This thesis focuses on drug use in the elderly, in particular those residing in Dutch nursing homes: the frail elderly. These elderly are especially prone to drug-related problems because of their age, frequently occurring co-morbidity and polypharmacy. Relatively little is known of drug use and drug-related problems in these frail elderly. The studies described in this thesis aim to increase the knowledge on drug use and drug-related problems in this population. The thesis comprises four main parts.

In chapter 1, the introductory chapter, the scope and the objective of this thesis are described and the problems of drug use in elderly people are outlined. Because of co-morbidity, reduced homeostatic mechanisms and the prescription of several drugs simultaneously, elderly people are at an increased risk of drug-related problems such as drug-drug interactions, drug-disease interactions and adverse drug effects. Drugs may also inadvertently be withheld from the elderly, sometimes as a result of underdiagnosing. In view of these considerations, prescribers need a thorough understanding of the risks and benefits of drug therapy in the elderly, especially in the frail elderly, most of whom will be residing in nursing homes. In the Netherlands, relatively few epidemiological studies on drug use in nursing homes have been carried out. The objective of this thesis is to provide insight in the extent, determinants and characteristics of drug use, as well as the outcomes of drug use in frail elderly. Section 1.2 gives an overview of the Dutch health care system for ambulatory and institutionalised elderly. The Dutch nursing home is a healthcare institution for chronically ill persons in need of permanent medical and paramedical attention and complex nursing care. The type of care can be characterised as continuous, long-term, systematic and multidisciplinary. Recently it was concluded that quality aspects should be more incorporated in medication distribution processes and in pharmaceutical care activities in Dutch nursing homes. Hospital pharmacists play a role in drug and therapeutics committees, the evaluation of prescribing practices on patient level, and development and implementation of drug formularies.

Chapter 2 describes several studies that investigated drug use in nursing home residents and elderly outpatients. The first part describes the studies performed in nursing home residents. In section 2.1 an introduction is given to the field of drug utilisation studies and studies that describe the quality of drug use in nursing homes. Many studies have investigated the extent of drug use, whereas only few studies used longitudinal prescription data to evaluate drug effects over time. The studies showed an average number of drugs prescribed per resident.
number of different drugs (based on 5th level of Anatomical Therapeutic Chemical (ATC) code) per resident was 8.9 (SD 4.9). Duration of drug use was relatively long: eight of the ten therapeutic drug groups prescribed most frequently were used for more than 50% of the time spent in the nursing home. In particular psycholeptic drugs, diuretics, and laxatives were used chronically (83%, 81% and 80% of the nursing home stay, respectively). Except for laxatives and diuretics, the prescribed daily dosages were relatively low. We concluded that drug use in the nursing homes was high and many drugs were used chronically. In view of possible adverse effects and the risks of parallel prescribing and drug-drug interactions, the prescribing of psycholeptic drugs, laxatives, loop diuretics, and ulcer-healing drugs should be re-evaluated. In section 2.4 a study is presented on drug-drug interactions (DDIs) in the nursing home. We developed prescribing indicators based on the frequency, nature and duration of DDIs to systematically assess potential DDIs in the cohort of nursing home patients. We found 32% of all residents were exposed to at least one clinically relevant DDI. The number of medications prescribed was a strong predictor of the occurrence of a potential DDI. Drug groups most frequently involved in DDIs were oral anticoagulants, antibiotics and theophylline. The interaction between non-steroidal anti-inflammatory drugs (NSAIDs) and loop diuretics, and between NSAIDs and oral anticoagulants were the potential DDIs most frequently encountered. The number of days on which drugs were prescribed concomitantly was relatively high. Nineteen out of 32 DDIs were prescribed for an average of 50 days or more per 100 days of index drug use. The prescribing indicators developed in this study provide the tools to audit DDI occurrence in nursing homes systematically. Finally, in section 2.5 a pilot study is presented that used several prescribing indicators, based on the studies in sections 2.3 and 2.4, to evaluate drug prescribing in Dutch nursing homes. We evaluated prescribing of benzodiazepines, NSAIDs, ulcer-healing drugs and diuretics. Prescribing indicators were used to identify prescribing that was potentially not in line with recommendations in national and regional prescribing guidelines. Both descriptive indicators, such as percentage of users, and indicators reflecting potentially suboptimal prescribing, such as use of drugs outside the drug formulary and prescription of drug dosages above recommended values were used. We found the majority of prescribing to be in line with recommendations upon which we based our prescribing indicators. Clinical information from the prescriber was necessary to get insight into actual prescribing appropriateness. The second part of chapter 2 describes two drug utilisation studies that were performed in ambulatory elderly, and partly in nursing home patients. Section 2.6 presents a study on the concomitant use of benzodiazepines and antidepressants in two cohorts of elderly outpatients and the nursing home cohort. We assessed whether differences in co-prescribing between tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) existed. Pharmacy dis-
drugs that exhibit moderately to strongly constipating effects and occurrence of constipation was found, the risk was not as high as seen in previous studies. In section 3.2 the clinical effect of a DDI was investigated. In a cohort of elderly outpatients attending the Groningen Outpatient Thrombosis Service, we studied the effects of the interaction between three NSAIDs (diclofenac, naproxen and ibuprofen) and the oral anticoagulant acenocoumarol on prothrombin time, expressed as the International Normalised Ratio (INR). Genotyping of cytochrome P450 2C9 was performed to determine whether genotype was a predictive variable for the occurrence of an increased INR as a result of this DDI. The study population consisted of 112 patients stable on acenocoumarol therapy, of whom 52 (46%) showed an elevation of the INR above the desired therapeutic level (average INR increase between 1 and 4 units). In 12 patients, the INR increased above 6, indicating a clinically relevant risk of severe haemorrhage. No association between CYP2C9 genotype and an increased INR as a result of the DDI was found, and no other predictive variables were identified. We recommend close monitoring of the INR of all patients receiving NSAIDs and acenocoumarol as at present we cannot predict who will and who will not be affected by this DDI.

In chapter 4 the results of the studies described in the thesis are placed in a broader perspective and suggestions for clinical practice and further study are given. For example, hospital pharmacists can play a leading role in the monitoring of drug-related problems in the frail elderly both on an individual and a population based level.