Chapter 1

General Introduction
Cardiovascular disease (CVD) is the leading cause of death in most industrialised countries. In 2004, approximately 45,000 persons died from cardiovascular disease in The Netherlands. Cardiovascular disease accounts for 33% of all deaths in both men and women.\(^1\) Therefore, efforts to optimise preventive therapy are warranted.

Hypertension and hyperlipidemia are the two most common risk factors for CVD that can be modified with lifestyle interventions and pharmacotherapy. Although the efficacy and safety of antihypertensive and lipid-lowering drugs have been extensively established in clinical trials, they appear not to be used to their full benefit in daily medical practice.

**Drug prescribing in daily medical practice**

Cardiovascular drugs should be targeted to the appropriate patients, and both undertreatment and overtreatment may occur.\(^2\) Undertreatment can be defined as inappropriately not receiving medication but also includes uncontrolled disease status despite pharmacological treatment. Undertreatment in high risk patients is common in cardiovascular medicine.\(^3^-^6\) Conversely, overtreatment may occur when guidelines restrict drug use to certain subpopulations while drugs are prescribed to a non-selective group of patients or newer agents are used with no proven benefit over other effective and longer available drugs. This appeared to have happened with regard to the newer classes of antihypertensives.\(^7^-^10\) Undertreatment should be prevented in order to gain optimal benefit in those most in need of therapy, whereas overtreatment should be avoided to limit unnecessary health risk and spending of health care resources.

To improve antihypertensive and lipid-lowering drug prescribing, insight in the patterns and determinants related to cardiovascular drug prescribing on the level of the individual patient and the physician is needed.

**Evidence and guideline recommendations related to cardiovascular drug prescribing**

The quality of drug prescribing is often assessed from an evidence-based medicine point of view. In the past decade, increasing attention has been paid to evidence-based medicine, and many guidelines have been developed based on systematically obtained, best available evidence. In the Netherlands, the Dutch College of General Practitioners and Dutch Institute for Healthcare Improvement (CBO) regularly publish and update national guidelines. These guidelines are designed to help physicians in making decisions about the care of individual patients.

In most of these guidelines, recommendations are given regarding screening, diagnosis, treatment and first-choice drugs. Therefore, they can serve as the ‘gold standard’ when
assessing the quality of pharmacotherapy in daily medical practice. This section will provide a short overview of the evidence and guideline recommendations for hypertension and hyperlipidemia management.

**Efficacy of antihypertensive and lipid-lowering drugs**

The benefits of antihypertensive and lipid-lowering therapy for the prevention of cardiovascular disease are well-known.\(^{11-13}\) The early studies documenting the beneficial effects of treatment of hypertension were carried out using diuretics or beta-blockers. Over the past two decades, it has been shown that drugs from newer classes also reduce major cardiovascular events. This is the case for angiotensin-converting enzyme (ACE) inhibitors and, more recently, the angiotensin II receptor blockers (ARBs).\(^{14-17}\) Moreover, these drugs have renoprotective effects beyond those resulting from lowering blood pressure alone.\(^{18-22}\) With regard to lipid-lowering therapy, the HMG-CoA reductase inhibitors (statins) have proven to be effective in reducing cardiovascular morbidity and mortality across a broad range of patient groups.\(^{23-27}\)

**Guidelines for hypertension management**

In the period 1996-2005, the Dutch College of General Practitioners released updates of their practice guideline on hypertension in 1997, 1999, and 2003.\(^{28-30}\) In addition, a new consensus guideline on hypertension was released by the Dutch Institute for Health Care Improvement (CBO) in 2000.\(^{31}\) In all guidelines, diuretics and beta-blockers remained the drugs of first choice in patients with uncomplicated hypertension. ACE inhibitors and calcium channel blockers may be added when the blood pressure remains too high. ACE inhibitors were recommended as first-choice drugs in all hypertensive patients with diabetes in the Dutch consensus guideline from 2000, while in the practice guidelines from the Dutch College of General Practitioners ACE inhibitors were only suggested for patients with diabetes and microalbuminuria. ACE inhibitors in combination with diuretics were recommended in hypertensive patients with heart failure in all guidelines. ARBs were first mentioned in the Dutch consensus guideline on hypertension from 2000, as alternative for patients who do not tolerate ACE inhibitors. Between 1997 and 2003, the threshold values for the diagnosis hypertension in the guidelines were lowered from 160/95 mmHg to 140/90 mmHg.

**Guidelines for hyperlipidemia management**

A revised consensus guideline on the management of hyperlipidemia by the Dutch Institute for Healthcare Improvement (CBO) was released in 1998, after the publication of the first landmark trials on the efficacy of statins.\(^{32}\) In 1999, the Dutch College of General Practitioners launched their own guideline, which differed only marginally from the consensus guideline.\(^{33}\) Both guidelines indicate lipid-lowering therapy for the primary prevention of CVD to patients at high risk for CVD: i.e. patients with a history of cardiovascular disease, patients with a
(suspected) hereditary lipid disorder or patients with a 10-year coronary heart disease (CHD) risk larger than 25%. To eliminate the need to calculate this risk, the guidelines incorporate risk tables that indicate the predicted CHD risk using six risk factors: age, cholesterol (as total cholesterol/HDL ratio), blood pressure, smoking, diabetes, and gender.

**Patterns of cardiovascular drug prescribing and patient-related factors**

Given the changes in recommendations regarding antihypertensive treatment, one might expect an overall increase in the use of antihypertensives in the past decade, whereas increases in the use of newer classes of antihypertensives are more likely in the specific patient groups for which they have been recommended. In other words, according to the recommendations increases in the use of ACE inhibitors and ARBs should have been largest in hypertensive patients who also have heart failure or diabetes mellitus, especially in the presence of microalbuminuria. To get better insight into the quality of antihypertensive treatment and potential overtreatment with newer agents, it is therefore important to investigate trends in prescribing of ACE inhibitors and ARBs as initial and second-line treatment for hypertension, and to clarify the role of comorbidity in explaining these trends.

Treatment decisions with regard to hyperlipidemia should be based on a combined assessment of multiple cardiovascular risk factors to target prevention to patients at high cardiovascular risk. There are doubts, however, that such a high-risk approach in the primary prevention of cardiovascular disease has been implemented in daily medical practice.\textsuperscript{34,35} Insight into whether patients with both elevated blood pressure and elevated lipid levels were more likely to receive lipid-lowering therapy, can help us to guide future efforts to improve the quality of lipid-lowering drug prescribing.

**Physician factors related to cardiovascular drug prescribing**

Much research has focused on the relation between physician characteristics and drug prescribing. General physician characteristics, such as age, gender or year of graduation, are sometimes found to be associated with specific prescribing patterns but these findings are not consistent.\textsuperscript{36-38} Moreover, these characteristics cannot be modified. Others have looked at internal factors related to the prescribing process, such as knowledge, attitudes and personal experience of the prescriber, showing that treatment choices are not always the result of carefully reasoned decision making.\textsuperscript{39-41} External factors, such as commercial information sources and the professional network, may influence drug choice and adoption of new drugs.\textsuperscript{42}
This section will address some issues related to these external factors relevant for understanding the dynamics of (new) drug prescribing.

**Influences of professional and commercial information sources**

The literature pertaining to the prescribing of new drugs by general practitioners clearly identified commercial information sources as one of the key influences on their adoption of new drugs.\(^{43-46}\) Over the past decade, however, there has been a growing emphasis on practicing evidence-based medicine in drug prescribing. This raises the question whether professional information sources currently counterbalance the influence of commercial information sources in the adoption process.

**Pharmaceutical drug advertising in medical journals**

In step with the growing popularity of evidence-based medicine, the pharmaceutical industry is incorporating clinical trial results and bibliographic references in drug advertisements more frequently than previously.\(^{47-49}\) Use of clinical trials is especially evident in promotion of antihypertensive and lipid-lowering drugs, as a way for pharmaceutical companies to succeed in an environment marked by intense competition between a host of similar drugs in the same therapeutic group.\(^{50}\) In fact, the use of clinical trials is now an important marketing strategy. Pharmaceutical companies use randomised clinical trials to obtain results on safety and efficacy on hard endpoints to distinguish their product from its competitors and to improve their product’s position in the market.\(^{48;51}\) The newest antihypertensive drug class, the ARBs, forms an interesting case to study how new research findings are presented in drug advertisements over time.

**Specialists’ attitudes towards treatment guidelines**

An important issue for drug choices in chronic diseases forms the interaction between general practitioners and hospital physicians. Hospital physicians can have a great impact on treatment at the general practitioners level. Nevertheless, they are often not included in efforts to improve treatment in primary care. In the year 2000, a program was set up in the Netherlands to improve the quality of treatment care across the primary-secondary care interface. The aim was to improve both quality and efficiency in health care by bringing the therapeutic care provided by general practitioners and specialists in line with each other. In some regions, joint treatment guidelines were developed recommending specific drug choices for a range of diseases. Previous research showed that hospital physicians expressed mixed attitudes towards such joint treatment guidelines, and their willingness to follow the recommendations seemed low.\(^{52-53}\) One might expect that the attitudes differ between hospital settings because of differences in organisational culture and patient populations.\(^{54-56}\) Better insight in differences in attitudes across hospital settings is needed to find ways to promote the use of joint treatment guidelines.
Aims and outline of this thesis

The main objective of this thesis is to explore trends in cardiovascular drug prescribing, and to assess whether antihypertensive drugs, in particular ACE inhibitors and ARBs, and lipid-lowering drugs were prescribed appropriately and according to the guideline recommendations in Dutch general practice. The studies in this thesis will show whether patient-related factors influence antihypertensive and lipid-lowering drug prescribing, and will give insight into factors which influence the general practitioners’ decision to prescribe (new) drugs.

The first part of this thesis consists of three studies focusing on patterns of antihypertensive and lipid-lowering drug prescribing and the influence of patient-related factors. Chapter 2 presents trends in prevalent and initial use of ACE inhibitors and ARBs in the treatment of hypertension, and clarifies the role of comorbidity. Chapter 3 emphasizes on prescribing of ARBs as initial and second-line therapy. Chapter 4 describes trends in initiating and intensifying antihypertensive and lipid-lowering therapy in type 2 diabetes patients and examines predictors of these treatment changes.

The second part of this thesis describes physician-related factors associated with prescribing (new) drugs. Chapter 5 describes which physician-related factors are associated with early adoption of ARBs. Chapter 6 evaluates how the pharmaceutical industry deals with this evolving clinical evidence in their advertising claims for the different ARBs. Chapter 7 addresses specialists’ attitudes towards cardiovascular treatment guidelines for primary and secondary care.

Finally, in chapter 8 the main findings and conclusions are discussed and put into a general perspective for further improvement of cardiovascular drug prescribing.
References


