PH.D. THESIS

CLINICAL PRACTICE GUIDELINE IN THE MEDICINAL THERAPY OF PATIENTS WITH CHRONIC HEART FAILURE

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Publications related to the subject of the thesis

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II. **Müller A,** Paulik E, Belicza É. Hazai fekvőbetegintézetekben krónikus szívelégtelenséggel kezelt betegek gyógyszeres terápiájának elemzése. Népegészségügy 2000;81(5):10-16.

III. **Müller A,** Paulik E, Belicza É, Boda K, Nagymajtényi L. Evaluation of the introduction of an american guideline on pharmacotherapy of chronic heart failure (ACE inhibition) in Hungary. Centr Eur J Occup Environ Med 2002;8(2-3):199-207.

IV. **Müller A.** Minőség az egészségügyben. In: Nagymajtényi L, Varga T (Szerk.) Közgazdaságtani, menedzsment, minőségügyi és jogi alapismeretek rezidensek számára. Szeged: 2003.123-31.

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Abbreviations

A	'after' investigation period
ACC/AHA	American College of Cardiology /American Heart Association
ACE	angiotensin-converting enzyme
AHCPR	Agency for Health Care Policy and Research
ATC	Anatomical, Therapeutic, Chemical
B	'before' investigation period
BORCSI	name of the program, an acronym coined from the names of the hospitals involved
Ca channel blocker	calcium channel blocker
CIBIS	Cardiac Insufficiency Bisoprolol Study
CONSENSUS	Cooperative New Scandinavian Enalapril Survival Study
DIG	Digitalis Investigation Group
EBM	evidence-based medicine
EF	(left-ventricular) ejection fraction
EMIKK	Consultation Center for Quality Improvement in Health Care
ESC	European Society of Cardiology
F	female
H1-H6	hospitals enumerated 1 to 6
HCT	hydrochlorothiazide
HOPE	Heart Outcomes Prevention Evaluation
HUF	Hungarian forint
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10^{th} revision (e.g. I50: Heart failure)
ISDN	isosorbide-dinitrate
ISMN	isosorbide-mononitrate
K	potassium
M	male
MERIT-HF	Metoprolol Randomised Intervention Trial in Congestive Heart Failure
Na	sodium
NYHA	New York Heart Association
RAS	renin-angiotensin system
SD	standard deviation
SOLVD	Studies of Left-Ventricular Dysfunction
SPSS	Statistical Package for the Social Sciences
USAID	United States Agency for International Development
VHeFT	Veterans Affairs Vasodilator Heart Failure Trial
yr	year
β blocker	beta blocker

Contents

1. Introduction and aim

The conflicting concepts of the "medically possible" and the "economically feasible" represent one of the crucial issues in modern medicine. Medicine today is able to offer cure for numerous diseases but even the wealthiest national economy in the world is unable to make the high technology used in health care available for all its citizens who are in need of it. In case of guaranteeing quality health care, it is essential to provide access for everyone to efficient procedures that are based on facts and to put a stop to inefficient or harmful practice [1].

"Evidence-based Medicine" (EBM) as the English-speaking world has labeled this philosophy prefers the application of the best evidences that are based on facts without encroaching upon the doctors' independence in decision-making. The evidence-based protocols can contribute to the establishment of health welfare and their application can optimize the utilization of financial and intellectual resources and diminish useless hospitalization and the practice of quantitatively unjustified and professionally objectionable drug prescription [2,3,4].

The main objective of quality health care is to guarantee the best possible health result at the lowest cost in such a way that those who are provided are satisfied with the nature and result of the rendered service.

The last decade saw the growing appreciation of attempts to achieve high quality health care in Hungary as well. The available resources are tight and the health condition of the population is quite poor. The regional differences can be seen not only in the practice of health care but in the development of health condition parameters as well [5,6,7].

An important systematic device of improving quality is to control the processes, and one of the possible ways by which it can be achieved is to apply evidence-based practical guidelines. Since the input in health care – the patient who needs the care – is a personal entity with features that influence the result of the care in several ways, the specification of processes that are most likely to be able to produce optimal results is rather difficult, and this task needs caution and the co-operation of several professions, and naturally it is time consuming. Nevertheless, even those practical guidelines that are produced according to the appropriate regulations, and applied in the appropriate manner can fail to achieve the expected results in certain cases [8,9].

By *practical guidelines* we mean series of systematically developed statements that are based on scientific evidence and expert opinion and they can present a suggestion with respect to the certain steps of health care for both the providers and those who are provided in case of specific, well-defined circumstances, and with regard to special categories of patients [10].

The guidelines make an attempt to standardize the processes by using scientific professional evidences, and their application render the achievement of optimal health and/or economic result probable. With the help of these guidelines the process of health care becomes controllable and the determination of quality indicators and the standards that derive from these becomes possible [11,12].

The *objective in using practical guidelines* can be manifold. Assisted decision-making, as mentioned in the definition, can be highlighted in the first place, in case of which those specific therapies and diagnostic methods are given preference that are able to guarantee the biggest possible improvement in the health condition of the patient. A further goal can be the balancing of the differences that can be seen in clinical practice, the promotion of quality guarantee, and the moderation of health care costs by implementing "the best for the first try" principle. The guidelines can serve as a basis for institutional certification, as evidences in connection with medical malpractice cases, they can promote research activities and they are important means in medical training and in post-graduate medical training as well [9,13].

One of the *criteria of guideline development and guideline application* is that the disease affects a large population of patients and it is a public health problem. The application of these guidelines is recommended in those fields of public health where there are considerable differences in clinical practice, where great variability is shown in the outcome of health care among the various health institutions and where significant costs are involved.

The development of practical guidelines and their application at a national level has not been integrated fully into the system of professional control in Hungary yet. In 1996 the Ministry of Welfare started a project in order to make advance on the activities in quality matters at a national level, and seven hospitals won the support. The Ministry initiated the adaptation and implementation of guidelines developed by the US Agency for Health Care Policy and Research (AHCPR) in 1994 in those institutes that volunteered to test the practical guidelines. The project was named "BORCSI" after the initials of the involved hospitals. The main objective of this initiation was on the one hand to examine with a 1-year follow-up surveyhow the foreign guidelines can be put into everyday practice, what effect they have on health care activities, how the practice and results of health care change, how the costs develop and on the other hand to monitor the documentation discipline in reflection of all these [14].

Following expert consultation we have joined the program namely the examination of the evidence-based practical guideline titled *"Heart Failure: Evaluation and Care of Patients with*

Left-Ventricular Systolic Dysfunction". This survey includes the examination of the impact study of this guideline and investigates how the guideline can be implemented in Hungary.

The aim of the study:

1. Evaluating the applicability of hospital documentation in terms of how the impact study of the practical guideline can be accomplished.
2. Analyzing the practice of Hungarian patient care before the implementation of guideline in case of patients with chronic heart failure on the basis of health documents found in the institutions.
3. Revealing the fields where changes can be experienced in the period after disseminating the recommendations of the guideline, comparing it to the period before in relation to treatment, care and therapy carried out according to the specifications of the practical guideline, irrespective of the institution.
4. Analyzing the clinical practice of the hospitals participating in the study in the periods before and after disseminating the guideline and consequently revealing those fields of the project where the leveling of basic differences between the hospitals can be attributed to the implementation and application of practical guideline.

The present study demonstrates the features of *medicinal therapy* as one of the treatment options in case of patients with chronic heart failure.

2. Literature review

2.1. Epidemiology of heart failure

Over the past several decades, cardiovascular diseases have become the leading causes of death in both sexes worldwide. It can be clearly seen that the most frequent causes of death and disability are cardiovascular diseases for middle-aged men. This disease has got a less dominant role among women before their menopause. In developed countries however, the number of age-specific cardiovascular deaths has decreased as a result of systematically planned and well-financed curative-preventive activity (e.g. in the USA by 50 % in the last 25 years). The clinical manifestation of these diseases and consequently the deaths connected to them appear later in life [15,16,17,18].

In the second half of the 20th century, the trends of premature death were strongly determined by premature death caused by the diseases of the circulatory system [19]. After the middle of the 1960's certain differences could be observed: while in developed European countries the favorable changes in premature death were mainly due to the fact that the number of deaths caused by cardiovascular diseases decreased, in the Eastern European population it was exactly this disease that played a significant role in the increasing number of deaths [20,21,22,23,24,25,26].

As regards premature death caused by diseases of the circulatory system in the adult population, from the Central European countries Hungary is the one that has fallen behind the developed European countries really drastically [19,27].

The "Johan Béla National Program Decade of Health" wishes to give high priority to the suppression of cardiovascular diseases and deaths within the framework of its preventable death section [28].

Today *heart failure* represents a significant and rapidly increasing public health problem worldwide even if mortality due to cardiovascular diseases has considerably decreased in developed countries. On the basis of current epidemiological research it can be seen that the incidence and prevalence of heart failure show an increasing tendency both in the USA and in Europe as well [15,29,30,31,32,33]. 1.5-2 % of the American population suffers from clinically diagnosed heart failure but the number of patients with left-ventricular (systolic or diastolic) dysfunction is even higher. Their condition can be verified by modern diagnostic methods but they either do not manifest the signs and symptoms of heart failure, or do not recognize the already existing signs and symptoms [29,30,31,34].

According to the results of the Framingham Heart Study the yearly incidence of heart failure in the average population is 1.6 ‰ and gradually increases with age: between the age of 35-65 there are 3/1000, while over 65 there are 10/1000 new cases every year. For the elderly, over 75 the incidence is 10 %, and heart failure is the most common cause for their hospital admission as well. The incidence of the disease is higher in men [31,33,35,36,37,38].

Heart failure is also notable for its high mortality rate. Although serious attempts have been made in order to investigate the etiology of this common disease, to diagnose and provide cure for it, the mortality is still high and the 5-year mortality rate exceeds 50 %. Its prognosis is the same as that of cancer. Death occurs in 40-70 % because of progressive circulatory failure, and it occurs suddenly in 30-60 % of all cases mainly due to malignant arrhythmia [33,35,36,39].

By the end of the third year after the onset of the symptoms only one fifth of the decompensated male patients are alive, and the number of those is high who have asymptomatic cardiac dysfunction and in their cases in the coming 1-5 years symptomatic heart failure can be expected to develop presumably [39,40,41]. The five-year survival rate is 25 % in men and 38 % in women. The average survival period is 1.7 years for men and 3.2 years for women [42].

According to the estimate of the National Heart, Lung and Blood Institute more than one million patients suffering from heart failure need clinical care annually, and more than 5 % of all hospital admissions are due to heart failure. One-third of the patients need re-admission and clinical care within 90 days [32,33,43].

The results of those European epidemiological studies that are few in number (carried out in North-Finland and Sweden) are similar to the outcome of the Framingham Study. According to a bulletin issued by the European Society of Cardiology in 1995 the number of patients receiving treatment for heart failure is minimum 2 million in the European countries but this number may as well exceed 10 million. The prevalence of heart failure in Europe is 0.6-17 ‰ for those under the age of 65 while it is 28-190 ‰ for those over 65 [33,44].

In Hungary there are no data available at population level on the basis of which the exact indicators of incidence and prevalence can be determined as far as diseases of the circulatory system are concerned. But it can be presumed that the situation cannot be better in Hungary than in the more developed countries since we know that the number of the main diseases that may lead to heart failure such as ischemic heart disease and hypertension is very high [35,36]. After extrapolating data of the Western world and taking into consideration the arteriosclerosis

mortality data it can be stated that the number of those suffering from heart failure in Hungary is at least 300 000 or even more [34].

The serious problem presented by heart failure had been neglected for a long time in health care. Today when a lot of hospital beds are occupied by patients with heart failure and this tendency seems to be increasing, more consideration has to be given this problem and the treatment of this disease has become a major challenge in health care [45].

2.2. The concept of heart failure, its characteristics and the basic theories in its therapy

From a *pathophysiological point of view* heart failure is a condition in which the inadequate pumping function of the heart muscle is responsible for not being able to transport oxygenated blood into the peripheral organs as the body's metabolic needs acquire.

From a *clinical point of view* heart failure is a complex clinical syndrome with reduced quality of life and shorter life expectancy. It is characterized by inadequate left-ventricular function and deficient neurohormonal regulation, exercise intolerance, fluid retention and shortened life expectancy. Typical features include complaints and symptoms (dyspnoea, basal wheezing, edema) related to the pathological expansion of intravascular and interstitial fluid space and the consequences of insufficient tissue perfusion [32,35,46,47].

The criteria set up by the Framingham study concerning congestive heart failure have proved to be useful i.e. for the establishment of the diagnosis the co-existence of two major criteria or one major and 2 minor criteria are necessary. In everyday practice a less quantitative evaluation is used, a functional classification, which classifies heart failure patients according to the severity of their cases on the basis of the recommendation made by the New York Heart Association (NYHA) [48,49].

In most cases heart failure is caused by the malformation and later the deficiency of the heart muscle, which is called left-ventricular dysfunction. There are two types: systolic and diastolic dysfunction, and their distinction is very important concerning the applied therapy.

The definition of chronic systolic heart failure comprises, apart from clinical symptoms, systolic dysfunction as well, where the ejection fraction (EF) is less than 35-40 %. In order to establish the diagnosis it is essential to be able to detect the objective signs of cardiac dysfunction besides the existence of the physical symptoms of heart failure either in rest or on exertion [32,35,46,50,51].

As regards the etiology of heart failure, valvular heart defects then hypertension were considered to be the most common causes for this disease earlier. Today however, ischemic heart disease is the most decisive etiological factor [35]. Chronic systolic heart failure and severe systolic left-ventricular dysfunction are of ischemic origin in 70 % of all cases, their prognosis is less favorable than that of non-ischemic origin, and modern medicinal therapy can improve these conditions only to a certain extent [52].

In recent years a number of official bodies and professional societies have dealt with heart failure management such as the European Society of Cardiology (ESC) or the American College of Cardiology/American Heart Association (ACC/AHA) thus everyday clinical practice is assisted by guidelines and practical recommendations elaborated by these American, European and other cardiologist societies [44,53,54,55].

Therapy options in case of heart failure include non-medicinal treatment, medicinal therapy, and invasive therapies, and heart transplantation [33]. The main purpose of medicinal treatment is to reduce mortality (ACE inhibitors, isosorbide-dinitrate/hydralazine), to ease complaints and to improve general physical condition (ACE inhibitors, diuretics, digoxin) [32].

Since the treatment strategy of heart failure has changed in recent years, the management has been altered as well [36,40]. Earlier the main purpose of medicinal treatment was to improve the left-ventricular systolic dysfunction (with positive inotropic drugs) and to stop fluid retention (with diuretics) because by doing so the key symptoms of the disease could be eased. Today mainly angiotensin-converting enzyme inhibitors (ACE inhibitors), aldosterone antagonists, beta blockers are used in order to have an effect on the pathologically increased functioning of the neuroendocrine system besides taking earlier purposes into consideration as well. The treatment aims at decreasing the symptoms, preventing heart failure, stopping progression, improving the quality of life in a complex way and making life expectancy longer [35,40,56].

Since cardiac dysfunction is always a progressive disorder, following early diagnosis a preventive intervention is necessary: treatment has to be started at the earliest possible stage by applying efficient dosage of drugs that have an effect on neurohormonal action in an aggressive way. Standard medication, which is a combination of drugs containing ACE inhibitors, diuretics and digitalis, with β blockers in NYHA II-III stages, is able to prevent the progression of asymptomatic left-ventricular dysfunction [34,40,49].

2.3. Description of the most important pharmaceutical combinations used in the treatment of heart failure

2.3.1. Diuretics

Diuretics have an undisputed benefit in the treatment of renal failure, renal diseases with salt-water retention and also in the failure of the heart's pumping function. They reduce plasma volume and venous reflux, thus moderating pulmonary congestion and dyspnoea [41, 57].

Even though they represent the most efficient treatment in congestive heart failure, their beneficial effect on the progression of the disease and on mortality has not been justified.

Three main types of diuretics are used in the treatment of heart failure.

Thiazides represent the first line therapy in mild congestive heart failure. They do not cause significant diuresis and can be administered orally due to their good absorptional characteristics. They are cheap and well combined with loop diuretics.

In moderate or severe congestive heart failure the use of *loop diuretics* is indicated. Administered either orally or intravenously their effect is fast and intensive but short, and the degree of the effect is always dependent on the applied dose. Loss of potassium due to the fast effect may lead to arrhythmias. In case of long-term administration of more than 80 mg daily, loop diuretics are to be combined with potassium-retaining diuretics and ACE inhibitors.

Potassium-retaining diuretics may not be used alone in heart failure, as their effect is slow and comparatively mild. However, given simultaneously with thiazides and loop diuretics they act synergistically as well as reduce the loss of potassium [53].

The American guidelines AHCPR and ACC/AHA focus on diuretics and ACE inhibitors in medicinal therapy.

According to the AHCPR guideline, complaints caused by volume overload can be significantly reduced by diuretics, the administration of which should be instituted immediately on the appearance of such symptoms. Patients with no volume overload should be given ACE inhibitors [32].

2.3.2. ACE inhibitors

Besides their antihypertensive features, they represent the first line therapy in the various forms of heart failure. ACE inhibitors are the most important pharmaceutical preparations in the long-term treatment of chronic heart failure; they have a favorable effect on functional capacity, therefore their use in left ventricular systolic dysfunction is indispensable. They are regarded as

the cardioprotective agents of the 1990s as, apart from their clinical use, their preventive effect slows down the progression of heart failure [15,40,58]. No other vasodilator can produce a similar reduction in heart frequency [47]. Large-scale, randomized studies prove their efficiency in the prevention and treatment of post-infarct circulatory failure [59,60,61,62,63].

Several studies have found that ACE inhibitors considerably reduce the morbidity and mortality of patients suffering from heart failure, and at the same time the duration of hospitalization is shortened. An ACE inhibitor mortality study closed in 1999 proved that captopril is as efficient as ß blockers and diuretics in the prevention of cardiovascular morbidity and mortality [59,62,64,65]. In asymptomatic patients with moderate or severe left ventricular systolic dysfunction – whose ejection fraction is lower than 35-40% - the administration of ACE inhibitors reduces the development of heart failure and hospitalization. Data on mortality show no difference. In symptomatic heart failure the administration of ACE inhibitors reduces symptoms, hospitalization and mortality [15,35,65,66,67,68,69,70,71].

Several multicenter trials – CONSENSUS, VHeFT II, SOLVD – have considered the favorable effects of ACE inhibitors, especially enalapril [72,73,74].

The HOPE study represents a new milestone in the prevention of cardiovascular diseases. Ramipril obviously and significantly reduced cardiovascular mortality and the number of infarcts and cerebrovascular accidents in the high-risk patients examined [15,75].

ACE inhibitors have a considerable role in several cardiovascular syndromes but they have almost revolutionalized the treatment of heart failure. Their significance in the treatment of post-infarct left ventricular dysfunction and also in diabetic neuropathy is constantly increasing [76].

According to the AHCPR guideline, the single use of ACE inhibitors may be satisfactory in patients complaining about exhaustion or exercise dyspnoe, or in case complaints and symptoms of volume overload do not occur. ACE inhibitors should be combined with diuretics when complaints persist in spite of pharmaceutical therapy or when symptoms of volume overload develop [32].

2.3.3. Cardiac glycosides

Digitalis glycosides have represented a well-known and widely used option in the treatment of cardiac failure for the past 200 years; however, their effect mechanism has not been understood until recently. Previously they were praised because of their positive inotropic effects; nowadays their neurohumoral effects are in the focus of attention.

The DIG-trial, dealing with the effect of digitalis, found that although it did not modify prognosis (overall mortality and cardiovascular mortality), the application of digitalis reduced morbidity and hospitalization. Digitalis involves no safety issues concerning long-term physical performance and quality of life [36,40,77,78,79,80,81].

In the treatment of chronic heart failure with systolic dysfunction, ACE inhibitors combined with digitalis still represent the basic components of pharmaceutical therapy [41].

According to the AHCPR guideline, digoxin should be combined with ACE inhibitors and diuretics in severe heart failure. Frequently, complaints caused by mild or moderate decompensation may be totally relieved by an optimal dose of ACE inhibitors and diuretics; in this case there is no need for digoxin. Digoxin should be used as a supplement when the optimal dose ACE inhibitor - diuretic treatment fails to relieve the patient's symptoms [32,41].

2.3.4. Anticoagulants

Patients with heart failure are prone to develop thromboembolic complications.

Several retrospective studies have analyzed anticoagulant therapy in the treatment of heart failure and according to their findings the effect of anticoagulants on mortality and on the development of thromboembolism is paradoxical, their regular administration may not be justified [82,83,84,85].

According to the AHCPR study, the application of a routine anticoagulant therapy is not indicated. Provided there is systemic or pulmonary embolism or recent atrial fibrillation in the history of the patient, it is indicated to start an anticoagulant therapy resulting in the 1.2-1.8 times lengthening of the prothrombin time [32].

2.3.5. Other pharmaceutical preparations

ß blockers are applied in order to prevent the activation of the parasympathetic system, which plays an important role in the development and progression of heart failure.

Previously these agents were not indicated in the treatment of circulatory failure due to their negative inotropic effect. Recently several studies (CIBIS I., CIBIS II. MERIT-HF Study) have found that long-term ß blocker therapy in heart failure improves both clinical symptoms and prognosis [35,40,42,71,86,87,88,89,90,91].

Initially, ß blocker therapies may have side effects; however, in case of prolonged administration they have the favorable effects of reducing the risk of progression and improving survival. Their application is contraindicated in unstable conditions and in NYHA Class IV [40].

According to the guidelines of the AHCPR, if the dose of ß blockers is increased gradually, they have a positive long-term effect on the symptoms of decompensated patients and on the prognosis of the disease.

The physiological background to the application of *vasodilators* in heart failure is the reduction of cardiac preload with venous and afterload with arteriolar dilation. Nitrates have been used as a medicine for centuries. Drugs with a direct vasodilator effect can be alternatives to ACE inhibitors [40,44,53]. If patients treated with an optimal dose of diuretics, ACE inhibitors and digoxin still have resistant dyspnoe, ACE inhibitors may be supplemented with vasodilators. Drugs with a direct vasodilator effect are especially effective in hypertensive patients. Nitrates are mostly indicated in rational therapy if symptoms indicate pulmonary congestion; such as orthopnoe, nocturnal cough attacks and dyspnoe, exertion dyspnoe, congestive murmur, dilated jugular veins, or if pulmonary congestion and a reduction in systolic blood pressure are dominant in the clinical picture [32,41].

Ca channel blockers are popular mostly because of their fast and efficient hypotensive effect; however, the safety of their long-term application has been questioned lately [42]. First generation Ca channel blockers are usually contraindicated in heart failure with systolic dysfunction due to their negative inotropic and neurohumoral activating effect. Second generation Ca channel blockers – felodipine, amlodipine – have practically no negative inotropic effects; they act similarly to vasodilators. They do not exacerbate symptoms or increase mortality; therefore their application in heart failure seems to be safe [92,93].

Heart failure is the subject of a wide range of cardiovascular research – from basic examinations concerning its pathophysiology to international studies analyzing the efficiency of therapeutic interventions in thousands of patients.

When treating a patient, apart from features concerning etiology and severity, several important factors should be taken into consideration, including age, familial background, lifestyle, nature of accompanying diseases, compliance, reaction to the pharmaceutical therapy introduced. On deciding which of the above mentioned pharmaceutical preparation(s) we are going to opt for, the significance of these factors is similar to that of the underlying disease.

3. Materials and methods

3.1. Background of the project

In 1996, the Hungarian Ministry of Welfare initiated a project in order to study the effectiveness of implementing of practice guidelines in Hungarian hospitals. Originally 6 practice guidelines developed by the AHCPR were introduced in Hungary with the assistance of the US Agency for International Development (USAID).

The Major Department III of the Hungarian Ministry of Welfare, and the Ministry's Consultation Center for Quality Improvement in Health Care (EMIKK) have had good professional relations due to previous successful co-operations, and the former as an academic coordinator, and the latter as a practical coordinator have been entrusted with undertaking this project. The Hungarian Ministry of Welfare initiated the survey named "BORCSI" (after the initials of the involved hospitals) in autumn, 1996, which was planned originally for a span of one year. This program was meant to assess the Hungarian implementation and adaptability of the guideline titled *"Heart Failure: Evaluation and Care of Patients with Left-Ventricular Systolic Dysfunction"* and the direct effects caused by the changes in clinical practice but it does not deal with the analysis of the effects on the health conditions of patients. We have joined the data collection, verification, data processing and assessment procedure of this guideline.

The guidelines developed by the AHCPR were issued and introduced in Hungary in three volumes. The first volume outlines the methodology of guideline development and the levels of familiar evidences; its aim is to make the application of the guideline accepted. The second volume gives a short description of the realization process of health provision for the service providers. The third volume informs the patients about what happens to them and why it happens during receiving health care in order to encourage patient compliance.

The financial support provided by the Ministry (HUF 1.5-2 million for each participating hospital) was able to cover the cost of translating the practice guideline developed for informing doctors (service providers) and patients into Hungarian, and the cost of organizing and accomplishing data collection in the hospitals i.e. they provided the financial background of the Hungarian implementation of this practice guideline.

The trial of this practice guideline was performed in six Hungarian institutions (H1-H6). The certain levels of Hungarian inpatient health care could be represented by initiating 3 municipal hospitals, 1 county hospital, 1 university teaching hospital and 1 national institute in this

program. (These institutions will be mentioned further in the text as hospitals, institutes or institutions regardless of their real status.)

The academic coordinator was to make a recommendation on the basis of the number of cases as to the assignation of "sample departments" in those institutes that volunteered to disseminate the uniform practice guideline. Local coordinators responsible for the project (head physicians or medical specialists) were assigned in the institutions. These program leaders had the appropriate level of authority to make decisions and to ask for reports, and their responsibility was to be in constant communication with the academic coordinator (Ministry of Welfare) and the practical coordinator (EMIKK). Their task included the co-ordination and controlling of the project within their institute, the local distribution of tasks, the assignment of people who took part in the accomplishment of these tasks, and they had to take part personally in the quarterly meetings and to report on the local experience. The organization of the project i.e. detailed planning of the survey, central data collection and assessment of results was accomplished by EMIKK.

3.2. Main steps of the project

3.2.1. Preparation of the project

In June 1997, the representatives of the hospitals participating in the program were summoned to the Ministry of Welfare in order to hold an expert forum and to give information about the program. Leading specialists of this special field, local coordinators of the involved institutes, representatives of the EMIKK and Ph.D. students, who did data processing and assessment work, took part in the meeting. The aim of this meeting was to compare the aspects of the guideline with the Hungarian conditions, to adapt these guidelines, to determine whether the guideline contained recommendations the implementation of which cannot be resolved within the Hungarian circumstances and to be able to prevent in time the incidental problems that may arise.

The institutions received the Hungarian translation of the guideline adapted to Hungarian conditions but the Ministry of Welfare did not regulate the process how the guideline was introduced and put into everyday practice, this task was complemented locally in the sphere of authority of the individual institutions taking the local conditions and facilities into consideration. The assigned local coordinators were informed about the schedule and the accomplishable tasks of the project beforehand.

3.2.2. Selection of data for data collection

At the planning of data collection, the following aspects had to be considered:

- Is it possible to trace the group of patients with this particular diagnosis category?
- How has the examination and treatment of this disease been documented?
- Is it possible to make a distinction between the documentation of this particular disease and that of other illnesses in case of individual patients?

Further important aspects included:

- the ability to observe clinical practice,
- the exact determination of the time limit of the survey,
- the consultation with the coordinators as to the method of data collection,
- the realization of data collection (the assignment of the leaders of this task and the organization of external and internal control).

Collectable data included the following fields:

- demographic characteristics of the patient,
- duration and scene of hospital care (hospital admission/discharge),
- required nursing,
- initial diagnoses/other illnesses,
- anamnestic data (complaints, previous medication, former hospital treatment, surgical interventions),
- parameters of physical status,
- examinations during hospital stay:
  - laboratory tests,
  - imaging procedures,
  - treatments, interventions.
- medicinal therapy applied during inpatient hospital stay.

3.2.3. Planning data collection, scheduling the study

In order to examine the effects of the practice guideline, the method of the 'before-after' epidemiological study was used, which had been preceded by a quite detailed pilot study.

3.2.3.1. Pilot study

The first phase of data collection was to design a data sheet in order to be able to observe the practice of hospital care. Before starting the actual study these data sheets were sent to the institutions for testing in order to find the final form. The participants filled in the data sheets retrospectively about their patients, to whom they previously provided care, on the basis of their documentation, the case-history sheets, according to the instructions concerning filling in.

In the course of the pilot study we visited all the scenes concerned, and personally checked the validity of the data indicated on the data sheets filled in in the various institutions by comparing them against the case-history sheets and other related documents (bedhead boards, nursing documentation, laboratory findings, final reports, etc.). During the pilot study 65 data sheets of 5 hospitals were checked. The validity of data collection concerning the introduction of the practice guideline was monitored by observing the completeness and appropriateness of data. For the assessment and objectivity of the information on the data sheets, we constructed two indices, which were used later as well. The extent to which the project could be followed was characterized by the "availability index", which indicated the availability of the information in the basic documentations needed for accomplishing the study. The "reliability index" referred to the filled in data sheets, which were qualified according to the following criteria:

1. fully correct group of questions
2. incomplete filling in but data can be found in source documentation
3. incorrect piece of data, not in accord with the case-history sheet
4. incomplete filling in, data cannot be found in the case-history sheet either
5. the piece of data cannot be found in the case-history sheet but the question was answered (source of information is unknown) [14].

We gave an account of the findings of the pilot study at a ministry meeting. Detailed description of our conclusions was presented to the individual data providing institutions respectively. We suggested that the local coordinators should acquaint the colleagues with the problems that arose, especially those colleagues who work in these particular problematic fields. Another suggestion was that hospital administrators should fill in these data sheets if possible since they could accomplish this task correctly and meticulously, as they previously proved it, and that it is necessary for them to receive assistance from physicians [14].

The findings of the pilot study revealed that the documentation principle considerably improved at the departments concerned, the assessment of the data sheets became easier and

their completeness increased. This change is the first, and in our opinion the most important step in the quality improvement of the institutions.

3.2.3.2. The 'before-after' study

The actual examination was carried out by the 'before-after' epidemiological study method. In the course of this examination we studied the health care practice before and after the dissemination of the guideline on the basis of health care documentation provided by the institutions. We examined whether the introduction of the guideline had any impact on health care practice in the given institutions, and if it had we wanted to know how and to what extent the care, treatment and medicinal therapy of patients with heart failure in inpatient institutions had changed.

The existing medical files made it possible for us to compare the collected data after the dissemination of the guideline with the documentation of patients provided before the adaptation of the guideline within the institutions respectively in order to be able to observe the effects. The collection of examination and control data was carried out simultaneously, in the period before the dissemination of the guideline it was done retrospectively and in the period after the dissemination of the guideline, prospectively.

The data sheet used for data collection acquired its final form after implementing the corrections deemed necessary on the basis of the findings of the pilot study. The data sheets together with the guidelines adapted to the Hungarian conditions were sent to the institutions in January 1998.

The actual examination can be divided into the following periods on the basis of the time of hospital admission:

- *'before' (B) ~ retrospective period*: 1 January 1997 – 28 February 1998, a period for studying the prevailing conditions: when the existing practical care was studied;
- *'after' (A) ~ prospective period*: 15 March 1998 – 15 March 1999; data provided in this period reflected on patient care of chronic heart failure after the institutions participating in the project had become familiar with the recommendations of the evidence-based practice guideline.

By the prospective period of data providing the physicians and the specialized staff of the hospital departments had got to know the practice guideline and the instructions for filling in the

data sheets in a uniform manner. The assigned program leaders in the inpatient institutions carried out the technical co-ordination of the project.

In both examination phases, data providing concerned those patients who were admitted to these particular inpatient institutions in the periods indicated above, with the initial diagnosis of chronic heart failure according to the ICD-10 [I50] or with any initial diseases that may lead to heart failure such as arteriosclerotic heart disease – [I20-I25], hypertensive heart disease – [I10-I11, I13], valvular heart disease – [I34-I35], or dilatative cardiomyopathy [I42]. All patients were represented in the program who had chronic heart failure regardless of the fact that their hospital admission was or was not the result of this particular condition.

With respect to the applied medication, the data collection included not only those drugs that were normally used in the management of chronic heart failure but all types of drugs that were prescribed during the hospitalization period. Since the practice guideline developed by the AHCPR recommends the use of diuretics, ACE inhibitors, cardiac glycosides and anticoagulants as the initial phase in medicinal treatment, primarily the analysis of these groups of drugs will be presented.

The data sheets contained information on the name of the drug applied during the inpatient hospital stay, its daily dosage, and the period of the therapy. The registration of the potency of drugs and the form of their packaging was not very precise.

We completed the categorization of the applied drugs according to the active agent on the basis of the Anatomical, Therapeutic, Chemical classification of drugs (ATC-code).

3.2.4. Processing and analyzing data

In the course of the entire research period, checking the validity of data was carried out at random. The coding and computerizing of data sheets filled in by the institutions were performed continuously. Processing and analyzing data with the help of a statistical program, SPSS 9.0 for Windows, could only be started after 15 March 1999. The statistical tests were accomplished with the help of Pearson's chi-squared test and the Mann-Whitney U test. The significance level was $p<0.05$. Examinations with more than one variable were carried out by logistic regression as a possible statistical modeling form. During the piloting the H4 county hospital was chosen as a reference hospital with regard to its intermediary position in progressive patient care.

4. Results

In the first part of this section following the structure of the data sheet the socio-demographic parameters of the surveyed population and the major patient state variables assessed before and at the time of hospital admission are presented *comparing the observed 'before-after' phases.*

In the course of the 'before-after' epidemiological study a total of 1386 data sheets have been filled in by the 6 hospitals. Finally, data of 1222 patients met the requirements. 46.3 % (566) and 53.7 % (656) of these patients constituted the database of the period before and after the dissemination of the guideline respectively.

4.1. Socio-demographic features

According to the socio-demographic parameters shown in Table 1 48.9 % of the 1222 patients were male and 51.1 % was female. In the before period the *sexes* were represented in 50.0-50.0 % but in the after period the proportion of women is slightly higher (52.0 %).

The *average age* was 67.3±12 years; the youngest patient was 22 and the oldest, 97.

Table 1 **Major socio-demographic features of the patients in the 'before' and 'after' periods**

Characteristics \ Investigation periods		Before	After	Altogether
Sex	Male (%)	50.0	48.0	48.9
	Female (%)	50.0	52.0	51.1
Age/mean ± SD/ (yr)		67.1 + 12.0	67.4 + 12.0	67.3 + 12.0
Age groups	< 65 yr (%)	36.9	36.3	36.6
	65-75 yr (%)	36.1	34.1	35.0
	> 75 yr (%)	27.0	29.6	28.4
Family background	Single (%)	16.2	16.5	16.4
	In family (%)	83.8	83.5	83.6

From an epidemiological point of view, the *age groups* are very significant and in patients with heart failure the age groups showed the following facts: nearly one-third of all patients (36.6 %) was under 65, and two-thirds of all patients (63.4 %) were over 65. With respect to the cardiovascular diseases we have to lay emphasis on the fact that 28.4 % of all patients were over 75. The proportions in the 'before-after' study periods did not change much.

The breakdown by *family background* showed that 83.6 % of the patients lived with their families and only 16.4 % lived on their own.

As far as socio-demographic parameters are concerned there was no statistically significant difference between the two study periods.

4.2. The period before hospital admission

Table 2 shows the *hospitalization indicators* of patients, almost half of them (49.3 %) were admitted as emergency cases. In the period after the dissemination of the guideline, the number of patients admitted as emergency cases significantly increased and the number of planned patient admissions decreased.

Table 2 **Major hospitalization indicators in the 'before' and 'after' periods**

Characteristics \ Investigation periods		Before	After	Altogether
Admission state *	Urgent (%)	42.1	56.4	49.3
	Non-urgent (%)	57.9	43.6	50.7
Nursing need	Bedridden (%)	24.8	24.2	24.5
	Self-catering (%)	75.2	75.8	75.5
Average nursing time /mean±SD/ (day) *		10.8 ± 7.9	8.6 ± 5.9	9.6 ± 7.1

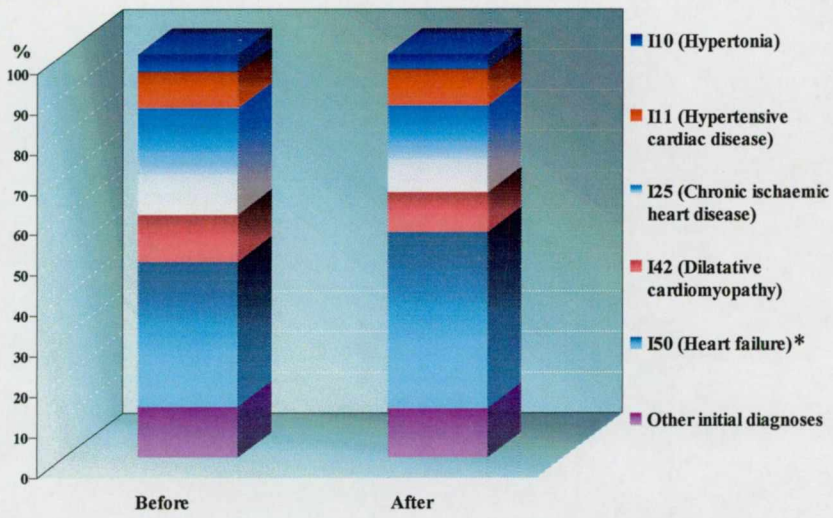
* $p<0.05$ (in the 'before' and 'after' period)

As for *required nursing*, almost three quarters of all patients did not need nursing in either period.

The *average number of days when nursing was required* 9.6; after the dissemination of the guideline this number dropped from 10.8 days to 8.6 days, thus a significant change was experienced. The shortest period spent in the inpatient institution in the 'before-after' periods was 1 day in both periods, and the longest stay was 82 and 64 days respectively.

40.1 % of all patients were admitted with the *initial diagnosis* of chronic heart failure [I50], a considerable proportion of patients were admitted with the initial diagnosis of chronic ischemic heart disease [I25] (23.8 %), dilatative cardiomyopathy [I42] (10.6 %), hypertensive heart disease [I11] (9.0 %) and hypertension [I10] (4.0 %), and 12.5 % of all patients was admitted with other initial diagnoses.

As Figure 1 demonstrates, in the period after the dissemination of the guideline the proportion of patients admitted with the initial diagnosis of heart failure significantly increased (B: 35.9 %, A: 43.8 %). At the same time the proportion of patients with the initial diagnosis of hypertension (B: 4.4 %, A: 3.7 %), chronic ischemic heart disease (B: 26.5 %, A: 21.5 %), dilatative cardiomyopathy (B: 11.5%, A: 9.9 %) decreased, the degree of the change in case of the latter ones cannot be assessed statistically.

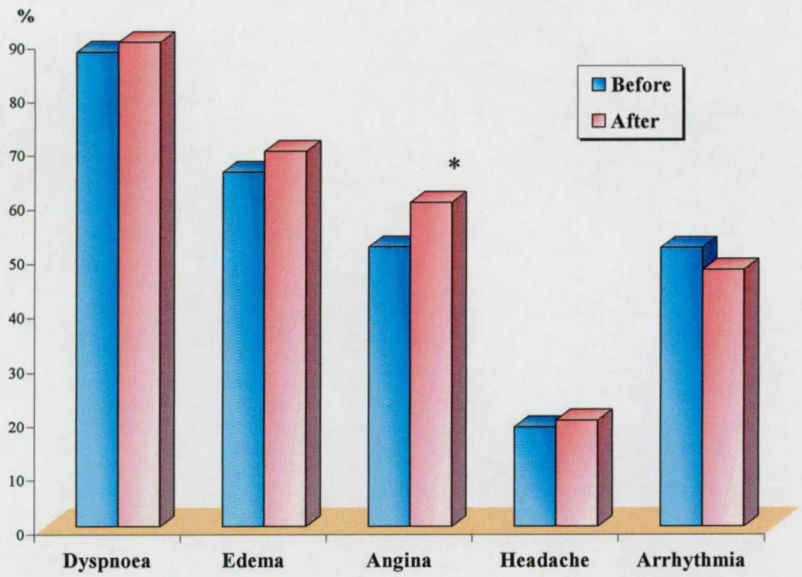


* p<0.05 (in the 'before' and 'after' period)

Figure 1 **Initial diagnoses of patients admitted in the 'before' and 'after' periods**

The number of *other diagnoses* was an average of 6.1±2.7. There were patients with no other illnesses besides the initial diagnosis, but sometimes the number of other diagnoses was almost twenty.

The examination of patient *complaints* comprised the existance of dyspnoea (88.8 %), edema (67.6 %), angina (56.1 %), headache (19.1 %) and arrhythmia (49.4 %).



* p<0.05 (in each period)

Figure 2 **Frequency of complaints in the periods before and after the dissemination of the guideline**

Figure 2 clearly shows that comparing the 'before-after' periods, significant difference occurred only in case of angina complaints; there was no considerable change in the frequency of other symptoms. The most frequent complaints among patients were dyspnoea and edema. The occurrence of arrhythmia complaints decreased in the 'after' period, and in case of the other complaints there was a slight rise in numbers.

It is worth having a look at one of the anamnestic data, the patients' *smoking habits*: on the one hand three quarters of them (B: 76.0 %, A: 75.5 %) have never smoked, on the other hand 15.0 % and 11.4 % of the patients, respectively, smoked during their existing disease as well.

Figure 3 demonstrates the main features of prescription in case of drugs that affect the cardiovascular system *in the period before hospital admission.* The applied drugs were categorized as follows:

- drugs listed in the recommendation of the practice guideline (diuretics, ACE inhibitors, cardiac glycosides, anticoagulants),
- frequently used cardiovascular drugs but not mentioned in the recommendation of the practice guideline (beta blockers, nitrates),
- other drugs affecting the circulatory system.

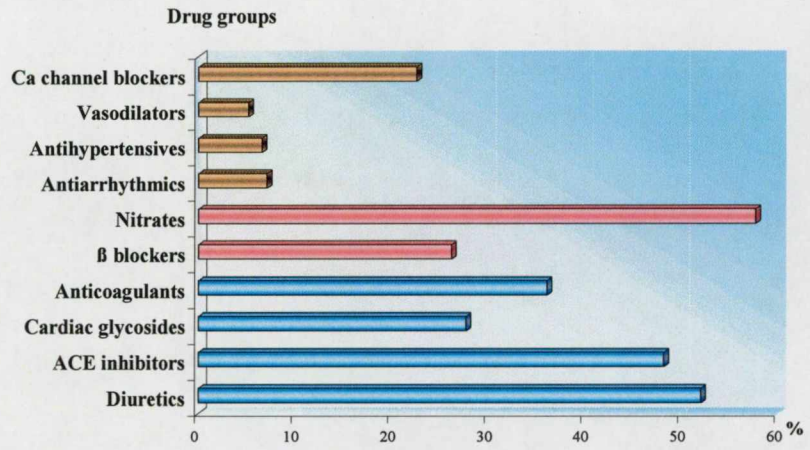


Figure 3 **Frequency of drug application before admitted to inpatient institutions (%)**

Every second patient (52.0 %) received *diuretic treatment*; 41.3 % of the patients received one type of diuretics, 9.8 % got two different types and in case of 0.9 % of all patients more than two types of diuretics were prescribed simultaneously. The most frequently used active agents were furosemide (38.4 %) and the hydrochlorothiazide+potassium-retentive diuretics /HCT+K-sparing/ (14.5 %) but the use of chlopamide (4.2 %) and spironolactone (4.4 %) was also

common. At the same time drugs containing thiazide (0.3 %) and K-cancreonate (0.2 %) were practically not prescribed.

48.2 % of all patients received *ACE inhibitors*. The use of one particular type of ACE inhibitor was predominant; only 0.6 % took two types of drugs simultaneously. Enalapril (28.0 %) and captopril (13.1 %) were the most popular and most frequently prescribed ACE inhibitors but the use of perindopril (4.4 %) cannot be neglected either. The other drugs within this particular group were not dominant; their frequency was under 1 %.

Cardiac glycosides were prescribed in case of 27.7 % of all patients; basically one type of drug was favored. The leading drug in this group was digoxin (26.1 %).

Anticoagulants were applied in case of one third of all patients (36.1 %) in the period before admission. 4.4 % of all patients received two or more drugs simultaneously. In this group of drugs the prescription of acenocumarol (19.4 %) and acetylsalicylic acid (18.3 %) was predominant.

β blockers were prescribed in case of 26.2 % of all patients. Mainly drugs with the active agents of metoprolol (19.5 %), bisoprolol (2.8 %) and atenolol (1.7 %) were used.

Organic nitrates were the most favored drugs in the period before admission to inpatient institutions: 57.7 % of all patients received them and 2.2 % took two types of them at the same time. Nitroglycerin (43.0 %) and isosorbide-mononitrate (16.0 %) are heading the list; the prescription of isosorbide-dinitrate (0.3 %) and pentaeritril-tetranitrate (0.6 %) was not significant.

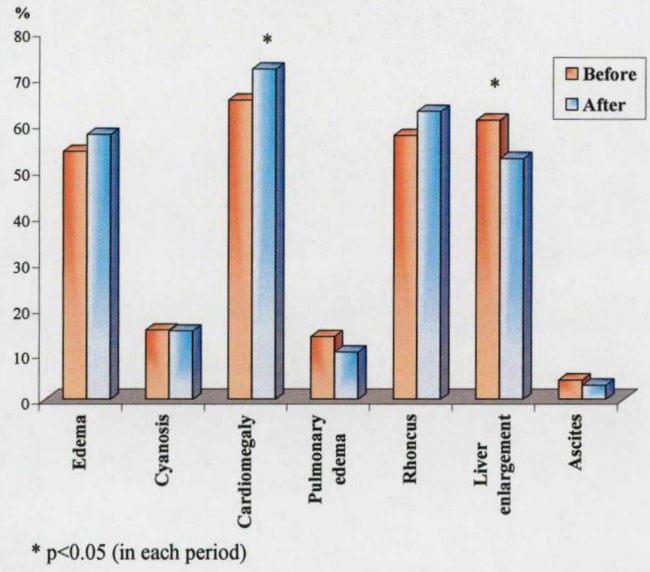
As for *other cardiovascular drugs*, Ca channel blocking agents were taken by 22.6 % of all patients.

4.3. Determination of physical condition of patients at time of hospital admission

The following parameters were taken into consideration when assessing the *physical status* of patients suffering from heart failure: *edema* was observed in 56.1 % of all patients (primarily in the form of crural edema), 15.3 % were *cyanotic*, 66.5 % had *cardiomegaly*, 12.0 % had *pulmonary edema*, 60.4 % had *rhoncus*, 56.4 % had *chronic liver enlargement*, and 3.7 % had *ascites*.

Figure 4 shows the patients participating in the project according to these physical status parameters in the 'before-after' periods.

The proportion of patients with enlarged hearts in one or both directions increased significantly in the period after the dissemination of the guideline (B: 65.2 %, A: 72.0 %). At the same time the proportion of patients admitted with chronic liver enlargement decreased (B: 60.9 %, A: 52.6 %). Both changes have to be considered significant.



* p<0.05 (in each period)

Figure 4 **Parameters of physical status in the 'before' and 'after' periods**

At hospital admission the patients were categorized according to the NYHA classification: 8.6 % of all patients belonged to NYHA I, 20.3 % to NYHA II, 31.1% to NYHA III and 40.0 % to NYHA IV. Figure 5 demonstrates the NYHA classification at the time of admission in the observed periods.

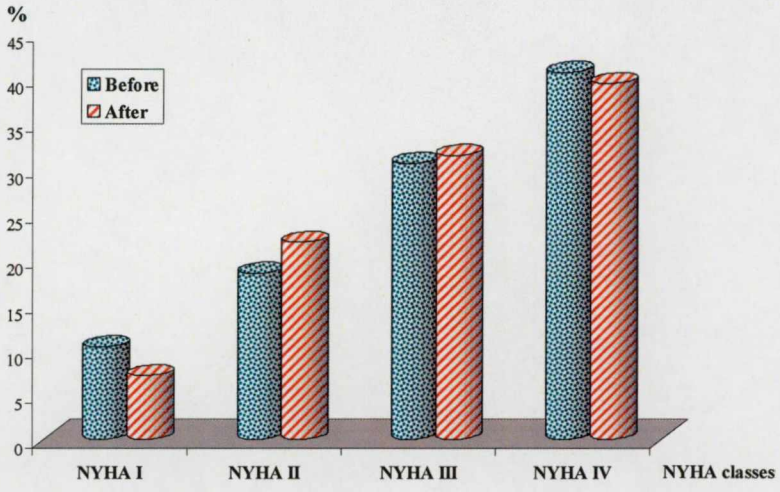


Figure 5 **NYHA classes of patients at the time of hospital admission in the 'before' and 'after' periods**

In both periods most patients were admitted with NYHA IV. The proportion of patients belonging to NYHA II and III increased in the period after the dissemination of the guideline (NYHA II – B: 18.5 %, A: 21.9 %; NYHA III – B: 30.6 %, A: 31.5 %). At the same time fewer patients were admitted with having NYHA I (B: 10.3 %, A: 7.1 %) and NYHA IV (B: 40.6 %, A: 39.4 %) in the after period. The change was not significant in either case.

4.4. Description of the pharmaceutical therapy of patients with chronic heart failure

The AHCPR guideline recommends the application of diuretics, ACE inhibitors, cardiac glycosides and anticoagulants in the introductory phase of heart failure treatment. This part of the study will cover the use of the above-mentioned pharmaceutical preparations before and after the dissemination of this guideline.

4.4.1. Diuretics

Out of the 82.6 % of patients who received diuretics, 50.8 % received one, 25.3 % two and 6.5 % three or more different types of diuretics simultaneously. 17.4 % of patients treated with chronic heart failure received no diuretics.

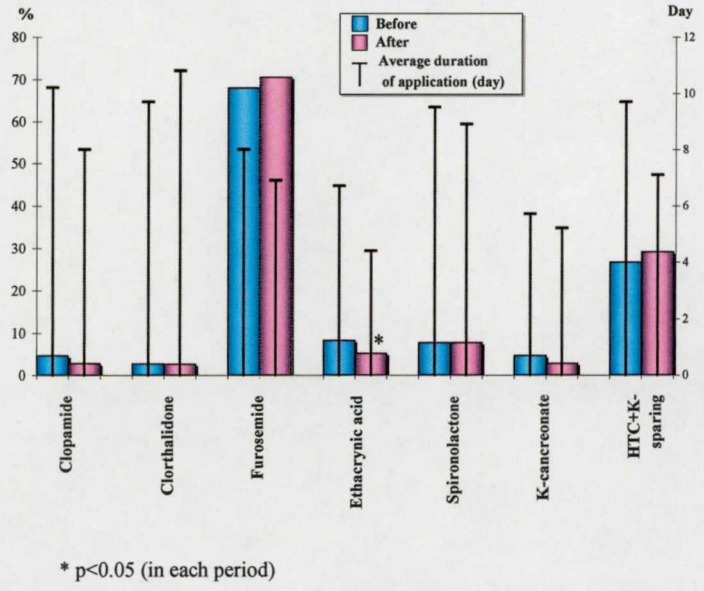
Before the dissemination of the AHCPR guideline, 81.4 %, after 83.5 % of the patients got diuretics.

As illustrated in Figure 6, the most frequently used diuretics were preparations containing a combination of furosemide (69.5 %) and (HCT) + K-retaining diuretic agents (27.9 %). Spironolactone (7.7 %) and ethacrynic acid (6.6 %) were less frequently used. Thiazides were practically unused in diuretic therapy (0.2 %) and preparations containing clopamide (3.6 %), chlorthalidone (2.6 %) and K-cancreonate were also seldomly applied [94].

After the dissemination of the AHCPR guideline, the use of preparations containing clopamide, chlorthalidone, ethacrynic acid and K-cancreonate was reduced; the reduction was most significant in case of ethacrynic acid. At the same time, furosemide and HCT + K-retaining diuretic agents were used in more patients. The increase in the number of diuretic treatment was due to the more frequent application of the two latter agents.

There were significant differences in the duration of application between the different types of diuretics. Clopamide, chlorthalidone and spironolactone were used longest; on the average they were used for 10.0, 9.3, 9.2 days, respectively (minimum 1 – maximum 27, 41, 22 days). The average duration of application in case of the most rarely used K-cancreonate was 5.5 days

(minimum 3 – maximum 11). After the dissemination of the AHCPR guideline, the duration of application of all diuretics shortened except for chlorthalidone.



* p<0.05 (in each period)

Figure 6 **The frequency of diuretics (%) and the average duration of their application (days) in the 'before' and 'after' periods**

Very short, one or two-day therapies for chronic heart failure mostly occurred due to the death of hospitalized patients; however, there were some cases of relatively longer hospitalization with short-term medication, the therapeutic benefit of which may be questioned.

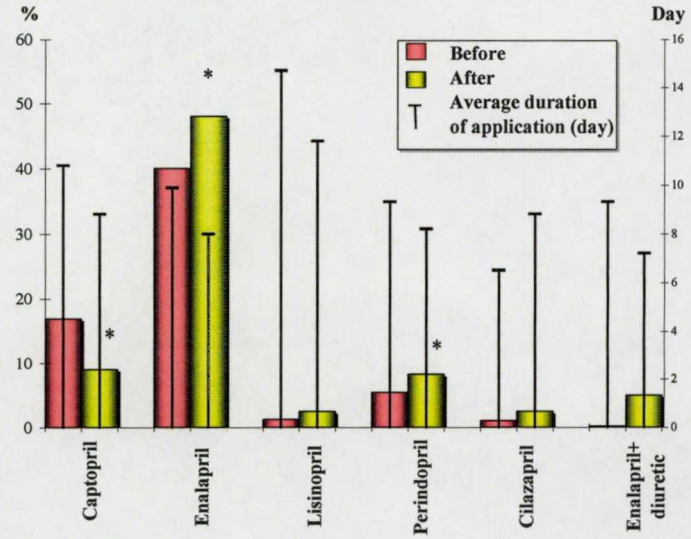
4.4.2. ACE inhibitors

68.0 % of patients hospitalized with chronic heart failure received ACE inhibitors and in most of the cases (65.2 %) these preparations were not combined with anything else. However, 32.0 % of patients received no ACE inhibitors. Before the dissemination of the AHCPR guideline, 64.7 % of patients with heart failure received ACE inhibitors, this number rose to 70.9 % in the 'after' period. The rate of increase is significant.

As illustrated in Figure 7, from all the ACE inhibitors registered and sold in Hungary, enalapril (44.4 %), captopril (12.7 %) and perindopril (6.9 %) were used in most ACE inhibitor therapies.

When considering the 'before' and 'after' periods, we can conclude that the use of captopril significantly decreased, resulting in the statistically increased use of enalapril and perindopril [94].

Regarding the duration of application of ACE inhibitors, all preparations except for cilazapril were used shorter after the dissemination of the guideline. Preparations containing lisinopril were used the longest ('before' 14.7, 'after' 11.8 days) [95].



* p<0.05 (in each period)

Figure 7 **The frequency of ACE inhibitors (%) and the average duration of their application (days) in the 'before' and 'after' periods**

According to the AHCPR guideline, the excessive use of diuretics should be avoided before the application of ACE inhibitors. If symptoms persist in spite of the ACE inhibitor therapy, or if symptoms of volume overload occur, the treatment should be supplemented with diuretics.

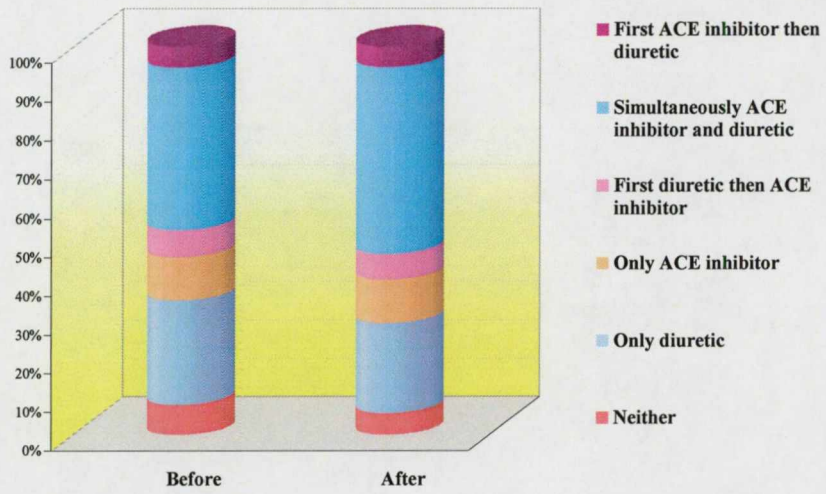


Figure 8 **The order of applying ACE inhibitors and diuretics in the 'before' and 'after' periods**

Figure 8 illustrates the results of examining the time passed before the institution of diuretic and ACE inhibitor therapy.

ACE inhibitors were given prior to diuretics only in 5.0 % of all cases. The simultaneous application of both types of preparations dominated in the 'before' as well as in the 'after' periods ('before' 41.7 %, 'after' 48.0 %). Monotherapy using only ACE inhibitors ('before' 11.1 %, 'after' 11.2 %) or diuretics ('before' 27.0 %, 'after' 23.3 %) was also frequent [94].

4.4.3. Cardiac glycosides

About half of the patients (47.2 %) received a cardiac glycoside monotherapy, while 52.8 % of the patients received no cardiac glycosides at all.

The application of these preparations was reduced after the dissemination of the guideline ('before' 48.9 %, 'after' 45.7 %).

Almost half of the patients (45.5 %) received digoxin. The use of digitoxin doubled after the dissemination of the guideline, still no more than 2 % of the patients received this preparation [94].

The average duration of the dominant digoxin application was reduced after the dissemination of the guideline ('before' 11, 'after' 9.2 days). Continuous application and the practice of missing two days weekly were both characteristic in the use of glycosides.

Dissemination of the guideline did not influence significantly the application of these preparations, i. e. no active agents of glycoside showed a considerable difference between the two periods of the examination.

4.4.4. Anticoagulants

Out of the 55.6 % of patients who received anticoagulants, 40.5 % received one, 12.2 % two and 2.9 % three or more different types of anticoagulants simultaneously.

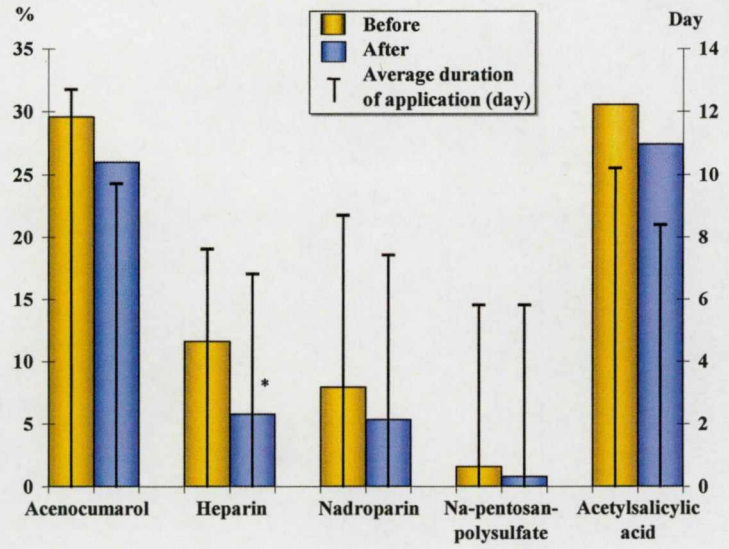
The 'before' and 'after' phases show a significant difference regarding the application of anticoagulants. Before the dissemination of the guideline 59.4 % of patients was treated with anticoagulants, their percentage dropped to 52.5 % in the 'after' period.

As illustrated in Figure 9, the most frequently used anticoagulant agents were acenocoumarol (27.7 %), heparin (8.5 %) and acetylsalicylic acid (28.7 %)[94].

All anticoagulants were used less frequently in the 'after' period; however, the reduction was significant only in the case of heparin.

The average duration of application was longest with acenocoumarol and acetylsalicylic acid ('before' 10.9, 'after' 9.4 days); however, there was a significant variation in the actual duration (minimum 2 days, maximum 65 days).

Except for Na-pentosan-polysulfate, all anticoagulant preparations were used shorter after the dissemination of the guideline.



* p<0.05 (in each period)

Figure 9 **The frequency of anticoagulants (%) and the average duration of their application (days) in the 'before' and 'after' phase**

4.4.5. Other pharmaceutical preparations

Even though the guideline do not directly deal with the administration of *ß blockers*, *organic nitrates* and *Ca channel blockers*, a short description of their application is important, partly because they represent a relatively high proportion in the therapy of cardiac failure both before hospitalization and in the 'before – after' periods and partly because, as a result of recent findings, ß blockers have been applied more frequently in the hospital setting as well.

32.0 % of patients received *ß blockers*, and 31.8 % of them received a monotherapy.

As illustrated in Figure 10, 26.1 % of patients with heart failure was given metoprolol, and bisoprolol was used in 3.2 % of all cases. After the dissemination of the guideline, both active agents were used more frequently.

Of all ß blockers, atenolol was used longest, which can be attributed to the low number of cases ('before' 6, 'after' 6 patients) and also to the maximum indication of 32 days in the 'before' period.

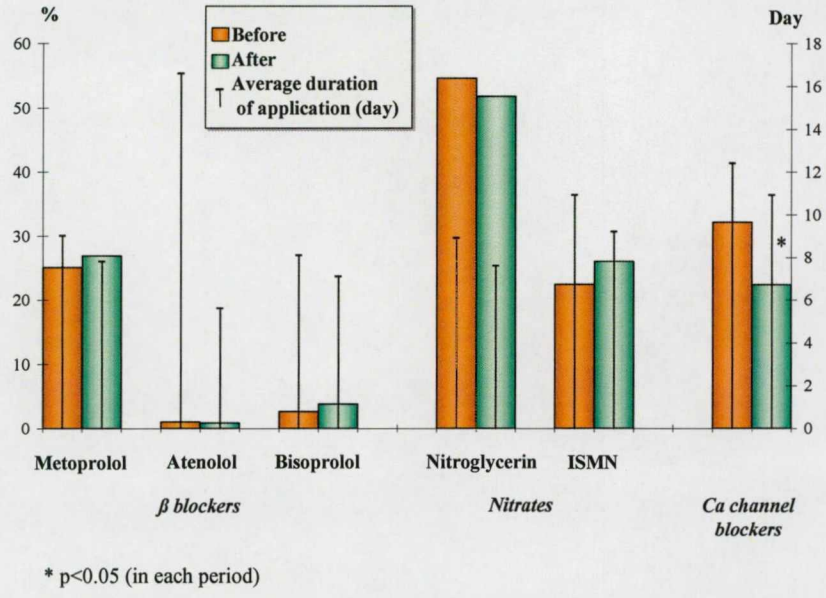


Figure 10 **The frequency of ß blockers and nitrates (%) and the average duration of their application (days) in the 'before' and 'after' periods**

The use of *organic nitrate preparations* was second only to the application of diuretics in the treatment of chronic heart failure. Out of the 71.8 % of patients who were given these preparations, 64.3 % received one, 7.5 % two different types of nitrates.

Nitroglycerin was applied in 53.1 % of the cases, and 24.4 % of patients received isosorbide-mononitrate (ISMN). The application of the former agent decreased, that of the latter one increased in the 'after' period, but the rate of difference is not significant in a statistically.

Preparations containing ISMN were applied longer. The duration of application of both active agents became shorter after the dissemination of the guideline; it varied between the minimum of 1 and the maximum of 47 days.

Ca channel blockers were used in 26.9 % of the cases. Significantly fewer patients received such preparations for a significantly shorter time ('before' 32.2 %, 'after' 22.4 %).

Summarizing the comparative results of the 'before' and 'after' periods, the following conclusions can be drawn:

- The patient population of the two examination periods can be considered homogenous regarding the most important sociodemographic parameters.
- The admission status showed a significant difference between the two examination periods.

- The average duration of hospital stay significantly decreased after the dissemination of the guideline.
- The percentage of patients hospitalized with the initial diagnosis of heart failure significantly increased in the 'after' period.
- Nitrates, diuretics and ACE inhibitors played the most important role in the pharmaceutical treatment preceding hospitalization. Anticoagulants, cardiac glycosides, ß blockers and Ca channel blockers were also frequently applied.
- The parameters of physical status recorded on admission showed a significant difference between the two examination periods in terms of patients admitted with cardio- or hepatomegaly.
- NYHA classification on admission showed no significant difference between the two examination periods.
- Regarding the application of the ATC groups highly indicated in the pharmaceutical treatment of heart failure (see Figure 11), dissemination of the guideline led to a statistically meaningful difference in the application of ACE inhibitors and anticoagulants. Comparisons between the two examination periods reveal that the use of ACE inhibitors increased and the application of anticoagulants decreased by the 'after' period. The shift in the use of these two preparations complies with the recommendations of the guideline [94,95].

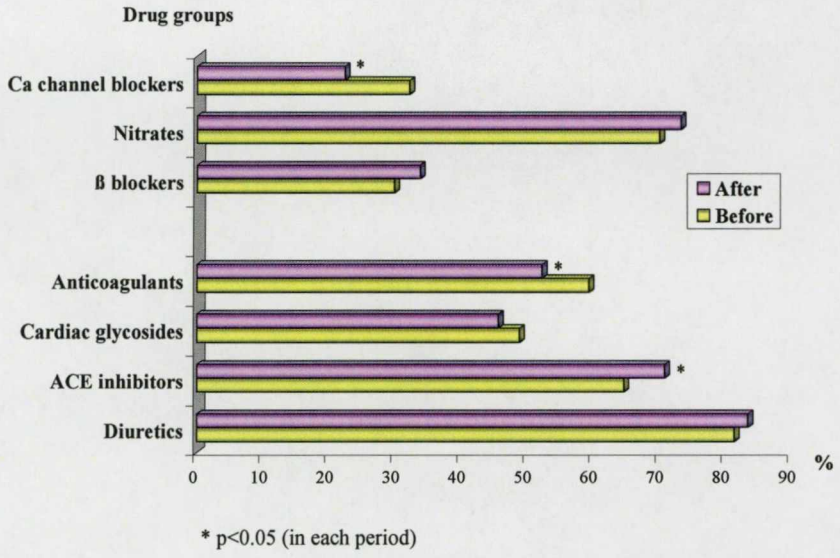


Figure 11 **Frequency of the most important groups of pharmaceutical preparations recommended by the guideline (%) in the 'before' and 'after' hospitalization periods**

- The more frequent use of diuretics in the 'after' period can be attributed to the increased application of furosemide and HCT+K-sparing diuretics.
- After dissemination of the guideline, the use of digoxin was reduced but the rate of decrease may not be considered significant.
- Regarding the use of other preparations that were not directly dealt with in the guideline, the use of ß blockers increased in the 'after' period, although not significantly.
- The use of nitrates in the pharmaceutical treatment of chronic heart failure was second to that of diuretics in both examination periods.
- In the 'after' period the use of Ca channel blockers decreased significantly.
- The average duration of application in case of all active agents studied was reduced after dissemination of the guideline.
- The AHCPR guideline recommends the initial use of ACE inhibitors before the institution of a diuretic therapy. According to our findings, these two preparations were given simultaneously in the everyday nursing practice; the initial use of ACE inhibitors alone did not dominate in either examination period.

How can we evaluate the effect of the guideline on the basis of our findings?

Analyzing the general practice of medication in chronic heart failure applied by the hospitals involved in this study we can conclude that it complies with the recommendations of the evidence-based guideline; therefore we cannot report on a significant change in medication after dissemination of the guideline. In the case of ACE inhibitors and anticoagulants there was a statistically meaningful difference between the two examination periods – but the direction of this change was parallel with the recommendations of the guideline. However, when evaluating such an impact study we should not disregard traditions determining the various fields of medicine, whose influencing or alteration may only be executed over a longer period of time - namely a couple of years - especially if the consideration of scientific evidence in the everyday nursing is not required.

It is difficult to take an unambiguous position when evaluating the comparative, 'before' and 'after' effect of the guideline based on the findings discussed above. Therefore, in the following we are going to present some parameters that may have influenced the outcome of study.

4.5. The institution-specific characteristics of the study

In this section we aim to analyze the inequalities present in the various fields of medicine and also in the health status of the general population in different regions. The location of the 6 hospitals involved in this study is rather heterogeneous, so we have to determine whether they can be treated as a homogenous unit or whether there exist some basic nursing differences that would influence the findings of this project.

Apart from the period-oriented examination aspects presented before, the consideration of some institutional parameters seems to be vital in order to be able to decide whether the change in the medication practice of patients treated with chronic heart failure can really be attributed to the influence of the dissemination of the guideline (as supposed earlier) or whether it is also the result of the different patient population and theoretical as well as therapeutical attitudes in the different hospitals [95].

4.5.1. The most important socio-demographic parameters

According to Table 3 the distribution of *sexes* was closest to that in the general population (M: 48.9 %, F: 51.1 %) in institutions H5 (M: 47.4 %, F: 52.6 %) and H6 (M: 49.5 %, F: 50.5 %). The most striking divergence occurred in the case of H2.

Table 3 **The institutional distribution of the most important socio-demographic indices**

Characteristics \ Institutions		H1	H2	H3	H4	H5	H6	Altogether
Sex *	**Male (%)**	40.7	**60.7**	51.9	51.9	**47.4**	**49.5**	48.9
	Female (%)	59.3	**39.3**	48.1	48.1	**52.6**	**50.5**	51.1
Age * /mean ± SD/ (yr)		**70.7 ± 10.4**	68.3 ± 11.7	68.2 ± 10.8	67.8 ± 11.0	**63.1 ± 13.2**	**69.7 ± 11.9**	67.3 ± 12.0
Age groups*	**< 65 yr (%)**	24.3	34.8	29.7	35.9	52.1	26.7	36.6
	65-75 yr (%)	**37.6**	36.0	42.9	36.4	**27.0**	**37.1**	35.0
	> 75 yr (%)	**38.1**	39.2	27.4	27.7	**20.9**	**36.2**	28.4
Family background *	**Single (%)**	10.5	15.9	**26.3**	20.7	11.2	**7.3**	16.4
	In family (%)	89.5	84.1	73.7	79.3	88.8	92.7	83.6

* $p<0.05$ (in H1-H6 institutions)

The *average age of patients* was also different in the different institutions. H5 had the 'youngest' patients with the average age of 63.1 and the 'oldest' ones came from H1 (70.7) and H6 (69.7).

The distribution is also heterogeneous concerning different *age groups*: in H5 47.9 % of patients was over 65 while in H6 and H1 73.3 % and 75.7 % of patients belonged to this age group, respectively.

Regarding *family background,* institutions H3 and H6 should be mentioned, as 26.3 % of the patients in the former hospital and 7.3 % in the latter one lived on their own.

Socio-demographic factors show a significant variation in case of the different institutions.

4.5.2. Hospitalization indices

As illustrated by Table 4 the *admission status* of patients to the different institutions reveals significant differences; 76.0 % of patients were brought to H3 as an emergency and less than one third of the patients in H1 and H5 were hospitalized with urgency. The regional variation in the system of referring patients to hospital highly contributes to the parameters of admission status.

Table 4 **Distribution of the most important hospitalization indices (%) in the different institutions**

Characteristics \ Institutions		H1	H2	H3	H4	H5	H6	Altogether
Admission state *	**Urgent (%)**	**25.0**	64.7	**76.0**	58.5	**29.5**	1.6	48.6
	Non-urgent (%)	75.0	35.3	24.0	41.5	70.5	98.4	51.4
Nursing need *	**Bedridden**	19.3	22.7	**5.2**	**52.0**	**12.0**	**47.3**	24.5
	Self-catering	80.7	77.3	**94.8**	48.0	**88.0**	52.7	75.5
Average nursing time * /mean±SD/ (day)		**6.1±3.2**	**13.3±9.8**	10.4±4.6	11.5±4.6	**7.8±5.2**	**14.6±12.8**	9.6±7.1

* $p<0.05$ (in H1-H6 institutions)

Some characteristic data can represent the difference between *nursing needs* in the hospitals: nearly half of the patients in institutions H4 and H6 was bedridden (52.0 % and 47.3 %), which means that the percentage of severe cases in these two hospitals considerably exceeded the nursing-need characteristics of all the patients involved in the study. In institutions H3 and H5 only 5.2 % and 12.0 % of patients was bedridden and, at the same time, 94.8 % and 88.0 % of them was ambulant.

These prominent data from Table 4 may not be explained by inequalities in morbidity. The question is whether these striking differences can be attributed to physicians' attitude and professional background or to the deficiencies in information and methodology in the period preceding the dissemination of the guideline, or whether the strong presence of traditions, the

age-related characteristics of physicians and the influence of the "alma mater" attended also play their role. Since the validity of the data was not controlled, the indices of nursing needs and admittance status (except for age and gender) can only be considered informative. It is very likely that both outstanding figures regarding bedridden status (5.2 % and 52.0 %) should be regarded as extremes.

The analysis of *average nursing days* reveals that institutions H1 and H5 treated their patients shorter than the average (6.1 and 7.8 days), while institutions H2 and H6 were characterized by longer hospitalization (13.3 and 14.6 days).

4.5.3. Initial diagnoses

As illustrated by Table 5, more than 70 % of patients in institutions H1, H2 and H6 were admitted to hospital with the initial diagnosis of heart failure [I50]. 88.4 % of patients in H3 were diagnosed initially as suffering from chronic ischemic heart disease [I25], while in H5 the most frequent initial diagnoses were hypertensive cardiac disease [I11] (29.5 %) and dilatative cardiomyopathy [I42] (24.5 %).

Table 5 **Distribution of the initial diagnoses (%) in the different institutions**

Institutions / ICD-10	H1	H2	H3	H4	H5	H6	Altogether
I10 (Hypertonia) *	4.9	5.6	0.9	6.9	1.9	7.6	4.0
I11 (Hypertensive cardiac disease) *	-	3.4	0.5	-	**29.5**	-	9.0
I25 (Chronic ischemic heart disease) *	3.1	4.5	**88.4**	14.7	17.3	4.8	23.8
I42 (Dilatative cardiomyopathy) *	1.3	2.2	7.1	8.7	**24.5**	1.9	10.6
I50 (Heart failure) *	**73.0**	**77.5**	0.5	55.4	13.6	**74.3**	40.1
Other initial diagnoses *	17.7	6.8	2.6	14.3	13.2	11.4	12.5

* $p<0.05$ (in H1-H6 institutions)

The institutions show a significant difference concerning the *other diagnoses* as well: in H6 an average patient had 3 other diagnoses, while in H4 the same figure was 8.5.

There were significant differences between the institutions regarding both the initial diagnosis and the average number of other diagnoses, which might be explained by methodological problems.

4.5.4. Classification of status on admission

Figure 12 showing the institutional *differences in NYHA classes on admission* reveals that almost half (46.1 %) of the patients in *H1* was evaluated as NYHA Class III.

NYHA Class IV dominated in *institutions H2 and H3* (50.0 % and 69.2 %).

Institutions H4 and H6 also admitted a high number of severe cases (H4 NYHA Class III: 31.2 %, NYHA Class IV: 41.1 %, H6 NYHA Class III: 51.5 %, NYHA Class IV: 33.3 %). More than 4/5 of the patients in the latter institution were admitted with severe heart failure (NYHA Class III-IV).

Institution H5 admitted most of the mild cases (NYHA Class I: 17.0 %, NYHA Class II: 25.6 %).

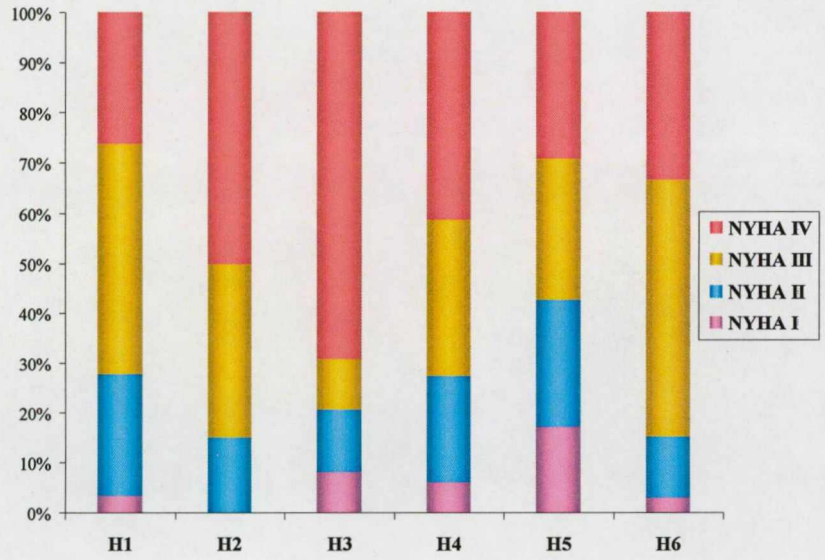


Figure 12 **The institutional distribution of NYHA classes on admission (%)**

4.5.5. Medicinal therapy

Tables 6-9 comprise information on the application of the different active agent groups, the use of which in the treatment of chronic heart failure was recommended by the guideline.

The application of *diuretics* (Table 6) reveals no significant differences between the two examination periods, nor can we detect any change in the practice of the individual institutions either. With a few exceptions, the hospitals applied the same active agents after the dissemination of the guideline as before. The rate of application did not change either.

However, there are some institution-specific uses of certain pharmaceutical preparations. In H2, furosemide, chlorthalidone and clopamide were used as diuretic agents in both examination periods. (Practically, this was the only hospital that applied a significant quantity of chlorthalidone.) In H5, all types of diuretics were used in both examination periods, and this was the only institution that used thiazide-based diuretics.

The most widely used diuretic agents were furosemide and HCT+K-retaining preparations in all institutions.

Table 6 **Institutional frequency of diuretics (%) in both examination periods**

Institutions	H1		H2		H3		H4		H5		H6	
Investigation periods / Active ingredients	B	A	B	A	B	A	B	A	B	A	B	A
Thiazides	-	-	-	-	-	-	-	-	**0.6**	**0.5**	-	-
Clopamide #	5.3	3.7	**8.9**	**6.8**	-	-	0.6	5.2	**1.2**	**1.5**	14.7	-
Chlorthalidone *	-	-	**24.4**	**22.7**	-	-	0.7	-	**1.9**	**2.5**	-	5.4
Furosemide *	71.1	76.1	**77.8**	**86.4**	68.9	90.3	88.1	83.5	**45.7**	**44.2**	72.1	86.5
Ethacrynic acid *	-	0.5	-	-	14.3	8.6	16.4	17.5	**1.9**	**3.0**	7.4	5.4
Spironolactone *	7.9	9.6	-	4.5	7.6	7.5	11.2	11.3	**2.5**	**2.5**	19.1	21.6
K-cancreonate *	2.6	1.6	-	-	-	-	6.0	1.0	**2.5**	**4.6**	19.1	13.5
HCT+K-sparing *	44.7	32.4	6.7	-	38.7	50.5	36.6	46.4	**10.5**	**16.2**	27.9	16.2

* $p<0.05$ (in H1-H6 institutions in both periods of time)

# $p<0.05$ (in H1-H6 institutions in the 'before' period)

When considering the differences in the application of *ACE inhibitors* (Table 7) between the institutions, we can see that H2 applied all ACE inhibitor preparations mentioned in the table. On the other hand, institutions H5 and H6 used only three preparations (captopril, enalapril, perindopril) while treating their patients.

Table 7 **Institutional frequency of ACE inhibitors (%) in both examination periods**

Institutions	H1		H2		H3		H4		H5		H6	
Investigation periods / Active ingredients	B	A	B	A	B	A	B	A	B	A	B	A
Captopril *	5.3	5.9	**4.4**	**6.8**	18.5	7.5	38.1	29.9	-	2.5	**27.9**	**10.8**
Enalapril *	42.1	52.1	**57.8**	**56.8**	24.4	43.0	33.6	28.9	**56.2**	**56.3**	**24.9**	**37.8**
Lisinopril *	-	-	**6.7**	**2.3**	-	3.2	1.5	3.1	**1.2**	**1.0**	-	18.9
Perindopril #	5.3	10.1	**13.3**	**15.9**	3.4	4.3	3.0	8.2	**8.6**	**7.6**	**1.5**	**5.4**
Benazepril #	-	-	**2.2**	**2.3**	-	1.1	3.7	-	-	0.5	-	-
Cilazapril	5.3	3.7	–	**2.3**	1.7	2.2	1.5	1.0	-	2.5	-	-
Trandolapril #	-	1.1	**2.2**	**4.5**	-	-	-	-	-	0.5	-	-

* $p<0.05$ (in H1-H6 institutions in both periods of time)

# $p<0.05$ (in H1-H6 institutions in the 'before' period)

Enalapril- and perindopril-based ACE inhibitors were widely used in both examination periods by all hospitals. In H2, these two active agents constituted about 3/4 of all ACE inhibitor therapies. Except for H5, captopril was also frequently used in the treatment of chronic heart failure by all institutions. The rare use of benazepril and trandolapril was only characteristic of some institutions.

We can conclude that after the dissemination of the guideline the pharmaceutical practice of the individual institutions did not change significantly, i. e. they applied the same active agents with more or less the same frequency in both examination periods [95].

The pharmaceutical practice of the individual institutions differed in the order of applying diuretics and ACE inhibitors as well.

Except for H3 (where diuretic monotherapy was preferred - 44.8 %), the simultaneous application of diuretics and ACE inhibitors dominated all hospitals. Institutions H1, H4 and H6 also had significant diuretic monotherapies (27.4 %, 27.3 % and 29.5 %, respectively).

In case of H5, besides the simultaneous application of these two agents, ACE inhibitor monotherapies also played a significant role (27.0 %).

Out of *cardiac glycosides*, *digoxin* was used in both examination periods by all hospitals. Digitoxin was almost exclusively applied in H2, where its application frequency changed significantly (from 13.3 % to 34.1 %) after the dissemination of the guideline.

Regarding the application of *anticoagulants* (Table 8) there was a significant difference between the individual institutions. The most types of anticoagulants were used in H4 in both examination periods; the other hospitals used 3-4 different types of anticoagulants. Acenocoumarol and acetylsalicylic acid were used in all institutions.

Table 8 **Institutional frequency of anticoagulants (%) in both examination periods**

Institutions	**H1**		**H2**		**H3**		**H4**		**H5**		**H6**	
Active ingredients \ Investigation periods	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**
Acenocumarol *	13.2	19.1	55.6	34.1	23.5	19.4	**45.5**	**39.2**	16.7	28.4	32.4	21.6
Heparin *	2.6	2.7	-	-	7.6	6.5	**32.8**	**10.3**	5.6	8.6	4.4	-
Antithrombin III	-	-	-	-	-	-	**0.7**	-	-	-	-	-
Nadroparin *	-	-	2.2	2.3	0.8	1.1	**31.3**	**34.0**	0.6	-	-	-
Na-pentosan-polysulfate	-	-	-	-	-	-	**6.7**	**4.1**	-	-	-	2.7
Ticlopidin	-	-	-	-	-	-	**3.7**	**3.1**	1.2	1.0	-	2.7
Acetylsalicylic acid *	13.2	13.3	11.1	18.2	30.3	29.0	**28.4**	**33.0**	45.7	42.6	22.1	5.4
Streptokinase	-	-	-	-	-	1.1	-	**1.0**	-	-	-	-

* $p<0.05$ (in H1-H6 institutions in both periods of time)

The institutional application of *ß blockers* and *nitrates* (see Table 9) can be summarized as the following:

The most frequently used ß blocker was metoprolol; however, there are significant differences in its application between the individual hospitals.

The most frequently used nitrates were nitroglycerin and isosorbide-mononitrate in both examination periods; nevertheless, their application shows significant differences between the institutions participating in this project.

Table 9 **Institutional frequency of ß blockers and nitrates (%) in both examination periods**

Institutions / Investigation periods / Active ingredients	H1		H2		H3		H4		H5		H6	
	B	A	B	A	B	A	B	A	B	A	B	A
ß blockers												
Propranolol	-	-	-	2.3	-	1.1	0.7	1.0	1.2	1.0	-	2.7
Sotalol	-	-	-	-	0.8	1.1	0.7	-	0.6	1.0	-	-
Metoprolol *	15.8	23.4	13.3	11.4	17.6	10.8	33.6	30.9	31.5	40.1	19.1	24.3
Atenolol	-	0.5	-	-	2.5	1.1	-	1.0	1.2	0.5	1.5	5.4
Betaxolol	-	1.1	-	-	-	1.1	-	1.0	-	0.5	-	-
Bisoprolol	-	4.8	-	2.3	0.8	3.2	4.5	4.1	4.9	4.1	-	-
Nitrates												
Nitroglycerin *	76.3	64.9	6.7	15.9	51.3	46.2	60.4	51.5	64.2	49.2	47.1	56.8
ISDN	-	0.5	-	-	-	-	0.7	-	-	-	-	-
ISMN *	18.4	20.2	15.6	29.5	17.6	20.4	50.7	56.7	11.7	21.3	7.4	10.8
Other nitrates	-	1.6	2.2	2.3	-	-	0.7	6.2	0.6	4.1	-	-

* $p<0.05$ (in H1-H6 institutions in both periods of time)

Table 10 shows the pharmaceutical practice of the individual hospitals according to the *main ATC groups.*

Table 10 **Institutional frequency of the most important ACE inhibitor preparations (%)**

Institutions / Drug groups	H1	H2	H3	H4	H5	H6
Diuretics *	93.8	97.8	91.0	92.2	**57.1**	94.3
ACE inhibitors *	71.2	**86.5**	**51.4**	69.3	71.3	64.8
Cardiac glycosides *	43.8	**74.2**	38.2	71.4	**29.8**	56.2
Anticoagulants *	**32.7**	59.6	44.3	**83.5**	61.6	41.9
Nitrates *	**86.7**	**32.6**	65.1	**87.0**	70.8	57.1
ß blockers *	27.4	**16.9**	19.8	38.1	**43.7**	25.7

* $p<0.05$ (in H1-H6 institutions)

Except for H5, all other hospitals used *diuretics* at a frequency of over 90 %. The use of *ACE inhibitors* was also frequent but the rate of application differs significantly. H3 used the smallest (51.4 %) and H2 used the highest amount of ACE inhibitors (86.5 %).

The most *cardiac glycosides* were used in H2 (74.2 %) and the fewest were applied in H5 (29.8 %).

The two extremes regarding the use of *anticoagulants* are H1 (32.7 %) and H4 (83.5 %).

The most frequent use of *nitrates* occurred in institutions H1 (86.7 %) and H4 (87.0 %), while H2 used the least of these preparations (32.6 %).

H5 used the most *ß blockers* (43.7 %) and the least was applied in H2 (16.9 %).

The application of the most important ACE inhibitor preparations showed a significant divergence between the six hospitals participating in the project. The data of Table 11 support

that there was no significant difference in the pharmaceutical practice of the individual hospitals between the two examination periods.

Table 11 **The institutional application of the most important pharmaceutical preparations in the two examination periods (%)**

Investigation periods	Before						After					
Institutions / Drug groups	H1	H2	H3	H4	H5	H6	H1	H2	H3	H4	H5	H6
Diuretics *	97.4	95.6	85.7	92.5	57.4	91.2	93.1	100.0	97.8	91.8	56.9	100.0
ACE inhibitors *	57.9	88.9	47.1	72.4	67.9	60.3	73.9	84.1	57.0	64.9	74.1	73.0
Cardiac glycosides *	52.6	73.3	34.5	70.1	32.1	54.4	42.0	75.0	43.0	73.2	27.9	59.5
Anticoagulants *	28.9	66.7	43.7	85.8	58.6	48.5	33.5	52.3	45.2	80.4	64.0	29.7
Nitrates *	94.7	24.4	65.5	87.3	73.5	52.9	85.1	40.9	64.5	86.6	68.5	64.9
ß blockers *	15.8	17.8	21.8	38.1	39.5	20.6	29.8	15.9	17.2	38.1	47.2	31.5

* $p<0.05$ (in H1-H6 institutions in both periods of time)

Summarizing the results of comparing the institution-specific factors, we can say that the hospitals participating in the study showed significant differences in terms of sociodemographic parameters, way and status of admission, and medicinal therapy.

4.6. Multivariate analyses

There is no doubt that we should consider the basic differences between the institutions participating in this project before evaluating the influence of the guideline on the medicinal therapy of heart failure.

In the following, we evaluate the influence of the guideline on the application of the mostly recommended pharmaceutical preparations (diuretics, ACE inhibitors, cardiac glycosides, anticoagulants) after adjusting for the differing parameters of the individual institutions both in the 'before' and 'after' examination periods.

The multivariate analysis was carried out with the help of logistic regression, which is a widely used model system in statistical analyses. The model describes the connection between a categorical dependent variable (the application of the different pharmaceutical preparations) and one or more (categorical or continuous) independent variables [96]. In the example illustrated in Table 12 the categorical independent variables are sex, the examination period and the institution, while the continuous independent variable is age.

Table 12 **Parameters influencing the application of the most important pharmaceutical preparations recommended in the treatment of heart failure**

Characteristics	Drug groups											
	Diuretics			ACE inhibitors			Cardiac glycosids			Anticoagulants		
	Estimated regression coefficient	Signifi-cance	Odds ratio	Estimated regression coefficient	Signifi-cance	Odds ratio	Estimated regression coefficient	Signifi-cance	Odds ratio	Estimated regression coefficient	Signifi-cance	Odds ratio
Sex ¤	0.3766	**0.0334**	1.4574	0.0016	0.9901	1.0016	0.4595	**0.0003**	1.5833	0.5222	**0.0000**	1.6857
Age	0.0417	**0.0000**	1.0426	-0.0016	0.7720	0.9984	0.0341	**0.0000**	1.0347	-0.0016	0.7667	0.9984
Invest. period ¤	-0.2567	**0.1506**	0.7736	-0.2459	**0.0621**	0.7820	0.0022	**0.9868**	1.0022	0.0825	**0.5276**	1.0860
Institution ¤	-	**0.0000**	-	-	**0.0000**	-	-	**0.0000**	-	-	**0.0000**	-
H1	0.0700	0.8546	1.0725	-0.0094	0.9650	0.9907	-1.2620	0.0000	0.2831	-2.2978	0.0000	0.1005
H2	1.2565	0.0981	**3.5132**	1.0304	0.0026	**2.8021**	0.0856	0.7656	1.0894	-1.2943	0.0000	0.2741
H3	-0.1768	0.6105	0.8379	-0.7629	0.0001	**0.4664**	-1.4543	0.0000	0.2336	-1.8782	0.0000	0.1529
H5	-2.0677	0.0000	0.1265	0,0528	0.7783	1.0543	-1.6583	0.0000	0.1905	-1.1405	0.0000	0.3197
H6	0.3345	0.4974	1.3972	-0.1852	0.4586	0.8310	-0.7407	0.0031	0.4768	-1.9712	0.0000	0.1393
Constant	-0.3116	0.5658	-	1.0647	0.0114	-	-1.6075	0.0002	-	1.4376	0.0007	-

¤ Reference categories: female
after period
H4

According to the results of the multivariate analysis, the examination period (i. e. the periods before and after the dissemination of the evidence-based guideline) did not influence significantly the application of the pharmaceutical preparations in any of the groups. However, the effect of the institution was statistically evident in all groups. In the case of diuretics and cardiac glycosides sex and age are the most influential factors, while anticoagulant application is influenced by sex mainly. We can also conclude that in H2 the chances of receiving a diuretic treatment are 3.5 times, while the chances of receiving an ACE inhibitor treatment are 2.8 times higher than they would be in H4, which was the reference institution. At the same time, in H3 only every second patient has the chance to receive an ACE inhibitor treatment, which would comply with the recommendations of modern pharmaceutical practice. These data emphasize the existence and the determining role of regional differences in health care.

5. Discussion

The concept of evidence-based medicine is not a new one. It means that in the course of patient care health service providers make their decisions meticulously with regard to the individual patient on the basis of the best available (literary, statistical, empirical) information.

The expertise and personal wisdom that medical practitioners may acquire during their work constitute the "personal component" in EBM. This personal component can manifest itself in efficient and effective diagnostic skills, in reasoned statements, in the personal empathy with the suffering of patients and their human dignity, and in decisions made in the best interest of the patient. By "external component" of EBM we mean the best available external theories that are exclusively based on relevant research results, which mainly come from patient-centered clinical research [97].

Congestive heart failure is a circulatory disorder, sometimes it is called "the silent epidemic"; this disease is the leading cause of death in developed industrialized countries. 22 million people are at risk worldwide and half of the patients will die within a 5-year period after establishing the diagnosis. The mortality rate is six times higher than it was 40 years ago [40]. The mortality and morbidity indicators are on the increase as well, the population is aging, the average life expectancy gets higher; the prevalence of heart failure is the highest in case of people 65 and over. Heart failure represents a major problem in health care all over the world since the chronic disease is accompanied by high mortality rate, and it carries reduced life quality, the incidence has increased, and the demand for treatment and hospital care of patients is immensely high. The large amount of required drugs, the devices that are implanted (pacemaker, defibrillator, resyncronizator), and in certain cases the only solution, the heart transplantation costs a lot, and they impose a great burden on health care. The care of patients suffering from heart failure presents a considerable task for cardiologists, internal specialists and general practitioners working in primary health care as well.

A large spectrum of cardiovascular research deals with heart failure with regard to its significance. As a result of these investigations a new approach has appeared in specialized literature called the "neurohormonal model" of heart failure. This model indicates that the concept of circulatory failure syndrome of cardiac origin includes all neurohormonal reactions that have an effect on the functioning of the whole body i.e. "heart failure is not only a failing heart". On the basis of this new approach the standard treatment of heart failure has been complemented, so today besides diuretics and digitalis, primarily ACE inhibitors are prescribed

that have an effect on the renin-angiotensin system (RAS) and research deals primarily with new therapies that influence the neurohormonal regulating systems [35,40].

It is expedient to carry out modern medicinal therapy of chronic heart failure on the basis of the results presented by comprehensive multi-centered clinical tests, and after establishing the correct diagnosis, the pathophysiological background, the initial disease, the precipitating factors and the state of clinical severity.

In the treatment of cardiovascular diseases nitroglycerin and acetylsalicylic acid have a leading role and they are a hundred years old, while digitalis is two hundred years of age but their exact effect mechanism is not yet fully understood. It is surprising that the first research findings in connection with the renin-angiotensin system were published in 1898 by scientists of the Karolinska Institute in Stockholm. The inhibition of the angiotensin-converting enzyme as a potential new group of drugs for hypotensive treatment was first described in 1977. Blocking RAS with ACE inhibitors is able to slow down the progression of several cardiovascular diseases, and improves life expectancy as well [98,99]. Over the past decade ACE inhibitors have become the favorites in the often "fashion-conscious" world of applied therapies. The use of ACE inhibitors in case of different syndromes of cardiovascular diseases, such as hypertension, heart muscle infarct, congestive heart failure, is not only recommended but also in most cases obligatory. This "fashion-consciousness" is not without foundation since EBM has provided numerous convincing data in connection with the indispensable use of ACE inhibitors; the only exception is the intolerance of these drugs [100].

Standard therapies should be performed with efficient dosages of medicine. It is characteristic of the Hungarian regional health care provision that the patients concerned are not always treated with the efficient, appropriate dosages of medicine. Further shortcomings are present in providing information and in patient education [40,101,102].

The present study demonstrates the practice of medicinal therapy in case of patients with chronic heart failure in Hungary. We have compared the medicine provision of hospitalized patients in two examined periods. Our comparison was of a rather epidemiological nature; the cardiologist aspect, in the strictest sense of the word was less prevalent. Our objective was to make a survey about the Hungarian practice of health care, to what extent it is able to keep pace with evidence-based medicine, and to examine what effect the dissemination of guideline had on the daily care of patients suffering from heart failure. On the basis of our findings we can say that in the six Hungarian health care institutions volunteering to participate in the project the

medicine provision of patients suffering from heart failure met the requirements of modern medicinal therapy in the period before the dissemination of the evidence-based practice guideline. In the period after the dissemination of the practice guideline developed by the AHCPR a significant change could be observed in the volume of drug use in case of 2 of the 4 main classes of drugs recommended for standard treatment of heart failure – diuretics, ACE inhibitors, cardiac glycosides and anticoagulants – in comparison with the period before the dissemination of the guideline. ACE inhibitors were more frequently used and anticoagulants were more rarely applied by the hospitals in the 'after' examination period than in the 'before' period. With regard to the use of other two classes of drugs – diuretics and cardiac glycosides – there was no statistically relevant change comparing the two periods.

One of the main objectives of the application of practice guidelines is the balancing of diversities in clinical practice besides supporting decision-making. Since we were well aware of the considerable differences that exist in the different fields of Hungarian health care, it was essential to be fully informed about the characteristics of medicinal therapy of the individual institutes participating in the project in both periods. On the basis of the findings of this examination we can say that the dissemination of the guideline did not have a considerable impact on the practice of medicinal therapy in the hospitals, since the differences that fundamentally exist between the inpatient institutions, and which can be experienced also in the therapeutic approach of heart failure, could not be balanced by the time of the 'after' period either. Regional health care differences (in our case differences in drug dispensation) can be observed in clinical practice. The leveling of these differences cannot be proved on the basis of our findings although it could have been expected from the application of the guideline.

This fact is highly unsatisfactory in itself. In order to form the final, research-based opinion about the impact of the practice guideline, it is inevitable that the different parameters of the institutions are taken into consideration as well. The multivariable analyses in the third major part of our experiment have shown that the examination period i.e. the fact that the guideline had been disseminated did not have any influence on the application of any group of drugs used in heart failure but in each case the institutions had a significant impact on the application of drugs. On the basis of the results of the logistic regression analysis it can be stated that the changes in drug application that were expected to be effects of the practice guideline were not due to the dissemination of the guideline but these changes were the result of the fundamental differences in medicinal therapy applied in the different institutions participating in the project. The

medicinal treatment of the inpatients with chronic heart failure is largely institution-specific and this was not influenced by the dissemination of the guideline. Similar results were provided by the analyses of echocardiography examinations, which are applied very successfully in the diagnosis of left-ventricular systolic dysfunction [51].

As far as the implementation methodology of the evidence-based practice guideline is concerned, the following conclusions can be made, which may affect the outcome of the examination. The Hungarian Ministry of Welfare - as an academic coordinator - and the Consultation Center for Quality Improvement in Health Care under the umbrella of the Ministry of Welfare - as a practical coordinator - took an active part in the Hungarian adaptation of the guideline developed by AHCPR. Due to their co-operation and mutual assistance their tasks such as translating the guideline into Hungarian, modifying the guidelines in order to make them adaptable in Hungary after a consensus seeking period, informing the project coordinators of the institutions participating in the project, carrying out a pilot study prior to the examination and performing the necessary modifications on the basis of the findings of the pilot study, completing the instructions so that the data sheets are filled in a uniform manner, sending the data sheets to the institutions, determining the time span of the examination periods and collecting the data sheets filled in by the hospitals on the basis of their patient documentation were all well coordinated and performed quite successfully. There was no central regulation by the Ministry as to the dissemination of the guideline within the hospitals and to the translation of the guideline into everyday practice. The hospitals performed these tasks individually within their own sphere of authority with the help of the project coordinators, and taking the local conditions and facilities into consideration as well. It seems that the individual, institution-specific implementation of the practice guideline could not achieve the expected results. Culture, customs, traditions and various interests in health care practice turned out to be stronger than the latest research results. The Health Act of 1997 made it compulsory to apply practice guidelines but there is no such forum that determines what practice guidelines mean. In addition, the control of professional work in hospitals is not carried out entirely either. The introduction of professional accreditation is a current issue lately, and it can considerably contribute to the regard for scientific evidences in the course of providing health care.

As for the documentation of drug application during inpatient hospital stay, the denomination, the daily dosage and the period of indication of the drug used in heart failure therapy were registered correctly but the form of application, the potency of the drug and the

packaging units were indicated rather incompletely. Therefore, due to the lack of reliable data, provision costs could not be examined although it had been one of the objectives of the project.

Precise and high-level documentation actually influences the quality of medical treatment in the given patient care unit/department favorably since it affects the physicians/staff performing the documentation, and the quality of patient care as well. At the various levels of health care, control is largely based on the examination of documentation. Continuous control of medical documentation is an integrated part in the system of quality assurance in health care. Even if the most sophisticated method is applied, the efficiency of this control can only be guaranteed if the control is permanently sustained and frequently performed. Unfortunately the publication of the continuous control in medical documentation, and the concrete results of this control are rather poor in Hungary [103].

On the basis of the results outlined in this study, we can claim that only the translation of professionally well-founded and internationally accepted practical guidelines into therapeutic practice can be justified. If we consider our examination as a model for approaching the impact study of evidence-based practical guideline from an epidemiological point of view, on the basis of our findings we can suggest a more extended regulation of conditions in the implementation of the guidelines, and quality improvement of data provision and documentation. If these aspects are taken into consideration, there is a hopeful possibility and a performable expectation that the implementation and application of practical guidelines will reduce regional differences and increase the standard quality of health care in Hungary.

6. Summary

Over the last decade great importance has been attached to the attempts for achieving quality patient care. The increase in regional differences can be detected in the changes in health condition and in patient care practice as well. A possible device for improving quality is the application of practical guidelines.

The objective of our research, the examination of the adaptability and impact study of the evidence-based practical guideline developed by the AHCPR, *"Heart Failure: Evaluation and Care of Patients with Left-Ventricular Systolic Dysfunction"* was to study the Hungarian health care of patients with chronic heart failure, and to examine the effect of the recommendations of the above mentioned guideline on the inpatient hospital care.

We used the 'before-after' epidemiological method in our study. The present thesis demonstrates the examination of one of the treatment options, the medicinal treatment of patients with chronic heart failure.

Our findings show that in compliance with the recommendations of the evidence-based practical guideline the application of ACE inhibitors has significantly increased, and the use of anticoagulants decreased. There was no statistically relevant change in the application of diuretics and cardiac glycosides in the period after the dissemination of the guideline.

In the six health institutions the drugs recommended for the treatment of chronic heart failure were used quite extensively – but at the same time quite dissimilarly in the various institutions. The diversity balancing effect of the practical guideline could not be detected either in the variety of the applied drugs or in their amount.

According to the findings of the multivariable examination, the examination period did not, but the institution did affect significantly the medicinal therapy in case of all groups of drugs.

Our results put great emphasis on the existence and strong predominance of regional differences in health care. Providing quality health care can only be achieved realistically if these differences are leveled, and careful and elaborated implementation and application of the practical guidelines and continuous monitoring of the hospitals are realized.

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APPENDIX