Summary

In Chapter 1 medication adherence is introduced and defined as a process by which patients take their medication as agreed upon with their health care provider. It comprises several components, referring to different phases of medication intake. Medication non-adherence is often categorised as intentional and unintentional. However, it has been argued that these types of non-adherent behaviour might be overlapping. Medication adherence is influenced by multiple and interrelated factors that have been categorised by the WHO in five dimensions: social/economic factors, patient-related factors, condition-related factors, therapy-related factors and health care team and system-related factors. Adherence can be measured with several methods, each having its own advantages and disadvantages. However, no method is considered the 'golden standard'. Therefore, a combination of methods is preferable in assessing medication adherence. The chapter continues with introducing hypertension and the problem of non-adherence to antihypertensive medication. Hypertension exists when systolic blood pressure is ≥140 mmHg and/or diastolic blood pressure is ≥90 mmHg. It affects over one billion people worldwide. The ability of antihypertensive medication to control high blood pressure, reduce the risk of cardiovascular events and decrease morbidity and mortality is well established. Unfortunately, adherence to antihypertensive medication is often suboptimal and substantial numbers of patients benefit from their medication only to a limited extent. In the past decades, numerous interventions in community pharmacies have been developed with the aim to enhance medication adherence. In spite of these efforts up till now little progress has been made in tackling this persistent problem. In order to effectively challenge antihypertensive medication non-adherence, the CATI intervention programme has been developed. The CATI study is a parallel-group randomised controlled trial in 20 community pharmacies aimed to evaluate the (cost-)effectiveness of the patient-tailored, pharmacist-led and theory driven CATI intervention programme by comparing it with usual care. The chapter ends with presenting the aim, research questions and outline of this thesis.

In Chapter 2 the results of a systematic literature review aimed to identify factors associated with antihypertensive medication non-adherence are presented. The databases MEDLINE, EMBASE, PsycINFO and The Cochrane Library were searched for observational studies reporting on factors associated with non-adherence to antihypertensive medication. Factors that were extracted from the included studies were categorised as factors with consistent or inconsistent evidence in order to put their potential importance into perspective. Eventually, 44 observational studies were included. Higher co-payment, side effects and a poor patient–health care provider relationship were identified as factors with consistent evidence since significant relationships were found for these factors whenever studied. In addition, multiple potentially relevant factors were identified. The results therefore suggest that patient-
tailored interventions focused on identifying and addressing patients’ specific barriers to adherence are needed to enhance adherence to antihypertensive medication.

Chapter 3 reports on an observational, cross-sectional study aimed to identify factors associated with non-adherence to cardiovascular medication. In total, 255 patients (≥45 years) using cardiovascular medication from 23 Dutch community pharmacies participated. Both an adherent sample (n=146) and a sample of patients non-adherent to their prescribed medication (n=109) as assessed by means of pharmacy dispensing data (proportion of days covered<80%) were selected. Data were collected on patient demographics, self-reported adherence, medication and disease characteristics, knowledge, quality of life, attitude towards medicines and satisfaction with information. Associations of factors with refill non-adherence were assessed using univariate and multivariate logistic regression analyses. Factors significantly associated with cardiovascular medication non-adherence in multivariate analyses included experiencing difficulties with medication use due to forgetting, having insufficient knowledge on what to do when a dose is forgotten and having an ambivalent attitude towards medicines (beliefs of high necessity and high concerns). The results indicate that interventions should be targeted mainly to the unintentional dimension of non-adherence. However, the possible effect of certain factors underlying intentional non-adherence, such as patients’ beliefs about medicines, on unintentional non-adherence should also be investigated and addressed.

Chapter 4 presents an observational, cross-sectional study aimed to explore the impact of cardiovascular medication on different aspects of daily life and to examine differences of these aspects between adherent and non-adherent patients. In total, 196 patients using cardiovascular medication from two Dutch community pharmacies participated, including 96 non-adherent patients according to pharmacy dispensing data. Data were collected by means of the Living with Medicines Questionnaire which was translated in Dutch for this study. The questionnaire measured the impact of medicines use on patients’ daily lives. A substantial proportion of patients experienced medication-related burden, mainly concerning the acceptance of long-term medicine use, medication-related concerns or dissatisfaction, the interference of medication-related effects with their social and daily lives, and the communication and actual interaction with health care providers. When comparing the impact on patients’ daily lives no statistically significant differences were found between adherent and non-adherent patients. The results suggest that health care providers must acknowledge the impact of multiple, long-term medication use on patient’s daily lives and really have to make an effort to diminish patients’ medication-related burden.

Chapter 5 describes the study protocol of the CATI study, a parallel-group randomised controlled trial in 20 community pharmacies evaluating the (cost-)effectiveness of the patient-tailored, pharmacist-led and theory driven CATI intervention programme as
compared to usual care. Patients aged 45–75 years using antihypertensive medication and considered non-adherent according to both pharmacy dispensing data and a self-report questionnaire, were eligible to participate. The CATI intervention programme consisted of two consultations with the pharmacist to identify a patients’ barriers to adhere to medication use and to inform and counsel patients in order to overcome these barriers and improve medication adherence. The primary outcome was self-reported medication adherence. Secondary outcomes were quality of life, illness perceptions, blood pressure and societal costs. Outcomes were measured at baseline, and after three, six and nine months.

**Chapter 6** evaluates the effectiveness of the CATI intervention programme as compared to usual care. Mixed-model and GEE analyses were used to assess the effects of the intervention programme. No significant differences between intervention and control groups were found in self-reported adherence (primary outcome), quality of life, illness perceptions, beliefs about medicines (concern scale) and blood pressure (secondary outcomes). After nine months patients in the intervention group had significantly stronger beliefs about the necessity of using their medicines as compared to those in the control group (mean difference 1.25 [95% CI: 0.27-2.24], p=0.012). On the basis of these results the CATI intervention programme in its present form should not be implemented in this study population. Further studies should focus on how to select eligible patient groups with appropriate measures in order to effectively target adherence-enhancing interventions.

In **Chapter 7** the cost-effectiveness of the CATI intervention programme is compared with usual care. Effect outcomes included self-reported adherence, beliefs about medicines and quality-adjusted life-years. Costs were assessed from a societal perspective. They included the cost related to the intervention, the provided health care and lost productivity. Missing cost and effect data were imputed using multiple imputation. Bootstrapping was used to estimate uncertainty around the cost-differences and the incremental cost-effectiveness ratios. Cost-effectiveness planes and acceptability curves were constructed. No significant improvements were found in adherence-related behaviour, beliefs about medicines and quality-adjusted life-years in the intervention group as compared to the control group. Total societal costs in the intervention group were not significantly higher than in the control group. The results show that, as compared to usual care, the CATI intervention programme is not cost-effective.

**Chapter 8** describes the process evaluation of the CATI intervention programme in order to clarify whether the lack of effectiveness was due to a poor implementation of the intervention. To assess implementation fidelity the conceptual framework proposed by Carroll *et al.* was used. In this framework the main element of implementation fidelity is the measurement of ‘adherence’ to the intervention, defined
as the degree to which the intervention has been delivered as intended by the developers. Adherence can be operationalised by addressing the following constituents: coverage, content, frequency and duration. The framework also suggests that moderating factors that might have influenced the implementation process and as such the level of fidelity, must be investigated. According to the rating of the researchers, for all key intervention components the implementation fidelity was moderate to high showing that most key intervention components were carried out as planned. However, the method to select patients was considered limited and pharmacists questioned whether certain participants were eligible for the intervention. Thus, the absence of effectiveness of the intervention programme on self-reported medication adherence cannot be explained by poor implementation of the intervention but the shortcoming of the selection method, the limited eligibility of some participants and a potential selection bias need to be considered. Extensive communication skills training, easy-to-use and system integrated intervention materials, time and an eligible patient group seem important to successfully implement adherence-enhancing interventions in daily practice.

In Chapter 9 the main findings and methodological considerations of this thesis are discussed. An overview of the clinical implications and recommendations for further research is also provided.