Connecting pre-marketing clinical research and medical practice. The case of the cardiovascular drugs

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Summary

Before new drugs are approved for marketing and doctors are allowed to prescribe them to patients, their efficacy and safety are extensively studied. An important part is formed by the clinical trials testing the new drug against placebo or other drugs. Administration of the study drug and its comparator should prevent identification by the patient and the physician. Application of this so-called double-blind methodology reduces bias in the trial results as much as possible. Clinical trials are conducted in different types of populations. For phase III trials populations are defined to resemble the recipient population after marketing. Phase III clinical trials are performed in selected patient populations. The exclusion from clinical trials of elderly and female patients, patients from ethnic minorities and patients with co-morbidity and co-medication, is often justified by the need for homogenous trial populations. As a result, by reducing the co-variables, the internal validity of trials is enhanced. At the same time, however, it reduces the applicability of trial results to medical practice, where large variation between patients exists. This gap between clinical research and medical practice has been widely recognised. It poses a problem to doctors, pharmacists and patients, who want the right drug to be prescribed to, delivered at and used by the right patient at the right time and in the right dosage. Other important actors in the pharmaceutical field also experience this problem, in particular the government, health care insurers and pharmaceutical companies.

The gap between clinical research and medical practice forms an important issue in the scientific debate about evidence-based medicine. The concept of evidence-based medicine is that diagnostic and therapeutic methods, which are applied by physicians, need to based on scientific evidence. Therefore, it is essential to use the results from systematic analyses of research data. Two core issues have been identified regarding systematic analyses. The first one refers to the assessment of the scientific quality of research data. The second issue refers to the generalizability of data from selected trial populations to populations in medical practice the results from the systematic analysis are applied to. A specific issue regarding the use of new drugs in the context of evidence-based medicine is the limited availability of published research data.

The issue of the gap between clinical research and medical practice, in particular regarding new drugs, is the central theme of this thesis. At present, few empirical studies have focussed on differences between populations in clinical trials and in daily practice using new drugs. Studies in this field focussed primarily on demographic patient characteristics, i.e., age, sex and ethnic origin. Also, most of the studies have been per-

formed in the United States. The aim of present study is to contribute in two ways to the scientific research regarding differences between pre-marketing clinical research and medical practice. Firstly, this study was designed to investigate the nature and size of demographic and disease-related differences between patients in pre-marketing research and medical practice. Cardiovascular drugs were chosen for the study, because they are widely used, by both younger and older patients, of whom the latter often present with co-morbidity and co-medication. Secondly, this study was designed to investigate the gap between clinical research and medical practice from the perspective of medical practitioners. Therefore, two approaches were used. The first approach was to study how academic and professional opinion leaders assess new drugs and whether they consider differences between patients in trials and in medical practice when they prescribe new drugs; in other words, the relevance of the issue. The second approach refers to the question which changes in drug regulation are considered necessary, according to the opinion leaders, in order to optimise the connection between research and practice from the perspective of evidence-based medicine. In summary, the research objectives were as follows:

1 To determine the discrepancies regarding age and sex distribution, ethnic origin of patients and patterns of co-morbidity and co-medication between phase III trial populations and patients in medical practice using cardiovascular drugs.
2 To investigate the considerations used by academic and professional opinion leaders in the assessment of new cardiovascular drugs, whether they are familiar with under-representation of subgroups of patients in pre-marketing trials, to assess its clinical relevance and which changes in drug regulation are considered necessary to improve the connection between pre-marketing clinical trials and medical practice.

To study the first research question, pharmaco-epidemiological methods were used. Thirty cardiovascular drugs were registered in the Netherlands in the period from 1985 to 1995 for the indications mild to moderate hypertension, angina pectoris, hypercholesterolaemia or myocardial infarction. Fifteen of these were selected for this study. Included were five ACE inhibitors/angiotensin-II antagonists, three calcium channel blockers, two beta-adrenergic blocking agents, one vasodilator, two HMG-CoA reductase inhibitors and two thrombolytics. Three drugs were registered for both hypertension and angina pectoris, bringing the total number of registration files included in the study to 18. A registration file is compiled by the pharmaceutical company applying for registration of the new drug. It contains all the information regarding the quality, efficacy and safety of the drug which is used for assessment by regulatory authorities to decide on marketing approval.

In this study, characteristics of the phase III trial populations were compared with those of patient populations in daily practice. As a reference population, data from the Registration Network Groningen (RNG) were used. This database was started in 1989 by general practitioners and contains all data from their practices. For this study data were used from 13 general practitioners with a total patient population of 22,199. All patients were selected who had received at last one prescription in 1994 or 1995 for a drug from one of the above mentioned therapeutic classes for the same indication as the trial populations

of the selected drugs. To define meaningful differences, the same classification was used as in a US study regarding the representation of female patients in clinical trials. Thus, moderate discrepancies were defined as differences of 10 to 20% in age and sex distribution and disease prevalences between the trial and RNG populations, large discrepancies were differences more than 20%.

Chapter 2 presents the results of the comparison of demographic characteristics. The age and sex distribution of all patients involved in 218 phase III trials were analysed and compared to those from the RNG patient populations. The ethnic origin of patients is not recorded in the RNG database. Therefore, a comparison of this patient characteristic was not possible. Clinical trial data regarding the ethnic origin of patients, and the male/female ratios of the populations, were analysed by region of trial performance.

Patients older than 65 years accounted for more than 50% of the population in daily practice using drugs for hypertension, angina pectoris and myocardial infarction. Elderly, as well as female patients, were under-represented in the clinical trials of the drugs registered for these indications. Trials performed in North America included relatively fewer female patients compared with European trials. In a limited number of registration files trial results were analysed by age or sex. These analyses generally involved only descriptive statistics.

Analysis by sex and age revealed over-representation of male patients younger than 45 years and female patients aged 45-65 years in the files of drugs registered for hypertension. Younger male patients were also over-represented in the files of drugs registered for hypercholesterolaemia. Discrepancies regarding elderly were found for male and female patients, but above 75 years they involved in particular female patients.

European trials included primarily Caucasian patients. North American trials of antihypertensive drugs included on average one-third non-Caucasian patients, whereas the trials with cholesterol-lowering drugs, representing a new drug class, included more than 90% Caucasians.

From the results it is concluded that clinically relevant subgroups of cardiovascular patients were under-represented in pre-marketing phase III trials of widely used drugs. Age, sex and the ethnic origin of patients are well-known modifiers of the efficacy and safety of cardiovascular drugs. Therefore, the use of drugs by patients with other characteristics than those in the trials may result in a different efficacy and/or safety. Data from phase III trials should be conclusively analysed in relation to demographic variables in order to provide a better understanding of such differences.

Chapter 3 focuses on the patterns of co-morbidity and co-medication of patients included in the phase III pre-marketing trials. Co-morbidity refers to one or more other diseases co-existing to the one the drug is indicated for. In the case of co-medication other drugs are used concomitantly to the study drug. Both are relevant factors which may alter the efficacy and/or safety of drugs. In this study, the availability of data in the registration files was investigated, and the patterns of co-morbidity and co-medication. Furthermore, differences in co-morbidity and co-medication of patients were studied according to the region of trial performance, and the impact of patient selection criteria regarding coexisting diseases on the actual inclusion of such patients.

Thirteen out of 18 registration files contained data regarding co-morbidity and co-medication of patients in phase III trials. The products involved were registered for hypertension, angina pectoris or hypercholesterolaemia. Large variation was found between the registration files in the reporting of data and in patterns of co-morbidity. In contrast to the general notion of exclusion from trials of patients with co-morbidity and co-medication, the results of this study show that pre-marketing trials were performed in populations which included such patients. Concomitant cardiovascular, endocrine and metabolic diseases were most frequently documented, in particular in the files of drugs registered for angina pectoris and hypercholesterolaemia. As expected, the patterns of co-medication corresponded to those of co-morbidity. Patients included in North American trials on average had more coexisting diseases and co-medication compared with European trials.

The patient selection criteria related to concomitant morbidity and medication varied in description and content. Differences in definitions of concomitant diabetes, heart failure or hypertension (the latter only regarding drugs registered for angina pectoris) resulted in different levels of inclusion. Also, trials were found to include patients when this was not allowed and vice versa. Therefore, the actual trial populations may differ from the intended populations, as defined by the selection criteria, with respect to co-variables which influence the disease prognosis.

The results of the study are discussed in relation to the question of whether the generalizability of pre-marketing trials can be enhanced by further utilisation of data from these heterogeneous populations. The issue to study is variability between safety and efficacy in patient groups with different patterns of co-morbidity and co-medication. In order to allow regulatory authorities to consider patterns of co-morbidity and co-medication during the evaluation of registration files, development of guidelines for uniform reporting of data in pre-marketing trials is recommended.

In **chapter 4**, the prevalences of concomitant cardiovascular, endocrine and metabolic diseases were compared between populations in the pre-marketing trials and the RNG database. Data from 13 registration files were available for analysis. Data were also collected about the number of trials focussing specifically on patients with co-morbidity.

Coexisting cardiovascular, endocrine and metabolic diseases were generally less prevalent in the pre-marketing populations as compared to patients in the RNG population. Ischaemic heart disease and lipid disorders formed an exception to this pattern, because these were more prevalent coexisting with angina pectoris and hypercholesterolaemia.

Discrepancies were found for all indications, but for different concomitant diseases. Prevalences of concomitant cardiovascular diseases of patients using antihypertensives in the RNG population were all less than 10%. Therefore, differences did not reach the threshold level at which discrepancies were classified. In contrast, discrepancies were found for the indications angina pectoris and hypercholesterolaemia. Patients with co-existing hypertensive disease and heart failure were under-represented in the trial populations, whereas patients with a history of myocardial infarction were over-represented. Regarding endocrine and metabolic diseases, discrepancies were found for

diabetes, which was more prevalent in the RNG populations. These discrepancies were present for drugs registered for hypertension and angina pectoris. Only in four registration files of antihypertensive products specific phase III trials focussing on patients with concomitant morbidity were performed.

These results suggest that the lack of reporting and under-utilisation of data regarding patients with co-morbidity appear to be a limitation in the external validity of pre-marketing phase III trials. With respect to a better understanding of safety issues of new drugs, our study re-emphasises the limited value of pre-marketing trials, because of the small numbers of patients with complex diseases such as heart failure. However, information about safety aspects in these patients are likely to be highly relevant in daily practice.

Chapter 5 presents the results of an analysis of the comparative phase III trials in the registration files, the nature of the comparator drugs and their dosing schemes. This analysis was conducted because a number of persons, who were interviewed for the second research question, had mentioned a lack of data from such studies when new drugs are marketed.

Sixteen out of 18 registration files were included in the analysis. In half of the 146 double-blind trials the new drugs was compared with another, active drug. Twelve registration files contained both placebo and active medication controlled double-blind trials, one file only placebo, and three files only active controlled trials. The majority of registration files included comparative trials with first choice drugs within the same and within other therapeutic classes. In six trials different dosing schemes were used. Furthermore, maximum doses were more often included for the test drug, than for the comparator drug.

The use of only active controlled double-blind trials and the differences found in dosing schedules for study and comparator drugs are in principle sources of bias in demonstrating efficacy of drugs. In general, this is likely to over-estimate the study drug's efficacy. Therefore, basic details of trial design, such as the choice of reference drug and dosing schemes, need to be stated when communicating data from pre-marketing trials to medical practice. The European Medicines Evaluation Agency, EMEA, aims to improve transparency of the regulatory process by publishing European Public Assessment Reports (EPARs) on the internet. EPARs contain a summary of the clinical trials used as a basis for approval and reflect the considerations for granting approval. To improve the interpretation of these data, it is recommended to develop uniform reporting on basic details of trial design.

To study the second research question, regarding the gap between clinical research and medical practice from the perspective of medical practice, qualitative research methods were used. This part of the study involved two approaches, i.e., the assessment of new drugs in practice and the relevance of data from research in various subgroups of patients, and the investigation of changes in drug regulation which were considered necessary in order to optimise the connection between research and practice. Semi-structured interviews were conducted with 47 specialists in internal medicine, cardiologists, general practitioners, hospital and community pharmacists throughout the Netherlands. The interviewees were involved in the pre- or post-marketing evaluation of cardiovascular

drugs, for example through clinical research or assessment of new drugs for therapeutic guidelines. In the interviews, the research issues were addressed in general and in the specific case of a newly marketed cardiovascular drug. Two semi-innovative drugs were chosen for the case study. Losartan was the first representative of a new class of antihypertensives and atorvastatin was a cholesterol-lowering drug which was claimed to have a stronger effect than the other products in its class.

In **chapter 6** the considerations were analysed which the professional and academic leaders used to assess the position of new cardiovascular drugs in the therapeutic regimen in relationship to their professional characteristics, and level of prescribing.

In each interview, the respondents were asked about either losartan or atorvastatin. Considerations to assess the therapeutic position of the drugs referred to their relative advantage, compatibility with the respondents' opinions and complexity of the drug. Characteristics of the interviewees, which were applicable or not, referred to: their profession, academic affiliation, involvement in the development of treatment guidelines, specific expertise in hypertension or hypercholesterolaemia, mentioning commercial sources of information to learn about losartan or atorvastatin, and self-reported qualification as (moderately) early adopter of new drugs. The self-reported levels of prescribing of losartan and atorvastatin were classified as frequent, occasional, or non-prescribing. Through the numbers of respondents mentioning advantageous, comparable and/or disadvantageous characteristics of losartan or atorvastatin, patterns were constructed to analyse the evaluation of the drugs in relationship to professional characteristics and the level of prescribing.

The results showed that the majority of considerations referred to the degree of relative advantage, but different subjects were emphasised for both drugs. The efficacy of atorvastatin was predominantly considered relatively advantageous or comparable to competing drugs, whereas the efficacy of losartan was considered relatively disadvantageous to such drugs. Losartan only scored more positive on side-effects. Therefore, many considerations used to assess the value of both drugs in the therapeutic regimen focussed on the claims that were made during marketing, i.e., fewer side-effects when using losartan and higher efficacy with atorvastatin. However, some respondents positively acknowledged these claims, whereas others were not convinced by the claims or disagreed.

The patterns of evaluation of the drugs generally showed an intermediate or negative assessment. A more positive evaluation was found in relation to the respondents' profession, the mentioning of commercial sources of information and self-qualification as (moderately) early adopter of new drugs. In contract, specific expertise and academic affiliation made no difference in the evaluation of the drugs. A number of characteristics resulted in a more positive evaluation in the case of losartan, but not of atorvastatin. This referred to the mentioning of commercial sources of information and self-qualification as (moderately) early adopter of new drugs. A possible explanation for these findings is that the evaluation of a drug with less perceived advantages is more likely to be influenced by commercial sources of information. Only in the case of losartan it was found that frequent prescribing physicians had a more positive evaluation of the drug, compared with the occasional and non-prescribing physicians.

From this study it was concluded that professional and academic opinion leaders critically evaluated the claims when assessing the position of new drugs in the therapeutic regimen, but did not show consensus in their considerations. Accepted principles for prescribing were considered, but resulted in varied tendencies for prescribing.

In **chapter 7** the clinical relevance of the gap between pre-marketing trials and medical practice was studied. The opinion leaders were asked about their familiarity with under-representation of elderly, female patients and patients with co-morbidity in pre-marketing trials of cardiovascular drugs, the relevance attributed to under-representation, the types of arguments used and the consequences of perceived representation for prescribing. Two approaches were used, addressing the issue in general and for the specific cases of losartan and atorvastatin. To address the issue in general, the respondents received written information containing the main results of the comparison between pre- and post-marketing populations using cardiovascular drugs.

The majority of interviewees reported to be familiar with the fact that elderly, female patients and patients with co-morbidity are generally under-represented in pre-marketing trials of cardiovascular drugs. They were less familiar with the details of representation in the cases of losartan and atorvastatin. Under-representation was not considered a reason not to prescribe these drugs to such patients. The clinical relevance of under-representation, specifically regarding elderly and patients with co-morbidity, was affirmed by the majority of respondents, but refuted by others. Arguments used to affirm or refute the clinical relevance of under-representation referred to trial methodology, applicability of trial results and patient treatment. Furthermore, preconditions were attached to the clinical relevance which referred to the aims of trials, the presence of sufficient patients to perform subgroup analyses, differences between therapeutic drug classes and the timing of trials prior to or after drug approval.

The arguments substantiating the clinical relevance suggest two strategies to optimise the connection between pre-marketing clinical research and medical practice. Firstly, clinical trials testing new drugs should focus more on patient populations that represent relevant target groups in daily practice. When such research is not considered feasible prior to drug registration, it should be conducted after marketing. Secondly, information about new drugs should allow the determination of variations in the relative treatment effect between sub-populations. Therefore, it is relevant to develop formats which provide such detailed information from pre-marketing trials. These developments should facilitate assessment of new drugs in the context of evidence-based medicine.

In **chapter 8** core issues were studied which contribute to the gap between pre-marketing clinical research and daily practice, proposed changes which may be necessary to bridge this gap, the actors involved and potential barriers to change.

The interviewees placed the issue of differences between populations in pre-marketing trials and in medical practice in the broader context of drug development, clinical research, reimbursement policies and prescribing. They appointed issues in drug regulation which generally referred to the standards used and the organisation of the regulatory system. In particular, these issues referred to (1) an insufficient focus of pre-marketing trials on patient groups and research issues relevant to medical practice; (2) the

discrepancy between requirements for drug approval, generally involving demonstration of efficacy on surrogate endpoints, and the prescribing of drug in medical practice which is increasingly based on evidence of effectiveness; (3) absence of the risk/benefit assessment when drugs are prescribed off-label; (4) the lack of possibilities to verify the quality of the regulatory process because of its confidential nature; (5) the limited possibilities of regulatory authorities for steering research and development of new drugs, in particular after marketing; (6) the lack of information among practitioners when they evaluate new drugs for application in daily practice.

According to the professional and academic opinion leaders in the cardiovascular field, drug regulation should focus more on the needs in medical practice. With respect to regulatory standards two major subjects were mentioned by the respondents, i.e., variability in drug response and demonstration of clinical effectiveness. Both issues are scientifically important and need to be dealt with in terms of drug regulation in the pre- or post-marketing phase.

A wide variety of changes and actors involved were proposed by the respondents in order to improve the connection between pre-marketing research and medical practice. Regulatory authorities were identified as primary actors to initiate changes. Furthermore, the pharmaceutical industry, clinical investigators, ethics committees, practice researchers, governmental health care authorities, practitioners and professional organisations need to be involved. Dependent on the nature of changes in drug regulation which may be aimed for, a number of potential barriers should be considered.

Based on the analysis of the results two strategies for change could be identified. Firstly, strategies which can be applied within the present system of drug regulation. These typically involve policies which aim to increase the focus of clinical research on subgroups of patients relevant to practice. The present development that regulatory authorities consult various organisations about certain policies also fits into this strategy. The second strategy introduces new basic principles to the process of drug regulation. Two fundamental principles were identified. In the first place, the introduction of an interactive post-marketing drug development process. A particularly important part of drug innovation takes place in the context of medical practice. However, apart from regulating post-marketing pharmacovigilance, regulatory authorities loose their active power to influence research and development after registration. It was considered necessary to reach a better balance between the interests of pharmaceutical companies and those of the public in post-marketing research. The second principle that was introduced, refers to the development of a regulatory system in which more parties participate than just the regulatory authorities and pharmaceutical companies, as is the case in the present system. Also, the current confidentiality of the present system was clearly recognised as a problem. Providing information on the scientific assessment of drug approval by publishing EPARs is in itself a positive development, but from the perspective of medical practice it can only be valued in terms of a first step towards openness and public debate.

The need for reorientation from a drug centred regulatory system towards a practice oriented process is also recognised within the regulatory authorities. From this study it is recommended that regulatory authorities develop their influence on the post-marketing

drug research process, together with other parties involved, in order to bridge the gap between pre-marketing research and medical practice.

Finally, **chapter 9** integrates the results of these studies. Based on the data from the pharmaco-epidemiological studies, it is concluded that phase III pre-marketing trials of cardiovascular drugs from widely used therapeutic classes were performed in highly selected patient populations. This results in clinical relevant discrepancies between populations in research and medical practice. From this study it is concluded that little research was performed to identify possible differences in efficacy and/or safety between subgroups of patients in the phase III pre-marketing trials of these drugs. Such data, however, are likely to be of great importance to practitioners, because they deal with patients who present with a wide variety of characteristics. To study variability in efficacy and safety of new drugs, it should become a core issue of pre-marketing research.

The gap between pre-marketing clinical research and medical practice was recognised in particular as a general problem and as such it was considered clinically relevant. In the case of a specific new drug, less than half of the interviewees stated to be familiar with details of representation of subgroups of patients in pre-marketing trials. Since the interviewees operated closely to the process of drug regulation, these findings can be indicative for the limited availability to medical practice of detailed information about new drugs shortly after marketing. To facilitate evidence-based medicine it is important that all information from clinical trials is available to medical practice.

A number of changes regarding drug regulation was suggested to improve the connection between pre-marketing clinical research and medical research. Changes referred to the standards which are applied in drug regulation and the organisation of the process. Issues which are relevant to medical practice, in particular variability in drug responses and demonstration of clinical effectiveness, should become core issues in drug regulation. Strategies for change can be applied within the present system of drug regulation, or require the introduction of new principles. In particular, regulatory authorities should develop influence on the post-marketing drug research process and create openness about requirements for, and the process of drug approval. Regulatory authorities should be the primary actors to initiate changes, but other parties need to be involved.