periods of remission and exacerbation. Readmission rates of up to 25% within six months after a previous hospital discharge for CHF have been reported in patients older than 65 years (9, 10). Relapse of CHF in patients with previously stable compensated heart failure may be caused by unpreventable deterioration of ventricular function, but several precipitating factors have been suggested (11, 12).

Some precipitating factors can be regarded as potentially preventable. Many studies have been performed on prognostic factors for mortality due to CHF, such as left ventricular ejection fraction, but research on precipitating factors leading to relapses of CHF, however, is scarce (11, 13, 14). Nevertheless, timely identification of potential precipitating factors may offer an important advantage in efforts to reduce morbidity and the number of hospital admissions attributed to the syndrome of CHF.

We conducted a search of the Medline database from 1966 to December 1997 and used lateral references to review the literature on potential precipitating factors. In this article, we focus on the role of precipitating factors that are relatively common in clinical practice and potentially modifiable: the effects of alcohol, smoking, psychological stress, uncontrolled hypertension, cardiac arrhythmias, myocardial ischaemia, lack of compliance, and inappropriate medical treatment.

PRECIPITATING FACTORS FOR RELAPSE OF CONGESTIVE HEART FAILURE

Knowledge of potential precipitating factors for relapse of CHF is crucial to prevent or postpone relapses. As indicated, only a few studies have addressed this issue and identified factors which may be related to the onset or exacerbation of symptoms of CHF in patients with previously compensated heart failure (11-15). In a descriptive study, Ghali et al. examined potential precipitating factors in 101 hospital readmissions for CHF (11). Precipitating factors were identified in 93% of patients. The most common factor was lack of adherence to the prescribed medical regimen with respect to both medication and diet (64% of patients). Other frequently identified precipitating factors were uncontrolled hypertension (44%), cardiac arrhythmias (29%), iatrogenic factors (21%), and pulmonary infections (17%) (table I). In a more recent study, Opasich et al. identified precipitating factors in 91% of 328 instances of non-fatal decompensation in 304 patients. All patients had a history of at least one previous episode of severe decompensation. Common precipitating factors were cardiac arrhythmias (24% of patients), poor compliance (15%), infections (23%), angina pectoris (14%), and iatrogenic factors (10%). Frequency differences in specific precipitating factors reflect the different study populations and designs of the two studies. In addition, the absence of a control group in these studies excludes assessment of the relative risk of these potential precipitating factors.

Table I
Factors that may precipitate relapses in patients with pre-existing CHF

lack of treatment compliance
myocardial infarction
angina pectoris or painless myocardial ischaemia
alcohol consumption
cardiac arrhythmias
inappropriate medical treatment
infections
anaemia
pulmonary embolism
thyroid disease
pregnancy
physical, dietary, fluid, and environmental excesses
emotional stress
systemic hypertension
smoking

Table II
Aetiology of congestive heart failure

Common causes:	coronary artery disease hypertension idiopathic dilated cardiomyopathy valvular disease
Uncommon causes:	hypertrophic cardiomyopathy restrictive cardiomyopathy alcoholic cardiomyopathy connective tissue diseases medication inherited diseases infectious diseases metabolic diseases metals neurological diseases volume overload anaemia shunts

Several diseases may induce the syndrome of CHF (Table II). Patients in whom CHF is diagnosed should be given optimal medical care to prevent clinical worsening while maintaining quality of life. An accurate evaluation of potential precipitating factors should also be routinely performed in patients with relapse of CHF. This evaluation may reveal important factors which may have contributed to the relapse of CHF. For instance, adequate treatment of anaemia or arrhythmias may strongly contribute to relief of symptoms of CHF and may prevent future relapses of CHF.

Although the haemodynamic effects of the above-mentioned potential precipitating factors have been well investigated in healthy subjects and in patients with coronary artery disease, only limited data are available on their specific haemodynamic effects in patients with CHF. Therefore, the haemodynamic effects of these precipitating factors are discussed within the framework of current views on the pathophysiology of CHF. Apart from the precipitating factors discussed here, CHF may also be precipitated by infection, anaemia, pulmonary embolism, thyroid disease, pregnancy, and physical, dietary, fluid, and environmental excesses (11-15). As most of these factors have either known causes, such as excessive salt intake and excessive intravenous fluid administration, or relatively uncommon causes, they are not discussed in further detail.

Alcohol

CHF resulting from alcoholic cardiomyopathy is a relatively common cause of non-ischaemic cardiomyopathy (16). The amount and duration of alcohol consumption required to induce alcoholic cardiomyopathy is not well defined, but has been estimated at 5 to 6 ounces. (1 ounce=28 ml) of ethanol daily for at least 10 years. Abstention from alcohol is crucial in patients with alcohol-induced cardiomyopathy (17). Echocardiographic studies show that major clinical improvement and normalisation of left ventricular function can be achieved after abstention from alcohol in patients with alcoholic cardiomyopathy (18, 19). Resumed alcohol intake may act as a precipitating factor for a relapse of CHF in these patients. There is no convincing evidence for absolute abstention from alcohol in patients with CHF not induced by alcohol. In a study in which the acute effects of moderate alcohol consumption (0,9 g/kg) in patients with New York Heart association (NYHA) class III-IV heart failure were assessed, small but significant reductions in arterial pressure, pulmonary artery pressure, pulmonary artery wedge pressure, and systemic vascular resistance were seen after a single dose of alcohol, but CHF did not deteriorate (20). It was suggested that reduction in afterload counterbalanced the negative inotropic effects of alcohol, leaving cardiac performance essentially unchanged. Chronic heavy alcohol consumption should be strongly discouraged in all patients with CHF, but there are no convincing reasons to warn all patients with CHF against incidental moderate consumption of alcohol (21). Clinical practice shows, however, that some patients with apparently non-alcohol induced CHF may have significant improvement after complete abstention from even incidental moderate alcohol-consumption. Therefore, evaluation of a period of complete alcohol abstention in patients with severe CHF may be worthwhile.

Smoking

Several studies have been performed on the acute haemodynamic effects of smoking, both in healthy subjects and in patients with cardiovascular disease. Cigarette smoking increases heart rate and blood pressure, both principal determinants of myocardial oxygen consumption (22). Increased heart rate as well as increased blood pressure are both associated with the intake of nicotine (23). Goldbarg et al. showed in healthy subjects that the left ventricular stroke index (ml/beat/m^2) decreased significantly at several levels of exercise after smoking, although there was no significant change of stroke index after smoking at rest (24). Aronow et al. investigated the effects of cigarette smoking and breathing carbon monoxide on cardiovascular haemodynamics in patients with angina pectoris (23). This study showed that an increased level of carboxyhaemoglobin had a negative inotropic effect and increased left ventricular end-diastolic pressure. There was a signifi-

cant decrease in the stroke index after smoking in these patients. Results from a study of Pentecost et al. indicated that cigarette smoking tends to decrease cardiac output especially in older patients with a history of myocardial infarction (25). Nicolozakes et al. investigated the effects of smoking in patients with NYHA class III CHF (26). Cardiac output remained unchanged after smoking, but other haemodynamic changes were seen. As expected, heart rate and systemic blood pressure (double product) increased substantially after smoking. In addition, there were mild increases in pulmonary artery pressure, ventricular filling pressures, and total systemic and pulmonary vascular resistance. The increased ventricular afterload probably accounts for the observed mild decrease in stroke volume. Thus, smoking increases oxygen demand but decreases myocardial oxygen supply because of reduced diastolic filling time and increased carboxyhaemoglobin level. This finding has important negative consequences for the myocardial oxygen supply. Patients with CHF should be strongly advised to stop smoking and should be informed that continued smoking may unfavourably affect CHF. It remains unclear, however, to what extent smoking may act as a precipitating factor for relapse of CHF.

Psychological stress

Several effects of psychological stress on cardiac function in patients with cardiovascular disease have been described in the medical literature. Mental stress in patients with ischaemic heart disease can induce transient myocardial ischaemia and transient wall motion abnormalities (27). Myocardial ischaemia in response to psychological stress is frequently painless (28). Rozanski et al. reported that wall-motion abnormalities occurred in 59% of patients with coronary artery disease during mental stress. A drop in ejection fraction of more than 5% was seen in 36% of patients. Wall motion abnormalities were seen in only 8% of normal controls during mental stress, and no clear effect on ejection fraction was observed in the controls (29). Mental stress may also induce transient changes of the electrophysiological properties of the myocardium, which may sensitise the heart to life-threatening ventricular arrhythmias (30). Emotional factors preceding hospitalisation for CHF have been reported in 49% of patients (15). Some cases of stress-induced heart failure have been described (31). Giannuzzi et al. reported that psychological stress induced changes in left ventricular diastolic function in patients with idiopathic cardiomyopathy (27). The effects of mental arithmetic on these patients were compared to those on controls. The ratio of transmitral peak flow velocity in early versus late diastole (E/A) significantly increased during mental arithmetic, while transmitral deceleration time markedly decreased. These findings suggest that left ventricular function is impaired during psychological stress. Neuroendocrine activation and a significant increase in arterial blood pressure, especially in hypertensive patients, may also contribute to the haemody-

namic effects of psychological stress. The full effects of psychological stress on cardiovascular function in patients with CHF are not known, but many of the discussed effects can be considered unfavourable.

Uncontrolled hypertension

Hypertension is an important and well-known risk factor for the development of cardiovascular disease, including CHF. Recent data from the Framingham Heart Study underscore its importance as a major risk factor for CHF (32). Hypertension may impair ventricular function by increasing afterload and impairing both systolic contraction and diastolic relaxation (33). Approximately 50% of patients with hypertension and a normal coronary angiogram have transient ST-segment depression during 24 hour Holter monitoring, usually without angina pectoris (34). As there was no relation with left ventricular hypertrophy, these findings seem to reflect a disturbed coronary microvasculature. This may also explain the increased coronary resistance and decreased maximal coronary blood flow after dipyridamole in these patients (34). Intervention trials have provided convincing evidence of the efficacy of hypertension treatment in reducing the incidence of CHF (35). Obviously, persistent hypertension in patients with CHF will have a detrimental effect on ventricular performance. Blood pressure in patients with end-stage CHF usually decreases because of low cardiac output. Uncontrolled hypertension despite antihypertensive therapy, defined as diastolic blood pressure of 105 mm Hg or more, was identified in 44% of patients readmitted to hospital for CHF (11). Adequate blood pressure control in patients with CHF is crucial because of the numerous haemodynamic effects of hypertension, although there are few data on the extent to which uncontrolled hypertension may account for relapse of CHF.

Cardiac arrhythmias

Cardiac arrhythmias are frequently present in patients with CHF and are regarded as a sign of impaired left ventricular function. Atrial fibrillation is the most prevalent cardiac arrhythmia in patients with CHF. Nevertheless, its prognostic significance is controversial. There have been studies in which atrial fibrillation did not increase morbidity and mortality as well as studies in which atrial fibrillation was a marker for an increased mortality risk (36, 37). Ghali et al. reported that cardiac arrhythmias, particularly atrial fibrillation, were present in 29% of patients readmitted for CHF and were considered to be directly responsible for relapse of CHF in 78% of these patients (11). Loss of atrioventricular synchrony and impaired rate control because of atrial fibrillation are usually regarded to be an unfavourable clinical characteristic in patients with CHF. Cardioversion of chronic atrial fibril-

lation to sinus rhythm in patients with NYHA functional class I or II significantly increased cardiac output during exercise, maximum oxygen uptake, and maximal tolerated workload (36). Successful cardioversion in patients with chronic atrial fibrillation and idiopathic dilated cardiomyopathy significantly improved left ventricular ejection fraction from 32% to 53% (38). Several studies have reported on patients with severe left ventricular dysfunction and atrial fibrillation with rapid ventricular response (39, 40). Left ventricular dysfunction in these patients may be completely reversed by controlling ventricular rate or restoring sinus rhythm. Supraventricular tachycardias are usually the underlying arrhythmia in this so-called tachycardia-induced cardiomyopathy. The unfavourable haemodynamic consequences of atrial fibrillation compared with those of sinus rhythm suggest that development of this arrhythmia may be a trigger for relapse of CHF.

Myocardial ischaemia

The detrimental effects of myocardial ischaemia on ventricular function have been well documented (41). The main cause of progressive myocardial failure is postulated as subendocardial ischaemia, even in patients with non-ischaemic CHF (42). Silent or symptomatic myocardial ischaemia can also be identified as part of the pathway relating other potential precipitating factors, such as psychological stress, smoking, cardiac arrhythmias, and hypertension, to relapses of CHF (28, 34). Impairment of systolic and diastolic ventricular function persists from hours to days after transient myocardial ischaemia (43). Hibernating myocardium is a widely accepted concept in modern cardiology, defined as a state of persistently impaired myocardial and left ventricular function at rest because of reduced coronary blood flow (41). Hibernating myocardium can be considered as a myocardial adaptation to reduced coronary blood flow, to prevent irreversible myocardial damage. The significant improvement of left ventricular function after coronary revascularisation which can be observed in patients with coronary artery disease and left ventricular dysfunction is mainly based on this principle. Although the exact frequency of hibernating myocardium is not known, Carlson et al. reported hibernating myocardium in 75% of patients with unstable angina pectoris and in 25% of patients with stable angina pectoris (44). Abolition of myocardial hibernation can improve left ventricular function (41). Although only limited information is available on the frequency of myocardial ischaemia in patients with CHF, it seems reasonable to assume that myocardial ischaemia may deteriorate ventricular function and may act as a precipitating factor for relapse of CHF. Therefore, prevention of myocardial ischaemia may contribute to the maintenance of haemodynamic homeostasis in patients with CHF.

Lack of treatment compliance

Ghali et al. identified lack of compliance to medication and diet as a major precipitating cause in 64% of the 101 patients presenting with decompensated heart failure (11). In this study, 97% of the patients were black and described as a predominantly working-class minority population. As both educational level and ethnic background are major predictors of compliance, it has been suggested that non-compliance in these patients may be attributed to differences in culture, language and health education (45). In contrast, in the study of Opasich et al. poor compliance as a precipitating factor for relapse of CHF was encountered in only 15% of all 328 instances of decompensation (12). These discrepensies seem to be attributable to difficulties in measuring compliance, differences in study population and study design. Non-compliance with long-term medication regimens has been found to be approximately 50% in several studies (46). This may represent an important impediment to effective treatment of CHF. Dietary intervention, particularly aimed at reducing sodium chloride intake to 3 g/day or less in combination with other non-pharmacologic treatment such as graduated exercise training and psychological therapy have shown to improve functional and emotional status in patients with CHF (47). Intensive medication counselling may improve compliance significantly (48). Interestingly, physicians' personal characteristics and characteristics of their practices also influence patients' adherence to medical treatment (49). Physicians' global job satisfaction positively influences patient compliance.

Non-compliance to medication and diet has repeatedly been identified as a frequent precipitating factor for admission to hospital for decompensated heart failure. Therefore, non-compliance deserves major attention from health professionals, as it may offer an opportunity to make a significant contribution to preventing relapse in patients with CHF.

Inappropriate medical treatment

Iatrogenic factors considered to be responsible for relapses of CHF were identified by Ghali et al in 21% of relapses and by Opaschi et al in 10% of relapses (11, 12). The most important causes of iatrogenic CHF are usually inappropriate medication and excessive intravenous fluid administration. Although not discussed in detail here, several categories of drugs, such as non-steroidal anti-inflammatory drugs, β-blockers, and anti-arrhythmics, may affect cardiovascular homeostasis, especially in patients with pre-existing left ventricular impairment. Rich et al. prospectively studied the occurrence of iatrogenic CHF in 401 patients hospitalised for CHF (50). CHF was considered to be iatrogenic in 28 (7%) patients. As a result of the inability of the researchers to reliably assess causality between suspected inade-

quate medication and the onset of CHF, most instances of iatrogenic CHF were attributed to excessive intravenous fluid administration. Therefore, the importance of inappropriate medication, such as withdrawal of ACE-inhibitors, seems to have been underestimated in this study.

Patients with CHF deserve optimal treatment and investigation. Intervention trials have provided clear evidence for the beneficial effects of ACE-inhibitors on survival in patients with CHF (6, 7). However, some studies have reported flaws in the management of patients with CHF. Clarke et al. carried out a retrospective study in six general practices among 505 patients receiving loop diuretics (51). Although 74% of 281 patients who fulfilled diagnostic criteria for CHF were referred to hospital, only one third had echocardiogram. Furthermore, 234 patients of the 281 patients who fulfilled the diagnostic criteria for CHF were not treated with ACE-inhibitors. Among them were 26 patients with documented evidence of left ventricular impairment. These findings strongly suggest shortcomings in the diagnosis and treatment of CHF, but lack of information on the severity of CHF in this study makes it difficult to draw definite conclusions. Hilles et al. reported in a review of the case notes of 343 patients discharged from hospital with a diagnosis of CHF that only 40% of patients received ACE-inhibitors (52). Of patients with NYHA class III and IV CHF, only 50% were treated with ACE-inhibitors at the time of discharge from hospital. Although retrospective studies may have methodological limitations, they clearly point out some aspects of the management of CHF that need to be improved.

Striving for optimal medical treatment deserves major interest from all who are involved in the care of patients with CHF. Prevention of iatrogenic CHF should be a major issue in optimising medical treatment in these patients.

CONCLUSIONS

Relapse in patients with CHF may result from deterioration of underlying cardiac disease. Clinical practice and observational studies, however, have shown that precipitating factors can be identified in many patients with increased symptoms of CHF. These precipitating factors may have contributed to or even induced symptoms of CHF. Few studies have investigated these precipitating factors despite their presence in relapse of CHF. Suboptimal medical treatment and poor patient compliance in particular deserve more attention, as these factors can be considered as potentially preventable determinants of relapse of CHF.

Most of the discussed factors are common in daily practice, but little is known

about their influence on cardiac performance in patients with CHF under everyday circumstances. Most studies on the haemodynamic effects of smoking, alcohol, or psychological stress have been laboratory experiments. Such findings do not always reflect the effects in clinical practice. Despite these limitations, the negative haemodynamic effects of most precipitating factors discussed here are sufficient for them to be considered as unfavourable. Therefore, the presence of potential precipitating factors as listed in table I should be routinely evaluated in patients presenting with CHF. Elimination of these precipitating factors, if possible, may contribute to prevention of relapse in patients with CHF.

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Drug-induced heart failure

ABSTRACT

Heart failure is a clinical syndrome that is predominantly caused by cardiovascular disorders such as coronary heart disease and hypertension. However, several classes of drugs may induce heart failure in patients without concurrent cardiovascular disease or may precipitate the occurrence of heart failure in patients with pre-existing left ventricular impairment.
We reviewed the literature on drug-induced heart failure, using the MEDLINE-database and lateral references. Successively, we discuss the potential role in the occurrence of heart failure of cytostatics, immunomodulating drugs, antidepressants, calcium channel blockers, non-steroidal anti-inflammatory drugs, anti-arrhythmics, beta-adrenoceptor blocking agents, anaesthetics and some miscellaneous agents.
Drug-induced heart failure may play a role in only a minority of the patients presenting with heart failure. Nevertheless, drug-induced heart failure should be regarded as a potentially preventable cause of heart failure, although sometimes other priorities do not offer therapeutic alternatives (e.g., anthracycline-induced cardiomyopathy). The awareness of clinicians of potential adverse effects on cardiac performance by several classes of drugs, particularly in patients with pre-existing ventricular dysfunction, may contribute to timely diagnosis and prevention of drug-induced heart failure.

INTRODUCTION

Congestive heart failure (CHF) is a complex clinical syndrome that results from cardiac dysfunction (1). Signs and symptoms that are frequently encountered in patients suffering from CHF are dyspnea, fatigue, pulmonary crepitations, and peripheral edema. Its clinical course is often characterised by periods of exacerbating symptoms, alternated with periods in which the patient experiences fewer or no symptoms. Epidemiological studies indicate that both the prevalence and the incidence of CHF increase (2-4). CHF is predominantly caused by cardiovascular diseases, such as coronary artery disease, hypertension and valvular heart disease (3, 5). However, in some patients the occurrence of CHF can be attributed to the cardiotoxic effect of a particular drug. Furthermore, as several categories of drugs may exert unfavourable haemodynamic effects, these drugs may act as a precipitating factor for relapse in patients with previously compensated CHF.

Pathophysiologically, CHF may result from drug-mediated effects on cardiac preload, cardiac afterload or myocardial contractility. Drugs that increase cardiac preload or cardiac afterload may have unfavourable effects on ventricular function, because increased cardiac preload or afterload intensifies the demand on ventricular performance. The ability of the heart to comply with this increased demand will depend on pre-existing ventricular function. Drugs may also have a negative inotropic effect as a result of their direct cardiotoxic properties. Similarly, the likelihood of the occurrence of heart failure induced by cardiotoxic drugs may depend on pre-existing ventricular function, although some drugs may have detrimental effects in patients with previously normal cardiac function. We will discuss the potential ability of several categories of drugs to induce or exacerbate heart failure.

CYTOSTATICS

Anthracyclines

The anthracyclines are effective antineoplastic agents that are used in the treatment of many types of malignancy. Daunorubicin and doxorubicin are among the most frequently used anthracyclines included in chemotherapeutic regimens (6). The anthracyclines are antibiotic agents which antineoplastic action results from the inhibition of the nucleic acid synthesis by binding to both strands of the desoxyribonucleic acid (DNA) helix. This binding prevents normal function of the ribonucleic acid (RNA) polymerase and DNA-polymerase. The introduction of

the anthracyclines has contributed considerably to the improvement of survival in patients with cancer. However, anthracycline-induced cardiotoxicity is a well-known adverse effect of this category of drugs and a major limitation to the total dose that can safely be administered (6). Cardiotoxicity is considered to be an adverse effect of all anthracyclines, although epirubicine may cause less cardiotoxicity as compared with doxorubicine (7). Formation of free oxygen radicals, disturbance of the mitochondrial energy metabolism and intracellular calcium overloading are considered mechanisms in the pathogenesis of anthracycline-induced cardiotoxicity (8). Based on the dose-dependency of the anthracycline-induced impairment of left ventricular function, an upper limit of the cumulative dose of 550 mg/m^2 is generally recommended. When this upper limit of the cumulative dose is exceeded, early heart failure may develop in approximately 30% of the patients receiving these high dosages (6). Anthracyclines as part of a combined chemotherapeutic regimen, however, may induce heart failure at a cumulative dosage below 550 mg/m^2 (9). In particular, combined chemotherapeutic treatment with cyclophosphamide seems to be associated with an increased risk of cardiotoxicity, even when the cumulative dose of the anthracycline remains below 400 mg/m^2. The addition of cytoprotective agents to chemotherapeutic schemes, such as the bispiperazinedione compound ICRF187, seems to reduce cardiotoxicity significantly without reducing antineoplastic action (10, 11).

Cardiotoxicity may develop at any moment during or after treatment with anthracyclines. Although anthracycline-induced cardiotoxicity is usually characterised by heart failure, cardiac arrhythmias might be the first manifestation in some patients. Early cardiac toxicity, which occurs during or soon after treatment with anthracyclines, is mainly dependent on the cumulative anthracycline dose (6). However, the development of heart failure several years after the last administration of anthracyclines is increasingly recognised. In a study among 201 children who had completed chemotherapy with anthracyclines, decreased fractional shortening on echocardiography was present in more than 60% of the patients who had received >500 mg/m^2 and were followed up for at least 10 years (12). Although an adequate control group was lacking, these findings indicate that anthracycline-induced heart failure may develop several years after completing treatment with anthracyclines. Interestingly, in those patients of whom an end-therapy echocardiogram was available, it could be demonstrated that decreased fractional shortening at the end of the therapy was strongly associated with decreased fractional shortening at long-term follow-up. Although numbers were small, more than 70% (10/14) of the patients with decreased fractional shortening at the end of the therapy still had decreased systolic function at long-term follow-up. In contrast, of patients with a normal echocardiogram at the end of therapy, only 12% (8/64) had decreased fractional shortening at long-term follow-up ($p<0.001$). Patients suffering from anthracycline-induced cardiotoxicity may finally develop signs and

symptoms of heart failure when impaired systolic function is unable to maintain haemodynamic homeostasis. Although anthracycline-induced heart failure is generally considered to be irreversible, some reports on complete recovery of cardiac dysfunction have been published (13).

The severity of anthracycline-induced cardiomyopathy can be quantified with the help of a morphological grading system (14). In an endomyocardial biopsy, anthracycline toxicity is characterised by sarcotubular dilatation and myofibrillar loss of actin and myosin. Long-term myocardial damage has also been identified in patients who had received doses of only 45 mg/m^2 (15). Therefore, all patients exposed to anthracyclines should be considered at risk for the development of heart failure as a result of the cardiotoxic properties of these agents. To evaluate cardiotoxicity, guidelines for monitoring cardiac function have been implemented in most anthracycline-containing chemotherapeutic regimens (16).

The treatment of anthracycline-induced heart failure does not differ from the general pharmacotherapeutical approach to heart failure patients. Diuretics, angiotensin-converting-enzyme-inhibitors and digoxin are the mainstays of treatment. In some patients with severe anthracycline-induced CHF, heart transplantation may finally remain the only therapeutical option.

Cyclophosphamide

Cyclophosphamide is an alkylating agent that causes cytotoxicity by its biologically active metabolites. Reports have been published on both completely reversible cases as well as on fatal cases of CHF attributed to cyclophosphamide-induced cardiomyopathy (17, 18). Cardiotoxicity of cyclophosphamide is thought to be due to toxic endothelial damage followed by extravasation of toxic metabolites with resultant myocyte damage and interstitial haemorrhage and edema (19). Symptoms of CHF usually appear within two weeks after administration of the drug. In patients who develop severe progressive CHF, this complication may lead to death within a few weeks. Based on analyses of the plasma-concentration time curves (area under the curve, AUC) in 19 women with metastatic breast cancer, treated with a continuous 96-hour infusion of cyclophosphamide, it has been shown that a low AUC and a low peak plasma level of cyclophosphamide were predictive for both an increased duration of response as well as for an increased risk of developing CHF. These findings suggest that patients with a more extensive metabolism of cyclophosphamide are more prone to develop cyclophosphamide-induced cardiotoxicity. Thus, measurement of the AUC may draw attention to patients who are most susceptible to develop heart failure. The numerous reports on both reversible and irreversible heart failure indicate a wide spectrum of cyclophosphamide-

induced cardiotoxicity, which can be influenced by pre-existing cardiovascular condition, other chemotherapeutic regimens received before treatment with cyclophosphamide, and the dose and method of administration of cyclophosphamide (20).

Paclitaxel

Paclitaxel belongs to an important new class of anti-cancer agents, the taxanes. Paclitaxel promotes the polymerisation of tubulin. Microtubules formed in the presence of paclitaxel are extraordinarily stable and dysfunctional. These dysfunctional microtubules interfere with normal cell division and interphase processes and may eventually lead to cellular death. Paclitaxel is increasingly used in the treatment of patients with advanced ovarian and breast cancer. Transient asymptomatic bradycardia appears to be the most frequent cardiovascular adverse effect, reported in up to 29% of the patients treated with paclitaxel (21). Clinically important cardiac bradyarrhythmias appear to have an incidence of only 0.1%.

In a case report, the onset of heart failure has been associated with the administration of paclitaxel (22). Furthermore, heart failure has been reported with a remarkable frequency in an uncontrolled study of Gianni et al. in which women with metastatic breast cancer who had never received chemotherapy were treated with the combination of paclitaxel by 3-hour infusion and doxorubicin (23). Six out of 33 patients (18%) developed symptomatic heart failure within 12 months after starting this treatment. The median received dose of doxorubicin in these patients was 480 mg/m^2. Based on previous studies, an incidence of symptomatic heart failure in the range of 1% to 10% should be expected within one year after treatment with doxorubicin at the commonly used total-dose limit of 550 mg/m^2. Therefore, an incidence of 18% has raised the question whether the combined treatment of paclitaxel and doxorubicin may account for this apparently increased risk. Other studies, however, in which different schedules of the combined administration of paclitaxel and doxorubicin were used did not indicate an increased risk of heart failure (23). This finding may suggest that the schedule used for the administration of paclitaxel and doxorubicin may influence the risk of CHF. On the other hand, as all patients who developed CHF in the study of Gianni et al. had cardiovascular risk factors or a history of radiotherapy of the cardiac region, baseline differences among the patients included in these studies may also account for differences in the risk of paclitaxel-induced CHF. In summary, unequivocal evidence of paclitaxel-induced CHF is lacking. However, due to the efficacy of paclitaxel as an antineoplastic agent, paclitaxel will undoubtedly be prescribed to an expanding group of patients outside the setting of clinical trials in the near future. As the risk of cardiotoxicity in patients with concomitant cardiovascular disease is unknown,

there is a need for additional information on the risk of CHF after administration of paclitaxel in patients with cardiovascular comorbidity.

Mitoxantrone

Mitoxantrone is structurally related to doxorubicin and has also been associated with the development of left ventricular impairment. In a study in 801 patients treated with mitoxantrone, a clinical diagnosis of CHF was made in 1,5% of the patients, whereas in another 1,5% of the patients reduced left ventricular ejection fraction developed without clinically overt CHF (24). Furthermore, cumulative mitoxantrone dose was associated with an increasing risk of cardiotoxicity. Conclusions should be drawn with caution, as a control group was not included in this study. Decreased left ventricular ejection fraction has also been observed in a study in which patients were treated with mitoxantrone and in which patients with pre-existing cardiac disease or previous exposure to anthracyclines were excluded (25). The findings from these studies and the strucural relationship with doxorubicin support the hypothesis that mitoxantrone should be regarded as a potentially cardiotoxic agent that may be associated with drug-induced CHF.

Other chemotherapeutic agents

Heart failure has been associated with several other chemotherapeutic agents such as 5-fluorouracil (5-FU) and cytarabin. Cardiac toxicity induced by 5-FU is usually characterised by chest pain and signs of ischaemia, which resemble angina pectoris and is generally accepted to be caused by 5-FU-induced coronary spasm (26). There have also been reports in which the occurrence of severe but reversible left ventricular dysfunction was attributed to use of 5-FU (27-29), although the extent to which 5-FU may have accounted for the occurrence of CHF is not always obvious. As a result of 5-FU-induced coronary spasm, decreased ventricular function may also be caused by myocardial ischaemia instead of by a direct toxic effect on the myocardium (30). In a retrospective study on cardiotoxic effects of 5-FU and folinic acid in 390 patients treated for gastrointestinal cancer, heart failure occurred in only one patient (31). Therefore, the association between heart failure and 5-FU should be evaluated in future studies. Cytarabine-induced reversible CHF seems to be very rare and has only been described in a case report (32).

Recently, Herceptin (recombinant humanised anti-HER2 antibody) has been approved for the treatment of breast cancer in the United States. Herceptin inhibits the growth of cancer cells overexpressing HER2. The HER2 gene encodes a transmembrane tyrosine-kinase receptor, designated $p185^{HER2}$. Antibodies directed at

$p185^{HER2}$ have shown to inhibit growth of tumors that express high levels of this receptor (33). As overexpression of HER2 appears to be present in a considerable number of patients suffering from breast, ovarian and gastric cancer, Herceptin may be of value in the treatment of several different cancers. A recent study has shown that patients whose tumor cells have increased levels of $p185^{HER2}$ do significantly better when Herceptin is added to standard chemotherapy. However, concern has been raised on cardiac toxicity, which occurred in a number of patients participating in a trial on breast cancer treatment. Approximately 27% of the patients using doxorubicine, paclitaxel and Herceptin experienced signs of cardiac dysfunction, compared with 6% of those using only doxorubicine and paclitaxel (34). Although Herceptin may be considered as a potential improvement in the treatment of cancer, its cardiac toxicity might restrict its applicability in clinical practice. Therefore, cardiac toxicity should be a major point of concern in ongoing and future trials.

ANTI-ARRHYTHMICS

The cardiodepressant adverse effects of anti-arrhythmic drugs can mainly be attributed to their negative inotropic properties. Particularly, in patients with pre-existent left ventricular impairment, anti-arrhythmics can induce or exacerbate CHF. Proarrhythmic effects that may occur during treatment with anti-arrhythmics may further contribute to the induction or worsening of CHF. The degree of negative inotropy may vary from drug to drug. Class III anti-arrhythmics, however, are usually considered as lacking these negative inotropic properties. Pathophysiologically, the negative inotropic effects of anti-arrhythmic drugs are mediated by alterations of the intracellular calcium content (35). The ultimate effect on myocardial contractility of anti-arrhythmics does not only depend on their true negative inotropic effect, but also on additional effects on the peripheral circulation, pre-existing myocardial function and their effect on the prevailing arrhythmia.

Patients with decreased left ventricular function are at increased risk of supraventricular and ventricular arrhythmias. Sudden death, attributed to the occurrence of an acute ventricular arrhythmia, is frequently encountered in patients with CHF. Not only are patients with impaired left ventricular function more prone to develop cardiac arrhythmias, but the cardiac arrhythmia itself may have a deleterious effect on left ventricular performance. Therefore, despite their potential negative inotropic effects and proarrhythmogenic effects, anti-arrhythmic drugs are frequently needed in patients with CHF (36).

Randomised double-blinded placebo-controlled trials have indicated an increased

risk of CHF for those patients assigned to treatment with an anti-arrhythmic drug (37, 38). Although most anti-arrhythmic drugs have intrinsic negative inotropic effects and have been associated with the occurrence of CHF (39-45), there seem to be differences among the various anti-arrhythmic agents (39-45). In a randomised crossover study in 21 patients with severe left ventricular impairment (mean left ventricular ejection fraction 21%), tocainide and encainide were significantly more likely to cause haemodynamic and clinical deterioration as compared with procainamide (46). Conclusions should be drawn with caution, however, as the results may have been influenced by dose and route of administration of the anti-arrhythmic drug and the evaluation of only the short-term effect of a single dose. Despite some differences among the various anti-arrhythmic agents, nearly all anti-arrhythmic drugs should be considered as potentially disadvantageous with respect to left ventricular contractility.

BETA-ADRENOCEPTOR ANTAGONISTS

CHF is a well-known adverse effect of beta-adrenoceptor antagonists (beta-blockers). The negative chronotropic and negative inotropic properties of these drugs can easily induce or exacerbate CHF in patients with a propensity to this condition. Interestingly, also the topical administration of beta-blockers in patients with glaucoma has been associated with the occurrence of CHF in some case reports (47-49). Convincing evidence of systemic effects after topical administration of beta-blockers has been provided (50-54). In a pharmaco-epidemiological study using automated databases, however, no relation between the use of topical beta-blockers and the occurrence of CHF could be revealed (55). Apart from methodological limitations, this finding only indicates that on a population level, the topical administration of beta-blockers does not appear to be associated with a significantly increased risk of hospitalisation for CHF. In susceptible individuals, however, the systemic effects of topical beta-blockers may suffice to induce or exacerbate CHF.

Interestingly, a relatively new approach to the management of CHF includes the use of beta-adrenergic antagonists. As activation of the sympathetic nervous system is considered to be an important pathophysiological mechanism in the progression of CHF, interference with the activated sympathetic nervous system appears to have beneficial effects in animal models of CHF (56, 57). Until recently, long-term trials on the effects of metoprolol and bisoprolol did not provide convincing evidence with respect to reduction of mortality in patients with CHF (58, 59), However, a clinical trial with carvedilol demonstrated a reduced risk of death and hospitalisation for cardiovascular causes (60). Carvedilol is one of the new beta-adrenergic agents with alpha-1-blocking and antioxidant properties. As a result

of these additional properties of carvedilol, it remains unclear whether its favourable effects should be attributed to its beta-adrenergic antagonistic effect or to these additional properties of this agent. Other recently published clinical trials have also reported improved survival when beta-blockers were added to optimum standard therapy (61, 62). To prevent acute beta-adrenergic antagonistic effects in patients with CHF, starting dosages should be low and can be gradually increased if tolerated.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

NSAIDs have been associated with fluid retention and the onset of CHF in several publications (63-68). CHF that is induced or exacerbated by NSAIDs is not mediated by a direct myocardial depressant effect of NSAIDs. The major mechanism of action of NSAIDs is the interference with prostaglandin biosynthesis by inhibiting the function of the enzyme cyclo-oxygenase (COX) (69). Furthermore, NSAIDs also interfere with the effects of diuretics and ACE-inhibitors (70-72). In healthy individuals, prostaglandins play a negligible role in maintaining renal blood flow and consequently, NSAIDs usually exert no significant effects on renal haemodynamics (73, 74). In patients with an impaired left ventricular function, however, prostaglandins play an important role in the maintenance of cardiovascular and renal homeostasis. Prostaglandins have a vasodilatory effect on the afferent arteriole, oppose the effects of angiotensin II on the systemic circulation, and decrease total body sodium and water. These effects of prostaglandins are considered to contribute significantly to the maintenance of compensated heart failure in patients with impaired left ventricular function. In these patients, NSAIDs may interfere with cardiovascular homeostasis and may induce or exacerbate CHF (75).

Two isoforms of COX have been identified, COX-1 and COX-2. COX-2 is predominantly involved in all stages of the inflammatory response, whereas COX-1 is mainly responsible for the synthesis of prostaglandin E_2 (PGE_2) and PGI_2 in kidney and stomach (69). To prevent the potentially adverse effects on renal function, so-called renal-sparing NSAIDs have been introduced, such as sulindac, nabumetone and meloxicam. These agents have been reported to exert less adverse effects on renal function (76-80). However, comprehensive data on the effects of these agents on renal function and cardiovascular homeostasis in patients with decreased left ventricular function are not yet available.

CALCIUM CHANNEL BLOCKING AGENTS

For many years, there has been concern about the extent to which calcium channel blocking drugs may contribute to exacerbation of CHF in patients with pre-existing left ventricular dysfunction. As calcium channel blocking drugs are widely prescribed for the treatment of angina pectoris in patients with pre-existing left ventricular impairment, this concern should be regarded as fully legitimated. Most calcium channel blockers currently approved for clinical use belong to three distinct chemical classes: the phenylalkylamines (e.g., verapamil), the dihydropyridines (e.g., nifedipine) and the benzothiazepines (e.g., diltiazem). In the SOLVD trial, calcium antagonists were prescribed to 30% of patients with CHF (81). Several pathophysiological mechanisms that contribute to the potential effects of calcium channel blocking on left ventricular function have been described (82). These mechanisms can be characterised by a negative inotropic effect on the heart, caused by impeding the transmembrane cellular calcium transport, and the activation of endogenous neurohormonal systems such as the renin-angiotensin system and the sympathetic nervous system. Marked haemodynamic and clinical deterioration can occur in patients with CHF when the negative inotropic effects of calcium channel blockers are not counterbalanced by their vasodilatory effects (83, 84). It has been postulated that the ability to improve the vascular compliance of the arterial tree may be a crucial determinant with respect to the effect of a particular calcium channel blocker on the natural course of CHF (85). This may also be an explanation for the observed effects of calcium channel blockers on the occurrence of CHF in some trials. In the Multicenter Diltiazem Postinfarction Trial (MDPIT), postinfarction patient with a baseline ejection fraction of less than 40% who were treated with diltiazem had a statistically significantly increased risk of subsequent CHF (86). The risk of CHF rose progressively with increasing impairment of left ventricular ejection fraction at baseline. Life table analysis excluded the possibility that the observed effect could be attributed to improved survival of those patients who were treated with diltiazem. However, some caution with respect to these findings is warranted, as the hypothesis was formulated after completion of the study. Furthermore, the diagnosis of CHF was not required to satisfy specific predefined criteria. Although the double-blind design of the study prevents any differential misclassification, a complex clinical syndrome such as CHF should preferably comply with well-defined diagnostic criteria. Although calcium channel blockers intrinsically depress myocardial contractility, increased left ventricular ejection fraction can be observed after the administration of dihydropyridines such as nefidipine. This can be explained by the reflex stimulation of the sympathetic nervous system that counterbalances the intrinsic negative inotropic effect of the dihydropyridines (87). However, it has been shown that chronic administration of nefidipine in patients with CHF may have deleterious effects (88). Recently, results from the PRAISE-trial (Prospective Randomized Amlodipine Survival Evaluation

Trial) indicated that amlodipine 5 to 10 mg/day in patients with CHF had no significant effect on cardiovascular events and mortality (89). Subgroup-analyses in this trial pointed out that the benefit of amlodipine was only seen in patients with non-ischaemic cardiomyopathy. In a similar trial (V-HeFT III), felodipine showed neither beneficial nor unfavourable effects as compared with placebo (90). Although the vasodilatory effects of calcium channel blockers should be regarded as beneficial for patients with CHF, the negative inotropic effect and activation of neurohormonal systems by calcium channel blockers have unfavourable effects in these patients. Amlodipine, one of the newer dihydropyridines, may be of benefit in patients with non-ischaemic cardiomyopathy.

ANAESTHETICS

During general anaesthesia, cardiovascular homeostasis will be subject to several influences. Patient characteristics, such as age and comorbidity, intravenous fluid administration, surgical procedures, and medication used during general anaesthesia may all affect cardiovascular homeostasis. Therefore, the occurrence or exacerbation of signs and symptoms of CHF in close relationship with general anaesthesia can not always easily be attributed to a specific agent used during general anaesthesia. Nevertheless, a number of agents which are used during general anaesthesia may have negative effects on myocardial contractility. The halogenated volatile anaesthetics halothane and enflurane have mild negative inotropic effects (91). Particularly, halothane has been associated with cardiodepressant effects (92). Negative inotropic effects, however, have been found to be more pronounced in patients with pre-existing left ventricular impairment (93). Cardiodepressant effects seem to be less frequent when using newer agents such as isoflurane and desflurane, although it has been suggested that these differences may apply only to young patients (94).

The intravenous barbiturate anaesthetics thiopental and methohexital may also depress myocardial contractility. In general, the haemodynamic consequences of usual plasma levels of these agents are limited (95). In patients who are more susceptible to the potential cardiodepressant effect of these agents, such as the elderly and patients with impaired left ventricular function, cautious dosages and proper fluid administration may prevent undesirable haemodynamic effects.

Propofol is an intravenous induction anaesthetic that is also used for sedation in intensive care units. Bradycardia and hypotension are the most frequently reported adverse effects. The hypotensive effect of propofol is considered to be brought about by peripheral vasodilatation, inhibition of the sympathetic nervous system,

and reduced myocardial contractility (96). Long-term sedation with propofol in children has been associated with fatal myocardial failure, whereas the use in adults appears to be safe with respect to this effect (97). It has been suggested that the relatively high dosages in children might be responsible for these deleterious effects.

IMMUNO-MODULATING DRUGS

Interferons

Three types of interferons, interferon alpha, interferon beta and interferon gamma, are used for clinical indications. Interferon alpha and -beta exert antiviral and antiproliferative activities, whereas interferon gamma acts primarily as an immunoregulatory cytokine. Interferon-alpha has been associated with cardiovascular adverse effects, such as hypotension and tachycardia during the first days of treatment in 5% to 15% of the patients (98). Cardiac adverse effects of the interferons are cardiac arrhythmias, cardiomyopathy and symptoms of ischaemic heart disease (99). There have been case reports on both reversible and irreversible severe CHF after treatment with interferon-alpha (100-102). A clear pathophysiological understanding of interferon-alpha-induced cardiomyopathy is lacking. Both impairment of myocyte metabolism as well as increased oxygen demand as a result of fever and tachycardia may be involved in the onset of CHF (100, 103). Until now, interferon-beta has not been associated with the onset of CHF (99). Cardiovascular effects attributed to treatment with interferon-gamma, such as hypotension and arrhythmia, have been observed in patients treated with high dose interferon-gamma. In most instances, these patients had a history of pre-existent cardiovascular disease. Although cardiovascular adverse effects seem to be infrequent, CHF has been reported as a possible adverse effect of interferon-gamma (104).

Interleukin-2

Interleukin-2 (IL-2), which has been approved for the treatment of metastatic renal cell carcinoma, may have serious cardiovascular adverse effects. Hypotension and tachycardia are almost invariably encountered in patients treated with IL-2. Reversible left ventricular dysfunction has also been reported in patients treated with IL-2, using echocardiography or radionuclide ventriculography (105, 106). It has been suggested that the production of cytokines may have a central role in the development of IL-2-induced cardiac dysfunction. Cytokines inhibit the accumulation of cel-

lular cyclic adenosine monophosphate, which may blunt myocardial contractility. Histological findings of eosinophilic and mixed lymphocytic-eosinophilic myocarditis attributed to IL-2 indicate a possible drug hypersensitivity syndrome (107).

ANTIDEPRESSANT DRUGS

Antidepressant drugs are usually divided into three main categories: classical antidepressants (mainly consisting of the tricyclic compounds), second generation antidepressants (including the selective serotonine re-uptake inhibitors), and monoamine-oxidase inhibitors. The cardiovascular effects of the tricyclic antidepressants (TCAs) have always been a source of concern, in particular when the prescription of a TCA is indicated in patients with cardiovascular comorbidity. Sinus tachycardia occurs in the majority of patients treated with TCAs and approximately 20% of the patients have postural hypotension (108). TCA-induced postural hypotension is attributed to the combined effect of its peripheral anti-adrenergic action, its myocardial depressant effect and its alpha-adrenergic blocking effect in the central nervous system. Compared with other TCAs, nortriptyline is only rarely associated with the occurrence of orthostatic hypotension (109). TCAs also affect atrioventricular conduction by prolongation of the conduction time in the His bundle and the bundle branches, and prolongation of the duration of both the QRS-interval and the corrected QT-interval (110). Second - and third-degree atrioventricular block may occur and may lead to asystole and sudden death. TCAs are highly concentrated in myocardial tissue, which partly explains their interference with heart rate, cardiac rhythm, and myocardial contractility. The effects of TCAs on myocardial function are mediated by several mechanisms, such as their anticholinergic and quinidine-like action, interference with the re-uptake of adrenergic amines, alternations of membrane permeability and direct myocardial depression (42). Several studies have been performed on the effects of TCAs on left ventricular function. There have been case reports of CHF attributed to the use of TCAs (111, 112). Experiments in animals indicate that TCAs may have a negative inotropic effect (113), particularly in higher doses, although the findings from these experimental animal studies are difficult to extrapolate to human subjects. Results from non-invasive studies in which systolic time interval measurements are used as a parameter of left ventricular function suggest that TCAs impair cardiac function (114, 115). However, the systolic time interval depends on cardiac conduction, which may have been influenced by TCAs. Therefore, these indirect measurements of left ventricular function do not provide convincing evidence of a direct TCA-induced cardiodepressant effect at the level of myocardial cells. More recent studies in which left ventricular contractility was assessed by radionuclide ventriculography failed to demontrate TCA-induced left ventricular impairment. In

20 non-depressed patients with moderate to severe baseline ventricular impairment who were treated with imipramine (mean daily dose 210 mg) or nortriptyline (mean daily dose 100 mg) for ventricular premature depolarisations, no significant changes in mean ejection fraction could be observed (116). Studies of Glassman et al. and Veith et al. also indicate that in patients with decreased baseline ejection fraction TCAs have no significant effects on left ventricular ejection fraction (117, 118). These studies, however, are characterised by a small sample size, selection of patients and a short period of follow-up. Despite these limitations, most studies indicate that the effects of TCAs on left ventricular function seem to have no major consequences for their applicability in everyday clinical practice. Even in patients with pre-existent left ventricular impairment, there is no convincing evidence indicating that TCAs are likely to have deleterious effects on left ventricular function. However, as CHF is frequently accompanied by disturbances of cardiac conduction or low arterial blood pressure, and long-term information on the effect on ventricular performance of TCAs in heart failure patients is scarce, clinicians should be aware of possible adverse cardiovascular effects when prescribing TCAs to patients with severe CHF.

Selective serotonin reuptake inhibitors (SSRI) have a very low rate of adverse cardiovascular effects. It has been estimated that the incidence of adverse cardiovascular events is less than 0,0003% (119). This estimate, however, is based on reported cases of cardiovascular events to pharmaceutical companies. Estimates of the incidence of adverse reactions that are based on the number of reported cases should be regarded with caution, but the overall impression is that SSRI have a very low incidence of adverse cardiovascular effects. Probably the most important effect of SSRI in patients with cardiovascular comorbidity is their potential to interact with drugs which these patients are taking for cardiac arrhythmias, CHF, or hypertension. The interaction between SSRI and several drugs is mediated by the inhibition of cytochrome P450 enzymes. The SSRI-induced inhibition of cytochrome P450 affects the metabolism of several classes of drugs, such as antiarrhythmics, beta-blockers, antihistamines, and calcium channel blockers. It has been suggested that this might have been the cause of some unexpected deaths in patients who had recently begun fluoxetine therapy (120). As SSRI are a relatively new class of drugs, no studies have been performed on their effects on ventricular function in patients with CHF. Currently available data on the cardiac effects of SSRI suggest that these agents do not have direct effects on myocardial function, but attention should be paid to potential interactions with several classes of drugs (119, 121).

Table I
Drugs associated with the onset or worsening of congestive heart failure.

Agents associated with the induction of CHF
- anthracyclines
- paclitaxel
- mitoxantrone
- interferons
- interleukin-2

Agents associated with the precipitation of CHF in patients with pre-existing ventricular dysfunction
- calcium channel blockers
- NSAIDs
- anti-arrhythmics
- beta-receptor antagonists
- anaesthetics
- steroidal hormones with mineralocorticoid effects
- drugs which may increase afterload:
  - sympathicomimetic drugs; e.g. adrenaline, dobutamine, dopamine
  - cyclosporine (122)
  - ketoconazol (123)

Agents which are only incidentically associated with the onset of CHF in case reports
- tricyclic antidepressants
- 5-fluouracil
- cytarabine
- polyethylene glycol-electrolyte lavage solution (124)
- aminocaproic acid (125)
- antidigoxine antibody fragments (126)
- sodium-containing antacids (42)
- amantadine (127)
- bromocriptine (42)
- foscarnet (128)
- megestrol (129)
- mannitol (130)
- hydralazine (42)
- edetic acid (42)
- deferiprone (131)
- dapsone (132)
- carbamazepine (42)
- cibenzoline (133)
- prostaglandin E_2 (134)
- methyl-sergide (42)
- ifosfamide (135)

MISCELLANEOUS AGENTS

Apart from the categories of drugs discussed in the previous sections, various other agents have been associated with the occurrence or worsening of CHF (see table I). Although the pathophysiological mechanism is rather straightforward with respect to some agents, for example, mineralocorticoid effects of steroidal hormones, in other instances their causal role remains more obscure. In particular, when a pathophysiological mechanism appears to be absent, the possibility of coincidence can hardly be ruled out. Nevertheless, detailed documentation of all clinical features of patients with suspected drug-induced CHF, even in the absence of a straightforward pathophysiological explanation, may finally contribute to an objective risk-benefit profile of the agents involved.

CONCLUSION

Several categories of drugs may potentially induce or exacerbate CHF. Pathophysiologically, drugs that increase cardiac preload, cardiac afterload, or have negative inotropic properties may be able to cause this adverse reaction. In table I, a distinction has been made between agents which are commonly regarded as being able to induce CHF in patients with previously normal ventricular function and agents which may precipitate CHF in patients with previously compensated CHF. Obviously, agents which may induce CHF can also precipitate CHF. Agents reported to induce CHF only very rarely are mentioned in this table as a third category. Particularly patients with pre-existing left ventricular dysfunction who already have the propensity to develop CHF appear to be at risk for drug-induced heart failure. Although the cardiotoxic effects of drugs such as the anthracyclines and cyclophosphamide are obvious and well-known, this is not always the case in all categories of drugs we discussed. Moreover, drug-induced cardiac rhythm disorders may also induce signs and symptoms of CHF in susceptible patients. Therefore, detailed documentation of the medication involved together with all clinical features of patients suspected from drug-induced CHF may contribute substantially to a reliable assessment of both the pathophysiological mechanism and the likelihood of causality. This may contribute to an appropriate risk-benefit profile of the drugs involved.

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2.3

Precipitating factors in patients hospitalised for congestive heart failure

ABSTRACT

Objective: Knowledge on potential precipitating factors may improve care and treatment of patients with CHF. The aim of this study was to determine the presence of precipitating factors in patients hospitalised for congestive heart failure (CHF), particularly with respect to medication compliance.

Methods and results: We analysed 318 hospital discharge letters of participants of the Rotterdam Study admitted to hospital for CHF. Medication compliance was assessed in patients with more than one hospitalisation by comparing dispensed medication after the first hospitalisation with the dispensed medication in the period preceding a readmission for CHF.

Potential precipitating factors were described in 60% of the first hospitalisations for CHF as compared with 43% of the readmissions. Among the most frequently encountered precipitating factors were atrial fibrillation/flutter, myocardial infarction or ischaemia, and pulmonary disease. Lack of medication compliance was notified in only 3% of the discharge letters of patients rehospitalised for CHF. Based on dispensed medication according to computerised pharmacy records, however, non-compliance to either digoxin, diuretics or ACE-inhibitors was observed in 46% of rehospitalised patients.

Conclusion: Little attention is paid in hospital discharge letters to potentially precipitating factors for CHF. In particular, lack of medication compliance appeared to be significantly more common as may be expected on the basis of the information provided by hospital discharge letters. As lack of medication compliance should be considered as a major impediment of optimal CHF treatment, information on this aspect should be notified in hospital discharge letters.

INTRODUCTION

Congestive heart failure (CHF) is a major health problem in western countries. Both aging of the population and improved survival in patients with cardiovascular disease contribute to the continuous increase in prevalence and incidence of CHF. This trend is also reflected in the hospitalisation rates for CHF. In 1993, CHF was the primary diagnosis in more than 875,000 hospital admissions in the United States, a number which is 5 times greater than it was 25 years earlier (1). Studies from Scotland (2), Spain (3) and the Netherlands (4) indicate a similar trend towards increasing numbers of hospital admissions for CHF over the last two decades in Europe.

Although many studies have been performed on etiology and prognosis of CHF, relatively little is known about factors which may precipitate hospitalisations in patients with congestive heart failure (5). However, knowledge on possible precipitating factors for hospitalisations of CHF may contribute to optimal guidance and treatment of these patients. This information may particularly be important for the general practitioner who has a critical role in the day-to-day treatment of patients with CHF. Moreover, the general practitioner will usually be the first physician who will be contacted when a patient experiences symptoms which may indicate relapsing CHF. Hospital discharge letters are the main source of information to GPs on hospital admissions of their patients. In addition, hospital discharge letters provide important information when patients are readmitted to hospital or attend the outpatient clinic. Therefore, all relevant clinical information on hospital admissions should be included in the hospital discharge letters.

The aim of this study was to determine the presence of precipitating factors in patients hospitalised for CHF. Therefore, we evaluated the information on precipitating factors for CHF in the discharge letters of participants of the Rotterdam Study hospitalised with a diagnosis of CHF. In addition, to evaluate the role of medication compliance as a potential precipitating factor in more detail and independently from the hospital discharge data, we analysed dispensed medication prescriptions in patients with at least one readmission for CHF during the study period.

SUBJECTS AND METHODS

The Rotterdam Study is a population-based prospective cohort study in 7,983 inhabitants aged 55 years or older living in the suburb Ommoord in Rotterdam, The Netherlands. Main areas of interest in the Rotterdam Study are cardiovascu-

lar, neurological, ophthalmological and locomotor diseases in the elderly (6). The first cross-sectional survey started in 1990 and was completed in 1993. Apart from cross-sectional surveys which were carried out periodically, follow-up information was gathered on all cardiovascular, neurological, opthalmological and locomotor diseases which have occurred since the start of the study. All available information on these diseases, such as hospital discharge letters and notes from general practitioners, were copied from the records of the general practitioner. Information on the events of interest were assessed independently by two research physicians with respect to the certainty of the diagnosis, rated as possible, probable or definite. A definite diagnosis of CHF was assumed if the diagnosis had been made by a medical specialist. If the two research physicians disagreed on the certainty of diagnosis, they re-evaluated these events during a consensus meeting. When disagreement on the certainty of diagnosis remained, a final decision was made by a cardiologist. In addition, the cardiologist re-evaluated all potential cases of CHF on which the two research physicians agreed during the first evaluation.

We analysed 318 hospital discharge letters of participants of the Rotterdam Study admitted to hospital with a definite diagnosis of CHF since the start of the Rotterdam Study in 1990 until 1997. A total of 249 hospital discharge letters pertained to a first hospitalisation for CHF within the study period, whereas 69 discharge letters concerned readmissions for CHF. Hospital discharge letters were examined with regard to the presence of potential precipitating factors for the onset of CHF.

All medication prescriptions dispensed to participants of the Rotterdam Study by the three automated pharmacies in the suburb of Ommoord are stored in a database as from January 1st 1991. To assess medication compliance independently from the hospital discharge letters, we compared in patients with more than one hospitalisation during the study period the dispensed medication in a 3-month period after the first hospitalisation for CHF with the dispensed medication in the period preceding the second hospitalisation for relapsing CHF. The analysis of dispensed prescriptions was restricted to digoxin, angiotensin converting enzym-inhibitors (ACE-inhibitors) and diuretics, and the time interval between first and second hospitalisation had to be at least 90 days (n=35). Patients were considered to be non-compliant to these drugs if they were dispensed at least once within 3-months after discharge from hospital and if the calculated legend duration of the last prescription did not overlap the date of the second hospitalisation for CHF. A similar analysis was carried out in patients with 3 or more hospital admissions for CHF (n=17).

RESULTS

Information on hospital admissions for CHF was obtained from 318 hospital discharge letters on 249 participants of the Rotterdam Study. The general characteristics of the study population are given in table I. Factors which may have precipitated the onset of CHF were reported in 60% of the hospital discharge letters of patients with a first hospitalisation for CHF (table II). Precipitating factors were described in 43% of the hospital discharge letters which pertained to readmissions for CHF (table III). In the remaining hospital discharge letters, no information on any potential precipitating factor could be identified. Atrial fibrillation or atrial flutter were supposed to precipitate CHF in 20% of the first hospitalisations. Acute myocardial infarction was diagnosed in 12% of the patients first hospitalised for CHF. Myocardial ischaemia, either symptomatic (angina pectoris) or asymptomatic (silent ischaemia), may have precipitated CHF in 11% of the first hospitalisations. Respiratory tract disease, in particular exacerbations of chronic obstructive pulmonary disease and lower respiratory tract infections, could be identified in 10% of the first hospitalisations. Anemia and hypertension were recorded as potential precipitating factors in respectively 4% and 2% of the first hospitalisations for CHF. Some rarer precipitating factors such as a total atrioventricular block accounted for the remaining number of precipitating factors.

Table I
General characteristics of the study population (N=249)

Age (years)	79.1	SD: 8.8
Gender:		
females	126	(51%)
males	123	(49%)
No. of hospitalisations for CHF:		
1st	249	(78%)
2nd	46	(15%)
3rd	14	(4%)
4th	6	(2%)
5th	2	(0.6%)
6th	1	(0.4%)
History of:		
myocardial infarction	72	(29%)
diabetes mellitus	38	(15%)
angina pectoris	41	(17%)
hypertension	57	(23%)
chronic obstructive pulmonary disease	47	(19%)

Precipitating factors for relapsing CHF in patients readmitted to hospital are given in table III. Myocardial ischaemia appeared to be the most frequently encountered precipitating factor for relapsing CHF. Atrial fibrillation or atrial flutter were identified as a precipitating factor in 6% of the rehospitalisations for relapsing CHF. Lack

Table II
Precipitating factors identified in hospital discharge letters of 249 first hospitalisations for CHF.

No precipitating factor identified	99	(39.8 %)
Atrial fibrillation/flutter	50	(20.2 %)
Myocardial infarction	29	(11.6 %)
Angina pectoris	24	(9.6 %)
Respiratory tract disease	24	(9.6 %)
Anaemia	9	(3.6 %)
Silent myocardial ischaemia	4	(1.6 %)
Hypertension	4	(1.6 %)
Atrioventricular blocks	3	(1.2 %)
Other precipitating factors *-chorda-rupture* *-tamponade* *-intravenous fluid administration*	3	(1.2 %)

Table III
Precipitating factors identified in 69 hospital discharge letters of patients with at least one previous hospital admission for CHF.

No precipitating factor identified	39	(56.5 %)
Atrial fibrillation/flutter	4	(5.8 %)
Myocardial infarction	4	(5.8 %)
Angina pectoris	9	(13.0 %)
Respiratory tract disease	2	(2.9 %)
Anaemia	4	(5.8 %)
Silent myocardial ischaemia	3	(4.3 %)
Hypertension	1	(1.4 %)
Atrioventricular blocks	1	(1.4 %)
Lack of medication compliance	2	(2.9 %)

Table IV
Medication dispensed in a 3-month period after a first hospitalisation for CHF compared with medication use (according to the calculated legend duration) at the time of second hospital admission in 35 patients with at least two hospitalisations*.

	Dispensed drugs in a 3-months period after a first hospitalisation for CHF	Patients not using the drug according to the legend duration at the time of the second hospitalisation	
ACE-inhibitors	27	10	(37%)
Digoxin	22	6	(27%)
Diuretics	33	7	(21%)

* interval between both hospitalisations ≥ 90 days

of medication compliance was notified in only 2 hospital discharge letters concerning a second hospitalisation for CHF (3%).

Table IV presents the dispensed medication, based on computerised pharmacy records, in a 3-months period after the first hospitalisation compared to the dispensed drugs of which the calculated legend duration overlapped the date of the second hospitalisation for CHF. According to the calculated legend duration, 37% of the patients who were prescribed an ACE-inhibitor after the first hospitalisation were not compliant to this drug at the time of the second hospitalisation for CHF. For digoxin and diuretics, these percentages were 27% and 21%, respectively. A total of 15 out of 35 patients (43%) were non-compliant on the basis of the legend duration to at least one of these three drugs. Based on a similar approach, non-compliance could be demonstrated prior to 9 out of 17 hospital readmissions in patients with more than two hospitalisations for CHF. Hence, non-compliance according to our definition was observed in 24 out of 52 hospitalisations for CHF (46%; 95% CI: 32% - 60%).

During 74% (n=234) of the hospital admissions, patients with CHF were treated by cardiologists, whereas in the remaining 26% (n=84) of the hospitalisations for CHF, patients were treated by other medical specialists, mainly internists. Over the years 1992 until 1996, the percentage of patients hospitalised for CHF who were primarily treated by a cardiologist remained stable at approximately 75%. Precipitating factors were described in 59% of the hospital discharge letters of patients treated by cardiologists compared to 49% of the hospital discharge letters of patients treated by other specialists (p=0.10).

Death attributed to congestive heart failure occurred in 13% of all hospitalisations (n=42).

DISCUSSION

From just over a half (60%) of the hospital discharge letters of patients with a first hospitalisation for CHF, information could be obtained on factors which may have precipitated the onset of CHF. In hospital discharge letters of patients readmitted to hospital due to relapsing CHF, precipitating factors could be identified in 43% of the hospital discharge letters. Non-compliance to the prescribed drug regimen was only rarely noted in the hospital discharge letters as a potential precipitating factor. Analysis of dispensed medication prescriptions, however, suggested substantial non-compliance to medication in patients readmitted to hospital for relapsing CHF.

Although the evaluation and prevention of factors which may precipitate CHF are important objectives in the care and management of CHF patients, few studies have addressed this issue (7, 8). Ghali et al. examined 101 hospital readmissions for CHF in a large public hospital, and demonstrated that precipitating factors could be identified in 93% of these patients. Non-compliance to the medical regimen (diet, medication, or both) was by far the most commonly identified responsible factor for readmission (64%). Opasich et al. followed patients referred to a specialised heart failure unit for assessment of indication for cardiac transplantation. During a mean follow-up period of 310 days, 328 cases of nonfatal decompensation were recorded. Precipitating factors could be identified in 91% of the cases. Most frequently encountered were cardiac arrhythmias (24%) and infections (23%), particularly pulmonary infections, whereas poor compliance was recorded in 15% of the cases.

Both the study of Ghali et al. and the study of Opasich et al. identified precipitating factors in over 90% of the patients with relapsing congestive heart failure, whereas in our study precipitating factors could be identified in only 43% of the hospitalisations for CHF. This may be due to a number of differences between our study and these two previous studies.

First, as both the study of Ghali et al. and the study of Opasich et al. were carried out prospectively and especially aimed at revealing precipitating factors for relapsing CHF, this may have contributed substantially to the disclosure of a very high percentage of precipitating factors as compared to our study, in which information on precipitating factors was obtained from hospital discharge letters which

were already available. Second, in contrast to the studies of Ghali et al. and Opasich et al., which evaluated only patients with a relapsing CHF, we included both patients with a first hospitalisation as well as patients with readmissions to hospital because of CHF. It may be conceivable that precipitating factors for CHF are more easily identified in patients with pre-existing CHF. However, in our study, precipitating factors could be found in only 43% of the hospital discharge letters of patients with at least one previous hospital admission for CHF. Third, a major point of difference between our study and the studies of Ghali et al. and Opasich et al. is the source of information on which the results of the study are based. We deliberately confined our information on precipitating factors to the hospital discharge letters which are added to the hospital medical record and sent to the general practitioner (GP). Hospital discharge letters provide the GP with all relevant information on the hospital admission. In addition, they are an important source of information in case of subsequent hospital admissions. The presence of precipitating factors which preceded the onset of CHF should be regarded as particularly relevant information. For instance, lack of medication compliance or preceding myocardial ischaemia may provide important clues to improve the management of patients with CHF. Therefore, such information on precipitating factors should be recorded in the hospital discharge letter. However, this information may have been notified in the medical record without mentioning it in the hospital discharge letter.

Poor medication compliance was regarded as a precipitating factor for CHF in 43% of the patients in the study of Ghali et al. and in 15% of the patients in the study of Opasich and al. Poor medication compliance will be encountered predominantly in patients with a previous hospitalisation for CHF. For this reason, we analysed patients with at least one previous hospital admission for CHF within the study period separately (table III). Poor medication compliance was specifically mentioned in the hospital discharge letters of only 3% of the patients readmitted to hospital because of a relapse of CHF. However, a considerable number of patients (46%) did not use the heart failure medication which had been prescribed following a preceding hospitalisation for CHF, according to the calculated legend duration at the time of rehospitalisation for CHF. ACE-inhibitors appeared not to be used in 37% of the patients who had been prescribed an ACE-inhibitor after their first hospitalisation. Comparable findings, although less pronounced, were observed with respect to the use of digoxin and diuretics. As drugs may have been discontinued by the physician because of adverse effects or an altered therapeutical regimen, the calculated legend duration has some limitations in exactly estimating medication compliance. On the other hand, filled prescriptions do not necessarily imply medication compliance. It has been demonstrated that among participants of the Rotterdam Study, there is a very high agreement between pharmacy records and actual use of cardiovascular drugs (9). Therefore, our findings

strongly suggest that lack of medication compliance seems to be much more prevalent as suggested on the basis of information in hospital discharge letters. In addition, the abovementioned studies of Ghali et al. and Opaschi et al. indicate that lack of medication compliance should be regarded as a relatively common problem in the treatment of chronic diseases such as CHF (10). The findings in our study, however, demonstrate that poor medication compliance is only rarely recorded in the hospital discharge letters. In view of the estimated frequency of poor medication compliance in the literature (7, 8, 10, 11) and the estimated medication compliance on the basis of the calculated legend duration of prescribed heart failure drugs, this may indicate that in our study population poor medication compliance is either rarely noted as a potential precipitating factor at the time of hospital admission or that poor medication compliance is rarely recorded in the hospital discharge letter despite its identification as a precipitating factor at the time of hospital admission. If poor medication compliance is rarely recognized at the time of hospital admission, it may be interesting to know whether physicians ask explicitely for medication compliance when patients are readmitted to hospital for CHF. Although this should be regarded as an essential part of the anamnesis of each hospital readmission for CHF, it remains unclear whether all patients are asked for medication compliance routinely. If poor medication compliance is only recorded in the medical records without any notification in the hospital discharge letter, the GP may not be able to pay attention to this aspect when the patient has been discharged from hospital.

Over the last few years, some studies have been published which aimed at improvement of care in patients with CHF (12-15). Main objectives of these studies were to reduce the number of hospital readmissions and to improve quality of life. Most of these studies were characterised by a relatively intensive counselling programme for patients discharged with CHF. Although the results of these studies are not consistent, there is a general impression that intensive counselling of patients with CHF may contribute to the prevention of hospital readmissions for relapsing CHF and may improve their quality of life. However, the opportunity to participate in such programmes can be offered to only a minority of patients. Under everyday circumstances, the GP has an important role in the counselling of CHF patients. Therefore, it is of professional importance for the GP to receive all relevant information, including information on precipitating factors, concerning patients discharged from hospital with a diagnosis of CHF. Such information may help the GP to draw his attention to patient's characteristics (e.g. lack of medication compliance, atrial fibrillation, myocardial ischaemia) which may have an unfavorable effect on the clinical course of CHF.

The presence of potential precipitating factors does not necessarily imply a causal relationship with the onset or worsening of CHF. In particular, the high percentage

(≥90%) of precipitating factors identified in previous studies might give rise to the impression that many hospital admissions for CHF may be preventable. However, the absence of control groups in our study and the studies of Ghali et al. and Opasich et al. prevents a meaningful estimation of the relative risk for the occurrence of CHF associated with the presence of these precipitating factors. Nevertheless, convincing evidence for a significant beneficial effect of pharmacotherapy on the prognosis of CHF has been provided by several randomised clinical trials (16-18). Hence, especially lack of medication compliance has to be regarded as a major impediment to optimal treatment of CHF.

In conclusion, the findings in our study suggest that information on precipitating factors for CHF could be obtained from a small majority (60%) of the hospital discharge letters of first hospitalisations for CHF and from only a minority (43%) of the patients hospitalised for relapsing CHF. In contrast to the results of previous studies and to the estimated medication compliance on the basis of computerised pharmacy records, lack of medication compliance was identified in only 3% of the patients with a previous hospitalisation for CHF. These findings strongly suggest that routine hospital discharge letters pay too little attention to undercompliance of heart failure medication.

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Chapter 3

The role of non-steroidal anti-inflammatory drugs in heart failure

3.1

Adverse cardiovascular effects of non-steroidal anti-inflammatory drugs in patients with congestive heart failure

ABSTRACT

Congestive heart failure (CHF) is a complex clinical syndrome, especially in the elderly, which results from cardiac dysfunction. Epidemiological studies have shown a gradual increase in age-adjusted hospitalization rates for CHF and overall population prevalence of CHF during the last two decades in western countries. The health-care costs associated with CHF are considerable and are likely to increase in the near future. Hence, identification of risk factors which could induce or exacerbate CHF is of major importance.

Non-steroidal antiinflammatory drugs (NSAID) are frequently prescribed in elderly patients for several rheumatological- and non-rheumatological indications. Numerous adverse reactions, mainly related to the gastro-intestinal tract and kidney function, have been described. Some case-reports have suggested a causal relation between the use of NSAID and the onset of CHF. The pathophysiology of CHF and the pharmacological properties of NSAID support this hypothesis. In particular, the inhibition of prostaglandin-synthesis may adversely affect cardiovascular homeostasis in patients with a propensity to develop congestive heart failure.

Notwithstanding the adverse effects, however, the prescription of NSAID in elderly patients is often desirable and justifiable. Therefore, further pharmacoepidemiological research is needed to quantify the risk for CHF attributable to the use of NSAID and to identify patients who are particularly susceptible to their adverse cardiovascular effects. In these patients, it may be advisable to avoid the use of NSAID.

INTRODUCTION

Over the years, several reports have been published in which the onset of congestive heart failure (CHF) was attributed to the use of non-steroidal anti-inflammatory drugs (NSAID) (1-3). Recently, a study with a record linkage data base showed that concomitant use of NSAID and diuretics doubled the risk for hospitalization because of congestive heart failure (4). In this review, we will discuss the putative relation between the use of non-steroidal anti-inflammatory drugs and congestive heart failure. First, we will provide background information on the definition, epidemiology and prognosis of congestive heart failure. We will also summarize current views on the pathophysiology of congestive heart failure. Second, we will discuss aspects of NSAID-utilization and pharmacology, paying special attention to their effects on prostaglandin-synthesis and renal function, since both provide important information on how NSAID may induce or exacerbate congestive heart failure.

CONGESTIVE HEART FAILURE

Definition and classification

Although many definitions of congestive heart failure exist, none is entirely satisfactory. Recently, the Task Force on Heart Failure of the European Society of Cardiology proposed that patients should have the following: symptoms of CHF, typically breathlessness or fatigue, either at rest or during exertion, or ankle swelling and objective evidence of major cardiac dysfunction at rest (5). Signs and symptoms of CHF may be difficult to interpret, especially among elderly and obese patients. To measure the severity of CHF, the classification of the New York Heart Association (NYHA-classification) is in widespread use. The NYHA-classification is based on anamnestic criteria only. But, although often used, the association between NYHA-classification and the severity of cardiac dysfunction is poor. Therefore, in the Framingham study and the Boston score, more detailed diagnostic criteria based on history, physical examination and chest X-ray were formulated (6, 7).

No gold standard diagnostic procedure is currently available in the detection of CHF. Echocardiography is now the key investigation in patients suspected of CHF as it gives direct information on ventricular function. Echocardiography provides also information about valve- and pericardial disease.

Epidemiology

Although epidemiological data concerning CHF are still rather sparse, there has been a gradually increasing interest during the last decade in the epidemiological background of CHF (8). Findings in the Framingham Heart Study showed that the prevalence of CHF roughly doubled with each decade in persons aged 50-89 years from about 1% prevalence in persons aged 50-59 years to 10% in persons aged 80-89 years (9). The incidence of CHF showed a similar pattern, from about 0,2% in persons 45-54 years of age, to 4,0% in men 85-94 years of age. The incidence in men exceeded that in women in all patient-groups aged under 75 years. Above the age of 75 years, the incidence in women showed a steep increase which eventually exceeded that in men (9).

Several sources indicate an important age-adjusted increase in hospitalization rates for CHF in western countries over the last twenty years (10, 11). In 1991, more than two million patients were discharged from hospital in the United States with a primary or secondary diagnosis of CHF (12). Total healthcare expenditure in 1991 for this group of patients was estimated at nearly 40 billion US-dollars. In the Netherlands, annual hospital admissions for CHF increased from 14.441 in 1980 to 24.368 in 1992 (11). Age-adjusted hospitalization rates showed an increase in the period 1980-1992 of 43% for men and 30% for women. Re-admissions due to recurrent CHF occur frequently, especially in elderly patients. Re-admission rates up to 25% within 6 months after discharge have been reported in patients over 65 years of age(13, 14). A recently published simulation model predicted that in the near future there will be a further shift from acute to more chronic cardiovascular disease, including CHF (15).

Despite advances in the treatment of various risk factors for CHF, the overall population prevalence of CHF increases (10). As shown in the Framingham study, hypertension was the major etiologic factor in the development of CHF, followed by coronary-artery disease and rheumatic heart disease (7). More recent data, both from the Framingham Study as well as from other studies, suggest that the predominant role of hypertension in the development of CHF may have shifted towards ischemic heart disease (16-18).

To explain the increase in the overall population prevalence of CHF, it seems reasonable to concentrate on medical and demographical developments. First of all, with increasing average age of the population, the risk of the ageing individual to develop overt cardiovascular disease, including CHF will rise. Second, a decrease in the fatality rate of acute myocardial infarction will result in more patients who are at an increased risk for developing CHF. Recent trends in acute coronary heart disease indicate that survival among patients hospitalized for acute myo-

cardial infarction has increased substantially during 1985-1990 (19). Furthermore, improved survival among patients with angina pectoris and hypertension as a result of modern medical treatment may have contributed to an increase in the prevalence of CHF, especially in those 65 years of age and older (20).

In conclusion, epidemiological data suggest that CHF will be an increasing cause of morbidity among the elderly. This also has important socio-economic implications, since growing morbidity gives rise to increasing health expenditures. The bulk of costs can be attributed to hospitalizations for CHF (first admissions as well as readmissions). Therefore, further research on primary and secondary prevention is of major importance. A further evaluation of the role of NSAID in CHF may contribute to this, as these drugs are often used in the elderly.

Prognosis

The prognosis of CHF remains quite poor. Recent analyses from the Framingham Heart Study showed no appreciable change in median survival after the onset of CHF from 1948 to 1988 (17). In the Framingham Heart Study, the median survival after the onset of CHF in an unselected population was 1,7 years in men and 3,2 years in women. The one- and five-year survival rates were 57% and 25% in men and 64% and 38% in women respectively. No significant improvement in median survival was found during the 40 year-period under study. However, the mean age at diagnosis of CHF increased from 57,3 years in the 1950s to 76,4 years in the 1980s. After adjusting for age and aetiology of CHF, survival after the development of CHF remains better in women than men. Advancing age was also a predictor of reduced survival in patients with CHF. When patients who died within three months after the diagnosis of CHF were excluded from the analysis, the results closely resembled those from the placebo-group in heart failure intervention trials such as the V-HeFT study, in which inclusion and exclusion criteria led to selected populations.

Several cohort studies of prognostic factors in patients with CHF have been performed (table I). Reduced left ventricular ejection fraction (21), diminished peak oxygen consumption during exercise (22), coronary artery disease (23), low plasma sodium level and NYHA-classification (24) are among the most important predictors of an unfavourable prognosis.

Pathophysiological aspects

It is now well-recognised that the clinical syndrome of CHF cannot always be

explained simply by reduction of left ventricular ejection fraction. Besides systolic dysfunction, characterised by impaired left ventricular contractility, the importance of diastolic heart failure is now widely accepted (25-27). These patients present with the syndrome of CHF and have normal, or near normal, resting systolic function. Fundamental to the diagnosis of isolated diastolic heart failure is the demonstration of a raised filling pressure, despite normal ventricular dimensions and systolic contractility (27). Impairment of diastolic ventricular filling may have various mechanisms (28). Diastolic dysfunction may result from impaired active relaxation of the ventricular wall and reduced compliance. Furthermore, mechanical resistance to ventricular filling, such as in constrictive pericarditis and mitral stenosis, may induce diastolic dysfunction. Hence, the pathophysiology of CHF cannot be explained in terms of impaired left ventricular contractility only. Although most investigations on hemodynamic changes in patients with CHF have concerned systolic dysfunction, parts of what we know may also apply to patients with diastolic dysfunction (29). However, we will focus our discussion on the pathophysiology primarily on patients with the syndrome of CHF due to systolic dysfunction.

In response to an initial injury to the heart, resulting in a loss of functioning myocardial cells, hemodynamic and neurohumoral mechanisms are activated to compensate for negative circulatory consequences (30). First, a decrease in the ability of the left ventricle to empty during systole increases the tension on non-injured parts of the heart during diastole. This increase in diastolic wall tension (preload) will enhance ventricular contraction, following the Frank-Starling curve. Second, a decreased ability of the left ventricle to eject blood in the aorta activates the sympathetic nervous system. Stimulation of beta-adrenergic receptors in the non-injured myocardium will result in increased force and frequency of contraction. These two mechanisms also have potential risks. Ventricular dilatation and sustained sympathetic activation will lead to a striking increase in internal wall stress during systole. This distorts ventricular architecture and accelerates energy expenditure. In response to this potential adverse effect, synthesis of myofibrillar proteins is stimulated which leads to an increase in wall thickness and a subsequent reduction of ventricular wall stress and dilatation (30). In an attempt to achieve balance between sympathetic activation and inhibition, increased diastolic wall stress in the atria suppresses the activity of the sympathetic nervous system. Atrial baroreceptors are stimulated and inhibit sympathetic outflow from the vasomotor centre in the central nervous system (31). Atrial stretch also leads to the release of atrial natriuretic peptide, which inhibits the release of noradrenaline and its actions on peripheral blood vessels (32). It also exerts vasodilator and natriuretic effects. These so-called stress-reducing mechanisms are essential in limiting the potential adverse consequences of sustained sympathetic activation and ventricular dilatation.

Table I
Cohort studies on prognostic factors in congestive heart failure

Ref.	Year publ.	First author	Size	Months of follow-up	Endpoints	Risk factors / Prognostic factors
1.	1983	Franciosa(103)	182	12	mortality	High LV filling pressure, CAD
2.	1994	Madsen(24)	190	24.5	mortality	LVEF, creatinine > 121 µmol, sodium ≤ 137 mmol, CAD, urea>7.6 mmol
3.	1992	Parameshwar(21)	127	14.6	mortality	plasma sodium concentration, LVEF, transplantation, peak oxygen consumption
4.	1993	Ho(17)	652	47	mortality	male, age, diabetes, cause of CHF, LVH,
5.	1993	Carson(104)	206	30	mortality	atrial fibrillation , hospitalization
6.	1993	Cohn(22)	1325	60	mortality	LVEF, CTR, peak oxygen consumption, ventricular arrythmias, plasma norepinephrine
7.	1993	Middlekauff(105)	491	12	mortality	syncope
8.	1993	Anguita(106)	130	15	mortality	intravenous inotropic requirements, maximal tolerated captopril dose, decreased systolic blood-pressure.
9.	1995	Stevenson(107)	737	12	mortality	
10.	1995	Roul(108)	50	21	mortality	exercise peak oxygen consumption, invasive haemodynamic data
11.	1989	Gradman(109)	295	16	mortality	LVEF, ventricular tachycardia
12.	1987	Likoff(110)	201	11	mortality	LEVF, maximal oxygen uptake, ischemic cardiomyopathy,
13.	1989	Romeo(111)	104	45	mortality	ventricular arrhythmia
14.	1990	Kelly(23)	133	29	mortality	coronary artery disease, syst. blood pressure < 120 mm Hg, congestion on chest-X-ray, age over 64 years

15.	1988	Juillière(112)	111	56	mortality	LVEF
16.	1988	Hofmann(113)	110	53	mortality	LVEF, cardiac index < 2.5 L/min/m^2, ventricular arrhythmia, atrial fibrillation
17.	1991	Middlekauff(114)	390	8	mortality	atrial fibrillation

LV = Left Ventricle; LVEF = Left Ventricular Ejection Fraction; CAD = Coronary Artery Disease; CTR = Cardiothoracic Ratio; Major event = heart failure, severe ventricular arrhythmia

In established CHF, systemic perfusion is maintained by peripheral vasoconstriction and sodium retention. Whereas the sympathetic nervous system is activated early in the disease process, the renin-angiotensin system is usually triggered only once symptoms develop (30). Besides circulating vaso-active factors, CHF is accompanied by an increased release of locally active vasoconstrictors like endothelin, which is produced by vascular endothelium. In patients without CHF, endogenous vasoconstrictors are counterbalanced by endogenous vasodilators. Atrial natriuretic peptide (ANP) normally inhibits the release of noradrenaline, renin and vasopressin as well as their effects on peripheral vessels. In early CHF, increased levels of ANP appear to prevent a rise in plasma renin concentration and plasma aldosterone concentration, because of the inhibitory action of ANP on these two hormones (33-36). In long-standing CHF, however, the release and effectiveness of ANP will gradually diminish and the actions of vasoconstrictors are left unopposed. This will eventually lead to mutual neurohormonal amplification resulting in increased plasma concentrations of renin, angiotensin and aldosterone (37).

Sodium retention, resulting from activation of the renin-angiotensin system, is another important feature of neurohormonal activation (30). Angiotensin leads to a constriction of the efferent arteriole and an increase in glomerular filtration fraction. The latter will enhance the proximal tubular sodium reabsorption by altering the peritubular balance of hydraulic and osmotic forces. In addition, angiotensin enhances sodium retention both directly and indirectly by stimulating the release of aldosterone. Angiotensin also gives rise to water retention by stimulating the cerebral thirst centre and enhancing the release of vasopressin from the pituitary. In healthy individuals, these endogenous salt-retaining systems are offset by endogenous salt-excreting systems, such as atrial natriuretic peptide and prostaglandins. In patients with congestive heart failure, ANP loses its inhibitory effects on the release and actions of renin and vasopressin (38). Renal hypoperfusion plays a central part in this attenuated natriuretic response. Renal hypoperfusion alters intrarenal haemodynamics and triggers the release of vasoconstrictors. It also leads to the release of prostaglandins which exert some natriuretic and diuretic effects (39). Both peripheral vasoconstriction and sodium retention are central mechanisms in the development of the circulatory state of decompensation.

Long-term haemodynamic stress and neurohormonal activation will progressively cause deterioration of ventricular function. It can cause irreversible structural remodelling of the heart. Progressive ventricular dilatation may lead to subsequent mitral regurgitation. Hypertrophic response to stress will increase energy demands while reducing energy supply (wall thickening may impair oxygen diffusion). In experimental models, high concentrations of noradrenaline and angiotensin II exert direct toxic effects on myocardial cells (40, 41). Increased production of oxygen free radicals may also be involved in progressive heart failure(42). Poten-

tially cardiotoxic cytokines such as tumour necrosis factor are increased in patients with CHF, especially in those patients with neurohormonal stimulation (43). Progression of CHF may thus be the result of a complex hemodynamic and neurohormonal response to an initial cardiac injury that gradually compromises cardiac performance (44).

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND CONGESTIVE HEART FAILURE

NSAID have numerous effects on renal and cardiovascular homeostasis. In particular in patients with CHF, there seems to be an increased susceptibility for the renal and cardiovascular effects of NSAID. As shortly mentioned in the introduction, several case reports have been published in which the onset of CHF was attributed to the use of an NSAID (45-47). In the following paragraphs, various aspects of NSAID and their potential effects on cardiovascular homeostasis in patients with CHF will be discussed.

Utilization of NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are a heterogeneous group of organic acids which exert analgesic, antipyretic, antiinflammatory and platelet-inhibitory actions. World-wide, over 100 NSAID are marketed or at an advanced stage of development (48). Although originally used predominantly for rheumatological conditions, current indications include many non-rheumatological conditions such as dysmenorrhoea, posttraumatic pain, colic pain or patent ductus arteriosus in infants. The effective relief of pain provided by NSAID makes this category of drugs popular among both users and prescribers. The overall NSAID-exposure in the Netherlands was valued at 10.8 defined daily dosages (DDD)/1000 persons/day in 1987, over-the-counter products not included (49). More than the NSAID utilization is in patients of 60 years and older. In patients older than 75 years, NSAID utilization increases to 45 DDD/1000 persons/day in women and 20 DDD/1000 persons/day in men. In the United States of America, 50 million Americans were expected to use NSAID intermittently or routinely in 1991 (50). Nevertheless, most presently available NSAID have a far from satisfactory risk/benefit profile. The adverse reaction profile of several NSAID has proved to be unacceptable and led to withdrawal from the market. Adverse drug reactions which are attributed to the use of NSAID are mostly related to the effects of these drugs on the upper gastro-intestinal tract and on kidney function.

Pharmacology

The major mechanism of action of NSAID is the inhibition of prostaglandin biosynthesis (51).

NSAID inhibit the function of cyclooxygenase, an enzyme essential for the transformation of arachidonic acid into prostaglandins. Arachidonic acid can be oxygenated by cyclo-oxygenase to prostaglandin G_2. A peroxidase component of cyclo-oxygenase reduces prostaglandin G_2 to prostaglandin H_2, which is the precursor of several specific prostaglandins. Finally, many different prostaglandins are produced in various tissues, such as tromboxane A_2 in platelets and prostacycline in vascular endothelium. Recently, two isoforms of cyclo-oxygenase (COX) have been identified, COX-1 and COX-2. COX-2 is an inducible isoform of cyclo-oxygenase and predominantly present throughout all stages of the inflammatory response, whereas COX-1 is mainly responsible for the production of prostaglandin E_2 and prostaglandin I_2 in kidney and stomach (51).

A new class of COX-2 selective NSAID such as meloxicam exhibit greater inhibitory action against COX-2 as compared with COX-1. The adverse effects of NSAID on renal function seem to be in part attributable to inhibition of COX-1 and subsequently decreased production of renal prostaglandin E_2. As renal prostaglandin E_2 is important in maintaining renal perfusion in patients with CHF, more selective agents may offer benefits for these patients (37). Animal studies in rats have shown that meloxicam exerts less inhibitory effects on urine PGE_2 excretion than most other NSAID (52). Furthermore, no effects of meloxicam on blood pressure could be observed in experimental studies rats and dogs (53). In 12 healthy human volunteers, indomethacine 25 mg 3 times daily for 8 days markedly reduced urinary PGE_2- excretion, whereas meloxicam 7,5 mg/day for 6 days had no effect (54). From a theoretical point of view, the new COX-2 selective agents may be more appropriate when treatment with NSAID is demanded in patients with CHF. However, further studies on these selective NSAID are needed in which patients at an increased risk of adverse renal effects are included , such as patients with CHF, before the evidence for this hypothesis can be provided.

Prostaglandins play a major part in the inflammatory response in tissues. Prostaglandins are also involved in the pyretic response by activating the hypothalamus. Apart from the inhibition of prostaglandin synthesis, another postulated mechanism explaining the therapeutic effect of NSAID pertains to the interaction with the adenylate cyclase system (51). Indomethacin and several other NSAID inhibit phosphodiesterase, thereby raising the intracellular concentration of cyclic AMP. Cyclic AMP has shown to stabilize membranes, including lysosomal membranes. By preventing the release of enzymes, this mechanism may have an important role

in modifying the inflammatory response.

Inhibition of the production of prostaglandins does not only explain to a large extent the beneficial antipyretic and antiinflammatory action of NSAID, but also many of their adverse reactions. For example, upper gastro-intestinal bleeding caused by NSAID results mainly from the inhibition of locally produced prostaglandins, since prostaglandins have a protective effect on the mucosa. In other cases, such as hepatoxicity due to diclofenac and other NSAID, the pathophysiological mechanism is less clear.

Role of prostaglandins in congestive heart failure

In patients with CHF, in particular the advanced stages, renal function is at risk because of a decrease in renal blood flow. Nevertheless, until the terminal stage of the disease, glomerular filtration rate is usually preserved within acceptable limits. This appears to be achieved in part by the synthesis of two vaso-active peptides within the kidney, angiotensin II and prostaglandins (39). These two substances are rapidly released in response to a fall in renal blood flow or an increase in renal sympathetic nerve stimulation. Although these two hormonal factors exert opposite effects on systemic and renal blood flow and on sodium and water excretion, both act to preserve glomerular filtration rate. Prostaglandins exert a vasodilator action on the afferent arteriole and angiotensin II leads to a vasoconstrictor effect on the efferent arteriole. There is a close correlation between circulating levels of prostaglandin metabolites and angiotensin II (37).

The kidneys release two types of prostaglandins that are important in the regulation of renal function, prostacyclin (PG-I_2) and prostaglandin E_2. Prostacyclin is produced mainly in the cortex, while prostaglandin E_2 is produced mainly in the medulla (55). Under basal conditions they possess minimal vasodilator activity. However, in case of prior vasoconstriction they act as potent vasodilators. A significant increase in the excretion of metabolites of prostaglandins occurs especially in patients with hyponatremia (37). Principal renal sites of prostaglandin synthesis are the vasculature, the glomerulus, the collecting tubule and the medullary interstitial cells (56). Besides the beneficial effect on the glomerular filtration rate, prostaglandins antagonize many extraglomerular actions of angiotensin II. Prostaglandins oppose the action of angiotensin II on the systemic circulation and decrease the afterload of the failing heart. Prostaglandins decrease total body sodium and water as a result of multiple interactions such as direct inhibition of sodium reabsorption in the renal tubules (PG-E_2) and counteraction of the stimulation of the thirst centre caused by angiotensin II. They also oppose the actions of vasopressin in the collecting duct (PG-E_2). To what extent these interactions

contribute to the maintenance of a clinical state of compensation in patients with left ventricular dysfunction remains unclear.

Interactions of NSAID with ACE-inhibitors and diuretics

Both ACE-inhibitors and diuretics are cornerstones of the pharmacotherapeutic treatment of patients with CHF. Because many patients suffer from multiple pathology, it is not unusual that these drugs are prescribed in combination with an NSAID. NSAID and ACE-inhibitors, however, may exert counteractive effects that may affect renal function (57). NSAID and ACE-inhibitors inhibit the synthesis of prostaglandins and angiotensin II respectively. Both angiotensin II and prostaglandins act to preserve glomerular filtration rate in patients with CHF: angiotensin II by a vasoconstrictor effect on the efferent arteriole and prostaglandins by a vasodilator effect on the afferent arteriole. Four specific factors have been identified that predispose patients with CHF to the development of functional renal insufficiency after treatment with ACE-inhibitors or NSAID: marked renal hypoperfusion, vigorous diuretic treatment, diabetes mellitus and the intensity of hormonal inhibition within the kidney (39). When combined treatment of these two drugs is indicated, these risk factors for renal impairment need to be considered.

In patients with CHF, functional renal insufficiency can easily induce intravascular volume overload and exacerbation of signs and symptoms of CHF. Hall et al. demonstrated that aspirin (dose 350 mg) interacted relevantly with the circulatory effects of enalapril in patients with severe heart failure (58). In this randomised double-blind crossover study in patients with severe CHF, enalapril given before aspirin led to a significant decrease in systemic vascular resistance, left ventricular filling pressure and total pulmonary resistance and an increase in cardiac output. However, combined with aspirin, no significant changes in these parameters could be observed. The combined effect of NSAID and ACE-inhibitors in patients with CHF should be considered as potentially harmful in patients with CHF. Therefore, co-prescribing an NSAID with an ACE-inhibitor in these patients should be done cautiously.

NSAID can also antagonize the effects of loop diuretics. Loop diuretics increase renal blood flow and block tubular sodium reabsorption, both of which contribute to natriuresis (59, 60). Urinary excretion of prostaglandins increases in response to loop diuretics. (60, 61). In the setting of administration of loop diuretics, inhibition of renal prostaglandins by NSAID can affect the tubular and/or the haemodynamic component of natriuresis. Sodium balance can be considered as a major determinant in the interaction between loop diuretics and NSAID (62). Sodium depleted patients seem to be at an increased risk for this interaction. The interaction between NSAID

and diuretics has been shown most clearly in conditions of circulatory volume depletion. In these states, NSAID may decrease glomerular filtration rate and blunt the action of diuretics, which may lead to severe fluid retention (63). Although the attenuation of the natriuretic response to loop diuretics as a result of NSAID is predominantly mediated by affecting prostaglandin dependent mechanisms, competition between NSAID and loop diuretics with respect to the active secretion into the proximal tubule may also alter the pharmacokinetics of loop diuretics (59, 63).

The effects of thiazides on renal prostaglandin synthesis and their interaction with NSAID are not as well investigated as the effects of loop diuretics on renal prostaglandin synthesis. Although some investigators demonstrated an increased prostaglandin excretion rate in both human and animal studies, others were unable to confirm these effects after administration of thiazides (64, 65). Nevertheless, NSAID may attenuate the diuretic response to thiazides. Apart from the effect of NSAID on prostaglandin synthesis, a possible mechanism by which NSAID can blunt the effects of hydrochlorothiazide may be the decreased chloride delivery to the diuretic's principal site of action in the distal tubule. Obviously, underlying disease, such as CHF, may also affect the potential interaction between thiazides and NSAID.

An interaction between NSAID and triamterene has been documented in some reports (66, 67). Creatinine clearance decreased significantly in two healthy individuals who received indomethacine and triamterene. In another report, acute renal failure developed when indomethacine was added to triamterene.

NSAID and hypertension

In the study of Ghali et al. on precipitating factors for congestive heart failure, uncontrolled hypertension was considered to be a causative factor for the re-occurrence of heart failure in 44% of the patients (68). This study was carried among merely black citizens where hypertension may have a high prevalence. Even so, the increase of cardiac afterload due to systemic hypertension can only be considered as harmful in patients with CHF. Several randomized trials have studied the effect of NSAID on blood pressure. As many trials were too small to provide conclusive results, Johnson et al. performed a meta-analysis on this issue (69). Their overall results suggest that NSAID elevate mean blood pressure by approximately 5.0 mm Hg. Mean blood pressure is defined as 1/3(2.diastolic blood pressure + systolic blood pressure). The hypertensive effect of NSAID was most marked in hypertensive patients taking antihypertensive medication. Sulindac and aspirin seem to have no appreciable effect on mean blood pressure as compared to placebo, whereas piroxicam was the only NSAID that gave rise to a statistically significant elevation of blood pressure. No

effects of NSAID on weight and creatinine clearance could be observed in this meta-analysis, but the wide 95% confidence intervals of the pooled mean changes of these parameters suggest different findings in various studies. For most NSAID, further studies are required to provide a conclusive assessment with respect to their effects on blood pressure. As different statistically non-significant effects are observed within various categories of persons (e.g. normotensive volunteers without antihypertensive treatment, normotensive volunteers on antihypertensive treatment), it remains unclear which patients are in particular at risk for the effects on blood pressure of NSAID. Since hypertension may exert negative effects on the gradually increasing group of patients with CHF, the effect on blood pressure of NSAID in heart failure patients should be subject to future research.

NSAID and renal function

The kidney is extremely active in the synthesis and metabolism of prostaglandins (70). Under normal conditions, prostaglandins play a negligible part in maintaining renal blood flow and consequently, NSAID exert no negative effects on renal haemodynamics (71, 72). In healthy individuals, NSAID have little effect on glomerular filtration rate (73). However, because of altered circulatory dynamics, prostaglandin production increases in patients with CHF and acts in a protective autoregulatory manner (74). Not only patients with CHF, but also those with an ineffective circulatory volume due to hepatic cirrhosis or other conditions are at risk for renal insufficiency during treatment with NSAID (75).There have been several reports of renal impairment and edema, both pulmonary and peripheral, probably induced by NSAID (1-3, 45).

NSAID are associated with a number of renal function abnormalities (table II). Among these renal function abnormalities, fluid and electrolyte disturbances appear to be the most frequently encountered renal function abnormalities in users of NSAID. Although some degree of fluid retention occurs in virtually all patients exposed to NSAID, clinically detectable edema can be demonstrated in approximately 3-5% of patients (50). The interference of NSAID with sodium and water excretion is mainly established by inhibition of the synthesis of prostaglandins (50, 56, 76). PGE_2 inhibits the reabsorption of sodium chloride in the thick ascending loop of Henle and in the collecting tubule and also antagonizes the antidiuretic effect of vasopressin in the collecting tubule (77). Therefore, inhibiting PGE_2 synthesis by NSAID increases both sodium and water reabsorption and usually results in a net fluid retention of approximately 0.5 - 1.0 liter. Although this fluid retention will be of little importance in healthy subjects, it may affect the unstable cardiovascular homeostasis in patients with congestive heart failure.

Table II
Potential renal and cardiovascular effects of NSAIDs

water and sodium retention
hyperkalemia
decreased renal blood flow
decreased glomerular filtration rate
interaction with the effects of ACE-inhibitors
interaction with the effects of diuretics
increased mean blood pressure
acute renal failure
acute tubular necrosis
interstitial nephritis
nephrotic syndrome
papillary necrosis
acute glomerulonephritis

Hyperkalemia is also a well known complication of NSAID. Although hyperkalemia is not frequently encountered among users of NSAID, patients with pre-existing renal impairment or cardiac failure and patients using potassium-sparing diuretics or ACE-inhibitors seem to be at an increased risk (50). Both PGI_2 and PGE_2 stimulate the release of renin in the kidney (71). The inhibition of the synthesis of prostaglandins by NSAID lowers renin secretion and will contribute to a state of hyporeninemic hypoaldosteronism. Apart from hyporeninemic hypoaldosteronism, inhibited synthesis of prostaglandins gives rise to decreased distal tubular flow rate, decreased distal sodium delivery and increased action of antidiuretic hormone, which may all contribute to the reduced ability of the kidney to secrete potassium (71).

As NSAID do not affect glomerular filtration in healthy subjects (78, 79), NSAID induced acute renal failure occurs predominantly in patients with concomitant diseases (80). Several risk factors for NSAID induced renal failure have been identified (50, 71, 75) (table III). NSAID associated acute renal failure accounts for nearly 40% of all cases of drug induced acute renal failure (81). In patients at risk of NSAID induced renal failure, renal function has become prostaglandin dependent. When in these patients the balance between vasoconstrictive effects (catecholamines and angiotensin II) and vasodilatory effects (prostaglandins) is disturbed by NSAID, the vasoconstrictive effects are left unopposed and renal failure may develop (70). The deterioration of renal function in these patients is usually reversible when treatment with NSAID is discontinued. (82). However, incomplete recovery has been reported in 20% of the cases of NSAID induced acute renal failure (83).

Table III
Risk factors for NSAID induced acute renal failure

Congestive heart failure
Hepatic cirrhosis
Renal insufficiency and renal diseases, including nephrotic syndrome
Diabetes mellitus
Anaesthesia and surgery
Advanced age
States of impending renal hypoperfusion:
sodium depletion
serious sepsis
diuretic use
hypotension

As discussed in the paragraph on the pathophysiology of CHF, the balance between vasoconstriction and vasodilatation is crucial in the maintenance of cardiovascular homeostasis in patients with CHF. The effects of decreased cardiac output and sodium depletion on renal blood flow have been studied in several experimental animal models. White et al. demonstrated that reduction of cardiac output by bradycardia in unanesthetized dogs induced marked vasoconstriction in mesenteric and iliac vascular beds without inducing renal vasoconstriction (84). Similar findings were reported by Higgens et al., who decreased cardiac output in unanesthetized dogs by reducing venous return to the heart (85). Oliver et al. performed a study in anesthetized dogs where cardiac output was decreased by inflating a balloon in the thoracic inferior vena cava (86). Although total peripheral vascular resistance increased significantly, renal blood flow and renal vascular resistance showed no significant changes. Plasma concentration of prostaglandin E_2 in renal venous blood showed a fourfold increase. However, after administration of an NSAID (diclofenac or meclofenamate), renal blood flow decreased and renal vascular resistance increased significantly, and plasma prostaglandin levels in renal venous blood also fell significantly. Experimental studies in anesthetized dogs have also shown that sodium depletion does not affect renal blood flow and renal vascular resistance despite a significant increase in total peripheral resistance and both arterial as well as venous renin and norepinephrine activity (87). Increased renal venous PGE_2 concentrations in the sodium depleted dogs seemed to be responsible for the maintenance of renal blood flow, because administration of indomethacin in sodium depleted dogs lowered renal blood flow and renal venous PGE_2 concentrations significantly, whereas no effect of indomethacin on renal blood flow could be observed in sodium repleted dogs. Dzau et al. demonstrated that the most explicit adverse hemodynamic effects of the inhibition of prostaglan-

din synthesis in patients with severe heart failure were observed in those with hyponatremia (37). These adverse hemodynamic effects pertained to decreased cardiac index and increased left ventricular filling pressure, mean arterial pressure and systemic vascular resistance.

Apart from the prostaglandin mediated renal function disturbances described in this paragraph, NSAID are also associated with nephrotic syndrome, acute interstitial nephritis, acute tubular necrosis, papillary necrosis and acute glomerulonephritis. (70, 72, 81, 88, 89)

Risk of NSAID induced renal function impairment

Data from interventional studies indicate that various NSAID can affect renal function in patients with an increased susceptibility to the inhibition of renal prostaglandin synthesis (90, 91). As these interventional studies are usually small and do not reflect everyday circumstances, reliable risk estimates for specific groups of patients at risk are difficult to infer from these studies. Therefore, larger pharmacoepidemiological studies are needed to provide insight with respect to the actual risk of renal function impairment under everyday circumstances in the population at large (92). However, the design of the epidemiological studies carried out on the association between NSAID and renal function impairment do not allow to make reliable estimates regarding the risk of NSAID induced renal impairment in the population at large. In most studies, there is a lack of sensitivity with respect to the ability to demonstrate impaired renal function. In a population-based study, Fox et al. found no hospital admission for renal parenchymal disease in more than 65,000 patients who received NSAID (93). Although this finding implicates that hospitalization for NSAID induced renal function impairment appears to be rare, this study does not allow any estimation of NSAID induced renal function impairment, as NSAID may have been discontinued based on increased serum creatinine concentrations during follow-up in the outpatient clinic. Apart from the lack of sensitivity in the determination of renal function impairment in pharmacoepidemiological studies, the exclusion of populations at risk for NSAID induced renal function impairment will also underestimate its incidence. Johnson et al. found no hospitalization for renal disease within 3 months after a prescription of ibuprofen in 13,230 patients (94) However, patients above the age of 65 years were excluded from the study. Similarly, Bonney et al. examined renal function in 1468 patients with arthritis on NSAID, but excluded all patients with major pre-existing disease (95). An incidence of approximately 5% of potentially significant elevations of renal function parameters was observed.

In conclusion, no reliable estimate of the incidence of NSAID induced renal func-

tion impairment is available at present. To obtain more insight in the actual risks of NSAID induced renal function impairment, epidemiological studies should be carried out in which more sensitive measures of renal function are used, such as serum creatinine concentration or creatinine clearance in stead of hospitalization for renal disease. These studies should also include those patients who are at an increased risk as a result of their prostaglandin dependent renal function.

Safety of NSAID in patients with congestive heart failure

In view of the pharmacological properties of NSAID and the important role of prostaglandins in the pathophysiology of CHF, it seems reasonable to assume that NSAID may exert adverse effects in patients at risk for CHF. Induction or exacerbation of CHF due to treatment with NSAID has been suggested in several publications (45-47). However, pharmacoepidemiologic studies concerning the association between CHF and the use of NSAID are scarce. The mechanisms discussed in the previous paragraphs may provide an explanation for the twofold increase in the risk of hospitalization in patients with a primary diagnosis of CHF during concomitant use of diuretics and NSAID compared with use of diuretics only (4). Heerdink et al. also showed that most hospitalizations for CHF occurred within 30 days of initiation of combined diuretic and NSAID therapy, with the highest risk during the first days of combined treatment. Analysis of the NSAID dosages showed no clear dose-response relationship. However, detailed information on renal function of those patients who developed CHF after using NSAID was not available in this study.

The actual risk of induction or exacerbation of CHF during treatment with NSAID is still unknown. (37, 76). Nevertheless, it is obvious that the increased prostaglandin synthesis in patients with severe CHF is important for the maintenance of cardiovascular and renal homeostasis. In view of the pathofysiology of CHF and the pharmacological properties of NSAID, the central mechanism by which NSAID influences cardiovascular homeostasis is their effect on renal function. Therefore, the potential effects of NSAID on renal function should be considered as the central criterium on which their suitability for patients with CHF has to be assessed. Efforts have been made to develop NSAID which may spare renal prostaglandin synthesis and thereby lack the prostaglandin mediated effects of NSAID on renal and cardiovascular homeostasis. Sulindac is an NSAID with potential renal sparing properties, despite controversy with respect to the extent of these renal sparing effects.

Several studies have been performed in which various NSAID were compared with respect to their effect on renal function. Whelton et al evaluated the renal effects

of ibuprofen, piroxicam and sulindac in patients with asymptomatic renal failure (90). In this study, only ibuprofen was associated with acute renal failure, which occurred within 7 to 10 days of initiating NSAID treatment. However, as both piroxicam and sulindac have a long half-life , the study may have been too short to assess the renal effects of these agents reliably. Although sulindac was not associated with acute deterioration of renal function in this study, a statistically significant increase of serum creatinine and decrease of urinary PGE_2 excretion was observed. Sedor et al. compared the effects of sulindac, indomethacine and placebo on renal prostaglandin synthesis in healthy females during a 4 days exposure to NSAID or placebo (96). Whereas a significant decrease in urinary prostaglandin excretion was observed in patients treated with indomethacine 25 mg 4 times a day, no significant decrease in urinary excretion of prostaglandin was demonstrated in those who were treated with sulindac 200 mg twice daily. Extrarenal cyclooxygenase activity, as assessed by platelet tromboxane β_2, was inhibited by both sulindac and indomethacine. All participants were pretreated with furosemide to induce negative sodium balance and enhance renal dependence on prostaglandin synthesis. Bunning et al. described three patients who experienced rapidly reversible renal failure related to the use of naproxen and ibuprofen (97). When NSAID treatment was resumed with full dose sulindac (200 mg twice daily), renal function remained stable. On the other hand, others have reported on renal function impairment attributed to sulindac (71). Apart from sulindac, namubetone has also been reported to have renal sparing properties (98). Further studies are needed to confirm the potentially greater tolerability of these agents. According to current opinion, sulindac and namebutone may induce less haemodynamic impairment as compared to other NSAID (99, 100), although they may still be potential causes of renal impairment. Results from studies with the new COX-2 selective agent meloxicam indicate that this agent may also exert renal sparing effects, but more studies have to be performed to give a meaningful judgement on the renal effects of meloxicam (54).

Aspirin is an NSAID which is frequently prescribed in patients with cardiovascular disease. Aspirin leads to an irreversible inhibition of cyclooxygenase, whereas other NSAID inhibit cyclooxygenase reversibly. Aspirin is usually prescribed in low doses (80-100 mg/day) to inhibit platelet aggregation in patients with cardiovascular disease. Similar to other NSAID, renal function impairment in patients at risk has been reported, whereas no effect could be observed in healthy subjects (73, 101, 102). In all these reports, however, aspirin was prescribed in clinical dosages, usually above 2000 mg/day. As platelets lack the possibility to generate cyclooxygenase, low dosages of aspirin are sufficient to inhibit platelet aggregation.

Summarizing the currently available data on NSAID, no clear hierarchy exists with respect to the potential adverse effects of NSAID on cardiovascular and renal

homeostasis. In particular, data on the safety of NSAID in patients with congestive heart failure are scarce. Interference with renal function seems to be the main pathophysiological mechanism by which NSAID may induce or exacerbate CHF. Therefore, in patients with CHF, newer agents with renal sparing properties may be of benefit, although firm and consistent evidence has still not been provided.

Monitoring treatment with NSAID in congestive heart failure patients

In view of the cardiovascular effects of NSAID, prescribing these drugs should be done carefully in patients with CHF. The first step in preventing undesirable effects on cardiovascular homeostasis in patients with CHF is the awareness of the prescriber that he or she prescribes a drug to a patient who is at an increased risk of experiencing such effects. Preconceiving that a prescription of an NSAID is indicated, the patient should be carefully monitored and instructed. Determination of baseline serum creatinine concentrations can be of value in assessing the effect on renal function of NSAID. As patients with elevated baseline serum creatinine concentration are at an increased risk of renal effects of NSAID, serum creatinine concentration should be monitored regularly. Whelton et al defined that a serum creatinine concentration above 180 μmol/l can be regarded as a risk factor for NSAID induced renal failure (90). However, the assessment of the risk of cardiovascular effects of NSAID is primarily based on clinical judgement of the clinician, and such criteria should be used cautiously. Acute renal failure can occur within one week after initiating treatment, therefore, weekly follow-up of renal function in patients at risk seems to be warranted. Furthermore, an increase in body weight and the occurrence or exacerbation of signs and symptoms of CHF also clearly indicate undesirable effects of NSAID in these patients. When patients are instructed to be attentive to these signs and symptoms, treatment with NSAID can be discontinued at an early stage. As most of the NSAID induced effects on renal function are reversible, discontinuation of NSAID at an early stage may prevent further morbidity such as an exacerbation of CHF. In order to lose fluid excess, a short course with a diuretic may be considered.

CONCLUSION

NSAID are prescribed for a wide range of indications. Despite their undisputed beneficial effects, many of them may also cause important adverse reactions. For both beneficial effects and most adverse reactions, inhibition of the synthesis of prostaglandins seems to be of major importance. In patients with congestive heart failure, in particular in those with severe disease, prostaglandin synthesis is increased

to maintain adequate renal perfusion. NSAID interfere with this increased prostaglandin synthesis. Therefore, these drugs may be an important risk factor for the onset of heart failure and patients with established heart failure are likely to be at an increased risk for the adverse circulatory effects of NSAID. However, currently available data do not allow a reliable quantitative assessment of the risk of adverse cardiovascular effects of NSAID. Pharmaco-epidemiological studies should provide further information necessary for clinicians to assess the risk of adverse cardiovascular reactions from NSAID under everyday circumstances.

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3.2

Heart failure and fluid retention attributed to the use of non-steroidal anti-inflammatory drugs: a case series

ABSTRACT

Background: NSAIDs have been associated with the onset and worsening of heart failure in previously published case-reports.
Objective: identification of NSAIDS as a potential risk factors for the onset or reoccurrence of signs and symptoms of CHF.
Methods: description of a case series of patients with symptomatic heart failure or fluid retention which was attributed to the use of NSAIDs. The case series consists of reports to the Drug Safety Unit of the Inspectorate for Health Care in The Netherlands.
Results: During the period 1985-1995, the Drug Safety Unit of the Inspectorate for Health Care received 4 reports of patients with symptomatic heart failure attributed to the use of NSAIDs. These 4 patients complied to the Framingham criteria of heart failure. In addition, 16 reports were received of fluid retention attributed to NSAIDs. All reports in this case series were considered to be at least probably associated with the use of NSAIDs.
Conclusion: There is convincing evidence that NSAIDs may induce fluid retention and CHF. These adverse effects seem to occur predominantly in patients with pre-existing cardiovascular or renal disease.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed for locomotor disorders, especially in elderly people. In The Netherlands, more than half of all prescribed NSAIDs are dispensed to patients of 60 years and older (1). Therefore, NSAIDs are both quantitatively and qualitatively an important class of drugs. Over the years, reports have been published in the literature on a possible association between the use of NSAIDs and the onset of fluid retention and congestive heart failure (CHF) (2). As CHF is an invalidating disease with an increasing incidence and prevalence, the identification of factors which may contribute to the onset or reoccurrence of signs and symptoms of CHF is of major importance (3, 4). In this study, we present a case series of patients in whom the onset of signs and symptoms of fluid retention and CHF was attributed to the use of NSAIDs.

CASE SERIES

During the period 1985-1995, the Drug Safety Unit of the Inspectorate for Health Care in The Netherlands received a number of reports on CHF which onset was attributed to the use of NSAIDs. An outline of these reports is presented in table I. In these patients, a clinical diagnosis of CHF could be made, based on the Framingham criteria. All patients were known with a history of cardiovascular disease, such as atrial fibrillation and coronary artery disease. Most reports concerned elderly women who were prescribed NSAIDs for locomotor disease. Apart from these four reports, the Drug Safety Unit received several reports on fluid retention and increase in body weight attributed to the use of NSAIDs. These reports did not fulfil the requirements for a clinical diagnosis of CHF according to the Framingham criteria. An outline of these reports is presented in table II. The increase in body weight and the occurrence of peripheral edema was attributed to the use of NSAIDs prior to the onset of these signs of fluid retention.

In all patients, a causal relation with the use of NSAIDs was considered to be at least probable. Discontinuation of the use of NSAIDs resulted in most patients in the disappearance of peripheral edema and a loss of body weight. However, a positive dechallenge may have been influenced by the prescription of diuretics to counteract fluid retention. As shown in table II, fluid retention may occur within only a few days after initiation of treatment with NSAIDs. Although the dosage of NSAIDs influences their pharmacological effects, the occurrence of fluid retention or symptomatic heart failure seems to depend predominantly on patient characteristics such as concomitant cardiovascular disease.

Table I
Reports of congestive heart failure attributed to the use of NSAIDs.

patient	age	gender	NSAID	concomitant use of diuretics	time interval since start of treatment	signs and symptoms
A	90 yrs	female	indometacine 50 mg every other day	yes	2 months	dyspnea, peripheral edema, pulmonary crepitations
B	82 yrs	male	naproxen 250 mg 2 dd	no	1 month	dyspnea, peripheral edema, pulmonary crepitations
C	63 yrs	female	ibuprofen 400 mg 3 dd	no	6 weeks	dyspnea, pulmonary crepitations
D	89 yrs	female	ibuprofen 400 mg 3 dd	yes	3 months	dyspnea, peripheral edema, pulmonary crepitations

Table II
Reports on edema and fluid retention attributed to the use of NSAIDs.

Patient	age	gender	NSAID	indication	adverse effect	time interval since start of treatment
A	65	female	naproxen	backache	edema, dyspnea	1 day
B	50	female	indometacine 25 mg 3 dd	left shoulder pain	edema	2 weeks
C	72	male	indometacine 25 mg 3 dd	right shoulder pain	edema	10 days
D	61	female	indometacine	rheumatoid arthritis	8 kg weight increase	----
E	45	male	diclofenac 50 mg 3 dd	pain right knee	oliguria, edema	3 days
F	40	female	naproxen	myalgia	4 kg weight increase, edema	10 days
G	52	female	phenylbutazon	arthritis left wrist	edema	4 days
H	76	female	ibuprofen	arthrosis	oliguria, edema	----
I	75	female	ibuprofen 400 mg 4 dd	gonarthrosis	fluid retention	5 days
J	52	female	ibuprofen 400 mg 4 dd	peri-arthritis	3 kg weight increase, oliguria, edema	1 day
K	47	female	indometacine 25 mg 3 dd	reumatic disease	2 kg weight increase, edema	1 day
L	42	female	ibuprofen	joint pain	edema	----
M	62	female	naproxen 250 mg 3 dd	----	edema	1 day
N	61	male	ibuprofen 400 mg 4 dd	backache	edema	3 days
O	75	female	diclofenac	spondylarthrosis	edema	2 weeks
P	41	female	ketoprofen 200 mg 1 dd	ischialgia	edema	2 days

DISCUSSION

During the period 1980-1995, the annual number of hospitalisations for CHF in The Netherlands increased from 14.441 to 25.324 (5). This finding corresponds with the results of epidemiological studies which indicate an increase in both incidence and prevalence of CHF, particularly in patients over 70 years of age. Main reasons for the increasing incidence and prevalence of CHF are aging of the population, improved survival after acute myocardial infarction and the availability of drugs such as the angiotensin converting enzyme inhibitors (ACE-inhibitors) which have proven to be effective in the treatment of CHF. Nowadays, ischaemic heart disease and hypertension are regarded as the most important causes of CHF.

In the past, some case reports have been published on the onset of CHF which was attributed to the use of NSAIDs (6-8). Both in these published case reports as well as in the case series presented here, fluid retention occurred during treatment with commonly prescribed dosages of NSAIDs. Peripheral edema is a well-known adverse effect of NSAIDs which is mentioned in the product information of most NSAIDS, and should be regarded as a direct consequence of NSAIDs induced fluid retention (9). Heart failure, however, is explicitely mentioned in the product information of only a few NSAIDs. The product information of most NSAIDs include only a statement that NSAIDs should be prescribed with caution to patients with impaired cardiac function.

In a retrospective study in 600 patients hospitalised for CHF, the use of NSAIDs was considered to be responsible for the onset of CHF in five patients (2). However, medication is not always exactly known at the time of hospitalisation, and some physicians tend to notify only those drugs which appear relevant to them. Therefore, the retrospective design of this study prevents a valid estimate of the incidence of NSAIDs induced CHF. In a study carried out with data from a record linkage system, a twofoldly increased risk of hospitalisation for CHF was demonstrated during concomitant use of diuretics and NSAIDs compared to use of diuretics without NSAIDs (10). The majority of the hospitalisations for CHF (56.8%) occurred within one month after start of concomitant use of diuretics and NSAIDs. It may be conceivable, however, that the true effect of NSAIDs on the occurrence of CHF may even be stronger if not only hospital admissions but also cases of CHF treated by the general practitioner are taken into account. In addition, the patients presented in table I indicate that NSAIDs may induce CHF in patients who do not concomitantly use diuretics.

The pathophysiological basis of NSAIDs-induced fluid retention has several aspects. The main effect of NSAIDs is characterised by their inhibition of the enzyme cyclo-oxygenase (COX). This enzyme is essential for the transformation of arachidonic

acid into prostaglandins and tromboxanes. The inhibition of the synthesis of prostaglandins causes both the therapeutical effects of NSAIDs as well as many of their adverse effects. It has been demonstrated that the enzyme COX has two isoforms, COX-1 and COX-2. The synthesis of prostaglandins in the stomach and kidney seems to depend predominantly on the activity of COX-1, whereas COX-2 has an important role in inflammatory processes. There are some indications that COX-2 selective NSAIDs, such as meloxicam, may have less gastro-intestinal and renal adverse effects (11). However, additional research has to be carried out before definite conclusions can be drawn on the risk-benefit profile of COX-2 selective NSAIDs. Among the commonly prescribed NSAIDs, indometacine appears to be relatively frequently associated with serious adverse effects (11). It is of interest, therefore, that indometacine is in vitro a potent inhibitor of the activity of COX-1.

Renal effects are considered to be very important in the pathophysiology of fluid retention due to the use of NSAIDs. Prostaglandin E_2 and I_2 are synthesized within the kidney and have vasodilatory properties which stimulate renal perfusion (12). As adequate renal perfusion may be jeopardised by decreased cardiac output, the synthesis of prostaglandins increases substantially in patients with CHF, in particular in those with hyponatremia (13). Hence, the increased synthesis of prostaglandins stimulates renal vasodilation and maintains renal perfusion within an acceptable range. In such situations, the use of NSAIDs will inhibit prostaglandin synthesis and may have detrimental effects on renal perfusion and cardiovascular homeostasis. Apart from the effects on renal perfusion, experimental studies show that prostaglandin E_2 antagonises the effects of antidiuretic hormone, and prostaglandin E_2 reduces the reabsorption of natrium and chloride in the proximal and distal tubulus and the loop of Henle (14). In most healthy individuals, inhibition of COX does not give rise to clinically relevant retention of water and sodium, although some asymptomatic sodium retention can be observed shortly after initiation of treatment with NSAIDs in healthy persons (15). NSAIDs may also interfere with the effects of diuretics (16). Organic acids inhibit the secretion of diuretics into the tubular lumen. Most diuretics, apart from spironolactone and triamterene, are only effective from the tubular lumen. As most NSAIDs are organic acids, the inhibition of the secretion of diuretics into the tubular lumen by NSAIDs may counteract the effects of diuretics (17).

Inhibition of prostaglandin synthesis may also lead to hyperkalemia, another adverse effect of NSAIDs. NSAIDs interfere with the stimulating effect of prostaglandins on renine release, which may lead to hyporeninic hypoaldosteronism and hyperkaliemia, particularly in patients with impaired renal function (18, 19). Finally, prostaglandins appear to be involved in the regulation of coronary perfusion. It has been demonstrated that indomethacine may increase arterial blood pressure and vascular resistance in the coronary artery (20). It remains unclear, however, to

what extent these effects attribute to the deterioration of cardiovascular homeostasis which may occur during treatment with NSAIDs.

The pathophysiological basis of NSAIDs-induced fluid retention and CHF suggests that these adverse effects of NSAIDs are uncommon in healthy individuals and will predominantly occur in patients with pre-existing cardiovascular or renal disease (21).

CONCLUSION

In view of published case reports and additional studies, and the plausible pathophysiological mechanism, there is convincing evidence that NSAIDs may induce fluid retention and CHF. These adverse effects seem to occur predominantly in patients with pre-existing cardiovascular or renal disease. NSAIDs are an important class of drugs which are highly effective in the symptomatic treatment of chronic locomotor disease. In particular, elderly patients may have a legitimated indication for the prescription of NSAIDs. However, the undoubted effectiveness of NSAIDs should counterbalance their potential adverse effects. Patients with cardiac or renal disease are particularly prone to NSAIDs induced fluid retention and CHF. NSAIDs should be prescribed only cautiously to these patients or should even be avoided if possible.

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3.3

Non-steroidal anti-inflammatory drugs and left ventricular systolic function

ABSTRACT

Background: NSAIDs are associated with the onset of symptomatic congestive heart failure (CHF). In particular patients with left ventricular (LV) dysfunction seem to be susceptible to this adverse effect of NSAIDs. However, little is known about the effect of NSAIDs on LV systolic function.

Objective: To study the effects of NSAIDs on fractional shortening (FS) of the left ventricle.

Methods: Data were retrieved from the Rotterdam Study, a population-based prospective cohort study among 7,893 participants aged 55 years and older. Echocardiographic measurements were carried out in a random sample of 1919 participants. The lower limit of normal LV function was considered to be FS ≥ 30%. Exposure to NSAIDs was determined on the basis of computerised medication histories. Participants were considered to be current use of NSAIDs when the date of echocardiography fell within the legend duration of a prescription of an NSAID. Past users were defined as participants with a prescription of NSAIDs in the 6 months preceding the date of echocardiography, but who were not current users. Non-use was defined as no prescription in the 6 months preceding echocardiography. Multiple linear regression and logistic regression analyses were carried out to assess the effect of NSAIDs on FS.

Results: In an overall analysis, current use of NSAIDs was associated with a small and statistically non-significant absolute decrease in FS with 1.6% (95% CI: -4.9%, 1.7%). In participants with a FS < 30%, current use of NSAIDs was associated with an absolute decrease in FS of 11.8% (95% CI:-1.3%, -22.3%), whereas in participants with FS ≥ 30% a decrease in FS of 1.7 % (95% CI: -4.4%, 1.1%) was demonstrated.

Conclusion: In patients with FS < 30%, current use of NSAIDs had a substantial negative effect on FS. In patients with normal LV function, current use of NSAIDs was associated with a negligible effect on FS.

INTRODUCTION

The use of non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with the onset of symptomatic congestive heart failure in several case reports (1-4). In most of these reports, congestive heart failure during treatment with NSAIDs occurred in patients with pre-existing cardiovascular disease. This suggests that pre-existing cardiovascular diseases may increase the susceptibility to cardiovascular effects of NSAIDs (5). Recently, a twofoldly increased risk of hospitalization for congestive heart failure has been found in patients who concomitantly used diuretics and NSAIDs (6).

Inhibition of prostaglandin synthesis is regarded as the main pathophysiological mechanism by which NSAIDs adversely affect cardiovascular homeostasis in patients with a propensity to congestive heart failure. Prostaglandins have an important role in maintaining adequate renal perfusion in patients with decreased cardiac output (7). NSAIDs interfere with prostaglandin synthesis by inhibiting the enzym cyclo-oxygenase. Fluid retention resulting from the use of NSAIDs is probably the main mechanism responsible for the onset of symptomatic congestive heart failure in susceptible patients.

Although an association between the use of NSAIDs and heart failure has repeatedly been established, little is known about the effect of NSAIDs on left ventricular function. More than half of the persons with impaired left ventricular systolic function are not found to have signs or symptoms of heart failure on thorough clinical evaluation (8, 9). Asymptomatic impaired left ventricular systolic function, however, is generally accepted to be a precursor of heart failure. Approximately 20% of the participants of the placebo-arm of the SOLVD prevention study developed heart failure or died within one year of follow-up (10). It seems reasonable to assume that patients with decreased ventricular function are more susceptible to NSAIDs-induced fluid retention, and hence overt heart failure. However, this hypothesis is mainly based on pathophysiological plausibility, as echocardiographic studies relating use of NSAIDs to left ventricular systolic function have not been published. In the present study, we evaluated the effect of current use of NSAIDs on fractional shortening of the left ventricle as determined by echocardiography.

METHODS

The Rotterdam Study is a prospective population-based cohort study (11). The first cross-sectional survey started in 1990 and was completed in 1993. All inhibitants of Ommoord, a suburb of Rotterdam, who were 55 years of age or older were invited

to participate. Of the 10,275 eligible subjects, 7,983 agreed to participate (78%) and signed informed consent. All participants were visited at home for a standardised questionnaire and were subsequently examined at the research centre.

During the first cross sectional survey taking place from 1990 to 1993, echocardiography was performed at the research centre in a group of 2,823 participants to assess systolic ventricular function. Echocardiography was carried out with the participant in the partial left decubitus position (echocardiographic device: Toshiba SSH-60A). Echocardiographic measurements were made according to the guidelines of the American Society of Echocardiography. Left ventricular internal dimension was measured at end diastole (LVIDed), as defined by the onset of the QRS complex and at end systole (LVIDes), as determined at the nadir of septal motion. The percentage fractional shortening (FS) was calculated as 100 * ((LVIDed-LVIDes)/LVIDed) and used as an index of systolic ventricular function. In 19.7% (n=556), the echocardiographic registrations were deemed inadequate to obtain a reliable measurement of left ventricular dimensions. These participants were more likely to be older, to have a higher body mass index and to use medication for chronic obstructive pulmonary disease. During the interview and at the research center, information was gathered on several potential confounders such as pre-existing cardiovascular disease, renal function, blood pressure, smoking behaviour and body mass index.

Computerised pharmacy data were available for all participants of the Rotterdam Study. Prescriptions dispensed to participants of the Rotterdam Study by the three automated drug dispensing outlets in the suburb of Ommoord are stored in a database as from January 1st 1991. To be eligible for the present study, at least six months medication history before the date of echocardiography had to be available. Therefore, those patients who underwent echocardiography before July 1st 1991 were excluded from this study (n=348). Hence, 1919 participants of whom both an adequate echocardiographic registration and a medication history of at least six months were available were included in this study. Patients were considered to be current users of every drug of which the date of echocardiography fell within the calculated legend duration. The legend duration was calculated by dividing the number of filled tablets / capsules of a drug by the prescribed daily number. Past users were defined as participants with a prescription in the 6 months preceding the date of echocardiography, but of which the date of echocardiography did not fall within the calculated legend duration. Non-users were defined as those participants who did not have a prescription in the 6 months preceding the date of echocardiography. Although exposure to NSAIDs was the main determinant of interest in this study, use of several cardiovascular and pulmonary drugs was also taken into account.

Statistical analyses were carried out with the statistical software package SPSS. Univariate comparisons between proportions were assessed by Chi-square statistics. For comparisons between continuous variables, Student-t-test was used, or the Mann-Whitney test when non-normally distributed. Multiple linear regression analysis was used to carry out multivariate analyses on the effect of NSAIDs on fractional shortening after adjustment for potential confounders.

RESULTS

In table I, the general characteristics of the study population are presented. The mean age of the 1919 eligible participants was 65 years. There was a slight female predominance among the participants (54%). Mean fractional shortening as determined by echocardiography was 39%. Dyspnea during normal daily activities was experienced by 26% (95% CI: 24% – 28%) of the participants, whereas 5% (95% CI: 4%-6%) had ankle edema on physical examination. Ankle edema at the end of

Table I
General characteristics of 1919 participants eligible to this study.

Gender:		
female	1034	(54%)
male	885	(46%)
Age (years)	65	(7.4)
Blood pressure:		
systolic (mmHg)	139	(22.4)
diastolic (mmHg)	75	(11.6)
Serum creatinine (μmol/l)	83	(20.4)
Fractional shortening (%)	39	(7.4)
Body mass index (kg/m^2)	26.0	(4.2)
Current smoker	404	(21%)
Alcohol-intake (g/day)	10.3	(14.1)
Ankle edema during physical examination	100	(5%)
Ankle edema at the end of the day	278	(15%)
Dyspnea during normal daily activities	498	(26%)
History of coronary artery bypass surgery	41	(2%)
History of myocardial infarction	113	(6%)

Values are means (SD) or numbers (%)

the day was reported by 15% (95% CI: 13%-17%) of the participants. A history of myocardial infarction was present in 6% (95% CI: 5%-7%) of the participants, and 2% (95% CI: 1% - 3%) had undergone coronary artery bypass surgery in the past.

Current medication on the date of echocardiography is shown in table II. Approximately 4% (95% CI: 3%-5%) (n=68) of the participants were current users of NSAIDs according to the calculated legend duration of the prescription. Beta-blockers were the most frequently prescribed cardiovascular drugs in this study population.

In a univariate analysis, no differences in fractional shortening were present in current users of NSAIDs (n=68) as compared to the combined group of past users (n=198) and non-users (n=1653) (38.7% in current users versus 38.8% in past and non-users). After adjustment for possible confounders in a multiple linear regression model (table III), both current and past use of NSAIDs were associated with a small non-significant decrease of the absolute value of the fractional shortening with 1.6% (95% CI: -4.9%, 1.7%) and 0.9% (95% CI: -2.9%, 1.1%) respectively as compared to non use of NSAIDs.

In table IV, results are shown of multiple linear regression analyses carried out separately in participants with a fractional shortening < 30% (n=207) and in participants whose fractional shortening was ≥ 30% (n=1712). In participants with a frac-

Table II
Current use of NSAIDs and other drugs on the date of echocardiography

Medication	Number of patients (%)
Beta blockers	214 (11%)
ACE-inhibitors	106 (6%)
Calcium antagonists	87 (5%)
Potassium sparing diuretics in combination with low ceiling diuretics	94 (5%)
Vasodilators	102 (5%)
NSAIDs	68 (4%)
COPD-medication	51 (3%)
Digoxin	40 (2%)
High ceiling diuretics	39 (2%)
Low ceiling diuretics	26 (1%)
Potassium sparing diuretics	7 (0,4%)

Table III
Results of multiple linear regression analysis on the association between current or past use of NSAIDs and fractional shortening in 1919 participants.

	Regression coefficient b	95% CI	
History of myocardial infarction	-4.79	-7.74	-1.83
Female gender	2.05	0.57	3.53
Current use of diuretics	-2.67	-5.20	-0.15
Current use of NSAIDs	-1.60	-4.91	1.71
Past use of NSAIDs	-0.93	-2.92	1.07

The regression coefficient b reflects the effect of the variables on fractional shortening after adjustment in the multiple linear regression model.
Variables which were not statistically significantly associated with fractional shortening in the multiple linear regression model: age, serum-creatinine (µmol/l), body mass index, current use of digoxin, ACE-inhibitors, beta-blockers or peripheral vasodilators, systolic and diastolic blood pressure, alcohol intake (g/day) and current smoking.

Table IV
Results of multiple linear regression analysis on the association between current use of NSAIDs and fractional shortening in participants with a fractional shortening < 30% and participants with a fractional shortening ≥ 30%.

	Coefficient b	95% CI
Fractional shortening < 30% (n=207)		
Current use of NSAIDs	-11.8	-22.3, -1.3
Fractional shortening ≥ 30% (n=1712)		
Current use of NSAIDs	-1.7	-4.4, 1.1

Adjusted for age, gender, body mass index, history of myocardial infarction, serum-creatinine (µmol/l), current use of digoxin, beta-blockers, diuretics, ACE-inhibitors or peripheral vasodilators, systolic and diastolic blood pressure, alcohol intake (g/day) and current smoking.

tional shortening < 30%, current use of NSAIDs was associated with an absolute decrease of fractional shortening of 11.8% (95% CI: -1.3% , - 22.3%) compared to non use, whereas in participants with a fractional shortening ≥ 30%, a decrease in fractional shortening of 1.7% (95% CI: -4.4% , 1.1%) was demonstrated compared to non use.

DISCUSSION

The results of this study indicate that current use of NSAIDs has an overall small and statistically non-significant negative effect on fractional shortening in persons over 55 years of age. However, in those with a fractional shortening < 30%, which is considered to be the lower limit of normal fractional shortening (12), current use of NSAIDs appeared to have a clear negative effect on fractional shortening. As the results of linear regression analysis reflect an absolute effect, fractional shortening in current users of NSAIDs with a fractional shortening < 30% appeared to be approximately 30% to 40% lower as compared to non-users.

These findings suggest that NSAIDs may exert a marked negative and clinically relevant effect on fractional shortening in patients with impaired left ventricular function, whereas the negative effect of NSAIDs on fractional shortening in persons with a fractional shortening ≥ 30% appears to be only very small.

These findings are consistent with the presumed pathophysiological mechanisms responsible for the association between the occurrence of signs and symptoms of congestive heart failure and the use of NSAIDs (5). NSAIDs inhibit the function of cyclo-oxygenase, an enzyme essential for the transformation of arachidonic acid into prostaglandins. Under normal conditions, prostaglandins play a negligible part in maintaining renal blood flow. In patients with decreased ventricular function, however, renal function may be compromised because of decreased renal blood flow. Under these circumstances, prostaglandins may improve renal haemodynamics and stimulate the excretion of water and sodium. In this way, prostaglandins (in particular PG-I_2 and PG-E_2) have an important role in preserving renal function and cardiovascular homeostasis in patients with decreased ventricular function. Consequently, inhibiting the production of prostaglandins by NSAIDs may adversely affect cardiovascular homeostasis and renal function in patients with decreased ventricular function. Retention of sodium and water may lead to increased intravascular - and extravascular volume and may precipitate congestive heart failure.

Most patients in case-reports in which the occurrence of congestive heart failure was attributed to the use of NSAIDs had pre-existing cardiovascular disease. The twofoldly increased risk of hospitalization for congestive heart failure during concomitant use of diuretics and NSAIDs in a recent record-linkage study was demonstrated in patients who also used diuretics, which again indicates pre-existing cardiovascular disease (6). Our finding that current use of NSAIDs has a stronger effect on fractional shortening and the risk of dyspnea in persons with a fractional shortening < 30% supports the clinical experience that patients with decreased ventricular function are more prone to adverse cardiovascular effects of NSAIDs.

In this study, exposure to NSAIDs on the date of echocardiography was based on the calculated legend duration of prescriptions. In the Rotterdam Study, drug exposure based on calculated legend durations accords to a large extent to actual drug use as recorded during the interview at home, indicating that dispensed prescriptions reliably reflect actual drug exposure (13). Therefore, significant underestimation of exposure to NSAIDs due to extensive use of over-the-counter NSAIDs as well as significant overestimation due to poor medication compliance seem to be unlikely.

The outcome variable in this study was fractional shortening. Fractional shortening is an outcome parameter which can be measured precisely and objectively during echocardiography. As both participants and research assistents were not aware of our study hypotheses, any misclassification of outcome may be considered as non-differential which will only lead to a conservative estimate of the risk estimates in our study.

The potential effects of NSAIDs on cardiovascular homeostasis may be influenced by several factors. In our study, we were able to adjust for a number of possible confounders, such as smoking, alcohol intake, blood pressure, history of myocardial infarction, renal function and concomitant medication. Due to the design of the Rotterdam Study, there may have been selection-bias based on the physical condition of those participating in the study. Old and diseased individuals were less likely to participate in the study. However, it seems improbable that this may have led to an overestimation of the effect of NSAIDs on fractional shortening, as these non-participating elderly are likely to have a relatively high prevalence of heart failure and use of NSAIDs. This might be an explanation for the limited number of current users of NSAIDs among the participants with a fractional shortening $\leq 30\%$ (n=4). Consequently, although current use of NSAIDs was associated with a clear and statistically significant effect on fractional shortening, confidence intervals were wide.

In conclusion, NSAIDs appear to have only a very small effect on fractional shortening in persons with normal left ventricular function. Therefore, congestive heart failure as an adverse effect to NSAIDs is likely to be rare in patients with normal systolic function. However, in patients with decreased ventricular function, NSAIDs may have a clinically significant effect on fractional shortening. NSAIDs should be avoided as far as possible in patients with impaired left ventricular systolic function.

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3.4

Non-steroidal anti-inflammatory drugs do not cause first occurrence of heart failure but are associated with relapsing heart failure

ABSTRACT

Introduction: NSAIDs have been associated with a first hospitalisation of congestive heart failure (CHF). Based on the pathophysiology of NSAID-induced CHF, however, it seems more likely that NSAIDs may precipitate relapsing CHF in patients with prevalent heart failure, and that NSAIDs are less likely to induce a first occurrence of heart failure (incident heart failure).
Objective: to estimate the risk of NSAID-induced CHF in patients with incident CHF as well as in patients with prevalent CHF.
Design: prospective population-based cohort study (Rotterdam Study).
Methods: 7,277 participants of the Rotterdam Study were followed from the interview date until the first of one of the following events: a diagnosis of incident heart failure, death, removal from the study area or institutionalisation, or end of the follow-up period. Incident heart failure was encountered in 345 participant during follow-up. Excluded from the study population were all participants with prevalent CHF at baseline or an uncertain diagnosis during follow-up. Exposure to NSAIDs and other medication was calculated on the basis of automated data on filled drug prescriptions in the pharmacies within the study area. In a second analysis, we followed all participants with incident heart failure until the first relapse or the end of followup.
Results: Current use of NSAIDs was associated with a relative risk of incident CHF of 1.11 (95% CI; 0.74 – 1.68), after adjustment for age, gender, and concomitant medication. In patients with prevalent heart failure who filled at least one NSAID-prescription since diagnosis of CHF, the univariate and multivariate risk estimates of NSAIDs-associated relapsing CHF were respectively 3.79 (95% CI: 1.13 – 12.73) and 9.89 (95% CI: 1.72 – 57.01).
Conclusion: NSAIDs are not associated with an increased risk of incident CHF. In patients with prevalent CHF, current use of NSAIDs is associated with a substantially increased risk of relapsing CHF, which is in accordance with the supposed pathophysiological mechanism.

INTRODUCTION

Heart failure is a syndrome that results from complex circulatory and neurohormonal responses to cardiac dysfunction (1, 2). The main causes of heart failure are ischaemic heart disease and arterial hypertension (3, 4). According to recent guidelines of the European Society of Cardiology objective evidence of cardiac dysfunction has to be present in addition to symptoms, such as shortness of breath or fatigue at rest or during exercise, and ankle swelling, to establish the presence of heart failure (5).

Non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with the occurrence of congestive heart failure in several case reports (6-9). Inhibition of the enzyme cyclo-oxygenase may result in a decrease of prostaglandin synthesis. Prostaglandins have an important role in renal physiology, and inhibition of their synthesis may give rise to fluid retention (10). Fluid retention due to NSAIDs may adversely affect cardiovascular homeostasis, and patients with a propensity for congestive heart failure seem to be particularly susceptible to the cardiovascular effects of NSAIDs. Moreover, NSAIDs may interfere with the cardiovascular effects of ACE-inhibitors and diuretics (10).

Previous studies demonstrated that NSAIDs may precipitate a first hospitalisation for CHF (11, 12) which suggests that NSAIDs may not only induce a relapse of pre-existing heart failure but also be a cause of a first occurrence of heart failure. In view of the pathophysiology of NSAID-induced heart failure, however, there can be doubt whether NSAIDs may induce heart failure in patients without pre-existing left ventricular impairment. We examined the extent to which NSAIDs may induce a first occurrence of CHF and a relapse of heart failure in patients with prevalent CHF. Hereto, we first studied the association between NSAIDs and a first occurrence of heart failure (incident CHF) in a population of elderly. Subsequently, we studied the association between NSAIDs and the first relapse of CHF in these same patients in order to investigate a potential different effect of NSAIDs on incident and prevalent heart failure.

METHODS

Setting

The study is a part of the Rotterdam Study, a population-based prospective cohort study on the prevalence, incidence, and determinants of cardiovascular, neurolog-

ical, ophthalmological and locomotor diseases in the elderly (13). The baseline examination started in 1990 and was completed in June 1993. All inhabitants of Ommoord, a suburb of the city of Rotterdam, The Netherlands, who were 55 years or older were invited to participate in the Rotterdam Study. Of the 10,275 eligible subjects, 7,983 (78%) agreed to participate and signed informed consent. Since the start of the Rotterdam Study, reexaminations have been carried out periodically by means of home interviews and periodic visits of participants to the research centre. In addition, all neurological, ophthalmological, cardiovascular and locomotor diseases which occurred since start of the follow-up in participants of the Rotterdam Study have systematically been gathered.

Study population

From the cohort of 7,983 participants of the Rotterdam Study, we excluded participants who were not registered at the pharmacy or who had an unknown date of death (n=48). Participants with *prevalent* heart failure at study entrance or participants who developed heart failure after start of the study but who did not fulfil the below-mentioned criteria of first occurrence of heart failure (*incident* CHF) were excluded from the analyses (n=453). In addition, baseline echocardiographic data were available of 2246 participants. We excluded from the analyses 205 participants with a baseline fractional shortening < 30%, defined as [(left ventricular internal dimension at end diastole – left ventricular internal dimension at end systole) / left ventricular internal dimension at end diastole] * 100%. A total number of 7,277 participants was included in the study population of this present study. The study period ran from July 1st 1991 through December 31st 1998. The cohort was followed from the date of entry in the study until the end-point of the follow-up which was the first of one of the following events: a diagnosis of incident heart failure, death, removal from the study area or institutionalisation, and end of the follow-up period. In a second analysis, we followed all participants with incident heart failure until the first relapse or the end of follow-up as defined.

Exposure definition

Computerised pharmacy records were available of all participants of the Rotterdam Study as of January 1st 1991. All prescriptions dispensed to participants of the Rotterdam Study by the three automated pharmacies in the study area were routinely stored in a database. Drugs were coded according to the Anatomical-Therapeutical-Chemical classification (ATC-classification) (14). Every prescription included a filling date, the product name, daily dosage, the number of filled tablets/capsules, and the prescribed daily number. For each member of the study population, use of

NSAIDs and concomitant cardiovascular and pulmonary medication was assessed during the follow-up period. The drug-exposure-window was defined as the legend duration (prescription length), calculated on the basis of the total number of filled tablets divided by the prescribed daily number, *plus* a carry-over period of 7 days. If the drug-exposure windows of consecutive prescriptions of the same drug overlapped, this was considered to be one single period of drug exposure. Hence, the follow-up period for each member of the cohort was divided into periods of exposure and non-exposure to the drugs of interest. Patients were considered to be current users of each drug of which the exposure window overlapped the date of diagnosis of incident heart failure.

Outcome definition

The outcome of the first analysis was defined as a diagnosis of *incident* heart failure, defined as the first occurrence of heart failure. Heart failure is one of the areas of special interest in the Rotterdam Study. The continuous follow-up of all participants of the Rotterdam Study, in close co-operation with the participating general practitioners, is aimed at identifying all events of interest, including heart failure. It is part of the routine follow-up procedure that all available data on the events of interest, such as hospital discharge letters and notes from general practitioners, are copied from the records of the general practitioner. Two research physicians independently evaluate all information on cases of heart failure that have occurred during follow-up of the Rotterdam Study. Certainty of diagnosis is rated as possible, probable or definite, based on the availability of additional information. A definite diagnosis of CHF is assumed if a firm diagnosis of heart failure has been made by a medical specialist. If the two research physicians disagree on the certainty of diagnosis, they re-evaluate these events during a consensus meeting. When disagreement on the certainty of diagnosis remains, a cardiologist makes a final decision. In addition, a cardiologist re-evaluates all potential cases of CHF on which the two research physicians agree during the first evaluation. In this present study, participants were only regarded as patients with incident heart failure if there was a first diagnosis of definite heart failure and no symptoms that might be compatible with prevalent heart failure. Apart from the follow-up procedure of the Rotterdam Study, we used hospital discharge diagnoses concerning the study population as gathered from all hospitals in the Rotterdam area. We considered hospital admissions for CHF after January 1st 1993 as incident heart failure if these patients had not been admitted to hospital for CHF in the period January 1st 1991-January 1st 1993. If participants were identified in both the follow-up procedure and the hospital discharge data base, we took the first date as the date of incident CHF. For the second analysis, we defined a relapse of CHF as a hospital admission because of heart failure in the patients that were followed since the occur-

rence of incident heart failure. As of that date, these individuals were considered as patients with prevalent heart failure.

Statistical analysis

For the data analysis was used a Cox regression model with time-dependent covariates. Drug exposure was entered in the model as segmented time-dependent covariates, with different values at different periods in time. The value of the time-dependent covariates could be calculated for each individual member of the cohort on each day during follow-up by splitting up the follow-up time into periods of exposure and non-exposure to the drugs of interest, based on the start date of filled drug prescriptions and the end date plus seven days. In the multivariate analyses, we adjusted for age, gender, concomitant cardiovascular and pulmonary medication.

RESULTS

General characteristics of the study population (n=7,277) are presented in table I. Mean age of the study participants at study entrance was 70 years. Of the study population, 62% was female. Mean follow-up was 6.0 years. The average baseline serum-creatinine level was 83 micromol/l. A total number of 749 participants had a history of myocardial infarction, and 164 patients had atrial fibrillation at study

Table I:
General characteristics of the study population.

Study population	7277	
Age	70.2 yr	SD 9.6
Female gender	4499	(62%)
Patients with incident heart failure	345	
Participants who filled at least one NSAID-prescription during follow-up	5062	(70%)
Follow-up	6.0 yr	SD 1.9
Serum-creatinine (micromol/l)	83.0	SD 21.7
History of myocardial infarction	749	(10.3%)
Atrial fibrillation	164	(2.3%)

Table II
Association between incident CHF and the use of NSAIDs.

	RR_{crude} (95% CI)	$RR_{adjusted}$* (95%CI)
Risk of CHF during current use of NSAIDs in the study population (n=7277) (events of CHF during follow-up: 345)	1.51 (1.00 – 2.27)	1.11 (0.74 – 1.68)
Risk of CHF during current use of NSAIDs among participants who received at least one prescription during follow-up (n=5062) (events of CHF during follow-up: 263)	1.40 (0.93 – 2.12)	1.20 (0.79 – 1.83)

*adjusted for age, gender, concomitant cardiovascular and pulmonary medication

entrance. A diagnosis of incident heart failure during follow-up was made in 345 participants.

Table II presents the results of the Cox regression model analysis with time-dependent variables. Current use of NSAIDs was univariately associated with the occurrence of incident heart failure (RR 1.51; 95% CI; 1.00 - 2.27). Adjusted for age, gender, and concomitant medication, the RR of the association between current NSAID use and the occurrence of incident heart failure declined to 1.11 (95% CI; 0.74-1.68). Among participants who filled at least one NSAID-prescription, these risk estimates were respectively 1.40 (95% CI; 0.93 – 2.12) and 1.20 (95% CI; 0.79 – 1.83).

Several classes of drugs were associated with the occurrence of incident heart failure (table III). Among the classes with the strongest association were digoxin, vasodilators (mainly nitrates), loop diuretics, and potassium-sparing diuretics.

Baseline serum-creatinine was available of 4,882 participants. In patients with a serum-creatinine < 100 μmol/l, the univariate RR of the association between NSAIDs and CHF was 1.35 (95% CI; 0.75-2.43). In patients with a serum-creatinine ≥ 100 μmol/l, the RR was 1.97 (95% CI: 1.97-5.50). Adjusted for age, gender, and concomitant medication, the risk estimates were respectively 0.96 (95% CI: 0.53-1.74) and 1.50 (95% CI: 0.51-4.40).

In the second analysis (table IV) in patients who were followed since the occurrence of incident heart failure during the follow-up period, the overall risk of NSAID-associated heart failure was 1.38 (95% CI; 0.50-3.82) in the univariate analysis and

Table III
Association between use of cardiovascular and pulmonary medication and the occurrence of incident CHF.

	Number of patients using the drug during follow-up	Crude RR	(95% CI)
Digoxin	633	6.58	(5.01 – 8.63)
Anti-arrhythmics	243	4.96	(3.19 – 7.71)
Vasodilators	1552	5.94	(4.70 – 7.50)
Thiazides	122	2.31	(0.74 – 7.21)
Low-ceiling diuretics (thiazides excluded)	245	1.14	(0.43 – 3.07)
Loop diuretics	1244	8.04	(6.37 – 10.15)
Potassium-sparing diuretics	250	6.49	(4.13 – 10.20)
Loop diuretics or low-ceiling diuretics combined with potassium-sparing diuretic	1399	1.43	(1.01 – 2.01)
Beta-blockers	2121	2.10	(1.66 – 2.65)
Calcium entry blockers	1293	2.94	(2.26 – 3.82)
ACE-inhibitors	1352	2.85	(2.19 – 3.70)
COPD-medication	1307	2.81	(2.10 – 3.76)
Acetylsalicylic acid (platelet aggregation inhibitor)	278	2.78	(2.22 – 3.50)

Table IV
Association between NSAIDs and relapsing CHF in patients with prevalent CHF (patients followed since diagnosis of *incident* CHF).

	RR_{crude} (95% CI)	$RR_{adjusted}$* (95%CI)
All patients with prevalent CHF (n=292) (events of CHF during follow-up: 64)	1.38 (0.50 – 3.82)	1.36 (0.49 – 3.82)
Patients with prevalent CHF who filled at least one NSAID prescription (n=85) (events of CHF during follow-up: 12)	3.79 (1.13 – 12.73)	9.89 (1.72 – 57.01)

*adjusted for age, gender, and concomitant medication

1.36 (95% CI 0.49-3.82) in the adjusted analysis. Among patients with prevalent CHF who filled at least one NSAID-prescription since diagnosis of CHF, the crude RR of NSAIDs-associated relapsing CHF was 3.79 (95% CI; 1.13-12.73). Adjusted for age, gender and concomitant medication, the RR was 9.89 (95% CI; 1.72-57.01).

DISCUSSION

The results of this study suggest that current use of NSAIDs is not associated with an increased risk of a first occurrence of heart failure. However, among patients who were followed since diagnosis of incident CHF (*prevalent* heart failure) and who filled at least one NSAID-prescription, the use of NSAIDs was associated with a substantially increased risk of NSAID-associated relapsing CHF.

To study the association between NSAIDs and incident CHF appropriately, it is of major importance to exclude all patients who might already have CHF before the first diagnosis of CHF (incident heart failure). This may be difficult because a substantial part of the patients with left ventricular impairment appears to be asymptomatic or are undiagnosed despite signs and symptoms of CHF (15). Our study population included 345 patients with a certain diagnosis of incident heart failure. We excluded all patients from the study population who might have a possible or probable diagnosis of CHF. This was achieved by an intensive follow-up procedure of all participants of Rotterdam Study, that provided the information on which we were able to decide whether participants were truly incident cases of CHF. Moreover, we excluded from the analysis 205 patients with a baseline fractional shortening less than 30% that is regarded as the lower limit of normality (16, 17). Hence, the study population consisted only of patients with either a certain diagnosis of truly incident CHF during follow-up or patients without any known suspicion of CHF. In this study population, no association between current use of NSAIDs and incident CHF was present.

Adverse effects of NSAIDs on cardiovascular homeostasis are well established (10). Particularly in the clinical setting of reduced renal perfusion that can be seen in patients with various disorders such as dehydration, cardiovascular disease and renal dysfunction, NSAIDs may impair the adequacy of renal prostaglandin production. In patients with reduced left ventricular function, renal prostaglandin production has a crucial role in compensatory renal hemodynamics (18). Inhibition of cyclo-oxygenase enzyme (COX) activity by NSAIDs will have an inhibitory effect on prostaglandin synthesis that may deteriorate cardiovascular homeostasis in these susceptible patients. Although not statistically significant, the stratified analysis on baseline serum-creatinine also indicated that impaired renal function, defined

as serum-creatinine ≥ 100 μmol/l, seems to be associated with an increased risk of NSAIDs-associated CHF.

Over the years, a number of case reports has been published in which the onset of congestive heart failure was attributed to the use of NSAIDs (6-9). In most of these reports, patients did have pre-existing cardiovascular disease that may have predisposed to the onset of heart failure. An earlier published record-linkage study has shown a twofoldly increased risk of a first hospitalisation for CHF during concomitant use of NSAIDs and diuretics as compared to use of diuretics only in patients older than 55 years (11). As this record-linkage study was carried out within a cohort of users of diuretics, it is likely that a number of these patients did have symptomatic left ventricular dysfunction in the period preceding the first hospitalisation for CHF. Many elderly patients are treated by their general practitioner because of mild to moderate signs and symptoms of CHF before hospital admission is indicated. This may explain the finding in the above-mentioned record-linkage study that the strongest increase in hospitalisation risk was seen in patients who were likely to have pre-existing CHF. Hence, a first hospitalisation for CHF is not by definition the same as truly incident CHF. In our study, we included not only first hospital admissions but all diagnoses of incident CHF whether admitted to hospital or not, and excluded all patients with an uncertain diagnosis of incident CHF.

In a recent matched case-control study (12), use of NSAIDs in the previous week was associated with a doubling of the odds ratio of a hospital admission for CHF. In patients with a first diagnosis of CHF, a threefoldly increased odds ratio was calculated. An even much stronger association was shown in patients with a history of heart disease. In view of the pathophysiology of NSAID induced CHF (18), it seems likely that a substantial part of the cases in this study did have pre-existing left ventricular impairment before hospitalisation. In addition, the remarkably high consumption of NSAIDs of nearly 30% in the week prior to hospitalisation among the cases may imply either recall-bias or significant comorbidity.

The univariate association between various cardiovascular drugs and the onset of heart failure (table III) reflect the presence of pre-existing cardiovascular disorders such as hypertension, atrial fibrillation and ischemic heart disease which predispose to the development of heart failure. Therefore, these associations can be explained by confounding by indication. Although we excluded from the analysis all patients who may have prevalent heart failure, we can not exclude the possibility that some patients in the study population did use these drugs because of heart failure. The presence in the study population of some patients with prevalent heart failure, however, is likely to overestimate the relative risk. Hence, it seems plausible that the risk estimate of the association between incident heart falure

and NSAID use might even be lower if we were able to exclude these patients. The findings in this study suggest that NSAIDs do not have a substantial additional contribution to the risk of incident CHF but that this is largely caused by cardiovascular comorbidity as reflected by cardiovascular comedication.

The second analysis in our study in patients who were followed since diagnosis of CHF (n=292) demonstrates the different effects of NSAIDs in patients with incident and prevalent CHF. In patients with prevalent heart failure who filled at least one NSAID prescription, current use of NSAIDs was associated with a substantially increased risk of relapsing CHF. From a pathophysiological point of view, the different effects of NSAIDs with respect to incident and relapsing CHF seem to be plausible, as cardiovascular homeostasis is much more likely to be prostaglandin dependent in patients with prevalent CHF as compared to patients with a unimpaired left ventricular function.

A cohort study lacks some of the intrinsic limitations of case-control studies. The availibility of prospectively collected drug exposure data from the automated pharmacies in the study area prevents potential differential misclassification of exposure that may occur in case-control studies. Intensive follow-up procedures of participants of the Rotterdam Study provided the possibility to include only patients with definite incident heart failure and to exclude from the study population those with a uncertain diagnosis. However, we can not exclude the possibility that some patients with asymptomatic left ventricular dysfunction have been included in our study population.
An important source of bias in cohort studies may arise from the degree of accuracy with which participants have been classified regarding their exposure and disease status. In this present study, a diagnosis of incident heart failure could only be made on the basis of information of a medical specialist. Two research physicians independently reviewed all available information before rating the event as a definite diagnosis of CHF. In addition, this decision of the two research physicians had to be confirmed by a specialist in cardiovascular medicine. Therefore, major misclassification of the diagnosis definite CHF seems to be unlikely.

Exposure to NSAIDs was based on the information on filled drug prescriptions in the three automated pharmacies in the study area. Information on over-the-counter use of NSAIDs was not available. In the Netherlands, however, only since 1995 a small proportion of total NSAIDs consumption consists of over-the counter drugs. Moreover, misclassification of exposure is likely to be non-differential, as signs and symptoms of CHF do not give reason to use NSAIDs.

NSAIDs are drugs that may have several beneficial effects, particularly for musculoskeletal diseases that occur frequently in the elderly. Despite their potential

adverse effects, several patients take advantage of the potent analgetic and anti-inflammatory properties. In view of the risk-benefit profile of drugs, our finding that NSAIDs were not associated with an increased risk of incident heart failure in a cohort of patients without pre-existing signs or symptoms of CHF is of clinical significance. This implies that, regarding the risk of CHF, these drugs can safely be prescribed to elderly patients with uncompromised left ventricular and renal function.

In conclusion, NSAID use appears not to be associated with incident CHF. In patients with prevalent CHF, however, a substantially increased risk of NSAID-associated CHF was demonstrated, implying that NSAIDs should be prescribed with caution to patients with prevalent CHF.

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3.5

Relapse of congestive heart failure associated with the use of non-steroidal anti-inflammatory drugs

ABSTRACT

Introduction: Several case reports have been published on CHF attributed to the use of NSAIDs. Results from an earlier study have demonstrated that concomitant use of diuretics and NSAIDs was associated with a twofoldly increased risk of a first hospitalisation for CHF.

Objective: To assess the risk of relapsing CHF associated with the use of NSAIDs in a cohort of patients aged 50 years and older with a history of one hospitalisation for CHF.

Subjects and Methods: Data were used from the PHARMO record linkage system. The study population was defined as the cohort of all residents aged 50 years or older who had one hospitalisation for CHF. For each individual in the cohort, exposure to NSAIDs and concomitant cardiovascular and pulmonary medication was assessed during the follow-up period. Patients were considered to be current users of each drug of which the prescription duration overlapped the date of hospitalisation for relapsing heart failure. The outcome of the study was defined as a readmission with a primary diagnosis of CHF of a member of the cohort during the study period.

Results: In the cohort of 1,405 CHF patients, the overall risk of hospitalisation for relapsing CHF associated with NSAID use was 1.41 (95% CI; 0.97-2.06), adjusted for age, gender and concomitant medication. Among patients who had received at least one NSAID prescription (n=559) during the follow-up period, use of NSAIDs was associated with an overall twofoldly increased risk for rehospitalisation for CHF (adjusted RR 2.20; 95% CI 1.44-3.36). A first NSAID prescription was associated with an adjusted RR of 3.30 (95% CI; 1.63-6.71), a second to fourth prescription with an adjusted RR of 1.85 (95% CI 1.00-3.45), and a fifth or more prescription with an adjusted RR of 2.18 (95% CI 1.07-4.46). As compared to non-use, the risks of low dosage NSAID (< 0.75 DDD/day), medium dosage (0.75-1.24 DDD/day), and high

dosage (≥ 1.25 DDD/day) were respectively 0.85 (95% CI; 0.35-2.08), 1.07 (95%CI; 0.58-1.99), and 1.99 (1.32-3.00). The calculated attributable fraction was 22.8%. ***Conclusion:*** the use of NSAIDs in patients with a previous hospitalisation for CHF was associated with an increased overall risk of rehospitalisation for CHF. Among users, a first prescription is associated with a threefoldly increased risk, whereas more regular use is associated with a lower risk estimate. This observation may be explained by the phenomenon *'depletion of susceptibles'*. The calculated attributable fraction indicates that in our study population approximately 23% of the rehospitalisations in patients with a history of CHF may be attributable to the use of NSAIDs.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed, particularly in elderly patients with locomotor disease. NSAIDs are very effective in providing relief of pain and in suppressing inflammation-mediated processes such as rheumatoid arthritis. Most of the pharmacological effects of NSAIDs can be attributed to their ability to interfere with the synthesis of prostaglandins by inhibiting the enzyme cyclo-oxygenase (COX).

Apart from their role in inflammatory processes, prostaglandins have a number of physiological effects on renal function and are extensively synthesized in renal tissues (1-5). Prostaglandin I_2 and prostaglandin E_2 are the most important prostaglandins in the regulation of renal function.

NSAIDs are associated with a number of renal function disturbances such as fluid retention, acute renal failure, and interstitial nephritis. In healthy individuals under normal circumstances, prostaglandins have little or no effect on renal haemodynamics, and the use of NSAIDs is unlikely to affect renal perfusion. In patients with congestive heart failure (CHF), however, adequate renal perfusion may be at risk as a result of decreased left ventricular output, and prostaglandins may have an important role in the maintenance of adequate renal haemodynamics. Hence, inhibition of the synthesis of prostaglandins by NSAIDs may adversely affect cardiovascular homeostasis in heart failure patients (6).

Several case reports have been published on CHF attributed to the use of NSAIDs (7-10). In an earlier study, we demonstrated that in patients without a known history of CHF, concomitant use of diuretics and NSAIDs is associated with a twofoldly increased risk of a first hospitalisation for CHF (11). The objective of the

current study was to assess the risk of a relapse of CHF associated with the use of NSAIDs in a cohort of patients aged 50 years and older with a history of CHF.

SUBJECTS AND METHODS

Setting

Data were used from the PHARMO record linkage system, a database containing drug-dispensing records from community pharmacies and linked hospital discharge records of 450,000 residents of 12 population-defined areas in The Netherlands (12). Medication records and hospital data were collected during the study period January 1986 until January 1996.

Study population

The study population was defined as the cohort of all residents aged 50 years or older who had one hospitalisation for CHF. Medication records and hospital data were collected during the study period that ran from January 1986 until January 1996. This cohort of patients with CHF was followed from the date of discharge for the first hospitalisation for CHF until the end-point of the follow-up period which was the first of one of the following events: re-hospitalisation for CHF, a last dispensing of any prescription in the pharmacy indicating that the patient was still eligible at that time, or end of the follow-up period which was January 1st 1996. A last drug dispensing date before the end of the follow-up period usually indicated a move from the study area, institutionalisation or death. To be eligible for the study, the time interval between the first hospitalisation for CHF and the first of the abovementioned end points of the study had to be at least 180 days for all members of the cohort.

Exposure definition

For each individual in the cohort, exposure to NSAIDs and concomitant cardiovascular and pulmonary medication was assessed during the follow-up period. Drugs were coded according to the Anatomical-Therapeutical-Chemical classification (ATC-classification). A start date and an end-date were assigned to each individual drug prescription, based on the legend duration of the prescription. The legend duration (prescription length) was calculated on the basis of the total

number of filled tablets or capsules divided by the prescribed daily number. The exposure window was defined as the legend duration of a drug prescription *plus* a carry-over period of 7 days. If the exposure window overlapped the start date of a next prescription of the same drug, this was considered to be one single period of exposure. In this way, the follow-up period for each individual member of the cohort could be split up in periods of exposure and non-exposure to the drugs of interest. Patients were considered to be current users of each drug of which the prescription duration overlapped the date of hospitalisation for relapsing heart failure. In addition, we calculated for each patient the total number of NSAID prescriptions during the follow-up. To assess the effect of dosage, we compared the NSAIDs dosage in patients who were current users at the time of rehospitalisation with the NSAID dosages on a random date in patients who were not readmitted. Hereto, all prescribed dosages were expressed in defined daily dosages (DDD), a standardized dosing unit which is defined by the World Health Organisation and which represents the average daily dosage for the main indication of the drug in an adult. This unit facilitates comparisons of dosages between products.

Outcome definition

The outcome of the study was defined as a readmission with a primary diagnosis of CHF of a member of the cohort during the study period. Hospital discharge diagnoses were coded according to the International Classification of Diseases (13).

Statistical analysis

The statistical analysis was carried out with a Cox regression model with time-dependent covariates. Drug exposure was entered in the model as segmented time-dependent covariates, with different values at different periods in time. For each individual member of the cohort, the value of the time-dependent covariates could be calculated on each day during follow-up by splitting up the follow-up time of each individual cohort member into periods of exposure and periods of non-exposure to the drugs of interest, based on the start- and end-dates of filled drug prescriptions. We separately evaluated the risk of relapsing CHF associated with a first NSAID prescription, a second to fourth NSAID prescription, and a fifth or more NSAID prescription which closely resembled a distribution in tertiles. For that reason, we added to the model three additional time-dependent covariates which defined whether NSAID users were exposed to a first, a second to fourth, or a fifth or more NSAID prescription. In the multivariate analyses, we adjusted for age, gender, and current use of concomitant cardiovascular and pulmonary medication.To evaluate NSAID dosages among users, we compared the prescribed

number of DDDs per day (DDDs/day) on the date of rehospitalisation in cases with the prescribed DDDs/day on a random date in non-hospitalised patients. The attributable fraction was determined by calculating the incidence-density (ID) of CHF during exposure and during non-exposure to NSAIDs. Therefore, we determined the total number of both exposed person-years of follow-up and non-exposed person-years of follow-up. Subsequently, we calculated the attributable fraction with the formula $(ID_{exposed} - ID_{unexposed}) / ID_{exposed}$.

RESULTS

During the study period, 1,405 patients were identified in the database with a first hospitalisation for congestive heart failure who complied with the eligibility criteria of the study. Of these 1,405 patients, 306 patients were rehospitalised during the study period because of relapsing CHF. The remaining number of 1,099 patients were not rehospitalised for CHF during the study period. The general characteristics of the study population are presented in table I. The average age of the study population was 74 years and a small majority (51%) was male. The mean follow-up period was 879 days. During the follow-up period, a total number of 3162 NSAID prescriptions were dispensed to 559 patients (40% of all patients). Of these 559 patients, 170 patients received one NSAID prescription, 191 patients received

Table I:
General characteristics of the study population (n=1405).

Age (yrs)	74.4 yrs	SD: 9.1
50 – 59 yrs	95	(7%)
60 – 69 yrs	307	(22%)
70 – 79 yrs	589	(42%)
≥ 80 yrs	414	(29%)
Male gender	719	(51%)
Follow-up (days)	879	SD: 693
Number of rehospitalisations for CHF during follow-up	306	
Number of NSAIDs prescriptions during the study period	3162	
Number of patients using NSAIDs:		
Patients with no prescription	846	(60%)
Patients with 1 prescription	170	(12%)
Patients with 2-4 prescriptions	191	(14%)
Patients with ≥ 5 prescriptions	198	(14%)

Table II:
Cox regression analysis with time dependent covariates on the association between current use of NSAIDs and the risk of CHF during follow-up.

	Crude RR (95% CI)		Adjusted RR* (95% CI)	
All cohort members (n=1405)	1.54	(1.06-2.24)	1.41	(0.97-2.06)
Ever use of NSAIDs (n=559)	2.57	(1.69-3.89)	2.20	(1.44-3.36)
1 prescription (n=170)	3.59	(1.77-7.26)	3.30	(1.63-6.71)
2–4 prescriptions (n=191)	2.18	(1.18-4.03)	1.85	(1.00-3.45)
≥ 5 prescriptions (n=198)	2.66	(1.32-5.35)	2.18	(1.07-4.46)

* Adjusted for age, gender, and use of digoxin, diuretics, beta-blockers, ACE-inhibitors, anti-arrhythmics (class I and III), vasodilators, calcium-entry blockers, salicylic analgetics, acetylsalicylic acid (platelet aggregation inhibitor) and COPD-medication. Statistically significant values are given in bold type

2-4 NSAID prescriptions and 198 patients received ≥ 5 NSAID prescriptions during the follow-up period.

Table II shows the results of the Cox regression analysis of the association between current use of NSAIDs and the risk of CHF. In the cohort of 1,405 CHF patients, the overall risk of hospitalisation for relapsing CHF associated with NSAID use was 1.41 (95% CI; 0.97-2.06), adjusted for age, gender and concomitant medication. In the sub-cohort of patients who had received at least one NSAID prescription (n=559) during the follow-up period, use of NSAIDs was associated with an overall twofoldly increased risk of rehospitalisation for CHF (adjusted RR 2.20; 95% CI 1.44-3.36). A first NSAID prescription was associated with an adjusted RR of 3.30 (95% CI; 1.63-6.71), a second to fourth prescription with an adjusted RR of 1.85 (95% CI 1.00-3.45), and a fifth or more prescription with an adjusted RR of 2.18 (95% CI 1.07-4.46).

Table III presents the results of the analysis with the concomitant medication. In the multivariate analysis, vasodilators and loop diuretics were associated with an increased risk of rehospitalisation. The use of combinations of potassium-sparing diuretics with other diuretics was associated with a decreased risk. The most frequently used NSAIDs were diclofenac (45%), ibuprofen (27%), and naproxen (11%). No differences among NSAIDs could be observed with respect to the risk of rehospitalisation during current use of these agents. Among patients currently using NSAIDs at the time of rehospitalisation for CHF (n=26), the average dosage of NSAIDs was 1.25 DDDs/day. On a random date in patients who were not rehospitalised, the mean NSAIDs dosage was 1.01 DDDs/day. This difference was not

Table III:
Concomitant medication associated with rehospitalisations for CHF among 1405 patients with a history of CHF.

	Crude RR (95%CI)		Adjusted RR* (95% CI)	
Digoxin	1.09	(0.86-1.37)	0.93	(0.73-1.18)
Anti-arrhythmics	1.35	(0.91-2.03)	1.13	(0.75-1.71)
Vasodilators	2.16	(1.72-2.71)	2.10	(1.65-2.68)
Thiazides	0.51	(0.07-3.64)	0.59	(0.08-4.31)
Low-ceiling diuretics without thiazides	0.88	(0.28-2.74)	1.04	(0.33-3.30)
Loop diuretics	1.87	(1.45-2.40)	1.41	(1.06-1.89)
Potassium-sparing diuretics	1.42	(1.08-1.86)	1.16	(0.87-1.55)
Loop diuretics or low-ceiling diuretcs combined with a potassium-sparing diuretic	0.44	(0.24-0.81)	0.53	(0.28-0.98)
Beta-blockers	0.73	(0.49-1.08)	0.68	(0.45-1.01)
Calcium entry blockers	1.05	(0.79-1.39)	0.89	(0.67-1.20)
ACE-inhibitors	1.26	(1.01-1.58)	1.05	(0.82-1.34)
COPD-medication				
Tracheal sympaticomimetic agents	1.62	(1.13-2.31)	1.43	(0.90-2.26)
Other tracheal agents	1.38	(0.98-1.94)	1.09	(0.70-1.70)
Salicylic analgesics	1.58	(0.84-2.97)	1.60	(0.84-3.03)
Acetylsalicylic acid (platelet aggregation inhibitor)	1.03	(0.76-1.40)	0.93	(0.68-1.27)

* Adjusted for age, gender, and other concomitant medication.

statistically significant (p=0.05). As compared to non use, the risks of low dosage (< 0.75 DDD/day), medium dosage (0.75-1.24 DDD/day), and high dosage (≥ 1.25 DDD/day) were respectively 0.85 (95% CI; 0.35-2.08), 1.07 (95%CI; 0.58-1.99), and 1.99 (1.32-3.00).

In the total cohort, 26 cases of CHF occurred during 218 person-years of follow-up with NSAID-exposure. The remaining 290 cases of CHF occurred during 3164 person-years of non-exposure to NSAIDs, indicating an attributable fraction of 22.8%.

DISCUSSION

The findings in our study indicate that a first prescription of an NSAID in patients with a history of CHF is associated with a threefoldly increased risk of rehospitalisation for CHF. In patients who use NSAIDs more regularly (2-4 prescriptions and $\geq$ 5 prescriptions during follow-up), a twofoldly increased risk estimate was found. High dosages (>1.25 DDDs/day) seem to be associated with an increased risk of rehospitalisation for CHF. In addition, the calculated attributable fraction indicates that 23% of the rehospitalisations for CHF in our study population may be attributable to NSAIDs.

The analysis carried out on the complete cohort of 1405 patients revealed a small and statistically not significantly increased risk (adjusted RR 1.41 95% CI; 0.97-2.06). However, this analysis provides a diluted risk estimate as all patients who have not been prescribed an NSAID during follow-up (n=846) will not have any period of exposure to NSAIDs.

Studies in record linkage databases have only limited information on potential confounders. Apart from age, sex and comedication, additional information on clinical parameters is usually not available. There may be differences in general health status between users and non-users of NSAIDs that may be associated with the risk of relapsing CHF, and there may also be differences in general health status among incidental and chronic users of NSAIDs. Therefore, patients within a certain stratum of NSAID use are likely to be more similar, which may reduce the influence of unknown confounders that may affect the results. Our findings are in agreement with an earlier study with data from the PHARMO data base which showed that in persons aged 55 years or older taking diuretics, concomitant use of diuretics and NSAIDs was associated with a twofoldly increased risk of a first hospitalisation for CHF (11). In our study, the interaction between loop diuretics and NSAIDs was not associated with an increased risk of rehospitalisation for CHF in the multivariate analysis, which may be explained by the fact that the vast majority of patients with CHF are using diuretics on a chronic basis. As the negative effects of NSAIDs on cardiovascular homeostasis are likely to be more pronounced in patients with a history of CHF (6), the finding of a threefoldly increased risk associated with a first NSAID prescription in patients with a previous hospitalisation for CHF is biologically plausible.

The finding that more regular use of NSAIDs was associated with a lower risk increase, may be explained by the occurrence of depletion of susceptibles in our study population (14). As a second hospitalisation for CHF was considered as the endpoint of follow-up for the cases, patients who are particularly susceptible to the adverse effects of NSAIDs on cardiovascular homeostasis will more readily develop

a relapse of CHF after receiving a single prescription for NSAIDs. Patients who are prescribed NSAIDs and apparently can tolerate these drugs are likely to receive further prescriptions during the follow-up period. Hence, a lower risk of rehospitalisation for CHF associated with NSAIDs was demonstrated in patients who could tolerate the potentially adverse effects of NSAIDs on cardiovascular homeostasis. Although this seems to be a plausible explanation, the role of chance can not completely be excluded because of overlapping confidence intervals.

The attributable fraction of 23%, calculated on the basis of differences in incidence density of relapsing CHF during exposure and non-exposure to NSAIDs, demonstrates that NSAIDs may be responsible for a substantial percentage of rehospitalisations for CHF. This finding should be regarded as an important indicator that NSAID use seems to have a considerable impact on the number of rehospitalisations in patients with prevalent CHF.

Validation of hospital discharge diagnoses of CHF which are included in the PHARMO data base has been carried out in a separate study (15). The hospital discharge diagnoses were compared with 2 validated sets of diagnostic models for CHF, the criteria from the Framingham Heart Study and a modification of the Boston criteria (16, 17). According to these two diagnostic models, the validity of hospital discharge diagnoses was shown to be high. Therefore, it is unlikely that misclassification of outcome has affected our study results. Moreover, any misclassification of CHF is likely to be independent of prior exposure to NSAIDs and such random misclassification of outcome will not affect the relative risk estimate in a cohort study. Misclassification of exposure may result from either the use of over-the-counter NSAIDs or non-compliance to the prescribed drug regimen. In The Netherlands, the use of over-the-counter preparations is relatively low, and NSAIDs have become available as over-the-counter drugs only during the last few years of the study period. Misclassification of exposure due to the use of over-the-counter NSAIDs will result in an underestimation of the risk estimate, as exposed patients are regarded as non-exposed on the basis of pharmacy records. In addition, filled pharmacy prescriptions have shown to provide a reliable estimate of actual drug exposure (18, 19). Although misclassification of exposure can not completely be excluded in this study, it seems unlikely that it had a substantial effect on the study results. Apart from the use of NSAIDs, several other factors may be associated with the occurrence of relapses of CHF (20-22). The severity of CHF should be regarded as a major determinant in the occurrence of relapses. As patients with severe CHF use more cardiovascular medication than patients with mild CHF, we also adjusted for current use of several classes of cardiovascular drugs and medication for chronic obstructive pulmonary disease.

The negative effect of NSAIDs on cardiovascular homeostasis in patients with CHF

might partly be explained by the interaction between NSAIDs and loop diuretics (23-25). NSAIDs may attenuate the natriuretic response to loop diuretics by interference with prostaglandin-mediated mechanisms. In addition, NSAIDs may compete with loop diuretics with respect to active secretion into the proximal tubule and alter the pharmacokinetics of loop diuretics. In this present study, however, no statistically significant interaction between NSAIDs and loop diuretics could be observed. NSAIDs are associated with a variety of renal function abnormalities, such as acute renal failure, interstitial nephritis, and papillary necrosis (2, 4, 26-28). Use of NSAIDs has been associated with a fourfold increase in risk of hospitalisation for acute renal failure (27). Renal function impairment may easily lead to fluid retention that may precipitate overt heart failure. Patients with elevated baseline serum creatinine levels are at an increased risk of adverse renal effects of NSAIDs. It has been shown that a serum creatinine level of above 180 μmol/l should be regarded as a risk factor for NSAIDs-induced renal failure (29). Patients with an ineffective circulatory volume, including CHF, have also shown to be at an increased risk of NSAID-induced renal function impairment. Future studies with more extensive clinical information should be carried out to evaluate in more detail the effect of renal function on the association between NSAIDs and CHF. The dose-effect relation in our study provides additional evidence for a direct pharmacological effect. As particularly patients using high dosages seem to be at an increased risk, NSAID dosages should preferably not exceed the defined daily dosage.

In conclusion, the use of NSAIDs in patients with a previous hospitalisation for CHF were associated with an increased risk of rehospitalisation for CHF. A first prescription was associated with a threefoldly increased risk, whereas more regular use was associated with a lower risk increase, which may be explained by depletion of susceptibles. Therefore, patients who do not experience a relapse of CHF while using a first prescription of NSAIDs are likely to have a better tolerance of these agents, although these patients are still at an increased risk of relapsing CHF during current use of subsequent NSAID prescriptions.

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Chapter 4

Ibopamine and mortality risk

Risk factors for mortality in users of ibopamine

ABSTRACT

Background: In September 1995, the indication for the oral dopamine agonist ibopamine was restricted in the Netherlands and in several other European countries to patients with NYHA-class II heart failure as a result of an interim analysis of the PRIME-II trial. This trial demonstrated an increased risk of mortality in patients with NYHA-class III / IV heart failure on ibopamine. In September 1995, we initiated a nationwide retrospective cohort study to assess the effects of ibopamine under everyday circumstances in a cohort of users of ibopamine in all NYHA-classes.
Methods: All 2147 community pharmacies and drug dispensing general practitioners received a request to list all patients to whom they had dispensed ibopamine in the preceding years. All responding drug dispensing outlets (DDO) received a questionnaire on cardiovascular risk factors and mortality for the general practitioner of a random sample of these patients. DDO were also requested to send an anonymised printout of the complete medication record. On the end-date of follow-up, February 15th 1996, mortality rates were compared across categories of ibopamine use, adjusted for potential confounders. To assess medication use, drug exposure was compared in a three-months period before date of death in the deceased, and before a random date in those patients who were still alive.
Results: In patients with NYHA-class III / IV heart failure, multivariate analysis indicated that current use of ibopamine was significantly associated with mortality (RR 1.37 ;95% CI: 1.15-1.64). In patients with NYHA-class I/II heart failure, however, multivariate analysis showed a 2.03 (95% CI: 1.10-3.72) risk of mortality in current users of ibopamine. Apart from current use of ibopamine, male gender and increased serum creatinine were also independent risk factors for mortality in all NYHA-classes. No statistically significant association was found between mortality and current use of amiodarone or use of amiodarone at baseline.

Conclusion: The increased risk of mortality in patients with NYHA-class III and IV heart failure on ibopamine seems to confirm the main finding of the recently published PRIME-II trial. However, our results indicate that also patients with NYHA-class I/II heart failure may be at an increased risk of mortality when using ibopamine. Additional research on the effects of ibopamine in these patients is warranted and the use of ibopamine in NYHA-class II heart failure patients may have to be reconsidered.

INTRODUCTION

Ibopamine is an orally administered dopamine agonist which was registered in the Netherlands in 1991 for the treatment of mild congestive heart failure (CHF) in combination with diuretics, and for moderate to severe heart failure in combination with diuretics, angiotensin converting enzyme (ACE) inhibitors or digoxin. Ibopamine has peripheral and renal vasodilatory properties, both in healthy volunteers as well as in patients with congestive heart failure (1, 2). Other pharmacological properties of ibopamine are mild positive inotropic activity, increased diuresis and inhibition of both renine-angiotensin-aldosteron activity and noradrenalin plasma levels when elevated at baseline (1-4). The inhibition of the neurohormonal response in patients with congestive heart failure was considered to be the main mechanism to which the favourable effects of ibopamine were attributed.

In view of the increasing prevalence and incidence of congestive heart failure in western countries, the introduction of ibopamine was regarded as a promising pharmacotherapeutic contribution to the treatment of patients with congestive heart failure (5, 6). Several studies confirmed the beneficial haemodynamic and neurohormonal effects of ibopamine in patients with congestive heart failure without revealing major adverse effects, although previous experiences with new drugs such as milrinone and vesnarinone urged caution with respect to ultimate effects on survival (7-10).

Until August 1995, only limited data were available on the effects of ibopamine on mortality (11). At that time, however, results from an interim analysis of the PRIME-II trial (Prospective Randomized studies of Ibopamine on Mortality and Efficacy) indicated a significantly increased risk of mortality in the group treated with ibopamine as compared to the control group. As a consequence, the safety committee decided to terminate the PRIME-II trial. This randomised placebo-controlled trial was started in 1992 in several European countries to study the effects on mortality and morbidity in patients with moderate to severe congestive heart failure

(New York Heart Association classes III and IV) during long-term ibopamine treatment. Recently, the final findings of the PRIME-II study were published (12).

In response to the findings of the interim analysis of the PRIME-II study in August 1995, the indication for ibopamine in the Netherlands was restricted to heart failure NYHA-class II patients only. At that same time, the Inspectorate for Health Care in the Netherlands initiated a nationwide retrospective cohort study, which aim was to provide information on utilization of ibopamine and on mortality and associated risk factors in patients treated with ibopamine. As we were especially interested in the effects of the use of ibopamine under everyday circumstances, we included patients of all NYHA-classes in our study .

PATIENTS AND METHODS

Early September 1995, all 2147 community-based drug dispensing outlets (DDO) in the Netherlands received a request to list all patients to whom they had dispensed ibopamine in the preceding years. These 2147 DDO comprised 1516 community pharmacies and 631 drug dispensing general practitioners (GP). A reminder was sent in November 1995. The 1983 responding DDO (92%) had dispensed ibopamine to 14,024 patients. Subsequently, all GPs with a DDO who had dispensed ibopamine to a total of 1573 patients received a questionnaire for each of these patients. In addition, a random sample of 1573 patients was drawn out of the remaining 12,451 patients to whom ibopamine was dispensed by their community pharmacist. The same questionnaire was sent to the community pharmacist of the patients in this sample with the request to forward the questionnaire to the patient's GP. This procedure was necessary because we did not dispose of the names of the GPs of the patients to whom ibopamine was dispensed by the community pharmacist. In this way, a total of 3146 questionnaires were sent to the GPs of patients to whom ibopamine was dispensed. The GPs were asked to complete the questionnaire and return it to the Inspectorate for Health Care. The questionnaire concerned questions on cardiovascular risk factors, such as previous myocardial infarction, angina pectoris, atrial fibrillation and diabetes mellitus, indication for ibopamine (NYHA-class), current use of ibopamine and mortality.

The DDOs were also asked to return a printout of the complete medication record of these patients to the Inspectorate for Health Care. Patients were followed from the date of the first prescription until death or the end of the study period which was February 15th , 1996, whichever came first. In order to assess medication use, a drug exposure window of three months was defined in each patient of whom a printout of the medication record was available (n=1146). Every patient still alive

at the end of the study period was assigned a random date in the printout of the medication record. Drug exposure within three months before the date of death in deceased patients was taken and compared to drug exposure in a similar three-months period preceding the random date in those patients who were still alive on February 15th 1996. For every prescription, the legend duration was calculated on the basis of the ratio of the total number of tablets or capsules and the prescribed daily number of tablets or capsules. A patient was considered to be exposed to every drug for which the date of a filled prescription fell within the three months drug exposure window or for which the end date of the legend duration overlapped the date of death in deceased patients or the random date in non-deceased patients. As mortality from all causes was the primary end point of interest, as it was in the PRIME II trial, we analysed risk factors for mortality in deceased patients and in those patients who were still alive at the end of the study period.

Continuous variables were analysed with a Student-t test or Mann-Whitney test when non-normally distributed. The prevalence of risk factors in both deceased and non-deceased patients were analysed and expressed as a relative risk with a 95% confidence interval (95%CI). Apart from crude and stratified univariate relative risk estimates, we performed multivariate analysis on the complete dataset with a risk ratio regression model using the GENMOD procedure of the SAS statistical software package. All variables which were significantly associated with mortality in the univariate analysis were entered into the model. In a second multivariate analysis, carried out in a forward stepwise fashion with the risk ratio regression model, we introduced dummy variables to adjust for confounding which might result from missing values. In the subset for which we obtained both questionnaire data and a printout of the medication record, additional multivariate analyses were performed to correct for potential confounding by severity. Hereto, we made extra dichotomous variables on the basis of two indicators of the severity of CHF. These two severity indicators were based on the simultaneous use within the three months drug exposure window of respectively: 1. an ACE-inhibitor, loop-diuretic and digoxin and 2. an ACE-inhibitor, loop-diuretic, digoxin, and a vasodilatory agent. All tests were two-sided with rejection of the null hypothesis at a p-value < 0.05.

RESULTS

More than 92% of the DDO responded to our request to list all patients to whom ibopamine was dispensed. Based on the 14,024 patients listed by the reacting DDO, the number of patients treated with ibopamine in the preceding years could be estimated at approximately 15,000. The mean number of patients per community

pharmacy was 9 (median:6; range 0-145), and per GP with a DDO 3 (median:1; range:0-20). Completely filled in questionnaires were obtained from the GPs on 2246 patients (71%), of which 1049 came from GPs via pharmacists (66%) and 1197 (76%) from drug dispensing GPs. Printouts of the computerised medication records were available of 1304 patients (41%). The analysis of risk factors for mortality apart from medication use was based on 2246 patients, while in a subset of 1146 patients for whom both a questionnaire and a printout of the medication record were available, the association between mortality and medication use could be studied in more detail. In table I, general characteristics are given of all 2246 patients on whom a questionnaire was obtained. Analyses were based on patients deceased before February 15th 1996 (n=625; mean follow-up 395 days) and those patients who were still alive on that date (n=1621; mean follow-up 679 days).

Of the patients deceased before February 15th 1996, 58% was male compared to 49% of the non-deceased (Table I). The average age of the deceased was 78,5 years compared to 75,6 years of the non-deceased. According to the GP, 47% of the deceased died from cardiac failure and 21% from sudden death. The remaining 32% died from other causes, or the cause of death was unknown. At least 75% of all patients treated with ibopamine were in NYHA class III or IV. The risk of mortality was strongly related to NYHA-class. Compared to patients in NYHA-class I/II, patients in NYHA-class III and NYHA-class IV had a relative risk of mortality of 1.86 (95% CI: 1.41-2.45) and 3.31 (95% CI: 2.52-4.33) respectively. Coronary artery disease and idiopathic cardiomyopathy as primary causes of heart failure were both significantly more prevalent in the deceased, with a relative risk of 1.17 (95% CI: 1.02-1.35) and 1.19 (95% CI: 1.03-1.37) respectively. Several other cardiovascular risk factors were significantly more prevalent in the group of deceased patients. A history of myocardial infarction, syncope within the last 5 years, angina pectoris, atrial fibrillation, chronic obstructive pulmonary disease (COPD) and diabetes mellitus were all significantly more frequent in deceased patients. Increased serum creatinine levels were also associated with a higher risk of mortality, especially when serum creatinine levels were above 151 µmol/l. Failure of ibopamine to improve cardiac status within 2 months after starting and a history of re-admissions to hospital for congestive heart failure were also associated with an increased risk of mortality. Current use of ibopamine was associated with a crude relative risk of 1.82 (95% CI: 1.57-2.12).

Table II describes drug exposure of 1146 patients of whom both a questionnaire and a printout of the medication record were available. Medication use within a drug exposure window of three months before decease or the random date was analysed in both deceased patients and patients who were still alive on February 15th 1996, the end of the study period. Cardiovascular drugs, such as nitrates, digoxin and loop diuretics, were all significantly more frequently used by deceased

Table I:
Descriptives of 2246 users of ibopamine

	deceased patients (n = 625)	non-deceased patients (n = 1621)	Relative risk [95% CI] / p-value
Mean daily dose	315 mg (11.7)*	310 mg (6.1)	p=0.6
Mean follow-up	395 days (62,8)	679 days (43.2)	**p<0.001**
Age (years)	78.5 (0.4)	75.6 (0.3)	**p<0.001**
≤ 64 years	59	223	1.0 [reference]
65-74 years	124	452	1.03 [0.78-1.36]
75-84 years	262	599	**1.45 [1.13-1.86]**
≥ 85 years	180	347	**1.63 [1.26-2.11]**
Gender:			
female	263 (42%)	824 (50,8%)	1.0 [reference]
male	362 (58%)	795 (49,1%)	**1.29 [1.13-1.48]**
unknown		2 (0,1%)	
Cause of death:			
cardiac failure	295 (47%)		
sudden death	128 (21%)		
other causes	145 (23%)		
unknown	57 (9%)		
NYHA – class			
NYHA I/II	52 (8%)	359 (22%)	1.0 [reference]
NYHA III	254 (41%)	827 (51%)	**1.86 [1.41-2.45]**
NYHA IV	253 (40%)	352 (22%)	**3.31 [2.52-4.33]**
unknown	66 (11%)	83 (5%)	

Primary cause CHF					
coronary artery disease	333	(53%)	819	(41%)	**1.17 [1.02-1.35]**
hypertension	93	(5%)	312	(31%)	0.83 [0.68-1.00]
cardiomyopathy	206	(33%)	475	(24%)	**1.19 [1.03-1.37]**
History of myocardial infarction	311	(49%)	706	(44%)	**1.31 [1.14-1.51]**
Syncope < 5 years	136	(22%)	256	(16%)	**1.42 [1.21-1.66]**
Angina pectoris	349	(56%)	850	(52%)	**1.18 [1.02-1.37]**
Atrial fibrillation	253	(40%)	547	(34%)	**1.34 [1.16-1.55]**
COPD	195	(31%)	451	(28%)	**1.21 [1.04-1.40]**
Diabetes mellitus	170	(27%)	370	(23%)	**1.23 [1.06-1.43]**
Serum-creatinine (µmol/l)	157.5	(4.3)	124.3	(1,7)	**p<0.001**
< 94 µmol/l	67	(11%)	366	(22%)	1.0 [reference]
94 - 115 µmol/l	92	(15%)	321	(20%)	**1.44 [1.08-1.91]**
116 - 151 µmol/l	115	(18%)	320	(20%)	**1.71 [1.30-2.24]**
> 151 µmol/l	173	(28%)	256	(16%)	**2.61 [2.03-3.34]**
unknown	178	(28%)	358	(22%)	
Ibopamine improved cardiac status within 2 months	250	(40%)	938	(58%)	**0.58 [0.50-0.67]**
History of readmissions to hospital for heart failure during the use of ibopamine	217	(35%)	317	(20%)	**1.89 [1.64-2.17]**
Current use of ibopamine according to the GP**	339	(54%)	675	(42%)	**1.82 [1.57-2.12]**

* Values are means (SE) or numbers (%).
** Current use of ibopamine is defined as exposure to ibopamine on the date of death in deceased patients and on the end-date of the study in non-deceased patients.

Table II:
Medication use in 1146 patients based on drug-prescriptions within three months before the date of death in deceased patients or random date in non-deceased patients.

Drug	deceased (n=289)	non-deceased (n=857)	RR [95% CI]
Coumarins	79	229	1.02 [0.82-1.28]
HMG-CoA-reductase-inhibitors	3	36	**0.30 [0.10-0.89]**
Trombocyte-aggregation-inhibitors	56	176	0.95 [0.73-1.22]
Digoxin	121	297	**1.25 [1.03-1.53]**
Anti-arrhythmics (class III)	22	52	1.19 [0.83-1.72]
Nitrates	118	283	**1.28 [1.05-1.57]**
Loop diuretics	216	525	**1.62 [1.28-2.05]**
Other diuretics	81	233	1.07 [0.86-1.33]
Beta-blockers	22	114	**0.61 [0.41-0.91]**
ACE-inhibitors	138	361	1.18 [0.97-1.45]
Glucocorticoids	31	53	**1.52 [1.13-2.05]**
Opioids	40	6	**3.84 [3.29-4.49]**
Salicylates	13	9	**2.41 [1.67-3.46]**
Inhalation corticoids	44	82	**1.45 [1.12-1.89]**

patients. Beta-blockers and HMG-CoA-reductase-inhibitors, however, were significantly more frequently used by non-deceased patients. Apart from cardiovascular drugs, glucocorticoids, opioids, salicylates and inhalation corticoids were all significantly more frequently used by deceased patients. Other categories of drugs did not reveal significant differences between both groups. In particular, no statistically significant difference was present between deceased and non-deceased patients with respect to use of anti-arrhythmics (e.g. amiodarone) during the drug exposure window.

In a separate analysis stratified for NYHA-class I/II and III/IV, crude relative risk estimates of mortality in current users of ibopamine according to the GP were statistically significant in both NYHA-class I/II patients (RR 2.30 95% CI: 1.33-3.99) and NYHA-class III/IV patients (RR 1.74 95% CI: 1.48-2.04) (Table III) . Furthermore, risk of mortality increased within each stratum of increased serum creatinine level. In patients with NYHA-class I/II congestive heart failure, renal impairment increased the risk of death more than in patients with NYHA class III/IV congestive

heart failure.

As we had a special interest in the adjusted relative risks of mortality in the pooled NYHA-classes I/II (n=411) and III/IV (n=1686), the risk ratio regression models for these groups were built separately (Table IV). In NYHA-class I/II, the univariately significant variables age (in 4 classes), gender, cardiomyopathy, syncope < 5 years, serum creatinine (in 4 classes), and current use of ibopamine according to the GP were entered in the model. Only gender, serum creatinine > 151 μmol/l and current use of ibopamine according to the GP remained statistically significantly associated with mortality. This led to an adjusted relative risk of mortality of 2.03 (95% CI: 1.10-3.72) for current use of ibopamine in patients with NYHA-class I/II CHF. In NYHA-class III/IV, the univariately significant variables age, gender, history of myocardial infarction, syncope < 5 years, atrial fibrillation, serum creatinine, and current use of ibopamine according to the GP were entered in the model. After adjustment in the risk ratio model, gender, history of myocardial infarction, serum creatinine >115 μmol/l and current use of ibopamine according to the GP were statistically significantly associated with mortality. The adjusted relative risk of mortality was 1.37 (95% CI: 1.15-1.64) for current use of ibopamine. In a second multivariate analysis, we used dummy variables to adjust for potential confounding by missing values. This led to an adjusted relative risk of mortality of 1.97 (95% CI: 1.22-3.16) in patients with NYHA-class I/II, whereas the adjusted relative risk in patients with NYHA-class III/IV remained actually unchanged (1.38 ;95% CI:1.22-1.56).

DISCUSSION

In accordance with a large randomized trial (12), we found an increased risk of mortality during use of ibopamine in patients with NYHA-class III and IV at baseline. Our relative risk estimation of 1.37 was only slightly higher than the 1.26 found in the trial. Although most trials are remote from the situation of drug use under everyday circumstances, the results from our cohort study support the trial results. Importantly, we also found a statistically significantly increased risk of mortality in patients with NYHA-class I/II at baseline, patients that were not included in the PRIME-II trial.

Several other risk factors for mortality in patients with congestive heart failure could be distinguished in the overall univariate analysis (Table I). Patients with a history of angina pectoris, myocardial infarction, atrial fibrillation, diabetes and COPD had an increased risk of mortality in our study. These findings are in accordance with several prospective follow-up studies in which patients with con-

Table III:
Univariate analysis of risk factors for mortality in a cohort of users of ibopamine, according to NYHA-class.

	NYHA class I/II (n=411)			NYHA class III/IV (n=1686)		
	deceased (n=52)	non-deceased (n=359)	crude RR [95% CI]	deceased (n=507)	non-deceased (n=1179)	crude RR [95% CI]
Age	80.0 (1.4)	76.3 (0.5)	**p=0.015**	78.3 (0.5)	75.5 (0.3)	**p<0.001**
≤ 64 years	4	42	reference	49	161	reference
65-74 years	8	92	0.92 [0.29-2.90]	104	343	1.00 [0.74-1.34]
75-84 years	22	151	1.46 [0.53-4.03]	208	416	**1.43 [1.09-1.87]**
≥ 85 years	18	74	2.25 [0.81-6.26]	146	259	**1.54 [1.17-2.04]**
Gender:						
Female	17	193	reference	210	593	reference
male	35	166	**2.15 [1.25 - 3.71]**	297	584	**1.29 [1.11-1.50]**
Primary cause CHF						
coronary artery disease	21	148	0.97 [0.58-1.62]	292	635	1.11 [0.96-1.29]
hypertension	6	78	0.55 [0.22-1.15]	80	221	0.86 [0.70-1.06]
cardiomyopathy	22	99	**1.75 [1.05-2.91]**	176	360	1.14 [0.98-1.33]
history of MI	21	121	1.30 [0.77-2.19]	274	541	**1.28 [1.10-1.48]**
syncope < 5 year	14	52	**1.97 [1.13-3.44]**	115	198	**1.32 [1.11-1.56]**
angina pectoris	24	145	1.17 [0.70-1.96]	305	670	1.08 [0.93-1.26]
atrial fibrillation	19	101	1.41 [0.82-2.41]	221	442	**1.28 [1.10-1.49]**
COPD	15	82	1.31 [0.74-2.29]	168	352	1.13 [0.97-1.32]
diabetes	13	61	1.47 [0.82-2.63]	145	295	1.13 [0.96-1.33]

serum creatinine:						
<94 µmol/l	5	109	reference	55	243	reference
94 - 115 µmol/l	5	65	1.63 [0.49-5.43]	79	243	1.33 [0.98-1.81]
116-151 µmol/l	11	55	**3.80 [1.38-10.46]**	102	243	**1.60 [1.20-2.14]**
>151 µmol/l	10	26	**6.33 [2.32-17.32]**	158	220	**2.26 [1.73-2.96]**
missing	21	104		113	230	
current use of ibopamine according to the GP*	30	138	**2.30 [1.33-3-99]**	293	507	**1.74 [1.48-2.04]**

* Current use of ibopamine is defined as exposure to ibopamine on the date of death in deceased patients and on the end-date of the study in non-deceased patients.

Table IV
Multivariate analysis of risk factors for mortality in a cohort of users of ibopamine, according to NYHA-class.

	NYHA class I/II (n=411)	NYHA class III/IV (n=1686)
	adjusted RR	adjusted RR
Age:		
≤ 64 years	reference	reference
65-74 years	1.35 [0.30-6.21]	0.86 [0.60-1.22]
75-84 years	2.39 [0.57-9.98]	1.19 [0.87-1.65]
≥ 85 years	2.97 [0.67-13.12]	1.36 [0.98-1.90]
Gender:		
female	reference	reference
male	**2.03 [1.02-4.04]**	**1.23 [1.02-1.49]**
Primary cause CHF:		
cardiomyopathy	1.68 [0.89-3.17]	
history of MI		**1.28 [1.07-1.52]**
syncope < 5 year	1.80 [0.90-3.63]	1.17 [0.96-1.43]
atrial fibrillation		1.07 [0.90-1.28]
serum creatinine:		
<94 µmol/l	reference	reference
94 - 115 µmol/l	1.16 [0.44-3.07]	1.25 [0.90-1.72]
116-151 µmol/l	2.08 [0.85-5.09]	**1.47 [1.08-2.00]**
>151 µmol/l	**2.86 [1.19-6.85]**	**1.82 [1.35-2.44]**
current use of ibopamine according to the GP*	**2.03 [1.10-3.72]**	**1.37 [1.15-1.64]**

* Current use of ibopamine is defined as exposure to ibopamine on the date of death in deceased patients and on the end-date of the study in non-deceased patients.

gestive heart failure were involved (13-18). Consistent with our findings, use of nitrates and inhalation corticoids was more frequently encountered in deceased patients as compared to the non-deceased. Not suprisingly, a very strong association was found with opioids in the deceased, as these drugs are frequently prescribed in the terminal stage of heart failure to relieve symptoms of respiratory distress. Ibopamine improved cardiac status within two months after the first prescription significantly more frequently in non-deceased patients as compared to the deceased. Hence, a rapid therapeutic response to ibopamine seems to be protective with respect to mortality, although this finding may have been subject to recall bias by its retrospective and subjective nature. A history of readmissions to

hospital for congestive heart failure and current use of ibopamine were also significantly more frequent in deceased patients. As the associations remained present in the analysis stratified for NYHA-class, the severity of congestive heart failure and thereby the liability of physicians to continue treatment in the most severe patients does not seem to be the sole explanation for these associations, as also in patients with NYHA class I / II at baseline death was associated with current use of ibopamine. It should be emphasized, however, that the NYHA-classification has limitations in correctly estimating the severity of congestive heart failure. In patients with NYHA-class I/II, significantly more patients died from other courses, such as cachexia or malignancies.

Interestingly, increased serum creatinine levels were associated with the risk of death in the stratified analysis independently from NYHA-class (Table III). In particular in patients with mild congestive heart failure (NYHA class I/II), a statistically significant association was found between various levels of renal impairment and the risk of death, also after adjustment for other risk factors. In patients with moderate to severe congestive heart failure, a similar association was found, albeit less explicit. In the recently published report on the PRIME-II trial, the role of renal function was not discussed. It has been suggested that impaired renal function might lead to high levels of epinine, the active metabolite of ibopamine, and that these high plasma concentrations might account for the increased mortality in patients treated with ibopamine (19).

With respect to concomitant medication, nitrates, glucocorticoids and inhalation corticoids were significantly more frequently used in deceased patients, but this finding can be explained by the higher prevalence of angina pectoris and COPD in the deceased. Loop diuretics and digoxin were significantly more frequently used by deceased patients, whereas beta-blockers seemed to have a protective effect with respect to mortality. These findings might be compatible with the assumption that the severity of CHF explains the increased risk of mortality during use of ibopamine. Adjustment in the multivariate analysis for severity of CHF, however, did not substantially change the risk estimate.

In a subgroup analysis of the PRIME-II trial, therapy with amiodarone at baseline was identified as an independent predictor of mortality in patients treated with ibopamine. We were able to analyse current use of amiodarone both in deceased and non-deceased patients within the drug exposure window as well as the concurrent use of amiodarone at baseline. Both at baseline as well as within the drug exposure window, no significant differences in the use of amiodarone between deceased and non-deceased patients could be observed. Therefore, our findings do not confirm the hypothesis of the investigators of the PRIME-II trial that a possible interaction between ibopamine and the anti-arrhythmic drug amiodarone might

contribute to the increased mortality to ibopamine.

The validity of epidemiological studies may be jeopardized by selection bias, information bias or confounding. Selection bias might explain a high mortality in the total cohort because of selective prescribing of ibopamine to high risk patients with heart failure. As we used non-deceased as a reference group of patients who had been subject to the same prescribing habits as the deceased, selection bias is not very likely. This is endorsed by the fact that the relative risk estimates of mortality during the use of ibopamine of 1.37 (GP-information) in NYHA-classes III/IV was very close to the risk estimate of 1.26 in the trial (12). Information bias of GP might be present if they have a different recall of concurrent illnesses or drug use of deceased patients as compared to non-deceased patients. As the pharmacy data on ibopamine use showed the same trend this is also unlikely, especially as such data were gathered unbiased and before disease onset. Because filled prescriptions are not always used, however, we think that the GP will have a more reliable picture of the medicines which have actually been taken by patients in the terminal phase of their illness. Misclassification of outcome (death) is unlikely, whereas random misclassification of exposure would result in a conservative estimate of the relative risk. The calculated relative risk of mortality may have been influenced by the fact that the questionnaires were filled in after the announcement that the indication of ibopamine had been restricted to patients with NYHA class II CHF only. However, we were able to perform an additional analysis which was based on the prescription data of the medication records and restricted to only these patients with a date of death or random index date before 1 september 1995. Based on this analysis, the use of ibopamine within the three months drug exposure window was associated with mortality in both patients with NYHA I/II CHF as well as NYHA class III/IV CHF, with a relative risk of 4.48 (95% CI 1.11-21.20) and 2.94 (95%CI 1.99-4.33) respectively. As this analysis pertains to a period before the results of the interim-analysis of the PRIME-II trial came available, the results of this analysis can not be influenced by any negative publicity with respect to ibopamine.

Potential confounding was dealt with by adjusting for all known independent risk factors for mortality in patients with heart failure. As the analysis with dummy variables for all variables with missing values yielded similar results, these can not be regarded as a source of substantial confounding. The non-response of GPs to questionnaires was 34% when sent via pharmacies, and 24% when sent directly to drug dispensing GPs. Although this was significantly different, it was not associated with a difference in mortality and adjustment did not change the risk estimates. Also, there was no substantial difference in overall mortality or risk factors for those patients of whom we had only a questionnaire, and those of whom we had both a questionnaire and a medication printout. Due to negative publicity, sur-

vivors might have gradually been withdrawn from ibopamine before the end of the study period and this could have overestimated the relative risk. For this reason, we used a random end-date in the non-deceased which showed that publicity did not bias our risk estimates. Finally, we were unable to validate the information on cardiovascular risk factors provided by the GP. However, as the vast majority of patients on ibopamine are also regularly seen by a cardiologist, it is likely that most information provided by the GPs came from consultant cardiologists.

In conclusion, in our nationwide cohort study we found similar risk estimates for mortality during current use of ibopamine in patients with NYHA-classes III/IV heart failure as found in the PRIME-II trial. In addition, we also found an increased risk of mortality in patients with NYHA-classes I/II heart failure. Although definitive proof of the causal nature of this association can only come from another randomized trial, we think that additional studies on ibopamine are warranted and that its therapeutic role in NYHA class I/II patients should be reconsidered.

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Confounding by contraindication in a study on mortality risk of ibopamine use

ABSTRACT

Background: Confounding by contraindication pertains to differences in outcome between treated and untreated patients which may be attributed to the presence of a contraindication for treatment in untreated patients. To have a confounding effect, this contraindication should be independently associated with the outcome of interest.

Objective: To evaluate in detail the effects of confounding by contraindication in the analysis of a cohort study on risk factors for mortality in users of ibopamine which resulted from a restriction of the indication of ibopamine early September1995.

Design: Retrospective cohort study

Setting: General practitioners and pharmacists in the Netherlands

Patients and methods: The study cohort consisted of 1146 patients with congestive heart failure who had received at least one prescription of ibopamine. Cardiovascular risk factors and clinical characteristics were assessed by a questionnaire, filled in by the general practitioner. Information on medication use was obtained from print-outs of the computerised medication records. Each patient was assigned an index date, which was the date of death in deceased patients or a random date in the medication record for patients still alive at the end of the study period. Separate analyses were carried out on the association between the use of ibopamine and mortality for patients with an index date before and after September 8th 1995.

Results: In patients with an index date before September 8th 1995, current use of ibopamine was univariately associated with a relative risk of mortality of 3.02 (95% CI: 2.12-4.30), whereas in patients with an index date after September 8th 1995, the relative risk of mortality during current use of ibopamine was 0.71 (95% CI: 0.53-0.96). In a multivariate analysis, these associations were 2.62 (95% CI: 1.76-3.90) and 0.93 (95%CI: 0.84-1.02) respectively.

Conclusions: In the absence of any other likely alternative explanation, the marked inversion of the relative risk estimate can be regarded as a practical example of confounding by contraindication in an epidemiological study.

INTRODUCTION

Confounding is one of the major threats to validity in epidemiological studies. The popularity of randomised clinical trials follows from the rigorous restriction of the potential for confounding by nature of this study design. In spite of the attraction of randomisation in research on drug effects, several research questions, particularly with respect to drug safety issues, can only be addressed efficiently with an observational study (1). Careful study design and appropriate data analysis may, however, strongly reduce the effects of potential confounding in observational studies (2). In particular confounding by indication and contraindication should be considered as major threats to validity in non-randomised comparisons of treatment effects (3). Confounding by indication pertains to differences in outcome between treated and untreated patients which are not attributed to the treatment effect, but which may occur when the indication for treatment is an independent risk factor for the study outcome. Then, non-comparability with respect to the indication for treatment between treated and untreated patients may account, at least in part, for the observed differences in outcome. Alternatively, in confounding by contraindication, differences in outcome between treated and untreated patients are, at least in part, attributed to the presence of a contraindication for treatment in the untreated patients. Confounding by contraindication will mostly lead to an underestimation of the relative risk, because patients at risk for the outcome of interest are withheld from treatment.

Recently, we completed a cohort study in the Netherlands on risk factors for mortality in users of ibopamine, an orally administered dopamine agonist (4). This cohort study was initiated in response to the results of an interim analysis of the PRIME-II trial (Prospective Randomised studies of Ibopamine on Mortality and Efficacy) in August 1995. These results indicated a significantly increased risk of mortality in patients with moderate to severe congestive heart failure (NYHA III-IV) treated with ibopamine as compared to placebo (5). Therefore, early September 1995, the indication for ibopamine in the Netherlands was restricted to patients with NYHA II heart failure only (6). In the cohort study, emphasis was given to the putative association between the use of ibopamine and the increased risk of mortality. The study was conducted retrospectively for a period running from the date of the first prescription of ibopamine until death or the end of the study period on February

15th 1996, whichever came first. As the date of the restriction of the indication of ibopamine, September 1st 1995, fell within the study period, this offered a unique opportunity to study the influence of the restriction of the indication for ibopamine on the association between the use of ibopamine and the risk of mortality.

In most studies in which confounding by contraindication is suspected, the extent to which this might have influenced the results is difficult to quantify. Therefore, the concept of confounding by contraindication is commonly discussed in merely theoretical terms. In the present study, however, we were able to quantify the effect of confounding by contraindication by covering a period with a known and abrupt change of the registered indication and contraindications.

PATIENTS AND METHODS

The methods of this retrospective cohort study have been described in more detail elsewhere (4). In summary, all 2147 community-based drug dispensing outlets (DDO) in the Netherlands were requested early September 1995 to list all patients to whom they had dispensed ibopamine in the preceding years. The 1983 responding DDO (92%) had dispensed ibopamine to 14,024 patients. Subsequently, all general practitioners (GP) with a DDO who had dispensed ibopamine to a total of 1573 patients received a questionnaire for each of these patients. In addition, a random sample of 1573 patients was taken from the remaining 12,451 patients to whom ibopamine was dispensed by their community pharmacist. The same questionnaire was sent to the GPs of the 1573 patients in this random sample. The questionnaire concerned questions on cardiovascular risk factors, indication for ibopamine (NYHA-class), current use of ibopamine and mortality. The DDOs were also asked to return a printout of the complete computerised medication record of these patients. Patients were followed from the date of the first prescription until death or the end of the study period (February 15th 1996), whichever came first. The first prescription of ibopamine for a patient in the cohort was on April 1st 1991. To assess medication use, a drug exposure window of three months preceding an index date was defined for each patient of whom both a questionnaire and a printout of the medication record was available (n=1146). Every patient still alive at the end of the study period was assigned a random date in the printout of the medication record. The index date was defined as the date of death in deceased patients or the random date in non-deceased patients. Drug exposure within three months before the index date in deceased patients was compared to drug exposure in a similar three-months period preceding the index date in those patients who were still alive on February 15th 1996. Patients were considered to be current users of every drug for which the date of a filled prescription fell within the three

months drug exposure window or for which the end date of the legend duration overlapped the index date, i.e. the date of death in deceased patients or the random date in non-deceased patients.

In the present study, we evaluated the potential influence of confounding by contraindication as a result of the restriction of the indication of ibopamine early September 1995 in 1146 patients of whom both a questionnaire and a printout of the medication record were available. We carried out separate analyses for patients with an index date before September 8th 1995 (n=739) and for patients with an index date after September 8th 1995 (n=407). On that date, all pharmacists and GPs with a drug dispensing outlet received a letter from the Inspectorate for Health Care in the Netherlands with the request to contact the prescribers of ibopamine of all patients to whom they were dispensing ibopamine and to discuss with the prescribers whether further continuation of ibopamine was still indicated in these patients .

Apart from crude and stratified univariate relative risk estimates, we performed multivariate analyses with a risk ratio regression model using the GENMOD procedure of the SAS statistical software package. All variables which were significantly associated with mortality in the univariate analysis were entered into the model. Additional multivariate analyses were performed to correct for potential confounding by severity. Potential confounding by severity was addressed by introducing two severity indicators into the statistical model which were based on actual drug use within the drug exposure window. These two severity indicators reflected the simultaneous use within the three months drug exposure window of respectively: 1. an ACE-inhibitor, loop-diuretic and digoxin and 2. an ACE-inhibitor, loop-diuretic, digoxin, and a vasodilatory agent.

RESULTS

Table I gives the characteristics of users of ibopamine with an index date before September 8th 1995 (n=739) and those with an index date after September 8th 1995 (n=407). No statistically significant differences in age, gender, NYHA-classification at baseline, any of the cardiovascular risk factors, and the numbers of missing values could be observed between both groups of patients. In table II, univariate analyses of risk factors of mortality are shown for deceased and non-deceased patients, stratified for index date before and after September 8th 1995. Male gender, NYHA-classification at baseline, history of myocardial infarction and increased serum creatinine were associated with an increased risk of mortality in both groups of patients. Increased age, the presence of severity indicator 2, and syn-

Table I
Characteristics of the cohort of 1146 users of ibopamine stratified for index date before and after September 8th 1995.

	patients with index date before September 8th 1995 (n=739)	patients with index date after September 8th 1995 (n=407)	RR 95% CI / p-value
Age	74.4 (0.4)*	75.6 (0.6)	p=0.08
Male gender	366 (49.5%)	191 (47%)	1.04 (0.95-1.13)
missing	1 (0.1%)		
NYHA-I/II	125 (17%)	78 (19%)	0.95 (0.84-1.06)
NYHA-III	362 (49%)	206 (51%)	0.98 (0.90-1.06)
NYHA-IV	208 (28%)	96 (24%)	1.08 (0.99-1.19)
missing	44 (6%)	27 (6%)	0.96 (0.79-1.16)
History of myocardial infarction	355 (48%)	175 (43%)	1.07 (0.99-1.17)
missing	14 (2%)	7 (2%)	1.03 (0.76-1.40)
syncope <5 years	151 (20%)	71 (17%)	1.07 (0.96-1.18)
missing	39 (5%)	16 (4%)	1.11 (0.93-1.32)
angina pectoris	415 (56%)	213 (52%)	1.06 (0.97-1.15)
missing	53 (7%)	28 (7%)	1.02 (0.86-1.20)
atrial fibrillation	271 (37%)	140 (34%)	1.04 (0.95-1.13)
missing	67 (9%)	43 (11%)	0.94 (0.80-1.10)
COPD	218 (30%)	105 (26%)	1.07 (0.97-1.17)
missing	69 (9%)	34 (8%)	1.04 (0.90-1.20)
diabetes mellitus	161 (22%)	91 (22%)	0.99 (0.89-1.10)
missing	67 (9%)	35 (9%)	1.02 (0.88-1.18)
Serum-creatinine:	129 µmol/l (2.8)	135 µmol/l (4.2)	p=0.22
missing	170	87	1.03 (0.93-1.15)
severity indicator 1	79 (11%)	34 (8%)	1.09 (0.96-1.25)
severity indicator 2	70 (10%)	41 (10%)	0.98 (0.84-1.13)

* values are means (S.E.) or numbers (%).

cope within the last 5 years were statistically significantly associated with an increased risk of mortality in patients with an index date before September 8th 1995.

Table II
Univariate analysis of risk factors for mortality in 1146 ever users of ibopamine, stratified for index date.

	patients with index date before September 8th 1995 (n=739)			patients with index date after September 8th 1995 (n=407)		
	Deceased (n=165)	non-deceased (n=574)	RR (95% CI)	deceased (n=124)	non-deceased (n=283)	RR (95% CI)
Age: ≤ 64 years	25 (15%)	88 (15%)	reference	14 (11%)	37 (13%)	reference
65-74 years	32 (19%)	185 (32%)	0.67 (0.42-1.07)	28 (23%)	90 (32%)	0.86 (0.50-1.50)
75-84 years	70 (43%)	214 (37%)	1.11 (0.75-1.66)	49 (39%)	99 (35%)	1.21 (0.73-1.99)
≥ 85 years	38 (23%)	84 (15%)	1.41 (0.91-2.18)	32 (26%)	55 (19%)	1.34 (0.79-2.26)
missing		3 (1%)		1 (1%)	2 (1%)	
mean age	76.8 (0.8)	73.7 (0.5)	**p = 0.002**	77.0 (0.9)	75.0 (0.7)	p = 0.09
Male gender:	96 (58%)	270 (47%)	**1.41 (1.08-1.86)**	68 (55%)	123 (44%)	**1.37 (1.02-1.84)**
NYHA-I/II	12 (7%)	113 (20%)	reference	12 (10%)	66 (23%)	reference
NYHA-III	64 (39%)	298 (52%)	**1.84 (1.03-3.30)**	53 (43%)	153 (54%)	1.67 (0.95-2.96)
NYHA-IV	73 (44%)	135 (23%)	**3.66 (2.07-6.46)**	49 (39%)	47 (17%)	**3.32 (1.90-5.79)**
Missing	16 (10%)	28 (5%)		10 (8%)	17 (6%)	
History of myocardial infarction	93 (56%)	262 (46%)	**1.49 (1.13-1.98)**	66 (53%)	109 (39%)	**1.54 (1.14-2.08)**
syncope <5 years	45 (27%)	106 (19%)	**1.54 (1.15-2.08)**	23 (19%)	48 (17%)	1.13 (0.77-1.64)
angina pectoris	101 (61%)	314 (55%)	1.29 (0.96-1.75)	65 (52%)	148 (52%)	0.96 (0.71-1.29)
atrial fibrillation	62 (38%)	209 (36%)	1.09 (0.82-1.46)	56 (45%)	84 (30%)	1.63 (1.20-2.21)
COPD	57 (35%)	161 (28%)	1.33 (0.99-1.78)	30 (24%)	75 (27%)	0.95 (0.66-1.35)
diabetes mellitus	43 (26%)	118 (21%)	1.29 (0.95-1.75)	35 (28%)	56 (20%)	1.35 (0.98-1.86)

Serum-creatinine (µmol/l) in quartiles						
< 94 µmol/l	16 (10%)	134 (23%)	reference	18 (14%)	66 (23%)	reference
94 - 115 µmol/l	34 (21%)	119 (21%)	**2.08 (1.20-3.61)**	16 (13%)	48 (17%)	1.17 (0.65-2.10)
116-151 µmol/l	28 (17%)	101 (17%)	**2.03 (1.15-3.59)**	24 (19%)	66 (23%)	1.24 (0.73-2.12)
> 151 µmol/l	47 (28%)	90 (16%)	**3.22 (1.92-5.40)**	38 (31%)	44 (16%)	**2.16 (1.35-3.46)**
missing	40 (24%)	130 (23%)		28 (23%)	59 (21%)	
mean serum-creatinine	152 (7.6)	123 (2.8)	**p<0.001**	161 (11.3)	124 (3.3)	**p = 0.002**
severity indicator 1	17 (10%)	62 (11%)	0.96 (0.62-1.50)	15 (12%)	19 (7%)	1.51 (1.00-2.27)
severity indicator 2	22 (13%)	48 (8%)	**1.47 (1.01-2.14)**	13 (11%)	28 (10%)	1.05 (0.65-1.68)
current use of ibopamine	132 (80%)	289 (50%)	**3.02 (2.12-4.30)**	56 (45%)	162 (57%)	**0.71 (0.53-0.96)**

Current use of ibopamine was associated with a relative risk of mortality of 3.02 (95% CI: 2.12-4.30) in patients with an index date before September 8th 1995, whereas in patients with an index date after September 8th 1995, the relative risk of mortality during current use of ibopamine was 0.71 (95% CI: 0.53-0.96). In patients with an index date after September 8th 1995 who received a new prescription of ibopamine after this date, the relative risk of mortality was 0.66 (95% CI 0.48-0.91) when compared to patients who did not receive a new prescription after September 8th 1995. These new prescriptions of ibopamine were mostly refills of a treatment initiated before September 8th 1995, and apparently continued by the prescriber in spite of the Inspectorate's warning. Severity indicators were present in 115 (27%) of the 421 current users of ibopamine with an index date before September 8th 1995 compared to 46 (21%) of the 218 current users of ibopamine with an index date after September 8th 1995 (RR 1.29 95%CI: 0.96-1.75). Results of the multivariate analyses (table III), in which all univariately significant variables were included in combination with both severity indicators, demonstrated for patients with an index date before September 8th 1995 an adjusted relative risk of mortality during current use of ibopamine of 2.62 (95% CI 1.76-3.90), and in patients with an index date after September 8th 1995 a relative risk of 0.93 (95% CI 0.84-1.02). In table IV, statistically significant differences are shown between current and past users of ibopamine, stratified for index date. In patients with an index date before September 8th 1995, current use of ibopamine was statistically significantly associated with the presence of both severity indicators, increased serum creatinine levels and an increased number of hospital admissions for CHF during the use of ibopamine. None of these associations remained statistically significant in patients with an index date after September 8th 1995. Serum creatinine level was statistically significantly higher in current users of ibopamine with an index date before September 8th 1995 (136 μmol/l versus 119 μmol/l), whereas in patients with an index date after September 8th 1995, no statistically significant differences in serum creatinine level between current and past users of ibopamine could be demonstrated.

Information on the actual use of ibopamine until the date of death was based on the questionnaires which were completed by the GPs. In 253 of the 289 deceased patients (88%), the GP was able to provide detailed information on the use of ibopamine until the date of death. In deceased patients with an index date before September 8th 1995, 76% used ibopamine until the date of death, whereas in deceased patients with an index date after September 8th 1995, 46% was on ibopamine until the date of death. Figure I shows the percentage of patients using ibopamine until the date of death of those patients who deceased in the last 7 months of 1995. In the months preceding September 8th 1995, most deceased patients used ibopamine until the date of death. After September 8th 1995, the percentage of deceased patients who used ibopamine until the date of death showed a clear decline. Mean

Table III
Adjusted relative risk of mortality in 1146 ever users of ibopamine with index date before and after September 8th 1995.

	patients with index date before September 8th 1995 (n=739)	patients with index date after September 8th 1995 (n=407)
	RR (95% CI)	RR (95% CI)
Age: ≤ 64 years	Reference	reference
65-74 years	**0.54 (0.32-0.91)**	0.93 (0.78-1.10)
75-84 years	1.07 (0.70-1.61)	1.01 (0.85-1.18)
≥ 85 years	1.48 (0.90-2.44)	1.05 (0.88-1.26)
Sex: female	Reference	reference)
Male	**1.50 (1.08-2.08)**	1.08 (0.98-1.20)
NYHA-I/II	Reference	reference
NYHA-III	1.24 (0.65-2.37)	**1.24 (1.04-1.48)**
NYHA-IV	**2.14 (1.13-4.06)**	**1.41 (1.17-1.69)**
History of myocardial infarction	**1.36 (1.01-1.84)**	1.07 (0.96-1.19)
syncope <5 years	0.93 (0.67-1.27)	----------
severity indicator 1	0.78 (0.48-1.25)	1.08 (0.88-1.32)
severity indicator 2	1.32 (0.90-2.44)	0.97 (0.82-1.13)
Serum-creatinine (µmol/l) in quartiles:		
< 94 µmol/l	Reference	reference
94-115 µmol/l	1.60 (0.91-2.82)	1.05 (0.90-1.23)
116-151 µmol/l	1.31 (0.73-2.38)	1.04 (0.90-1.20)
>151 µmol/l	**2.32 (1.35-3.97)**	1.09 (0.93-1.26)
current use of ibopamine	**2.62 (1.76-3.90)**	0.93 (0.84-1.02)

dosage of ibopamine in patients with an index date before September 8th 1995 was 319 mg/day, whereas in patients with an index date after September 8th 1995, mean dosage of ibopamine slightly decreased towards 293 mg/day (p=0.03).

DISCUSSION

In current users of ibopamine with an index date before September 8th 1995 (n=739), a statistically significantly increased risk (adjusted RR 2.62; 95% CI: 1.76-3.90) of mortality could be demonstrated. In patients with an index date after September

Table IV
Univariate analysis of statistically significantly associated risk factors for mortality in current and past users of ibopamine, stratified for index date.

	patients with index date before September 8th 1995 (n=739)			patients with index date after September 8th 1995 (n=407)		
	Current users of ibopamine (n=421)	Past users of ibopamine (n=318)	RR (95% CI)	Current users of ibopamine (n=218)	Past users of ibopamine (n=189)	RR (95% CI)
severity indicator 1	63 (15%)	16 (5%)	**2.97 (1.75-5.05)**	20 (9%)	14 (7%)	1.24 (0.64-2.38)
severity indicator 2	52 (12%)	18 (6%)	**2.18 (1.30-3.66)**	26 (12%)	15 (8%)	1.50 (0.82-2.75)
Serum-creatinine (µmol/l) in quartiles						
< 94 µmol/l	74 (17%)	76 (24%)	reference	47 (22%)	37 (19%)	reference
94-115 µmol/l	87 (21%)	66 (21%)	1.16 (0.93-1.46)	44 (20%)	20 (11%)	1.38 (0.91-2.08)
116-151 µmol/l	88 (21%)	41 (13%)	**1.55 (1.17-2.06)**	41 (19%)	49 (26%)	0.82 (0.61-1.09)
>151 µmol/l	84 (20%)	53 (16%)	1.29 (1.00-1.67)	40 (18%)	42 (22%)	0.86 (0.64-1.18)
missing	88 (21%)	82 (26%)	0.81 (0.62-1.05)	46 (21%)	41 (22%)	0.94 (0.70-1.26)
mean serum-creatinine	136 (4.2)	119 (2.9)	**p=0.001**	133 (6.5)	138 (5.1)	p=0.58
no. of hospital admissions for CHF during use of ibopamine:						
0	332 (79%)	266 (84%)	reference	175 (80%)	156 (83%)	reference
1	49 (12%)	36 (11%)	1.08 (0.72-1.61)	28 (13%)	19 (10%)	1.27 (0.74-2.19)
≥2	40 (9%)	16 (5%)	**1.90 (1.08-3.31)**	15 (7%)	14 (7%)	0.96 (0.48-1.93)

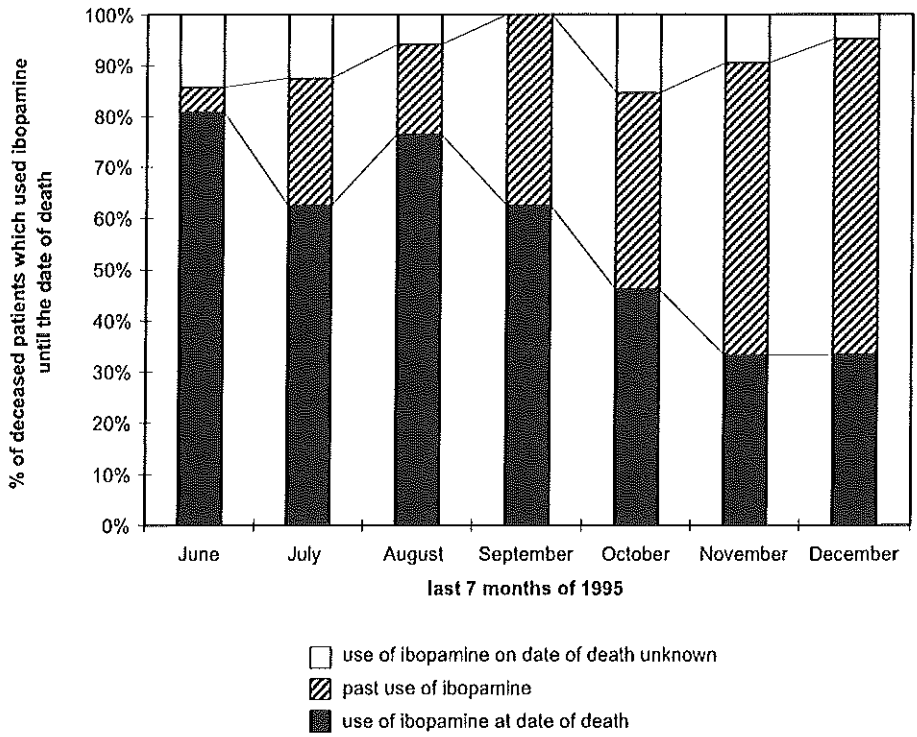

Figure I
Use of ibopamine until date of death.

8th 1995 (n=407), however, current use of ibopamine was associated with a neutral or even a protective effect with respect to mortality, although not statistically significant in the multivariate analysis (adjusted RR 0.93; 95% CI: 0.84-1.02). These seemingly contradictory findings can be explained by confounding by contraindication, resulting from the restriction of the indication of ibopamine early September 1995, and two direct mailings with regard to this issue to physicians and pharmacists by the Inspectorate for Health Care in the Netherlands. Until September 1995, ibopamine was regarded (and marketed) as a useful drug in the treatment of CHF. Therefore, the analysis of patients with an index date before september 8th could not have been influenced by the negative publicity on ibopamine. The unexpected reversal of the relative risk towards a neutral or even protective effect of ibopamine with respect to mortality in current users of ibopamine with an index date after September 8th 1995 constitutes, in the absence of any other likely explanation, a practical example of confounding by contraindication in an epidemiological study. In the current study, confounding by contraindication led to an underestimation of the relative risk. Theoretically, confounding by contra-indication may also lead to an overestimation of the relative risk if the contraindication has an effect on the

outcome into the same direction as treatment. We think, however, that such a situation is likely to be less common than the opposite.

Although the restriction of the indication was officially implemented on September 1st 1995, earlier experience with acute drug safety issues such as with acitretine has learned that prescribers themselves are unable to track all patients to whom they have prescribed a specific drug (7). Therefore, we used in our analyses September 8th 1995 as a cut-off date, as around that date all pharmacists and GPs with a DDO were requested to contact the prescribers of ibopamine of all patients to whom they were dispensing ibopamine.

Until September 8th 1995, ibopamine seemed to have been used relatively more frequently in patients with severe CHF as compared to patients with less severe complaints. Additional analyses of our data support this hypothesis. In patients with an index date before September 8th 1995, both severity indicators were statistically significantly associated with current use of ibopamine (crude RRs respectively 2.97; 95% CI 1.75-5.05 and 2.18; 95% CI 1.30-3.66), whereas in patients with an index date after September 8th 1995, no statistically sigificant association between the presence of severity indicators and current use of ibopamine could be observed. In addition, there is a trend towards a higher prevalence of severity indicators in current users of ibopamine with an index date before September 8th (27%) compared to current users of ibopamine with an index date after September 8th 1995 (21%) (RR 1.29; 95% CI: 0.96-1.75). In patients with an index date before September 8th 1995, current use of ibopamine was statistically significantly associated with ≥ 2 hospital admissions for CHF during the use of ibopamine (RR 1.90; 95% CI: 1.08-3.31) and increased mean serum creatinine levels (136 µmol/l in current users versus 119 µmol/l in past users; $p<0.001$). These effects were not demonstrable in patients with an index date after September 8th 1995. In the questionnaire, we asked for NYHA-classification on the date of the first prescription of ibopamine. In more than 98% of the patients, this date fell before the restriction of the indication of ibopamine early September 1995. Therefore, the first prescription of ibopamine has been based on similar considerations and indications in nearly all patients. Consequently, major differences in the distribution of NYHA-class between patients with an index date before or after September 8th 1995 could not be demonstrated (Table I).

Apart from demonstrating the phenomenon of confounding by contraindication, our data also gave the opportunity to gain insight into the effect of the restriction of the indication on the use of ibopamine after early September 1995. According to the information obtained from the GPs, 76% of the patients who deceased before September 8th 1995 used ibopamine until the date of death, whereas after September 8th 1995, only 46% of the deceased patients used ibopamine until the date

of death ($p<0.001$). As patients with severe CHF are most susceptible to dying, this finding indicated that patients with severe CHF were gradually withdrawn from ibopamine after September 8th 1995 (Figure I). This also nicely illustrates the phenomenon of depletion of susceptibles, a concept which directly relates to confounding by contraindication. Patients who are most susceptible to the outcome of interest, i.e. death, are withdrawn from exposure, i.e. the use of ibopamine, and move to the untreated category. Consequently, the association between exposure and outcome may disappear or even a seemingly protective effect of the exposure of interest may result, as shown in the analysis of patients with an index date after September 8th 1995.

Apart from the potential effect of depletion of susceptibles, it seems plausible that since September 8th 1995, ibopamine is preferably prescribed to patients who experience a substantial relief of symptoms when using this drug. Discontinuation of ibopamine was considered to be undesirable in these patients. This hypothesis is supported by the observation that after September 8th 1995, current use of ibopamine was statistically significantly associated with improvement of symptoms during the first two months of treatment with ibopamine (RR 1.57; 95% CI: 1.24-1.99), whereas such association was not found before September 8th 1995 (RR 1.06; 95% CI: 0.92-1.22). Apparently, after September 8th 1995, ibopamine was discontinued in users of ibopamine who did not experience favourable subjective effects of ibopamine. The mean dosage of ibopamine appeared to be higher in patients with an index date before September 8th 1995 compared to those with an index date after September 8th 1995 (319 mg/day versus 293 mg/day $p=0.03$). Apparently, apart from stopping ibopamine after the safety warning of the Inspectorate of Health Care, there has also been a small reduction in the mean dosage of ibopamine in those patients still using ibopamine after September 8th 1995 . Although statistically significant, this reduction in mean dosage of ibopamine after September 8th 1995 is only 8%. Therefore, it is very unlikely that this slight dose reduction may have influenced the results of our study substantially.

One of the strenghts of this study is the unbiased collection of data on both exposure and outcome. Information on medication use came from the computerised printouts of the medication record and can be considered as unbiased, as this information was gathered and automated before the occurrence of the outcome of interest. Although filled prescriptions do not guarantee medication compliance, exposure based on the legend duration of filled prescriptions provides a valid approximation of the actual drug exposure (8). Although substantial misclassification of exposure seems unlikely, it will probably be random and will lead to a more conservative risk estimate. Substantial bias with respect to the outcome death should be considered as unlikely.

In the period between September and December 1995, current use of ibopamine based on the legend duration in the medication record may have overestimated the actual use of ibopamine, as ibopamine may have been discontinued in the meantime due to the negative publicity early September 1995. In an univariate analysis restricted to patients with an index date after September 8th, the relative risk of mortality in patients with CHF who obtained a new prescription of ibopamine after September 8th 1995 was 0.66 (95% CI; 0.48-0.91), which confirms the hypothesis that after September 8th 1995, ibopamine was predominantly started or continued in patients who were at a lower mortality risk.

In conclusion, confounding by contraindication may have a profound effect on the risk estimates in epidemiological studies. In most studies, however, the data do not offer the opportunity for a detailed quantification of this confounding effect and its impact remains speculative. Thanks to widespread communication of an abrupt regulatory decision, we were able to quantify the effects of confounding by contraindication on the risk estimates.

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4.3

Heart failure treatments: issues of safety versus issues of quality of life

ABSTRACT

Congestive heart failure (CHF) is an important cause of morbidity and mortality in western countries. The profound impact that CHF has on life expectancy and quality of life has been a continuous stimulus for the development of new drugs for the treatment of this condition. Despite favourable effects on (aspects of) quality of life in short-term studies, several of these new agents have been shown to reduce survival in mortality trials.

However, patients with severe CHF may experience such incapacitating symptoms that the question should be raised as to whether an improvement of quality of life makes the increased risk of mortality associated with these new agents acceptable. Drugs which improve quality of life at the expense of an increased risk of mortality can be of value in the treatment of patients with severe CHF. However, this is only the case if the probability of improvement in quality of life *and* prolongation of life expectancy for those using the drug exceeds the probability of improvement in quality of life *and* prolongation of life expectancy for those not using the drug. Unfortunately, most clinical trials in which both mortality and quality of life are evaluated fail to provide information on this composite probability.

Despite disappointing results of some recent mortality trials on new pharmacological treatments of CHF, sound and well-designed clinical trials on innovative heart failure treatments in which these composite probabilities are also assessed should be carried out.

INTRODUCTION

Congestive heart failure (CHF) has a profound impact on quality of life and life expectancy. Dyspnea and exercise intolerance pose major limitations to the daily activities of patients with CHF. In the management of CHF, loop diuretics and angiotensin converting enzyme (ACE)-inhibitors are the mainstays of therapy. Depending on the characteristics of the disease for the individual patient, a beneficial effect may also be obtained by adding digoxin and vasodilators to the treatment regimen. However, even with the most optimal treatment currently available, many patients experience incapacitating symptoms and their life expectancy is reduced significantly. Furthermore, epidemiological studies indicate a marked increase with age in both the incidence and the prevalence of CHF (1-4). Apart from the therapeutic progress made with the introduction of the ACE-inhibitors, the expanding knowledge of the pathophysiology of CHF has failed to provide substantial progress to the usual pharmacotherapeutic treatment of this condition. Hence, the prognosis of patients with CHF has remained poor, both in terms of life expectancy and quality of life.

Over the years, several promising new drugs developed for the treatment of CHF have been shown to decrease survival in double-blinded randomised clinical trials (table I). Regardless of the pharmacological differences among agents such as xamoterol, milrinone, flosequinan and ibopamine, their ultimate effect on survival in patients with CHF can only be considered as unfavourable. Despite the inability

Table I
Double-blinded randomised clinical trials on drugs associated with a statistically significantly increased risk of mortality in patients with CHF.

Trial	Total number of patients in the trial	Drug
Xamoterol (28)	516	Xamoterol 200 mg 2dd1
Enoximone (22)	151	Enoximone 50-100 mg 3dd1
PRIME-II (24)	1906	Ibopamine 100 mg 3dd1
PROMISE (29)	1088	Milrinone 40 mg/day
VEST (30)	3833	Vesnarinone 30 mg/day Vesnarinone 60 mg/day
PROFILE (31)	2304	Flosequinan 75-100 mg/day
FIRST (32)	471	Epoprostenol (median dose 4 ng/kg/min)

of these drugs to exert favourable or even neutral effects on survival in patients with CHF, many of them may improve exercise tolerance and relieve symptoms. This raises the key question as to whether we are willing to accept improved quality of life at the expense of decreased survival, assuming that both the beneficial effect on quality of life and the unfavourable effect on survival of the drug involved have unequivocally been demonstrated.

SAFETY OF PHARMACOLOGICAL TREATMENT OF HEART FAILURE

Safety, effectiveness and efficacy are central issues in the development of new drugs. Safety can be regarded as a measure of the absence of adverse drug effects, but is always considered in relation to effectiveness, that is, the wanted pharmacological effect of the drug. Efficacy of the pharmacological treatment of CHF is essentially characterised by two aspects: improvement of symptoms and prolongation of life expectancy. In the evaluation of CHF treatment, a strict distinction between efficacy and safety is of little relevance, as both concepts refer largely to similar effects.
In CHF, prolongation of survival has been demonstrated with ACE-inhibitors and the combination of hydralazine and isosorbide dinitrate (5-7). Furthermore, results from recent trials with beta-blockers indicate favourable effects on mortality, although the effect may depend on the aetiology of CHF and on characteristics of the beta-blocker involved (8-10). Results from a recently published meta-analysis have confirmed the favourable effect of beta-blockade on all-cause mortality in patients with CHF (11).

The effect of diuretics on survival in patients with CHF has not been subject to randomised double-blind placebo-controlled studies, as these drugs are the cornerstone of the treatment of fluid retention in patients with CHF and a placebo-controlled study would be unethical. Moreover, their beneficial effects are not seriously questioned (12). Results from a recent trial on the effect of digitalis on mortality and morbidity in patients with CHF indicated that digoxin did reduce the rate of hospitalisation both overall and for worsening heart failure, but did not affect mortality during 4 years of follow-up (13).

In response to disappointing results of recent mortality trials on several new agents which were assumed to have, at least theoretically, beneficial effects on the failing heart (table I), it has recently been suggested that it is now time for a moratorium on human studies that investigate drugs which stimulate the catecholamine receptor and their post-receptor pathways until convincing animal

data endorse a beneficial effect on survival (14). In our opinion, however, the judgement of heart failure treatments deserves a more balanced approach. First, comparability between human and animal studies is subject to limitations. For instance, differences in catecholamine receptors among species may restrict any valid extrapolation from animal studies towards the human situation and is only one example why mortality in animals may differ from mortality in human beings. Second, the establishment of such a moratorium may give rise to serious delays in the development of innovative pharmacological approaches to CHF. Since we face an important increase in the prevalence of CHF, such a delay in the development of new drugs is undesirable. Third, prolongation of survival should not be regarded as the only objective in the treatment of CHF. In particular, patients with severe CHF may experience such incapacitating symptoms that improvement in their clinical condition by a new pharmacological treatment may counterbalance the possibly unfavourable effect on survival. In some patients with severe CHF, the wish for relief of symptoms (quality of life) may even strongly dominate the wish to prolong life (quantity of life).

QUALITY OF LIFE IN PATIENTS WITH CHF

Quality of life is a broad concept that can be considered as the sum of all negatively and positively valued aspects of life. Although mental and physical health status are dominant determinants of quality of life, other aspects of life such as the socio-economic situation, the presence of relatives and satisfying social contacts, and religious conviction may also contribute to quality of life. The appreciation of these aspects, however, can easily be influenced by changes in physical health status. Therefore, quality of life is generally considered as strongly physical health-related.

Improvement of quality of life is a very important aspect of CHF treatment. Several tests can be applied to measure (aspects of) quality of life in patient with CHF, such as the 6-minute walk test, the chronic heart failure questionnaire, and the Minnesota Living with Heart Failure Questionnaire (15, 16). In the past, patient self-assessment of quality of life was considered to be of little relevance in clinical trials and emphasis was given to objective clinical outcomes. Nowadays, however, questionnaires on quality of life are increasingly included in the evaluation of the efficacy of CHF treatments. Symptomatic well-being of patients is much better reflected by quality of life questionnaires than by objective measurements of cardiac function (e.g., left ventricular ejection fraction). In a study on quality of life in patients with advanced heart failure (predominantly NYHA III-IV), no significant association could be found between left ventricular ejection fraction and measures

of quality of life, such as functional status, physical symptoms, emotional state, and psychosocial adaptation (17). Among the numerous questionnaires available for the assessment of quality of life, the Minnesota Living with Heart Failure Questionnaire appears to provide the most suitable measurement of quality of life in patients with CHF (15, 16, 18).

Effects on quality of life have been examined during treatment with ACE-inhibitors, a class of drugs for which a favourable effect on survival in patients with CHF has unequivocally been established (19, 20). Valid comparisons among trials of the effect of ACE-inhibitors on quality of life are almost impossible as a result of the various measures of quality of life. However, the overall impression is that ACE-inhibitors exert a modest but consistent improvement of quality of life as compared with placebo. Beneficial effects on quality of life, additional to the improvement of quality of life achieved by optimal treatment with ACE-inhibitors, have also been reported with flosequinan and with enoximone. Unfortunately, both flosequinan and enoximone were associated with increased mortality (21-23). As a matter of fact, the results of the large-scale mortality trial on flosequinan (PROFILE-trial) have never even been properly published in an official medical journal, something which can only be regarded as regrettable. The recent results of the PRIME-II-trial on mortality and efficacy of ibopamine in patients with NYHA III and IV CHF indicated that mortality increased with 26% in patients treated with ibopamine as compared to placebo (24). These findings have once again demonstrated that most of the newer CHF treatments fail to combine short term improvement of quality of life with long term improvement of survival.

SAFETY VERSUS QUALITY OF LIFE

Improvement of quality of life and prolongation of life expectancy (quantity of life) are the main objectives in CHF treatment. As pointed out before, some of the newer treatments of CHF have been shown to improve quality of life at the expense of increased mortality. When treating an individual patient with CHF, physicians should decide on the primary aim of the treatment of that specific patient. This actually implies a translation of state-of-the-art knowledge on safety and quality of life issues into a therapeutical approach in which all the relevant patient characteristics are also taken into account. Of course, the patient must have an important role in this decision process. Obviously, an increased risk of mortality in a clinical trial does not necessarily mean that every individual patient with CHF will die earlier. Likewise, an average improvement of quality of life in a clinical trial does not necessarily mean that every individual patient will experience relief of symptoms. The prescription of drugs which have been demonstrated to decrease

survival in patients with CHF can only be accepted, however, when the probability of improvement of quality of life *and* prolongation of life expectancy for those using the drug exceeds the probability of improvement of quality of life *and* prolongation of life expectancy for those not using the drug.

In table II, the intention-to-treat analysis of exercise capacity data from the PICO-trial demonstrates that, despite a trend towards higher mortality in patients started on pimobendan, this probability is larger for those using the drug (63%) as compared to those not using the drug (59%). Unfortunately, only few clinical trials in which both survival and (aspects of) quality of life were evaluated offer the possibility for such a comparison (25). The adoption of an intention-to-treat approach to design and analysis instead of a per-protocol approach in the evaluation of repeated measurements of (aspects of) quality of life (e.g., exercise capacity), and the use of composite ranked endpoints as in the PICO-trial, may contribute to a joined evaluation of the actual drug effect (26). It should be stressed that this analysis is only possible when all patients are followed until the planned end of the trial and, depending on clinical condition, the quality of life measures are obtained irrespective of study medication status.

Prescribing the most suitable treatment for patients with CHF implies a careful process of weighing the pros and cons of the therapeutical strategies against each other, in relation to the individual needs of the patient. In this process, there should be no *a priori* hierarchy between quality of life and prolongation of life expectancy in all patients with CHF. To combine the dimensions quality and quantity of life, the concept of quality-adjusted life years (QALY) has been introduced in the field of clinical decision analysis. Quality-adjusted life years reflect the number of years in full health that would be valued equivalently to the number of years of survival that

Table II
Data adapted from the pimobendan in congestive heart failure (PICO) trial (25). Intention-to-treat analysis of exercise capacity after 24 weeks of treatment with pimobendan 2.5-5 mg or placebo.

	Placebo		pimobendan	
Exercise capacity maintained or improved	64	(59%)	132	(63%)
Exercise capacity deteriorated	34	(31%)	48	(23%)
Too sick to exercise	4	(4%)	5	(2%)
Dead	6	(6%)	24	(12%)
Total	108	(100%)	209	(100%)

are expected, including any morbidity during these years. This concept implies that the patient values the various health states on a scale of 1 to 0, where perfect health would be assigned the value 1 and a state as bad as death a value near 0. Multiplication of life expectancy in a certain health status with the appreciation of the health status as represented on the 1 to 0 scale, usually called the utility of the health state, leads to the number of quality-adjusted life years (quality adjusted life years = expected number of years of survival × utility). By using a method of health scale ranking with mutually exclusive categories, Olsson et al. demonstrated that measures could be derived from clinical trials that allow direct adjustment of life expectancy for quality of life (27). The use of such measures may contribute to a clearer understanding of the actual effects on health status of the treatment studied. In addition, the number of hospitalisations for worsening congestive heart failure might also indirectly reflect aspects of both quality of life and life expectancy.

Despite the methodological limitations of measuring quality of life in terms of reliability and validity, the concept of quality-adjusted life years may offer additional support to a quantitative approach to issues of life expectancy and quality of life in heart failure treatment. Obviously, these considerations will be particularly relevant in patients with severe CHF and debilitating symptoms. In patients with less severe CHF, prolongation of life expectancy should be the predominating aim of treatment.

In the absence of an established hierarchy between quality of life and prolongation of life expectancy in the treatment of patients with severe CHF, priority may shift from improvement of survival towards improvement of symptoms. Patients with invalidating CHF may choose to use drugs that may improve their symptoms even if that leads to an increased risk of death. In our opinion, this is acceptable provided that the patient is adequately informed of the risk-benefit profile of the drug involved. The patient should be regarded as the right person to judge whether the severity of symptoms is such that emphasis should be given to improvement of quality of life instead of prolongation of life expectancy. This does not mean that the patient's judgement is always well founded and that the clinician should agree with this judgement without any further comment. In most instances, however, patients and their physicians will agree on this. Based on this judgement and the characteristics of the individual patient, the clinician should choose the most appropriate therapeutic strategy, bearing in mind these issues of safety and quality of life.

CONCLUSION

Improvement of life expectancy and quality of life are both mainstays of CHF treatment. In severe CHF, however, the patient's wish for improving symptoms may prevail over any need for expanding life expectancy. Therefore, drugs that improve quality of life at the expense of an increased risk of mortality can be of value in the treatment of patients with severe CHF, provided that the probability of improvement of quality of life *and* prolongation of life expectancy for those using the drug exceeds the probability of improvement of quality of life *and* prolongation of life expectancy for those not using the drug. Appropriate treatment in these patients may imply that relief of symptoms becomes the primary aim instead of prolongation of life expectancy.

The seriousness of CHF, both at the level of the individual patient as well as in epidemiological terms, justifies continuous research on new therapeutical strategies. Aspects of quality of life deserve major attention in the evaluation of new drugs, attention that is increasingly obtained in clinical trials. However, most clinical trials in which both survival and quality of life are evaluated fail to provide a risk assessment in which both aspects are properly included. Assessment of a balanced risk-benefit profile of new drugs implies careful consideration of aspects of safety and quality of life, because survival alone should not considered to be synonymous to overall clinical effect. Only when both aspects are evaluated thoroughly, a balanced assessment of the risk-benefit profile can be made. Based on this risk-benefit profile, clinicians will be able, in dialogue with their patients, to choose the most appropriate treatment available.

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Chapter 5

Heart failure treatment; how can it be improved

INTRODUCTION

Congestive heart failure (CHF) is generally recognised as a major health problem. Aging of the population and improved survival after acute myocardial infarction are among the most important contributors to its increasing prevalence and incidence (1, 2). In particular severe CHF has to be regarded as an invalidating condition with a poor prognosis. The substantial morbidity which results from CHF leads to a significant increase in health care demands (3).

Although lifestyle modifications, such as sodium restriction, cease smoking advice, only modest amounts of alcohol, and promotion of physical activity, may play a role in CHF treatment, pharmacotherapy is the mainstay of its treatment (4). Distinction has to be made between the treatment of acute and chronic heart failure. There are substantial differences between acute and chronic heart failure in both clinical characteristics and pharmacotherapeutic treatment. We will restrict our discussion to the pharmacotherapeutic treatment of chronic heart failure.

To reduce the burden of morbidity and health care expenditures caused by CHF, and to improve life expectancy of heart failure patients, several new drugs for the treatment of CHF have been introduced over the years, such as milrinone, vesnarinone, flosequinan, pimobendan and ibopamine (5-9). Although it was assumed that these drugs would have favorable effects on mortality, clinical trials demonstrated a negative effect on survival in patients with CHF. More recently, results from clinical trials have shown that beta-blockers, formerly considered to be contraindicated in CHF, may improve survival (10-12).

Both disappointing as well as encouraging results from randomised clinical trials (RCT) on heart failure treatments may provide valuable clues to future research. Results from recently published RCTs on positive inotropic agents demonstrate substantial differences between the intuitive appropriateness of a pharmacological agent and its actual effects on morbidity and mortality. After summarizing some main findings of clinical trials on heart failure drugs, particularly with respect to morbidity and mortality, we discuss which implications these findings may have on current and future developments of heart failure treatment.

MAIN FINDINGS FROM RANDOMISED CLINICAL TRIALS ON HEART FAILURE TREATMENT

Diuretics

Fluid retention, the main clinical feature of most patients with CHF, can only be controlled adequately with diuretics. Although diuretics are generally regarded as the cornerstone of the pharmacotherapeutic treatment of CHF, long-term randomised clinical trials on their effects on mortality and morbidity are not available (13). Only a few short-term studies have demonstrated that diuretics improve cardiac function, symptoms and exercise tolerance in patients with CHF (14). Despite the lack of solid evidence for their long-term effects on mortality and morbidity, the favorable effects of diuretics in patients with CHF are not seriously questioned. However, monotherapy with diuretics is unable to obtain long-term clinical stability in patients with CHF (15). Therefore, diuretic therapy in heart failure patients should preferably be combined with ACE-inhibitors.

Angiotensin-converting enzyme inhibitors (ACE-inhibitors)

ACE-inhibitors interfere with the renin-angiotensin system by inhibiting angiotensin converting enzyme (ACE) responsible for the conversion of angiotensin I to angiotensin II.

In addition, ACE-inhibition interferes with degradation of kinins, because ACE is identical to kininase II that is responsible for the degradation of kinins. Table I presents the results of some major trials on the effects of ACE-inhibitors in patients with CHF due to systolic dysfunction. Findings from these trials and other clinical trials clearly demonstrate that ACE-inhibitors are able to decelerate the progression of CHF, and improve clinical status and survival in patients with mild, moderate and severe CHF. Therefore, all patients with CHF due to systolic dysfunction should receive an ACE-inhibitor, unless they can not tolerate this drug.

Digitalis

The digitalis glycosides inhibit the enzyme Na^+K^+-ATPase, which results in an increase in myocardial contractility. However, inhibition of Na^+K^+-ATPase in non-cardiac tissues also seems to contribute to the beneficial effects of digoxin in heart failure patients, particularly by attenuating the activation of neurohormonal systems. Several short-term placebo-controlled studies have shown that digoxin may

Table I
Randomised controlled clinical trials on the effects of ACE-inhibitors in heart failure patients.

Name	Year	Patients	Severity of CHF	Drug / daily dosage	Main findings
CONSENSUS	1987	253	NYHA IV	enalapril 40mg *vs* placebo	31% reduction of mortality one year after randomisation (p=0.001; 95% CI not published)
SOLVD	1991	2,569	mainly NYHA II-III	enalapril 20 mg *vs* placebo	16% risk reduction (95% CI: 5%-26%) of mortality at the end of scheduled follow-up
V-HeFT-II	1991	804	mainly NYHA II-III	enalapril 20 mg *vs* hydralazine 300 mg + isosorbide dinitrate 160 mg	28% reduction of mortality two years after randomisation (p=0.016; 95% CI not published)

CONSENSUS-trial (36) : Cooperative North Scandinavian Enalapril Survival Study
SOLVD-trial (37) : Studies on Left Ventricular Dysfunction
V-HeFT-II-trial (22) : Second Veterans Administration Cooperative Vasodilator-Heart Failure Trial

have beneficial effects on ejection fraction, exercise tolerance and functional capacity in heart failure patients (16, 17). Results from the Digitalis Investigation Group (DIG) trial indicate that digoxin has no beneficial effect on mortality in CHF patient with normal sinus rythm. Although the risk of being hospitalised for any reason decreased with only 6%, fewer patients randomised to digoxin were hospitalised for worsening CHF (Table II). Hence, digoxin may provide clinically relevant symptomatic relief to patients with CHF, and may reduce the risk of hospitalisation for worsening CHF. However, digoxin does not improve survival in patients with CHF.

Beta-adrenergic receptor blockers

In recent years, there has been a growing interest in the use of beta-adrenergic receptor blockers for the treatment of CHF. Activation of the sympathetic nervous system plays a major role in the pathophysiology of CHF. Norepinephrine has several effects on the cardiovascular system which are considered to be harmful to heart failure patients, such as peripheral vasoconstriction, impairing renal sodium excretion, and inducing myocardial hypertrophy (18-20). In addition, norepinephrine may stimulate apopthosis of cardiac myocytes. Results from RCTs have demonstrated that beta-blockers improve survival and reduce morbidity in patient with mild to moderate CHF due to systolic dysfunction (Table III). These beneficial effects of beta-blockers were observed in patients who were already on maintenance therapy with digoxin, ACE-inhibitor and diuretics. Until now, only few patients with severe CHF (NYHA class IV) have been treated with beta-blockers. Ongoing research such as the COPERNICUS-trial has to clarify their potential role in the management of patients with severe heart failure. Therefore, beta-blockers are currently recommended for all patients with stable mild to moderate CHF due to left ventricular systolic dysfunction unless these patients have a contraindication for their use or have shown to be unable to tolerate beta-blockers.

Angiotensin-II receptor blockers

Angiotensin receptor blockers are a new class of drugs which interfere with the effects of angiotensin II by means of blockade of the angiotensin II receptor (AT_1-receptor). Formerly, the benefits of ACE-inhibitors were mainly attributed to the suppression of angiotensin II formation, whereas their adverse effects were related to the accumulation of kinins. Currently, accumulation of kinins is increasingly regarded as essential to the beneficial effects of ACE-inhibitors. Only few studies have compared the effects of ACE-inhibitors and AT-II antagonists on mortality and morbidity (table II). Based on currently available information, there is no evi-

Table II
Randomised controlled clinical trials on the effects of digoxin and losartan in heart failure patients.

Name	Year	Patients	Severity of CHF	Drug / daily dosage	Main findings
DIG	1997	6,800	mainly NYHA II-III	digoxin 0.25mg *vs* placebo	digoxin did not affect mortality digoxin reduced number of hospitalisations for worsening CHF (RR 0.72; 95% CI:0.66-0.79)
ELITE	1997	722	mainly NYHA II-III	captopril 150 mg *vs* losartan 50 mg	46% reduced risk of mortality (95% CI: 5-69%) no statistically significant reduction of risk of hospitalisation or combined risk of death and hospitalisation
ELITE-II	2000	3,152	NYHA-II-IV	Captopril 150 mg vs losartan 50 mg	No significant differences in all-cause mortality or sudden death or resuscitated arrests between both treatments

DIG-trial (38) : Digitalis Investigation Group
ELITE (39) : Evaluation of Losartan in the Elderly Study
ELITE-II (47) : Losartan Heart Failure Survival Study

Table III
Randomised controlled clinical trials on the effects of beta-adrenergic receptor blockers in heart failure patients.

Name	Year	Patients	Severity of CHF	Drug / max. daily dosage	Main findings
MDC	1993	383	mainly NYHA II-III	metoprolol 150 mg *vs* placebo	no reduction of hospitalisations or mortality due to CHF
CIBIS I	1994	641	NYHA III-IV	bisoprolol 5 mg *vs* placebo	20% reduction of mortality (statistically non-significant) 34% reduced risk of hospitalisation for CHF ($p<0.01$)
CIBIS II	1999	2,647	NYHA III-IV	bisoprolol 10 mg *vs* placebo	34% reduction in mortality ($p<0.0001$) 20% reduced risk of hospitalisation ($p=0.0006$) 32% reduced risk of hospitalisation for CHF ($p<0.0001$)
MERIT-HF	1999	3,991	mainly NYHA II-III	metoprolol 200 mg *vs* placebo	35% reduced risk of mortality ($p=0.00015$)
†	1996	366	NYHA II-III	carvedilol 100 mg *vs* placebo	48% reduced risk of clinical progression ($p=0.008$) 77% reduction in mortality ($p=0.048$)
‡	1997	415	NYHA II-III	carvedilol 50 mg *vs* placebo	26% reduction in clinical progression of CHF ($p=0.02$) 23% reduction in risk of hospitalisation ($p=0.05$)
PRECISE	1996	278	mainly NYHA class II-III	carvedilol 100 mg *vs* placebo	no effect on exercise tolerance 39% reduction in combined risk of death or hospitalisation ($p=0.019$)

MOCHA	1996	345	mainly NYHA class II-III	carvedilol 50 mg *vs* placebo	no effect on exercise tolerance 49% reduction in combined risk of death or hospitalisation (p=0.002)

CIBIS-1(11) : First Cardiac Insufficiency Bisoprolol Study
CIBIS-II (41) : Second Cardiac Insufficiency Bisoprolol Study
MERIT-HF (28) : Metoprolol CR/XL Randomised Intervention Trial in Heart Failure
† (42) : US Carvedilol Heart Failure Study Group
‡ (12) : Australia / New Zealand Heart Failure Collaborative Group
PRECISE (43) : Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise
MOCHA (10) : Multicenter Oral Carvedilol Heart Failure Assessment

dence supporting a superior efficacy of AT-II-antagonists in comparison with ACE-inhibitors in heart failure patients, as shown by the recently published results from the ELITE-II trial.

Phosphodiesterase inhibitors

Cyclic adenosine monophosphate phosphodiesterase inhibitors (cAMP-PDE-inhibitors) prevent the breakdown of intracellular cAMP by their binding to cAMP-PDE. The rise in intracellular cAMP level was thought to have, at least theoretically, beneficial effects in patients with CHF as cAMP leads to an increase in myocardial contractility and relaxation of vascular smooth muscle. Results from several randomised clinical trials (table IV), however, clearly indicate that cAMP-PDE-inhibitors reduce survival in heart failure patients. Although favorable effects on parameters of quality of life have been reported, the consistent finding in several randomised clinical trials that cAMP-PDE-inhibitors reduce survival has substantially minimized their applicability in clinical practice.

Other agents in the treatment of CHF

Results from the V-HeFT I-trial (21) demonstrated that compared to placebo, the combination of the vasodilators hydralazine (predominantly arterial dilation) and isosorbide dinitrate (predominantly venous dilation) reduced mortality in patient with mild to moderate CHF who were already treated with digoxin and diuretics. ACE-inhibitors have shown to provide further improvement of mortality in the V-HeFT II-trial as compared to the combination of hydralazine and isosorbide dinitrate (22).

Calcium antagonists dilate arterial resistance vessels in the coronary and systemic circulation. Despite these vasodilatory properties, most clinical trials have not revealed any benefit from calcium antagonists in heart failure patients. On the contrary, several calcium antagonists were associated with an increased risk of worsening CHF and death in patients with decreased left ventricular function (23-25). Amlodipine, however, a relatively new calcium antagonist, appeared to have no adverse effect on survival. This agent was even associated with a trend towards decreased all-cause mortality, a finding which needs confirmation in ongoing research (26).

Inhibiting the effects of aldosterone may exert favourable effects in heart failure patients. In patients with severe CHF, treatment with spironolactone was associated with both a 35% decrease in hospitalisation rate as well as a 30% decrease

Table IV
Randomised controlled clinical trials on the effects of phosphodiesterase-inhibitors in heart failure patients.

Name	Year	Patients	Severity of CHF	Drug / daily dosage	Main findings
VEST-1	1993	477	NYHA class I-IV	vesnarinone 120 mg or 60 mg *vs* placebo	120 mg vesnarinone increased the risk of mortality 60 mg vesnarinone 50% risk reduction for death or worsening heart failure (95% CI:20-69%)
PROMISE	1991	1088	NYHA class III-IV	milrinone 40 mg *vs* placebo	28 % increase in mortality (95% CI: 1-61%) increase in hospitalisations (p=0.041)
ENOXIMONE	1994	151	NYHA class III-IV	enoximone 300 mg *vs* placebo	increased risk of mortality (p<0.05)
VEST-2	1998	3833	NYHA class III-IV	vesnarinone 60 mg or 30 mg *vs* placebo	

PROMISE (7) : Prospective Randomized Milrinone Survival Evaluation
VEST-1 (6) : First Vesnarinone Evaluation of Survival Trial
VEST-2 (44) : Second Vesnarinone Evaluation of Survival Trial
ENOXIMONE (5)

Table V
Randomised controlled clinical trials on miscellaneous pharmacological agents in heart failure patients.

Name	Year	Patients	Severity of CHF	Drug / daily dosage	Main findings
FIRST	1997	471	NYHA III-IV	epoprostenol i.v. *vs* conventional treatment	increased risk of mortality
PRIME-II	1997	1,906	NYHA III-IV	ibopamine 300 mg *vs* placebo	26% increased risk of mortality (95% CI: 4%-53%)
PICO	1996	317	NYHA II-III	pimobendan 2,5 – 5 mg *vs* placebo	hazard ratio for death 1.8 (95% CI: 0.9-3.5)
PROFILE	1993	2,304	NYHA III-IV	flosequinan 100 mg *vs* placebo	43% increased risk of mortality ($p<0.05$)
XAMOTEROL	1990	516	NYHA III-IV	xamoterol 400 mg *vs* placebo	increased risk of mortality ($p=0.02$)

Xamoterol (45) : The Xamoterol in Severe Heart Failure Study Group
FIRST (46) : Flonan International Randomised Survival Trial
PICO (9) : Pimobendan in Congestive Heart Failure Trial
PROFILE : RCT on the effects of flosequinan on survival in heart failure patients
PRIME-II (8) : Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy

in mortality during 2 years of follow-up (27). Therefore, the use of spironolacone may be considered in patients with severe CHF, although its safety and efficacy in patients with less severe CHF remains unknown. Patients with CHF tend to have frequent and complex ventricular arrhythmias and are at an increased risk of sudden death. However, due to their negative inotropic and pro-arrhythmogenic properties, anti-arrhythmisc are not recommended for heart failure patients with only asymptomatic or nonsustained ventricular arrhythmias. If indicated, class III anti-arrhythmics seem to be the most suitable class of anti-arrhthmics for patients with CHF.

Table V shows a number of drugs with various pharmacological effects applied in the treatment of CHF. Despite their theoretical benefits, these agents have shown to reduce survival in patients with CHF.

WHAT SHOULD BE STATE OF THE ART HEART FAILURE TREATMENT

For a long period of time, conventional treatment of CHF consisted of diuretics and digoxin. During the seventies, vasodilatory therapy was gradually included in most pharmacotherapeutic regimens of CHF. Results from the V-Heft I-trial and the CONSENSUS-trial demonstrated that both the combination hydralazine-isosorbide dinitrate as well as ACE-inhibitors improved survival in heart failure patients. Then, results from the V-HeFT II-trial revealed that reduction in mortality with enalapril was significantly greater in comparison to hydralazine-isosorbide dinitrate. The beneficial effects of ACE-inhibitors were confirmed in the SOLVD-trial on prevention and treatment of CHF, which convincingly showed favorable effects of ACE-inhibitors on both mortality as well as on the progression of the disease. Triple drug therapy (diuretic, digoxin and ACE-inhibitor) appeared to be the most appropriate treatment for patients with CHF due to left ventricular dysfunction.

Over the last few years, beta-blockade has gained growing interest as an option of treatment in CHF patients. Result from a number of clinical trials carried out over the last few years indicate that beta blockade may lessen symptoms and improve survival in heart failure patients. However, several questions with regard to beta-blockade in CHF are still under investigation in ongoing trials, such as the effects on efficacy resulting from pharmacological differences among beta-blockers, and the role of beta-blockade in patients with severe CHF.

A recently published consensus report on the treatment of CHF recommends the prescription of beta-blockers to patients with stable NYHA II / III heart failure due

to left ventricular systolic dysfunction (28). Hence, a four-drug regimen (diuretic, digoxin and ACE-inhibitor and beta-blocker) may now be regarded as the state-of-the-art treatment of most patients with NYHA II / III CHF. Recent results from the RALES-trial indicate that spironolactone substantially reduces the risk of both morbidity and mortality among patients with severe heart failure (47). Future research has to show whether spironolactone is also effective in less severe heart failure. In addition, more need to be learned about the combined use of beta-blockers and spironolactone in severe heart failure.

With respect to current treatment of CHF treatment, some issues seem to be of particular interest. Despite the unarguable benefits of ACE-inhibitors, several studies have shown that ACE-inhibitors are considerably underutilised in the treatment of CHF. Overall treatment rate remains far too low at approximately 50-60% (29). Underutilisation of ACE-inhibitors should be regarded as a major impediment to a state-of-the-art treatment of CHF. One may wonder why poor application of convincing results from well-designed clinical trials seems to be so prevalent in view of the attention currently paid to evidence-based medicine. Presuming that physicians do not deliberately deny a well-proven beneficial treatment to their patients, lack of education seems to be at least partially responsible for the underutilisation of ACE-inhibitors. Education by means of courses and up to date treatment guidelines may be of great value in the effort to reduce underutilisation of ACE-inhibitors. In several countries, physicians are obliged to participate in educational programmes. Whether or not such educational programmes are mandatory, physicians involved in the treatment of CHF patients, either general practitioners or specialists, should consider it their professional duty to prescribe state-of-the-art treatment to their patients. Deviating from well-considered recommendations and guidelines on CHF treatment is only legitimate if this results from a careful decision of the physician, and not from his or her ignorance of state-of-the-art CHF treatment.

Although placebo-controlled double-blinded randomised clinical trials are generally regarded as the most appropriate design to study treatment effects, their results can not always be applied uncritically to each individual patient with CHF. Old patients and patients with substantial comorbidity are usually excluded from these trials. However, it may seem reasonable to assume that results from RCT may also be, at least to some extent, applicable to many patients different from the study population. Although this may be true, elderly patients with CHF and substantial comorbidity are usually taking drugs for a number of other disorders, such as diabetes mellitus, chronic obstructive pulmonary disease or locomotor disorders. When state-of-the-art treatment of CHF implies a four-drug regimen, as proposed recently, patients with substantial comorbidity have to be prescribed a large number of different drugs which may lead to undesired drug interactions and

poor medication compliance. Poor medication compliance is an important problem in the treatment of chronic diseases under everyday circumstances, and a major impediment to optimal CHF treatment Hence, optimal treatment of CHF should always be tailored to individual patients. Physicians have to take into account both merits and limitations of RCT, and their treatment should be a synthesis of evidence-based medicine and the individual characteristics of their patients.

Over the years, several agents considered to be beneficial to patients with CHF have shown to reduce survival despite short-term favorable haemodynamic effects. In particular phosphodiesterase inhibitors (e.g. milrinone, vesnarinone, enoximone) were associated with increased mortality. In addition, ibopamine (dopaminergic agent), pimobendan (phosphodiesterase inhibitor with calcium sensitising activity), flosequinan (vasodilator), and xamoterol (beta-blocker with intrinsic sympathicomimetic activity) have all shown to increase mortality risk in placebo-controlled RCT. Nevertheless, several of these agents have been associated with improvement of quality of life. It can be questioned whether conventional RCT are the most appropriate design to evaluate quality of life aspects. Even if aspects of quality of life have been assessed in clinical trials, only few trials provide risk estimates in which effects on mortality and quality of life are evaluated simulaneously. The 'trial and error approach' which characterises drug therapy in clinical practice might be able to select those patients who may benefit most from these treatments, perhaps even without substantial negative effects on survival. In daily clinical practice, treatment may be continued only if the patient has symptomatic relief. Hence, there may be place for some selected agents which have convincingly shown to be capable of providing symptomatic relief in patients with severe CHF, even if these agents are associated with an increased risk of death (30). For example, these agents might be of value when used concomitantly with beta-blockers in patients with severe CHF who can not tolerate betablockade without additional positive inotropic drugs (31). After a period of stabilisation, treatment with positive inotropics may gradually be discontinued in these patients, offering the benefits of betablockade without the long-term risk of positive inotropics. However, additional research is needed before this approach can be applied in daily clinical practice.

Obviously, positive inotropic agents will have only a very restricted indication in the treatment of CHF. This raises the question what might be the next step forward in CHF treatment. Now we have learned that inotropic therapy appears to be unable to improve long-term survival, and that favorable effects on survival have only been obtained with ACE-inhibitors and beta-blockers, the most appropriate approach seems to aim at interference with neurohormonal responses and cardiac remodelling. The increased knowledge on the pathophysiology of CHF has revealed that stimulation of both the renin-angiotensin-aldosterone system and the sympathetic nervous system has deleterious effects on long-term cardiovascu-

lar homeostasis. Norepinephrine and angiotensin II are among the factors which may contribute to cardiac remodelling, a process regarded as fundamental to the progression of CHF. ACE-inhibitors, spironolactone, and beta-blockers directly interfere with respectively the renin-angiotensin-aldosterone system and the sympathetic nervous system. Over the years, several factors have been identified which may contribute to the process of cardiac remodelling, such as endothelin, inflammatory cytokines and oxidative stress (32). Endothelin receptor antagonists, anticytokines and antioxidant therapy might be of value for patients with CHF. Similarly, endopeptidase inhibitors which elevate the level of circulating atrial natriuretic peptide may be a valuable new approach in the therapy of CHF (33). However, much research and many future trials have to be carried out before any reliable estimation can be made on the clinical applicability of these agents in the treatment of heart failure patients. There is also insufficient information to assess whether calcium sensitisers (e.g. levosimendan), a relatively new class of drugs with positive inotropic activity, might be of value to patients with CHF (34). Prior experience with pimobendan, which had some calcium-sensitising properties gives no reason for optimism despite pharmacological differences between levosimendan and pimobendan.

There is little reason to suppose that the start of the third millenium will coincide with a major breakthrough in heart failure treatment. However, this does not imply that no further improvements can be achieved. It seems likely that in the short term the most important improvement can be obtained when available knowledge on optimal treatment, particularly the prescription of ACE-inhibitors, beta-blockers, and spironolactone is actually applied to all patients who may have the benefits from it. Apart from this, primary prevention of CHF, based on optimal treatment of its most important etiological factors, ischaemic heart disease and hypertension, should be one of the main objectives of physicians involved in the management of patients with cardiovascular disease (35).

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Chapter 6

General discussion

INTRODUCTION

Heart failure is an incapacitating disorder with a poor prognosis, despite recent advancements in treatment. Patients are usually prescribed several cardiovascular drugs, such as diuretics, digoxin, and angiotensin converting enzyme inhibitors (ACE-inhibitors). In addition, other classes of drugs are frequently prescribed because of comorbidity. In this thesis, two issues have been studied concerning medication use in heart failure patients.

First, we studied the potentially negative effect of NSAIDs in patients with a first occurrence of heart failure (incident heart failure) and in patients with prevalent heart failure. According to our findings, and in line with pathophysiologic plausibility, NSAIDs did not induce a first occurrence of heart failure, but appeared to be associated with relapses in patients with *prevalent* heart failure. The cohort study described in chapter 3.5 demonstrated an increased risk during current use of NSAID in patients with prevalent heart failure. Among patients with a first occurrence of heart failure (chapter 3.4), no association between the occurrence of heart failure and NSAIDs could be observed.

Second, we assessed in a nationwide cohort study mortality risk in heart failure patients who had been prescribed the dopaminergic agent ibopamine (1). We hypothesized that an increased mortality risk may not only be present in the severe stages of heart failure, as demonstrated in the PRIME-II trial, but also in patients with mild heart failure who were excluded from the trial (2). Our finding that ibopamine was not only associated with an increased mortality risk in patients with moderate to severe heart failure, but also in patients with mild heart failure, led to the conclusion that the mortality risk of ibopamine should be evaluated first in a randomised clinical trial with mild heart failure before a final judgement can be made on the safety of this agent in these patients.

This final chapter will discuss these findings against the background of aspects of drug safety, the limitations of clinical trials in heart failure, and the emerging heart failure epidemic in western countries.

DRUG SAFETY

Monitoring safety aspects of drugs is a major and continuous concern for registration authorities, for organisations such as the Drug Safety Unit of the Inspectorate for Health Care and the LAREB Pharmacovigilance Foundation in The Netherlands, and for pharmaceutical companies. It is well-recognised that pre-marketing safety

studies are unable to provide a definite benefit/risk-profile of drugs newly introduced on the market (3). Pre-marketing studies are usually not large enough to detect rare adverse drug reactions. Nevertheless, relatively rare adverse drug reactions may have a considerable impact on the benefit/risk-profile of drugs. In most pre-marketing studies, follow-up is too short to detect adverse drug reactions associated with long-term drug use or adverse drug reactions which occur after a long delay, such as vaginal carcinoma in the daughters of mothers who had been treated with diethylstilboestrol (DES) during pregnancy (4). In addition, pre-marketing studies usually exclude potential users that might be more at risk for an increased frequency of adverse drug reactions such as children and aged patients. Moreover, multiple drug use, which may be a source of potentially life-threatening interactions, is common under everyday circumstances but is much less likely to occur in clinical trials.

The limitations of pre-marketing studies clearly underscore the need for post-marketing surveillance. Pharmacovigilance and pharmacoepidemiological studies are the two main forms of postmarketing surveillance. Pharmacovigilance refers to the obligations of the marketing authorisation holder and the regulatory authorities to set up and maintain a system in order to collect, evaluate and collate information about suspected drug reactions. In The Netherlands, there is a spontaneous reporting system of suspected adverse drug reactions, and the obligation to marketing authorisation holders to report all suspected serious adverse events within 15 days to the regulatory authorities. Pharmacoepidemiological studies refer to research on drug safety aspects as well as on the effectiveness of drugs under everyday circumstances in the post-registration phase.

Published case reports, spontaneous reporting systems, non-experimental studies (commonly referred to as observational studies), and phase IV clinical trials reflect different approaches to postmarketing surveillance, and may all contribute to knowledge on the benefit/risk-profile of drugs. Published case reports are particularly valuable to distribute knowledge on previously unknown serious ADRs. However, depending on the characteristics of the ADR, case reports can usually not be regarded as a definite evidence of causality. Similar to published case reports, spontaneous reporting systems may be effective in revealing unusual or rare adverse drug reactions such as Steven-Johnson syndrome, hepatic necrosis or anaphylactic shock although details of such reports are not always generally available. Causality assessment may be straightforward when there is a clear temporal association and a characteristic clinicopathological pattern of these events. However, when symptoms occur several years after initial drug exposure, an association may be more difficult to recognize. Moreover, underreporting (false-negative) and false-positive reporting of suspected adverse reactions can make it impossible to calculate the incidence of ADR. Therefore, post-marketing clinical trials or

observational pharmacoepidemiological studies have to be performed to assess the actual risks of ADRs associated with drug exposure. Post-marketing clinical trials, however, are usually unable to detect rare ADRs. Moreover, inclusion- and exclusion criteria may have as a consequence that the potential ADRs are only studied in eligible patients which may limit the generalizability of the results. From a health care point of view, however, it is of major importance to assess the risks associated with drug exposure under everyday circumstances, as clinical trials are usually unable to provide this information.

Randomised clinical trials are generally regarded as the gold standard in the evaluation of treatment effects. The design of randomised clinical trials inherently minimises bias and confounding. Drug safety aspects, however, can often only be adequately evaluated with an observational (=non-experimental) study design. Over the years, several observational studies have been published on potential adverse drug reactions. Observational studies provide an important contribution to the evaluation of a balanced benefit/risk-profile of drugs, but their validity is frequently being challenged because of potential bias and / or confounding. A careful design, however, may reduce or even prevent bias and confounding in observational studies (5).

Most registration authorities are particularly focussed on results obtained from randomised clinical trials. However, extrapolation of results from randomised clinical trials to community patients should be done cautiously. With respect to heart failure trials, the average clinical trial patient differs substantially from the average community patient with respect to age, gender, and comorbidity (6); aspects generally regarded as major determinants of clinical outcome. Registration authorities will increasingly be confronted with the results from observational pharmacoepidemiological studies. Although the interpretation of results from observational studies may appear less straightforward than from clinical trials, careful evaluation of their results, in view of their strengths and limitations, will provide valuable additional information on the risk - benefit profile of individual drugs.

HEART FAILURE

(Congestive) heart failure (CHF) is a rapidly growing public health problem. Currently, heart failure is one of the most common cardiovascular disorders among elderly in western societies (7-9). Despite improved treatment, the prognosis of heart failure with respect to survival remains poor (10, 11). Signs and symptoms of moderate to severe CHF may have a significant impact on quality of life. Poor prognosis and the impact on quality of life, next to the economic consequences of

increasing health care expenditures, justify the numerous efforts to improve prospects of patients with CHF. The morbidity, mortality and health care costs associated with CHF make prevention a more attractive and effective public health strategy than treatment. Adequate treatment of the major etiologic factors, ischaemic heart disease, hypertension, and valvular disease may postpone or prevent the onset of heart failure (12). Unfortunately, for patients attending their general practitioner or cardiologist with signs and symptoms of heart failure, prevention is no longer an option.

Over the years, several new drugs have been developed in an attempt to prolong survival and preserve quality of life of heart failure patients. Positive inotropic agents were thought to improve left ventricular performance, but most of them turned out to be associated with increased mortality risk as compared to placebo (13-16). Currently, ACE-inhibitors and loop diuretics are the mainstays of heart failure treatment. Recent trials have shown additional beneficial effects of beta-blockers and spironolactone (17-21). Optimising heart failure treatment does not only imply ongoing research on new treatment strategies, but also the implementation of these results from clinical trials in clinical practice.

IBOPAMINE AND HEART FAILURE

The limitations of clinical trials as discussed before regarding the benefit/risk- profile of drugs under everyday circumstances have motivated us to initiate the nationwide cohort study among heart failure patients who used the dopaminergic agent ibopamine. Results from an interim-analysis of the placebo-controlled PRIME-II trial indicated an increased mortality risk associated with ibopamine (2). However, only patients with NYHA III and IV heart failure were included in this trial, whereas ibopamine was also registered in The Netherlands for the treatment of NYHA II heart failure. Therefore, the results of this trial did not provide an answer to the question whether ibopamine was safe in patients with NYHA II heart failure.

The results of the nationwide cohort study described in chapter 4.1 were consistent with the PRIME-II-trial, indicating an increased mortality risk in patients with moderate and severe heart failure (1). Interestingly, we also found an increased mortality risk in NYHA class II heart failure patients. These patients were excluded from the PRIME-II trial. Based on the findings of the PRIME-II-trial, the indication of ibopamine in The Netherlands was restricted to mild congestive heart failure (NYHA II) only. The Dutch Medicines Evaluation Board decided to maintain NYHA class II as an indication for ibopamine, mainly because the increased mortality risk

in NYHA class II that was demonstrated in the nationwide cohort study would in their view have to be confirmed by results of a randomised double-blinded clinical trial (22). In addition, the observational design was regarded to be subject to potential biases and confounding, although others did not share this opinion (23). This decision of the Dutch Medicines Evaluation Board can be questioned. First, NYHA class II is still a registered indication for ibopamine despite the lack of mortality data from randomized clinical trials that convincingly demonstrate that ibopamine is safe in patients with NYHA II CHF. The Dutch Medicines Evaluation Board, however, is fully aware of the fact that it is unlikely that there will ever be reliable mortality data on ibopamine in NYHA II heart failure patients (22), and that the follow-up in available studies on ibopamine in NYHA II CHF was far too short to provide useful information regarding mortality. Second, European guidelines clearly state that there is no place for ibopamine in the treatment of CHF (24), and ibopamine is not even mentioned in recent American guidelines on heart failure treatment (25). Third, everyday clinical practice has learned that since the publication of the PRIME-II trial in 1995, ibopamine has gradually disappeared from the pharmacotherapeutical repertory without leaving behind the impression that a valuable drug was lost. Finally, it is remarkable that a former indication of a drug becomes a strict contraindication to the moderate and severe stages of a disease, while its use in the mild stages is *not* contraindicated. As clinical practice learns that drugs which are once prescribed are likely to be continued, maintaining NYHA class II as an indication for ibopamine can easily lead to continuing use in the more severe stages of this progressive disease.

NSAIDS AND HEART FAILURE

A substantial part of this thesis concerns the potential negative effects of NSAIDs on cardiovascular homeostasis in heart failure patients. Case-reports describing the onset of CHF associated with NSAIDs and an earlier study indicating a twofoldly increased risk of first hospitalisation for CHF during concomitant use of diuretics and NSAIDs suggested a negative effect of NSAIDs on cardiovascular homeostasis (26-30). Recently, a case-control study also demonstrated an increased risk of first hospitalisation for CHF in patients who were using NSAIDs in the period preceding hospital admission (31). Our cohort study in patients with a history of one hospitalisation for CHF (chapter 3.5) also revealed an increased risk of hospitalisation for relapsing CHF during NSAID use. This study suggested that the so-called process of 'depletion of susceptibles' may play a role, indicating a decreasing risk with prolonged exposure to NSAIDs. This finding implies that patients who are particularly susceptible to the cardiovascular effects of NSAIDs are more likely to have relapsing CHF after a first prescription. As this study was

carried out in a record linkage database, no clinical information was available on the severity of CHF. This phenomenon of 'depletion of susceptibles' might reflect a group of patients with severe left ventricular dysfunction that is particularly prone to develop relapsing CHF in response to NSAID exposure.

In view of the pathophysiology of CHF, it seems plausible that NSAIDs may in particular induce relapses in patients with *prevalent* heart failure. However, NSAIDs have also been associated with first hospitalisations for heart failure, suggesting that NSAIDs may cause a first occurrence of heart failure. In these studies, risk of hospitalisation was more pronounced in patients with a history of cardiovascular disease (30, 31). This may indicate that these patients may have already had impaired left ventricular function before their hospitalisation for CHF. As described in chapter 3.4, we used data from the Rotterdam Study, a prospective population-based cohort study characterised by a stringent individual follow-up procedure of all cohort members (32). The intensive follow-up procedures of the Rotterdam Study provided the possibility to include in the study population only participants with a certain diagnosis of heart failure and participants without any known suspicion heart failure. This study showed no association between NSAIDs and a first occurrence of heart failure. In an additional analysis in which participants were followed from the date of diagnosis of the first occurrence of heart failure until a first relapse or end of the study period, an association between NSAIDs and relapsing CHF was demonstrated that was compatible with the increased risk found in the study among patients with prevalent heart failure (chapter 3.5). These findings are clinically relevant, as NSAIDs are agents with potent anti-inflammatory and analgesic properties which are often used in the relief of pain from common musculoskeletal disorders in elderly patients. Any finding that NSAIDs might cause a first occurrence of heart failure would have far-reaching consequences. However, their use in patients with prevalent heart failure should be discouraged, as their liability to cause a relapse is substantial.

FUTURE MANAGEMENT OF CHF

Optimal heart failure management pertains to both pharmacological and non-pharmacological treatment of the disease. There can be no doubt that pharmacotherapy remains the mainstay of heart failure treatment. Although several new approaches are currently under study, they will probably not be introduced in the next few years and will not be discussed here (33). In the meantime, much can be gained by treating heart failure patients in accordance with present knowledge. Underutilisation of ACE-inhibitors is a well-recognised problem, indicating suboptimal heart failure treatment (34, 35). Another challenge is to put the results into clinical prac-

tice from recent trials on beta-blocker and spirolactone.

There is a growing interest in multidisciplinary interventions aiming at the prevention of hospital readmissions and improvement of the quality of life (3, 36-40). Studies with these interventions have shown favorable effects on these clinically relevant outcomes. In addition, positive effects have been demonstrated on cost-effectiveness. Until now, only few patients have the opportunity to participate in multidisciplinary heart failure management programs. Despite the beneficial effects of these programs, several important aspects still need to be addressed. The diversity of the studied multidisciplinary interventions complicates a critical evaluation of the individual contribution of the various components. Hence, it remains unclear what multidisciplinary approach is the most appropriate in terms of patient's benefits and cost-effectiveness. A second issue is that it remains to be discovered which patients with heart failure are most likely to benefit from a multidisciplinary intervention. It can be questioned whether these interventions are able to improve clinical outcome in patients with end-stage heart failure. On the other hand, patients with mild heart failure may be adequately treated with standard care. Psychosocial factors and living circumstances may also affect clinical outcome in heart failure patients (41). Providing optimal care, both pharmacologically as well as non-pharmacologically, is likely to improve prospects of many patients with heart failure.

CONCLUSION

The prevention, postponement and optimal treatment of heart failure will be one of the most important challenges of cardiovascular medicine in the next future. Contributions from both clinical trials as well as observational studies are needed to define optimal care. Despite disappointing results in the past regarding several promising cardiovascular drugs for the treatment of heart failure, pharmacological treatment remains to be the mainstay of therapy. Future research should demonstrate which combinations of pharmacological and non-pharmacological interventions yield the best results with respect to survival, quality of life, and cost-effectiveness. Prevention of relapses of heart failure in patients with prevalent heart failure may substantially contribute to quality of life and costs-effectiveness. Awareness of potentially preventable causes of relapsing heart failure such as use of NSAIDs will play an important role in optimal heart failure management.

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Chapter 7

Summary

The general objective of the work presented in this thesis was to study adverse cardiovascular effects of drug use in patients with heart failure. After a literature review on precipitating factors for either first or relapsing heart failure and the effects of medication, two safety aspects of drug use in heart failure patients were evaluated in further detail. First, we evaluated the potential adverse cardiovascular effects of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with heart failure. Second, we studied risk factors for mortality in patients with heart failure who had been prescribed the dopaminergic agent ibopamine.

A number of factors that may precipitate relapses of heart failure are discussed in chapter **2.1**. Although relapses of heart failure occur frequently and have serious consequences in terms of mortality, morbidity and health care expenditures, only limited data are available on the role of precipitating factors that may trigger relapses. Alcohol, smoking, psychological stress, uncontrolled hypertension, cardiac arrhythmias, myocardial ischaemia, poor treatment compliance, and inappropriate medical treatment are among the factors that may precipitate heart failure. Poor treatment compliance is frequently encountered in patients with relapsing heart failure. However, iatrogenic causes of relapsing heart failure such as inappropriate medication and excessive intravenous fluid administration may also precipitate heart failure.
The identification of precipitating factors may contribute to optimal treatment of patients with heart failure, and may reduce the number of relapses.

Although heart failure is predominantly caused by cardiovascular disorders such as ischaemic heart disease, valvular disease and hypertension, several classes of drugs have the potential to induce heart failure in patients with previously normal myocardial function or to precipitate relapses in patients with compensated heart failure. Cytostatics, immunomodulating drugs, antidepressants, calcium entry blockers, NSAIDs, anti-arrhythmics, beta-blockers and anesthetics are among the agents discussed in chapter **2.2** that are associated with the onset of drug-induced heart failure. Drug-induced heart failure should be regarded as a potentially preventable cause of heart failure. However, sometimes other priorities offer no therapeutic alternatives (e.g., anthracycline-induced cardiomyopathy). Awareness of clinicians of potential adverse effects on cardiac performance by several classes of drugs, particularly in patients with pre-existing ventricular dysfunction, may contribute to timely diagnosis and treatment or prevention of drug-induced heart failure.

Knowledge on potentially precipitating factors may improve treatment and care of patients with heart failure. Chapter **2.3** describes a study which evaluates the presence of precipitating factors in patients hospitalised for heart failure, particularly with respect to medication compliance. We analysed 318 hospital discharge letters

of participants of the Rotterdam Study admitted to hospital for heart failure. Medication compliance was assessed in patients with more than one hospitalisation by comparing dispensed medication after the first hospitalisation with the dispensed medication in the period preceding the first readmission for heart failure.
Potentially precipitating factors were described in 60% of the first hospitalisations for heart failure as compared to 43% of the readmissions. Among the most frequently encountered precipitating factors were atrial fibrillation / flutter, myocardial infarction or ischaemia, and pulmonary disease. Lack of medication compliance was notified in only 3% of the discharge letters of patients rehospitalised for heart failure. Based on dispensed medication according to computerised pharmacy records, however, non-compliance to either digoxin, diuretics or ACE-inhibitors was observed in 46% of rehospitalised patients.
Little attention is paid in hospital discharge letters to potentially precipitating factors for heart failure. In particular, lack of medication compliance seems to be significantly more common than may be expected on the basis of the information provided by hospital discharge letters. As lack of medication compliance should be regarded as a major impediment of optimal heart failure treatment, information on this aspect should be notified in hospital discharge letters.

In chapter **3.1**, the cardiovascular effects of NSAIDs in patients with heart failure are discussed. NSAIDs inhibit the function of cyclo-oxygenase, an enzyme essential for the transformation of arachidonic acid into prostaglandins. The inhibition of the production of prostaglandins does not only explain the beneficial effects of NSAIDs to a large extent, but also many of their adverse reactions.
In patients with heart failure, particularly the advanced stages, renal function is at risk because of a decrease in renal blood flow. Until the terminal stages of heart failure, glomerular filtration rate is usually preserved within acceptable limits. Prostaglandins have an important role in the maintenance of adequate renal function. The kidney releases 2 types of prostaglandins that are particularly important in the regulation of renal function, prostaglandin-I_2 and prostaglandin-E_2. These prostaglandins have vasodilatating activity in patients with heart failure, and inhibition of their synthesis may adversely affect cardiovascular homeostasis. In addition, prostaglandins reduce renal sodium and water reabsorption, which is considered to be beneficial to patients with heart failure.

During the period 1985 - 1995, the Drug Safety Unit of the Inspectorate for Health Care in the Netherlands received a number of reports of patients who developed heart failure which was attributed to the use of NSAIDs. A description of these cases is given in chapter **3.2**. This case series pertains to patients who developed definite heart failure as well as to patients who developed fluid retention without overt heart failure. In all patients, a causal relation with the use of NSAIDs was considered to be at least probable. Most reports concerned elderly women who

were prescribed NSAIDs for locomotor disease. All patients with definite heart failure had a history of cardiovascular disease, such as atrial fibrillation and coronary artery disease. Although the dosage of NSAIDs influences their pharmacological effects, the onset of significant fluid retention or symptomatic heart failure seems to depend predominantly on patient characteristics such as concomitant cardiovascular disease.

In particular patients with left ventricular (LV) dysfunction seem to be susceptible to the adverse cardiovascular effects of NSAIDs. Chapter **3.3** presents a study which evaluates the effects of NSAIDs on fractional shortening (FS) of the left ventricle.
Data for this study were obtained from the Rotterdam Study, a population-based prospective cohort study among 7,983 participants aged 55 years and older. Echocardiographic measurements were carried out in a random sample of 1919 participants. A fractional shortening of 30% was considered to be the lower limit of normal LV systolic function. Exposure to NSAIDs was determined on the basis of computerised medication histories. Participants were considered to be current users of NSAIDs when the date of echocardiography fell within the legend duration of a prescription of an NSAID. Multiple linear regression was carried out to assess the effect of NSAIDs on FS. In an overall analysis, current use of NSAIDs was associated with a small and statistically non-significant absolute decrease in FS with 1.6% (95% CI: -4.9%, 1.7%) . In participants with a FS < 30%, current use of NSAIDs was associated with an absolute decrease in FS of 11.8% (95% CI: -22.3%, -1.3%) whereas in participants with FS ≥ 30% a decrease in FS of 1.7% (95% CI: -4.4%, 1.1%) was demonstrated. Current users of NSAIDs with a FS < 30% were using a mean daily dosage of 1.63 DDDs/day as compared to 0.98 DDDs/day in current users with a FS ≥ 30%. In patients with FS < 30%, current use of NSAIDs had a substantial negative effect on FS. In patients with normal LV function, current use of NSAIDs was associated with a negligible effect on FS.

The association between the use of NSAIDs and *incident* heart failure was evaluated in a study presented in chapter **3.4.** Data were obtained from the Rotterdam Study. A diagnosis of *incident* heart failure during follow-up was made in 345 participants. Current use of NSAIDs was associated with a RR of *incident* heart failure of 1.11 (95% CI: 0.74 - 1.68), adjusted for age, gender, and concomitant medication. To study the effect of NSAIDs in *prevalent* heart failure, patients with incident heart failure were followed from the date of diagnosis until the end of the study. In patients with prevalent heart failure who filled at least one NSAID-prescription since diagnosis of heart failure, the adjusted risk estimate of NSAIDs-associated relapsing heart failure was 9.89 (95% CI: 1.72 - 57.01).

In chapter **3.5,** a cohort study is presented that assesses the risk of relapsing heart

failure associated with the use of NSAIDs in a cohort of patients aged 50 years and older with a history of one hospitalisation for heart failure. Data were used from the PHARMO record linkage system, a database containing drug-dispensing records from community pharmacies and linked hospital discharge records of 450,000 residents of 12 population-defined areas in The Netherlands. For each individual in the cohort, exposure to NSAIDs and concomitant cardiovascular and pulmonary medication was assessed during the follow-up period. The cohort was followed from the date of discharge of the first hospital admission until the second hospitalisation because of relapsing heart failure or end of the study period. The outcome of the study was defined as a readmission with a primary diagnosis of heart failure of a member of the cohort during the study period.
In the cohort of 1,405 patients with heart failure, the overall risk of hospitalisation a relapse of heart failure associated with NSAID use was 1.41 (95% CI: 0.97 - 2.06), adjusted for age, gender and concomitant medication. Among patients who had received at least one NSAID prescription during the follow-up period, use of NSAIDs was associated with an overall twofoldly increased risk for rehospitalisation for heart failure (RR 2.20; 95% CI: 1.44 - 3.36). A first NSAID prescription was associated with an adjusted RR of 3.30 (95% CI: 1.63 - 6.71), a second to fourth prescription with an adjusted RR of 1.85 (95% CI: 1.00 - 3.45), and a fifth or more prescription with an adjusted RR of 2.18 (95% CI: 1.07 - 4.46). The calculated attributable fraction was 22.8%.
The results of this study indicate that the use of NSAIDs in patients with a previous hospitalisation for heart failure was associated with an increased overall risk of rehospitalisation for heart failure. Among users, a first prescription is associated with a threefoldly increased risk, whereas more regular use is associated with a lower risk estimate. This observation may be explained by *'depletion of susceptibles'*. The calculated attributable fraction indicates that in the users of NSAIDs in our study population approximately 23% of the rehospitalisations because of heart failure may be attributable to the use of NSAIDs.

In September 1995, the indication for the oral dopamine agonist ibopamine was restricted in the Netherlands and in several other European countries to patients with NYHA-class II heart failure as a result of an interim analysis of the PRIME-II trial. This trial demonstrated an increased mortality risk in patients with NYHA-class III / IV heart failure randomised to ibopamine. In chapter **4.1**, a nationwide retrospective cohort study is presented to assess the effects of ibopamine under everyday circumstances in a cohort of users of ibopamine in all NYHA-classes in The Netherlands. All 2147 community pharmacies and drug dispensing general practitioners received a request to list all patients to whom they had dispensed ibopamine in the preceding years. All responding drug dispensing outlets (DDO) received a questionnaire on cardiovascular risk factors and mortality for the general practitioner of a random sample of these patients. DDO were also requested to

send an anonymised printout of the complete medication record.
In patients with NYHA-class III / IV heart failure, multivariate analysis indicated that current use of ibopamine was significantly associated with an increased risk of mortality (RR 1.37; 95% CI: 1.15 - 1.64). In patients with NYHA-class I/II heart failure, however, multivariate analysis showed a twofoldly increased risk of mortality in current users of ibopamine (RR 2.03; 95% CI: 1.10 - 3.72). Apart from current use of ibopamine, male gender and increased serum creatinine were also independent risk factors for mortality in all NYHA-classes. These results indicate that ibopamine seems to be associated with an increased risk of mortality not only in patients with moderate to severe heart failure, but also in patients with mild heart failure.

Confounding by contraindication pertains to differences in outcome between treated and untreated patients which may be attributed to the presence of a contraindication for treatment in untreated patients. In chapter **4.2,** we evaluated in detail the effects of confounding by contraindication in the analysis of the nationwide retrospective cohort study on risk factors for mortality in users of ibopamine. On september 8th 1995, the former indication for ibopamine NYHA class III and IV heart failure became a strict contraindication. In patients with an index date before September 8th 1995, current use of ibopamine was univariately associated with a relative risk of mortality of 3.02 (95% CI: 2.12 - 4.30), whereas in patients with an index date after September 8th 1995, the relative risk of mortality during current use of ibopamine was 0.71 (95% CI: 0.53 - 0.96). In the multivariate analysis, these associations were 2.62 (95% CI: 1.76 - 3.90) and 0.93 (95% CI: 0.84 - 1.02), respectively. These differences were statistically significant. In the absence of any other likely alternative explanation, the marked inversion of the relative risk estimate can be regarded as a practical example of confounding by contraindication in an epidemiological study.

In chapter **4.3,** the aspects of safety and quality of life of heart failure treatment are discussed. Heart failure has a profound impact on life expectancy and quality of life. This has been a continuous stimulus for the development of new drugs for the treatment of heart failure. Despite favourable effects on quality of life parameters, several of these new agents have been associated with reduced survival in large-scale mortality trials. However, patients with severe heart failure may experience such incapacitating symptoms that the question may rise whether an improvement of quality of life makes an increased risk of mortality associated with some heart failure drugs acceptable. Drugs which improve quality of life at the expense of an increased risk of mortality may be of value, provided that the composite probability of improvement of quality of life *and* prolongation of life expectancy for those using the drug exceeds the probability of improvement of quality of life *and* prolongation of life expectancy for those not using the drug. Most clinical trials,

however, fail to evaluate this composite probability.

Chapter 5 discusses some current and future aspects of the treatment of heart failure. Heart failure is generally recognised as a major health problem. Over the years, several new drugs have been introduced for the treatment of heart failure. However, a number of these agents (e.g. phosphodiesterase-inhibitors, ibopamine, flosequinan) appeared to be associated with an increased mortality risk. On the other hand, encouraging results have been obtained from clinical trials with ACE-inhibitors and beta-blockers. Recently, spironolactone showed to have a beneficial effect on survival in patients with heart failure. The role of new drugs such as calcium sensitizers in the treatment of heart failure has to be established in future research. It seems likely that in the short term the most important improvement can be obtained when available knowledge on optimal treatment is actually applied to all patients who may benefit from this.

In the general discussion (chapter 6), the findings of the studies in this thesis are discussed against the background of aspects of drug safety, strengths and limitations of clinical trials in heart failure, and the emerging heart failure epidemic in western countries.

Hoofdstuk 8

Samenvatting

Het onderwerp van dit proefschrift betreft de bestudering van cardiovasculaire bijwerkingen van niet-steroidale anti-inflammatoire geneesmiddelen (NSAIDs) en ibopamine bij patiënten met hartfalen. Na enkele inleidende hoofdstukken over luxerende factoren voor het ontstaan van (recidief) hartfalen en de rol die medicatie-gebruik hierbij vervult, wordt een tweetal onderwerpen aangaande cardiovasculaire bijwerkingen van bovengenoemde medicatie bij patiënten met hartfalen nader bestudeerd. Ten eerste werd het verband tussen het gebruik van non-steroïdale anti-inflammatoire geneesmiddelen (NSAIDs) en het ontstaan van (recidief) hartfalen onderzocht. Ten tweede werd onderzoek gedaan naar risicofactoren voor sterfte bij patiënten met hartfalen die de orale dopamine-agonist ibopamine voorgeschreven hadden gekregen.

Een aantal factoren die recidief hartfalen kunnen luxeren wordt beschreven in hoofdstuk 2.1. Hoewel recidief hartfalen frequent optreedt en belangrijke gevolgen heeft met betrekking tot mortaliteit, morbiditeit en kosten van de gezondheidszorg, zijn er relatief weinig gegevens bekend aangaande factoren die een recidief hartfalen kunnen luxeren. Alcoholgebruik, roken, psychische spanning, ongecontroleerde hypertensie, cardiale arrhythmieën, myocard-ischaemie, onvoldoende medicatietrouw en onjuiste medische behandeling behoren tot de factoren die een recidief hartfalen kunnen luxeren. Onderkenning van luxerende factoren kan belangrijk bijdragen aan een zo optimaal mogelijke behandeling van patiënten met hartfalen, en biedt aan behandelende artsen de mogelijkheid om de kans op recidief hartfalen te verminderen.

Hoewel hartfalen in hoofdzaak wordt veroorzaakt door cardiovasculaire aandoeningen zoals coronairlijden, hypertensie en kleplijden, zijn er een aantal geneesmiddelen die hartfalen kunnen veroorzaken bij patiënten die tevoren een normale linker ventrikelfunctie hadden of die recidief hartfalen kunnen luxeren bij patiënten met gecompenseerd hartfalen. Cytostatica, immuno-modulerende geneesmiddelen, antidepressiva, calcium-antagonisten, NSAIDs, anti-arrhythmica, beta-blokkers en anaesthetica behoren tot de geneesmiddelen die besproken worden in hoofdstuk 2.2. Het gebruik van deze geneesmiddelen wordt in de literatuur geassocieerd met hartfalen. Hartfalen door geneesmiddelen moet worden beschouwd als een potentieel vermijdbare oorzaak. In een aantal gevallen bieden andere prioriteiten evenwel nauwelijks een alternatief (bv. anthracycline-geïnduceerd hartfalen). Kennis van mogelijke bijwerkingen van geneesmiddelen op de cardiale pompfunctie, in het bijzonder bij patiënten met reeds verminderde linker ventrikelfunctie, kan bijdragen aan preventie en tijdige diagnose en behandeling van geneesmiddelen-geïnduceerd hartfalen.

Kennis betreffende mogelijk luxerende factoren kan bijdragen aan de zorg en behandeling van patiënten met hartfalen. Hoofdstuk 2.3 beschrijft een studie

waarin wordt onderzocht in welke mate mogelijk luxerende factoren worden vermeld in ontslagbrieven, met name wat betreft medicatie-trouw. Hiertoe werden 318 ziekenhuis-ontslagbrieven bestudeerd van deelnemers aan het ERGO-onderzoek die waren opgenomen wegens hartfalen. Medicatie-trouw werd beoordeeld bij patiënten met meerdere ziekenhuisopnames wegens hartfalen door de verstrekte medicatie direct na de eerste opname te vergelijken met de verstrekte medicatie in de periode voorafgaande aan de tweede opname. Potentieel luxerende factoren werden beschreven bij 60% van de eerste ziekenhuisopnames wegens hartfalen in vergelijking met 43% van de recidief opnames. De meest vermelde luxerende factoren waren atriumfibrilleren/atriumflutter, myocardinfarct/ischaemie en longlijden. Gebrekkige medicatie-trouw werd slechts vermeld in 3% van de ontslagbrieven van patiënten die opnieuw werden opgenomen wegens recidief hartfalen. Op basis van de geautomatiseerde medicatiegegevens werd het vermoeden van medicatie-ontrouw echter geconstateerd bij 46% van de patiënten die werden opgenomen vanwege een eerste recidief hartfalen.
In het algemeen wordt weinig aandacht besteed aan mogelijk luxerende factoren voor hartfalen in ziekenhuisontslagbrieven. Vooral medicatie-ontrouw blijkt veel vaker voor te komen dan verwacht kan worden op basis van de ontslagbrief uit het ziekenhuis. Aangezien medicatie-ontrouw moet worden beschouwd als een belangrijke belemmering voor een optimale behandeling van hartfalen, dient deze informatie zo veel mogelijk te worden vermeld in de ontslagbrieven, zodat dit onder de aandacht van de huisarts wordt gebracht.

Hoofdstuk 3.1 beschrijft de cardiovasculaire effecten van NSAIDs bij patiënten met hartfalen. NSAIDs hebben een remmende werking op het enzym cyclo-oxygenase, een enzym dat essentiëel is voor de omzetting van arachidonzuur in prostaglandines. De remming van de aanmaak van prostaglandines verklaart niet alleen voor een groot deel de gunstige effecten van NSAIDs, maar ook veel van de bijwerkingen.
Bij patiënten met hartfalen, in het bijzonder ernstig hartfalen, kan een adequate nierfunctie in gevaar komen ten gevolge van een verminderde renale perfusie. Tot in het eindstadium van hartfalen blijft de glomerulaire filtratie veelal op een acceptabel niveau. Prostaglandines leveren een belangrijke bijdrage aan de handhaving van een voldoende nierfunctie. In de nieren komen prostaglandine-I_2 en prostaglandine-E_2 vrij die een belangrijke rol spelen bij het reguleren van de nierfunctie. Deze prostaglandines hebben vaatverwijdende eigenschappen en remming van hun synthese kan het cardiovasculaire evenwicht bij patiënten met hartfalen ongunstig beïnvloeden. Bovendien remmen deze prostaglandines de renale natrium- en water-reabsorptie hetgeen als gunstig beschouwd dient te worden bij patiënten met hartfalen.

Gedurende de periode 1985 - 1995 ontving de afdeling Geneesmiddelenbewaking

van de Inspectie voor de Gezondheidszorg een aantal meldingen betreffende patiënten die tekenen van hartfalen hadden ontwikkeld die werden toegeschreven aan het gebruik van NSAIDs. Een beschrijving van deze patiënten wordt weergegeven in hoofdstuk 3.2. Het betreft zowel patiënten die evident het klinische syndroom van hartfalen hadden ontwikkeld als patiënten die vochtretentie hadden zonder verdere verschijnselen van hartfalen. Bij alle patiënten werd de causaliteit met betrekking tot het voorafgaande gebruik van NSAIDs als ten minste waarschijnlijk beoordeeld. De meeste meldingen hadden betrekking op oudere vrouwen waaraan NSAIDs waren voorgeschreven vanwege klachten van het bewegingsapparaat. Alle patiënten met een zekere diagnose hartfalen hadden een voorgeschiedenis van cardiovasculaire ziekte zoals atriumfibrilleren en coronarialijden. Hoewel de dosering van NSAIDs invloed heeft op het farmacologische effect lijkt het risico op vochtretentie of hartfalen met name afhankelijk te zijn van cardiovasculaire comorbiditeit.

In het bijzonder patiënten met linker ventrikel dysfunctie lijken gevoelig te zijn voor de ongunstige cardiovasculaire effecten van NSAIDs. Hoofdstuk 3.3 beschrijft een studie waarin het effect van NSAIDs op de fractionele verkorting van de linker ventrikel is onderzocht. De gegevens van de studie zijn afkomstig van het ERGO-onderzoek, een prospectief cohort-onderzoek onder 7983 deelnemers van 55 jaar en ouder in de wijk Ommoord te Rotterdam. Echocardiografische gegevens van 1919 deelnemers werden geanalyseerd, waarbij een fractionele verkorting van 30% als ondergrens van een normale systolische ventrikelfunctie werd beschouwd. Gebruik van NSAIDs werd vastgesteld op basis van geautomatiseerde prescriptiegegevens afkomstig van de apotheek. Deelnemers werden geacht actueel gebruiker van een NSAID te zijn wanneer de datum van echocardiografie lag binnen de prescriptieduur van het NSAID-recept. Multiple lineaire regressie analyse werd verricht om het effect van NSAID-gebruik op de fractionele verkorting te onderzoeken. Bij deelnemers met een fractionele verkorting van < 30% was actueel gebruik van NSAIDs geassocieerd met een absolute vermindering van de fractionele verkorting met 11.8% (95% BI: -22.3%, -1.3%), terwijl bij deelnemers met een fractionele verkorting ≥ 30% een vermindering van de fractionele verkorting met 1.7 % (95% BI: -4.4%, 1.1%) werd vastgesteld. Actuele gebruikers van NSAIDs met een fractionele verkorting van < 30% gebruikten een gemiddelde dagelijkse dosering van 1.63 DDDs/dag in vergelijking met 0.98 DDDs/dag bij actuele gebruikers met een fractionele verkorting ≥ 30%, een statistisch significant verschil. Bij patiënten met een fractionele verkorting kleiner dan 30% lijkt actueel gebruik van NSAIDs een negatief effect te hebben op de fractionele verkorting. Bij patiënten met een normale systolische linker ventrikelfunctie is het gebruik van NSAIDs niet geassocieerd met een belangrijk negatief effect op de fractionele verkorting.

Het verband tussen NSAID-gebruik en een eerste optreden van hartfalen (*inci-*

dent hartfalen) wordt beschreven in hoofdstuk **3.4.** De gegevens van deze studie zijn afkomstig van het ERGO-onderzoek. Om het effect van NSAIDs separaat te bestuderen bij patiënten met prevalent hartfalen werden in deze studie tevens patiënten na de diagnose hartfalen gevolgd tot het optreden van recidief hartfalen of eind van de follow-up. Actueel gebruik van NSAIDs was geassocieerd met een relatief risico op incident hartfalen van 1.11 (95% BI: 0.74-1.68), gecorrigeerd voor leeftijd, geslacht en comedicatie. Bij patiënten met prevalent hartfalen die ten minste één prescriptie voor een NSAID ontvingen was het risico op NSAID-geassocieerd recidief hartfalen in de gecorrigeerde analyse 9.89 (95% BI: 1.72 - 57.01), een statistisch significante toename.

Hoofdstuk **3.5** beschrijft een cohort-onderzoek waarin het risico op recidief hartfalen tijdens gebruik van NSAIDs werd bestudeerd in een cohort patiënten van 50 jaar en ouder met een voorgeschiedenis van één ziekenhuisopname wegens hartfalen. Gegevens van deze studie zijn afkomstig van de PHARMO-database, die medicatiegegevens bevat van openbare apotheken met daaraan gekoppeld ziekenhuisontslagdiagnoses betreffende 450.000 inwoners uit 12 verschillende bevolkingsgebieden in Nederland. Voor ieder individu in het cohort werd het gebruik van NSAIDs en cardiovasculaire en pulmonale comedicatie vastgesteld gedurende de follow-up periode. Het cohort werd gevolgd vanaf de ontslagdatum van de eerste opname wegens hartfalen tot aan de datum van een tweede opname wegens recidief hartfalen of eind van de studie periode. De uitkomst van de studie was gedefinieerd als een heropname met als hoofddiagnose hartfalen.
In het totale cohort van 1405 patiënten bedroeg het risico op heropname wegens recidief hartfalen geassocieerd met NSAID gebruik 1.41 (95% BI: 0.97-2.06), gecorrigeerd voor leeftijd, geslacht en comedicatie. Bij patiënten aan wie tenminste éénmaal een NSAID was verstrekt gedurende de follow-up periode (n=559) was het actuele gebruik van een NSAID geassocieerd met een ruim tweemaal verhoogde kans op een heropname wegens recidief hartfalen (RR 2.20; 95% BI: 1.44-3.36). Een eerste NSAID prescriptie was geassocieerd met een gecorrigeerd RR van 3.30 (95% BI: 1.63-6.71), twee tot vier prescripties met een gecorrigeerd RR van 1.85 (95% BI: 1.00-3.45), vijf of meer prescripties met een gecorrigeerd RR van 2.18 (95% BI: 1.07-4.46). De berekende attributieve fractie bedroeg 22.8%.
Het resultaat van deze studie geeft aan dat het gebruik van NSAIDs bij patiënten met bestaand hartfalen geassocieerd is met een verhoogd risico op het ontstaan van recidief hartfalen. Een eerste prescriptie was geassocieerd met een drievoudig verhoogd risico, terwijl regelmatig gebruik geassocieerd is met een verdubbeling van het risico. Deze bevinding kan worden verklaard door 'depletion of susceptibles'. Bovendien wijst de berekende attributieve fractie uit dat een substantieel deel van het aantal heropnames wegens hartfalen mogelijk is toe te schrijven aan het gebruik van NSAIDs.

In september 1995 werd de indicatie voor de orale dopamine agonist ibopamine in Nederland en een aantal andere Europese landen beperkt tot patiënten met NYHA-II hartfalen als gevolg van de resultaten van een interim-analyse van het PRIME-II-onderzoek. Dit onderzoek toonde een verhoogd sterfte-risico aan ten opzichte van placebo bij patiënten met NYHA III / IV hartfalen die ibopamine gebruikten. In hoofdstuk **4.1** wordt een landelijk cohort-onderzoek beschreven naar de effecten van ibopamine bij gebruik onder alledaagse omstandigheden in een cohort van gebruikers van ibopamine afkomstig uit alle NYHA-klassen. Alle 2147 openbare apotheken en apotheekhoudende huisartsen ontvingen het verzoek een uitdraai te maken van alle patiënten aan wie zij ibopamine hadden verstrekt. Alle responderende apotheekhoudenden ontvingen vervolgens een vragenlijst aangaande cardiovasculaire risicofactoren en mortaliteit voor een aselecte steekproef van de patiënten. Verzocht werd deze door de huisarts te laten invullen. Apotheekhoudenden werden bovendien verzocht een uitdraai op te sturen van de medicatiehistorie van deze patiënten.
Bij patiënten met NYHA III/IV hartfalen bleek actueel gebruik van ibopamine significant geassocieerd te zijn met een 37% verhoogd sterfte-risico (RR 1.37; 95% BI: 1.15 - 1.64). Patiënten met NYHA II hartfalen bleken bij multivariaat analyse een verdubbeld sterfte-risico te hebben tijdens gebruik van ibopamine (RR 2.03; 95% BI: 1.10-3.72). Naast actueel gebruik van ibopamine vormden het mannelijk geslacht en een verminderde nierfunctie risicofactoren voor een toegenomen sterfte-risico. Dit onderzoek geeft aan dat ibopamine niet alleen een toegenomen risico op sterfte geeft bij patiënten met matig- tot ernstig hartfalen, maar ook geassocieerd is met een toegenomen sterfte-risico bij patiënten met mild hartfalen.

Confounding by contraindication is een epidemiologisch begrip dat aangeeft dat verschillen in studie-uitkomst tussen behandelde en niet-behandelde patiënten zouden kunnen worden toegeschreven aan de aanwezigheid van een contra-indicatie voor behandeling bij de niet-behandelde patiënten. In hoofdstuk **4.2** wordt het effect beschreven van confounding by contraindication in de analyse van de landelijke cohort-studie naar risicofactoren voor sterfte bij gebruikers van ibopamine. Bij patiënten met een index datum voor 8 september 1995 was actueel gebruik van ibopamine geassocieerd met een relatief risico op sterfte van 3.02 (95% BI: 2.12-4.30), terwijl patiënten die een index datum hadden na 8 september 1995 dit relatief risico 0.71 (95% BI: 0.53-0.96) was. In de multivariate analyse waren deze relatieve risico's respectievelijk 2.62 (95% BI: 1.76-3.90) en 0.93 (95% BI: 0.84-1.02), een statistisch significant verschil. Bij afwezigheid van een andere plausibele verklaring kan deze opvallende omslag van het relatieve risico worden beschouwd als een praktisch voorbeeld van confouding by contraindication in een epidemiologische studie.

In hoofdstuk **4.3** worden overwegingen besproken die betrekking hebben op de

veiligheid van geneesmiddelen voor de behandeling van hartfalen in het licht van de kwaliteit van leven. Hartfalen geeft in zijn algemeenheid een belangrijke verkorting van de levensverwachting en een vermindering van de kwaliteit van leven. Dit gegeven is altijd een belangrijke stimulans geweest om nieuwe geneesmiddelen te ontwikkelen ter behandeling van hartfalen. Hoewel een aantal nieuwe geneesmiddelen een gunstig effect hadden op parameters van kwaliteit van leven, bleken deze geneesmiddelen vaak geassocieerd te zijn met een toegenomen sterfte-risico in grootschalige klinisch onderzoek. Ernstig hartfalen kan echter als dermate invaliderend worden ervaren dat de vraag gerechtvaardigd is onder welke omstandigheden de kans op verbetering van kwaliteit van leven zou kunnen opwegen tegen een toegenomen sterfte-kans. Geneesmiddelen die de kwaliteit van leven verbeteren ten koste van een toegenomen sterfte-kans kunnen van waarde zijn, vooropgesteld dat de samengestelde kans op verbetering van kwaliteit van leven *en* langere overleving voor diegenen die het geneesmiddel gebruiken groter is dan de samengestelde kans op verbetering van kwaliteit van leven *en* langere overleving voor diegenen die het geneesmiddel niet gebruiken. De meeste klinische onderzoeken verstrekken echter niet voldoende informatie om bovengenoemde afweging te kunnen maken.

Hoofdstuk **5** bespreekt een aantal aspecten aangaande de farmacotherapeutische behandeling van hartfalen. Hartfalen wordt algemeen beschouwd als een zeer belangrijk gezondheidsprobleem. In de afgelopen jaren zijn verschillende nieuwe geneesmiddelen geïntroduceerd voor de behandeling van hartfalen. Een aantal van deze geneesmiddelen bleek echter geassocieerd te zijn met een verhoogd sterfte-risico. Anderzijds werden positieve resultaten gemeld uit klinisch onderzoek naar de effecten van beta-blokkers. Bovendien werd recentelijk aangetoond dat spironolacton een gunstig effect heeft op de overleving bij patiënten met hartfalen. Deze geneesmiddelen zullen een belangrijke rol krijgen als aanvulling op de standaard therapie met diuretica, ACE-remmers en veelal digoxine. De rol die nieuwe geneesmiddelen zoals de zogenaamde calcium sensitizers kunnen gaan vervullen bij de behandeling van hartfalen vereist nog verder onderzoek. Zonder twijfel kan op de korte termijn de meeste winst worden verkregen wanneer de reeds beschikbare kennis aangaande de meest optimale behandeling van hartfalen ook daadwerkelijk wordt toegepast op zoveel mogelijk patiënten met hartfalen.

Hoofdstuk **6** (algemene discussie) bespreekt de resultaten van de studies zoals weergegeven in dit proefschrift tegen het licht van diverse aspecten van geneesmiddelenbewaking, kracht en beperkingen van gerandomiseerd klinisch onderzoek en de voorziene toename van hartfalen in de westerse wereld.

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Curriculum vitae

De schrijver van dit proefschrift werd geboren op 10 december 1965 in Ede. Na het behalen van het VWO-diploma aan het Christelijk Streeklyceum te Ede in 1984 ging hij geneeskunde studeren aan de Katholieke Universiteit Nijmegen alwaar hij in 1991 het arts-examen behaalde. In de periode 1991-1993 werkte hij als arts-assistent chirurgie en gynaecologie/verloskunde in het ziekenhuis de Tjongerschans te Heerenveen. Na een korte militaire opleiding bij het Opleiding Centrum Militair Geneeskundige Dienst in Hollandsche Rading was hij in de periode 1993-1995 werkzaam als kapitein-arts binnen het Perifeer Militair Team Heerenveen, onderdeel van de Krijgsmacht Hospitaal Organisatie. Gedurende deze periode werden arts-assistentschappen cardiologie en interne geneeskunde in bovengenoemd ziekenhuis te Heerenveen vervuld. In oktober 1995 werd een aanvang gemaakt met het in dit proefschrift beschreven onderzoek en werd hij aangesteld als arts-onderzoeker bij de afdeling Epidemiologie & Biostatistiek van de Erasmus Universiteit Rotterdam. Daarnaast was hij werkzaam bij de Afdeling Geneesmiddelenbewaking van de Inspectie voor de Gezondheidszorg, thans gevestigd te Den Haag. In de periode 1996-1997 werd de Master of Science-opleiding in klinische epidemiologie gevolgd. Sinds september 1999 is hij werkzaam als arts-assistent interne geneeskunde in het Albert Schweitzer Ziekenhuis lokatie Amstelwijck in Dordrecht, alwaar hij in opleiding tot internist is.