Chapter 8

Summary and General Discussion
Although the efficacy and safety of antihypertensive and lipid-lowering drugs have been extensively established in clinical trials and results from such trials have been incorporated into evidence-based practice guidelines, antihypertensive and lipid-lowering drugs appear not to be prescribed at optimal rates in daily medical practice. This thesis presents a series of studies exploring trends in cardiovascular drug prescribing in Dutch general practice. We have focussed on whether antihypertensive drugs, in particular ACE inhibitors and ARBs, and lipid-lowering drugs were prescribed appropriately and according to the guideline recommendations on hypertension and hyperlipidemia. We studied the influence of patient-related and physician-related factors on (new) cardiovascular drug prescribing. In the previous chapters, each specific study was described in detail, including the shortcomings and merits. In this final chapter, the most important findings are summarized and some methodological considerations are discussed. In addition, implications of this research for physicians, policymakers and future research are discussed.

Main findings

Patterns of cardiovascular drug prescribing and patient-related factors

The first part of this thesis focussed on patterns of antihypertensive and lipid-lowering drug prescribing in Dutch general practice and the influence of patient-related factors. Trends in choice of antihypertensive drug classes were assessed in chapter 2. This study was conducted in a cohort of hypertensive patients who were identified from the Integrated Primary Care Information (IPCI) database in the Netherlands. Between 1996 and 2000, prevalence of antihypertensive drug use increased steadily in hypertensive patients (from 68% to 73%). Also, the average number of antihypertensives prescribed per patient increased (from 1.4 to 1.5). Time trends showed that there was a significant increase in prevalent use of beta-blockers (from 38% to 43%) and ARBs (from 2% to 11%), whereas prevalent use of calcium channel blockers somewhat decreased (from 22% to 21%), and prevalent use of diuretics (41%) and ACE inhibitors (31%) remained stable over the years. While prevalent use of ACE inhibitors had stabilized, we observed an increased use of ACE inhibitors (from 33% to 41%) in patients for whom such drugs were recommended, i.e. hypertensive patients who also have heart failure, diabetes mellitus, proteinuria and/or renal insufficiency. By contrast, trends in prescribing of ARBs were not in agreement with evidence-based guidelines at that time. ARB use significantly increased immediately after its introduction in hypertensive patients with and without specific comorbidities. In addition, ARBs were used while benefits on cardiovascular morbidity and mortality were still uncertain and sufficient evidence-based alternatives were available.

In chapter 3 we assessed whether the start of ARB use during the period 1996-2000 was in agreement with the recommendations of Dutch guidelines for hypertension. ARBs were only
recommended as alternative for patients who do not tolerate ACE inhibitors. The objective of this study was to examine trends in prescribing of ARBs as initial and second-line treatment of hypertension. Prescribing data for 3,102 newly treated hypertensive patients were extracted from the Integrated Primary Care Information database. During the period 1996-1999, initial ARB use increased significantly from 4% to 10%. The use of ARBs as second-line treatment was much lower. ARBs were used as second-line treatment in less than 4% of all hypertensive patients who were initially treated with an antihypertensive drug other than an ARB: 2% switched to an ARB (mostly from ACE inhibitors) and 1% received ARBs as add-on treatment. From this study, we can conclude that ARBs have achieved a position in the treatment of hypertension as initial rather than second-line therapy which was not in accordance with guideline recommendations for hypertension that were effective during this study period.

Trends in initiating and intensifying antihypertensive and lipid-lowering therapy in the period 1998-2004 in type 2 diabetes patients were investigated in chapter 4. Information on drug prescribing and on cardiovascular risk factors was obtained from the Zwolle Outpatient Diabetes project Integrated Available Care (ZODIAC)-study in The Netherlands. In this project, general practitioners were supported by hospital-based diabetes specialist nurses for the annual control of approximately 2,400 type 2 diabetes patients. We observed an overall increased use of antihypertensive and lipid-lowering drug therapies and better control of risk factors between 1998 and 2004. The percentage of hypertensive patients decreased only slightly (≥ 150/85mmHg; from 58% to 51%), whereas the percentage of patients with elevated TC/HDL ratio (> 6) decreased considerably (from 29% to 4%). The proportion of type 2 diabetes patients initiated on antihypertensive therapy increased (from 20% to 29%), as did the percentage of intensifications in patients already on antihypertensive therapy (from 19% to 35%). However, still two-thirds of patients with insufficiently controlled blood pressure in 2003 did not receive an initiation or intensification of antihypertensive treatment. The proportion of patients who were initiated on lipid-lowering therapy increased substantially (from 12% to 35%), whereas intensification of lipid-lowering therapy remained low (12% in 1999 vs. 7% in 2004). The number of patients with insufficiently controlled lipid levels was already quite low by the year 2004, leaving not much room for further improvement in this group of patients. Among patients with both elevated blood pressure and lipid levels, and therefore at increased risk of cardiovascular disease, we did not observe higher initiation rates for lipid-lowering therapy. The decision to increase pharmacological treatment was influenced by the level of the risk factor itself, but not by the presence of other risk factors.

**Physician-level factors related to cardiovascular drug prescribing**

The second part of this thesis focussed on physician-level factors relevant for understanding the dynamics of cardiovascular drug prescribing. Special attention was given to physician-level
factors related to the adoption of ARBs, since we aimed to explore possible reasons for variation in ARB prescribing among Dutch general practitioners.

To gain insight into possible reasons underlying the rapid increase in prescribing of ARBs observed in chapters 2 and 3, we linked physician-related characteristics to their actual prescribing behaviour in chapter 5. A questionnaire was completed by 70 general practitioners (GPs) contributing data to the Integrated Primary Care Information (IPCI) database (response rate: 96%). This questionnaire consisted of the following domains comprising factors that may influence drug choice and the adoption of new drugs, i.e.: use of information sources, perceived benefits and risks of different antihypertensive drug classes, the importance attached to specific drug characteristics, professional network, and general physician characteristics.

Prescribing data of antihypertensive drugs were obtained from the Integrated Primary Care Information database. GPs who reported frequent use of commercial information sources were more likely to prescribe ARBs routinely in preference to other antihypertensives, whereas GPs who used a prescribing decision support system and those who were involved in pharmacotherapy education were somewhat less likely to prescribe ARBs. Other factors that were associated with higher levels of ARB adoption included a more positive perception of ARBs regarding their effectiveness in lowering blood pressure, and working in single-handed practices or in rural areas. Many of the other potential determinants could not explain the observed variation in ARB prescribing, indicating that the adoption of ARBs was not driven by a preference for ARBs based on a rational decision process nor by influence of hospital physicians nor by pressure from patients.

Interactions between pharmaceutical industries and physicians are inevitable but not always undesirable. At market introduction an information asymmetry about the new drug’s clinical profile exists between the drug company and health care providers. The drug companies have been collecting information about the drug’s efficacy and safety for years through extensive clinical testing, while the drug is rather unknown to physicians. Once on the market, new information may become available about side effects and long-term outcomes. Drug companies use this information in their marketing campaigns to inform physicians about their products. In chapter 6, we evaluated how the pharmaceutical industry dealt with evolving clinical evidence in their advertising claims for the different ARBs. We identified a total of 290 advertisements for ARBs during the period 1996-2004 in the Nederlands Tijdschrift voor Geneeskunde (Dutch Journal of Medicine). While awaiting the results of large clinical trials, ARBs were mostly promoted using claims of their efficacy in lowering blood pressure and their excellent safety profile. These claims were all substantiated by clinical evidence already available at the time of regulatory approval. Starting in 1999, claims suggesting beneficial effects on long-term outcomes were observed in 12 different advertisements, most using general statements as ‘favourable effects on end-organs’, ‘protection’ or ‘risk reduction’. In eight cases (57 appearances), these claims were not supported by the information in the
summary of product characteristics or evidence from a cited clinical trial. In some cases these claims were not supported by any reference at all, in other cases the drug was recommended in a patient group other than that assessed in the cited trial. The self-regulatory Code of Practice authority received complaints regarding two of these claims only. These findings are troublesome, since research shows that drug advertising serves as an important source of information for physicians.\textsuperscript{1,2}

In chapter 7, we investigated whether specialists’ attitudes towards cardiovascular joint treatment guidelines for primary and secondary care differed between hospitals. A questionnaire was completed by 31 general internists and cardiologists in the Groningen region of The Netherlands (response rate: 52\%). In general, physicians from nonteaching hospitals (n=14) viewed the joint treatment guidelines less favourably than did physicians from teaching hospitals (n=17). Physicians from nonteaching hospitals more often believed that the guidelines are too restrictive (64\% vs. 18\%) and too rigid to apply to individual patients (14\% vs. 6\%) and that they oversimplify medical practice (79\% vs. 35\%). Physicians from teaching hospitals more often agreed that good recommendations for first-choice drugs had been made (76\% vs. 50\%) and that these guidelines are a convenient source of advice (94\% vs. 57\%), can facilitate communication with general practitioners (94\% vs. 71\%), and can improve the quality of pharmacotherapeutic care (88\% vs. 43\%).

Methodological considerations using general practice databases for drug research

General practice data
This thesis describes several studies exploring trends in cardiovascular drug prescribing in Dutch general practice. Most of these studies used data from the Integrated Primary Care Information (IPCI) database in the Netherlands. The IPCI database is a longitudinal observational general practice research database containing the complete electronic medical records from approximately 200,000 patients. We used the IPCI database to explore trends in antihypertensive drug prescribing for the following reasons. Firstly, we had access to a large population of hypertensive patients that were followed over time. Secondly, as the IPCI database contains the complete electronic medical records, information on patient demographics, diagnosis, comorbidity, and drug prescriptions can be retrieved. In addition, the IPCI project gave us the opportunity to collect additional information on physician-related factors that may influence drug choice and the adoption of new drugs. Therefore, we were able to link physician-related factors to their actual prescribing behaviour to identify determinants for adoption of ARBs in routine prescribing for hypertension.
Data from the ZODIAC-study were used to investigate trends in initiating and intensifying antihypertensive and lipid-lowering therapy. An important strength of this study is that we had access to a large population of type 2 diabetes patients that were followed over time. Secondly, this study provided information on medical history (including year of onset diabetes and history of myocardial infarction and/or angina pectoris), measurements of blood pressure and weight, and laboratory findings (i.e.: HbA1c, total cholesterol, HDL cholesterol, and LDL cholesterol), besides data on patient demographics and drug prescriptions. Therefore, we were able to study which patient factors influence general practitioners to prescribe antihypertensive and lipid lowering drugs in a routine practice setting.

**Internal and external validity**

The validity, or the degree to which a finding is likely to be true, is very important. Commonly, two aspects of validity are considered namely the internal and external validity.

The internal validity of a study refers to the integrity of the study design, i.e. the ability to measure what is set out to be measured. In observational studies there is always a potential for selection bias, information bias and confounding, which undermines the internal validity of epidemiological research.

An important form of selection bias is referral bias where patients voluntary refer themselves to take part in epidemiological research. As the IPCI database encompasses the total patient population and the data are gathered prospectively, without knowledge of the later formulated research questions, the magnitude of selection bias is negligible. With regard to the type 2 diabetes patients in the ZODIAC-study, working groups of physicians participated with their type 2 diabetes population in the study as a whole. Although patients themselves had to give their informed consent and had to visit the diabetes specialist nurse yearly, patient participation rate remained high throughout the study period (90% of the patients responded to the invitation for a consultation with the diabetes specialist nurse at least twice during the first three years). It is possible that patients who volunteered for yearly screening are generally more health-conscious than those who did not volunteer. Another possibility is that some of the patients who volunteered for screening may have volunteered because they were especially worried about their health. These biases counteract one another, but because neither one is easy to quantify, the net selection bias is unknown.

Information bias, also known as misclassification bias, measurement bias or recall bias, results from an incorrect determination of exposure or outcome. This information bias might be random (non-differential) or systematic (differential). Non-differential misclassification almost always results in an underestimate of the true strength of the relationship, whereas differential misclassification may result in overestimation as well as underestimation of the
actual risk. In general, information bias is a much smaller problem in routinely collected patient data compared with interview and questionnaire data. Data on patients’ demographics, diagnosis, comorbidity and referrals was gathered from the IPCI database independently of prescribing data for antihypertensive drugs. We might have underestimated actual prescribing rates, since we used prescribing data from a general practice research database that did not include specialists’ prescriptions. With regard to risk factor levels, it may happen that laboratory results are more likely to be documented in patients with insufficiently controlled risk factor levels than in well-controlled patients. This bias was mainly avoided in the ZODIAC-study since diabetes specialists’ nurses used standardized report forms to document annual control findings. We might have underestimated actual prescribing rates, since our outcome assessment was mainly based on patient reported use of drugs.

Overall, we may have misclassified some of the exposure and outcome measurements. However, it is likely that exposure and outcome misclassification was mainly non-differential and therefore the reported association estimates are an underestimate of the true risk.

Confounding is one of the major concerns in epidemiologic research, as it is one of the most difficult biases to detect and control for. Confounding can lead to an overestimation or underestimation of the true association between exposure and outcome. We mostly applied multivariable techniques (e.g. mathematical modelling via multivariable logistic regression analysis or proportional hazard analysis) to control for confounding.

External validity of epidemiologic research implies that the observed findings can be generalized to the general population. As we used data from the IPCI database, a large general practice research database, we believe that our results regarding the choice of antihypertensive treatment can be extrapolated to the general population of hypertensive adults. Furthermore, trends in the choice of antihypertensive treatment in the period from 1996 to 2000 corresponded with the general trends in antihypertensive prescriptions in The Netherlands. Results from the ZODIAC-study on trends in initiating and intensifying antihypertensive and lipid-lowering therapy should be seen in the light that these improvements were achieved within a shared-care project. Hospital-based diabetes specialist nurses, who performed the annual control of type 2 diabetes patients, may have facilitated physicians to provide better care. The findings of this study may therefore reflect a best-case scenario and cannot simply be extrapolated to the management of hypertension and hyperlipidemia in Dutch general practice in general.

**Undertreatment of hypertension and hyperlipidemia**

Although the use of antihypertensive and lipid-lowering drug therapies has increased in the past decade, undertreatment of hypertension and hyperlipidemia is still present (chapters 2 and 4). We observed that about two-third of type 2 diabetes patients eligible for the
pharmacological treatment of hypertension in 2004 was either untreated or was uncontrolled. Physicians did not increase lipid-lowering drug therapy adequately for patients with both uncontrolled blood pressure and lipid levels. Suboptimal management of hypertension or hyperlipidemia is especially alarming in type 2 diabetes patients. Type 2 diabetes patients have high rates of hypertension and hyperlipidemia, contributing to the two- to four-fold increased risk of cardiovascular disease.6

Several causes have been proposed why physicians may not initiate or intensify therapy appropriately. It has been ascribed to clinical inertia – recognition of the problem of hypertension and hyperlipidemia, but failure to act.7 Proposed explanations for clinical inertia include physicians’ overestimation of their adherence to guidelines, or acceptance of elevated risk factors in their patients, lack of training on achieving therapeutic goals, possible lack of motivation to treat asymptomatic conditions, pharmacotherapy pill burden, and time limitations.7-9 Barriers related to carrying out cardiovascular risk assessment have also been reported. Physicians were not used to risk estimation, and physicians had more confidence in their own clinical judgement than risk tables or charts.10 Barriers relating to the content and format of the risk tables were also present.11 Furthermore, physicians were confused by the lack of agreement with other (inter)national risk guidelines.11 Many different Dutch practice guidelines existed for hyperlipidemia, hypertension and type 2 diabetes, and as a result various guideline recommendations for the prevention of cardiovascular disease were given. By the year 2003, it was realized that effective cardiovascular risk management would require more agreement between guideline recommendations. This led to the development of an integrated cardiovascular risk management guideline.12 This recently published guideline is already an important step forward. It may reduce the lack of consistency and can provide better support for health care providers.

**Adoption of new drugs**

According to the guideline recommendations for hypertension regarding first-choice antihypertensive drug classes in 2000, ARBs should have been prescribed only in patients unable to tolerate ACE inhibitors. However, ARBs achieved a marked position as initial treatment for hypertension in the period 1996-2000. Moreover, this position was not restricted to patients with relevant comorbidities (chapters 2 and 3). Thus, ARBs were already used as initial treatment in uncomplicated hypertensive patients before trials on cardiovascular endpoints became available. A different picture emerged regarding the prescribing of ACE inhibitors. Prescribing of ACE inhibitors seems to have developed into a pattern that is more in accordance with guideline recommendations, since increases in the use of ACE inhibitors were only observed in patients for whom these drugs were recommended. Differences in prescribing patterns between ACE inhibitors and ARBs suggest that increases in use of new drugs shortly
after their introduction are largely not specific but, in later years, become more confined to patients for whom this is more evidence-based.

Marketing of pharmaceutical industries is the main explanatory variable for the rapid adoption of new drugs as reported in chapter 5 and repeatedly shown by others.\textsuperscript{13-15} Pharmaceutical companies succeeded in launching ARBs in the market as ‘ACE inhibitors without cough’ instead of a new class of antihypertensive drugs.\textsuperscript{16} ACE inhibitors were already proven useful in the treatment of hypertension, the treatment of heart failure, and the prevention of renal failure progression.\textsuperscript{17-20} Furthermore, studies showing that ARBs were better tolerated and had higher persistence rates than other antihypertensive drug classes probably encouraged prescribing of ARBs as the initial treatment.\textsuperscript{21-24}

However, many patients may have been exposed to uncertain risks during the early post-marketing period of ARBs. Use of new drugs in daily medical practice can, and often does, unveil unknown effects that were not detected during clinical testing before market approval. New drugs are approved on the basis of studies of usually limited duration, relatively small numbers of patients, using strict inclusion criteria resulting in a study population far different from patients in daily medical practice. There is still a high degree of uncertainty at the moment of market introduction about the new drugs’ effectiveness and safety profile when used in large populations. Although newer drugs are nowadays relatively safe when they receive market authorisation, several new drugs (for example, mibefradil, cerivastatin and rofecoxib) were withdrawn after being on the market for only a few years. This advocates restraint in prescribing during the early post-marketing period.

**Implications**

Treatment of hypertension and hyperlipidemia has improved in the past decade but is still far from optimal. Many type 2 diabetes patients with hypertension remained untreated and many treated patients did not achieve target levels of these risk factors. Moreover, the increase in pharmacological treatment was only influenced by the level of the risk factor itself, but not by the presence of other risk factors. Programs or strategies to improve treatment of these important cardiovascular risk factors are needed because risk factors continue to contribute to disease progression and impaired prognosis. In addition, drug choices have been shifted to newer and less extensively evaluated drugs.

Traditional approaches to improve uptake of research findings have focused on better availability and presentation of evidence by identifying, synthesising, and disseminating evidence to doctors in practical accessible formats (e.g. clinical guidelines, reviews in medical journals, and better access to electronic sources of information). Although this approach may be all that is needed to ensure the uptake of some simple changes, most changes in practice
require further efforts. Adherence to guidelines may be hindered by a variety of barriers, such as method of development used, content of the recommendations, source of dissemination and implementation.\textsuperscript{25-27} One promising approach to implement evidence-based medicine into routine general practice are educational interventions, such as continuing medical education courses and pharmacotherapy peer review groups (in Dutch called FTO) that set goals about optimising pharmacotherapy and audit prescribing.\textsuperscript{28-29} However, not all educational programs have direct impact on improving prescribing practice.\textsuperscript{30} Interventions on implementing evidence-based medicine may not be generalizable, since barriers in one setting may not be present in another.\textsuperscript{25;31} Other interventions to achieve optimal management of cardiovascular risk factors include disease management, educational outreach visits, and computerized reminder systems.\textsuperscript{32-35} Also, providing information to patients about risk factors and medical treatment recommendations may be effective for initiating and maintaining therapy.\textsuperscript{36}

The problem of overprescribing with newer and less extensively evaluated drugs should be further addressed at the level of policy and education. Marketing of pharmaceutical industries is still the main explanatory variable for the adoption of new drugs.\textsuperscript{15;37} Although many doctors acknowledge that the pharmaceutical industry tries to influence their prescribing, only few recognise themselves as being susceptible.\textsuperscript{38} Thus, educational programmes aiming at a better understanding and analysis of pharmaceutical promotion strategies are certainly needed. In addition, professional organisations should try to provide objective, scientific information to physicians soon after the introduction of a new drug. In line with marketing campaigns that are completely tuned to special features of a new drug, educational programs to influence new drug prescribing need to be tailored to every new drug individually. Furthermore, there should be a stricter control of the self-regulatory system for pharmaceutical drug promotion. Regulations and self-regulatory systems are probably effective in preventing some drug promotion abuses by providing the opportunity to submit complaints and by ruling against code violations.\textsuperscript{39} However, there should be an active monitoring system for recognizing violations, independent monitoring committees, and effective sanctions for code violations.\textsuperscript{40-43} Aside from a stricter control of the regulations, it has also been recommended to tighten them up.\textsuperscript{44} Some specific requirements could be formulated to counter the observed problem of vague, suggestive claims. One could think of rules for mentioning the approved indication as well as the studied patient population on which claims are based clearly in pharmaceutical promotional materials. Furthermore, a clear warning statement could be required for drugs that have not yet proven efficacy on relevant long-term outcomes. This would be on par with the European Medicines Agency guidelines from 1997 which state that the summary of product characteristics should explicitly mention when beneficial effects on mortality and cardiovascular morbidity are unknown until the results from adequate trials supporting this effect are available.\textsuperscript{45}
We noted that only a small group of physicians seemed to be accountable for the early adoption of ARBs, as found in earlier studies as well. From these studies it has become clear that prescribing new drugs was very much dependent on the new drug in question and not so much on the prescriber. Physicians who rapidly adopt one new drug do not necessarily adopt other new drugs quickly. This lack of predictability has important implications for policy makers who would like to control prescribing of new drugs. The interaction between the new drug and the physician needs to be analysed and used as starting point before developing any policy to ensure optimal use of new drugs.

Final considerations
The studies describes in this thesis provide sufficient opportunities for interventions aiming at the improvement of pharmacotherapy of hypertension and hyperlipidemia, including initiating and intensifying cardiovascular drugs to improve attainment of treatment goals, targeting cardiovascular drugs to those benefiting most from them, and prescribing newer antihypertensive drug classes when necessary. Ongoing monitoring and measurement of the quality of care, empowering physicians with medical decision-support tools and evidence-based information about new drugs are essential to improve uptake of research findings in routine general practice.
References


