24 Chan TY. Prolongation of prothrombin time with the use of indomethacin and warfarin.
25 Haasse KK, Rojas-Fernandez CH, Lane L, Frank DA. Potential interaction between celecoxib and warfarin
significantly alter the pharmacokinetics or hypoprothrombinemic effect of warfarin in healthy subjects.
28 Stading JA, Skrabal MZ, Faulkner MA. Seven cases of interaction between warfarin and cyclooxygenase-2

Chapter 4

General discussion
and perspectives
Pharmacotherapy in frail elderly

People residing in Dutch nursing homes are mostly frail, elderly people who are dependent on continuous nursing and medical attention. Pharmacotherapy in this elderly group is an important aspect of medical care. Drugs obviously have beneficial effects in the very old. For example, the use of statins should not be limited to people younger than 70 years, as statins can reduce the risk of myocardial infarction even in the very old [1,2]. In addition, the benefits of oral anticoagulant therapy in patients suffering from atrial fibrillation, have been well acknowledged. For some therapies, such as hormone-replacement therapy in elderly women for reducing the risk of osteoporosis [3], it is not yet clear who will receive the most benefit. However, the impact of adverse effects of pharmacotherapy in the frail elderly is generally higher than in other populations. Non-steroidal anti-inflammatory drugs (NSAIDs) may lead to renal dysfunction [4], anticholinergic drugs to confusion and delirium [5], and psychotropic drugs to falls and fractures [6], often with significant impact on the quality of life. Therefore, the risks of drug therapy should be carefully weighed against the potential beneficial effects, especially in this vulnerable group of elderly persons. Pharmacoepidemiologic studies can provide insight into this delicate balance. The benefits of drug use are mainly studied in randomised controlled clinical trials (RCTs). Observational studies are less suitable for evaluating the benefits of drug use in view of biases and confounding issues such as selection by disease severity. However, observational studies are often used to study adverse drug effects. This is due to various considerations. These include differences between the experimental RCT setting and prescribing in daily clinical practice such as co-morbidity and comedication profiles and differences in patient age. This thesis is largely based on observational studies.

Pharmacoepidemiology in frail elderly

Organisational differences between nursing homes in the Netherlands and in other countries, in particular the United States, will have an impact on drug utilisation. Consequently, findings from one health care setting cannot automatically be considered true for another setting. Therefore, to gain insight into local drug use, it is important that drug utilisation studies are performed within the applicable health care system. This thesis reports on an investigation of drug use and drug-related problems in the elderly in the Netherlands, in particular those residing in nursing homes. To draw conclusions regarding drug use and safety, a sufficiently large number of subjects is needed. We collected pharmacy dispensing data from 6 nursing homes. In this way, we were able to study the extent of drug use, problem areas in drug prescribing and the potential risks associated with drug use in these nursing homes. Pharmacy dispensing data for 2355 residents were retrieved. It was found that the hospital pharmacy data were, in general, accurate, although completeness of discharge and admission date recording could be improved. With these data, the duration of stay in the nursing home could be calculated, as well as the duration of drug use. Hospital pharmacy data proved to be an important data source, enabling the performance of drug utilisation and drug safety studies. We demonstrated the importance of accurate and precise recording in the hospital pharmacy, of prescription data for individual nursing home patients in order to reliably determine drug exposure. The main findings and implications of these studies are described below. First, a drug utilisation study was performed. We found high numbers of drug users and the chronic use of many drugs. This study revealed several potential problem areas regarding the prescribing of drugs in the nursing home setting. Prescribing of loop diuretics, laxatives, psychotropic drugs and ulcer-healing drugs deserved attention, in view of high dosages, long-term use and a high proportion of users. Prescribing practices in individual nursing homes regarding these drug groups may subsequently be evaluated in pharmaconerapeutic discussion meetings or, on the level of an individual patient in a one-to-one discussion with the prescriber. Hospital pharmacists can play a key role in these evaluations since they have the tools to analyse individual prescription data. From the drug utilisation studies, several determinants of drug use were found. Sex was found to be a determinant of drug use in several cases, as was the type of care. It was shown that in drug utilisation studies it is important to distinguish between nursing home residents residing in psychogeriatric nursing homes, and those residing in somatic nursing homes as drug use substantially differs between these populations. As expected, nursing home residents residing in psychogeriatric nursing homes use more psycholeptic drugs (psychotropics and anxiolytics) and less antithrombotic drugs, diuretic drugs and antacids than residents residing in somatic nursing homes. Also, somatic residents showed a higher risk for the occurrence of potential drug-drug interactions (DDIs). Female residents were more likely than male residents to experience a potential DDI and were more likely to receive NSAIDs, antirheumatic drugs and psychoanaleptic drugs. Male residents were more likely to receive psychotropic drugs. Other determinants of drug use found were the number of medications prescribed. Residents with a higher number of medications were more at risk for the occurrence of potential DDIs than residents with fewer drugs. Patients with Parkinson’s disease were less likely to be exposed to potential DDIs.

In view of the high frequency of drug use, we studied the potential risks of polypharmacy by carrying out a descriptive study on the extent and occurrence of potential DDIs. Several prescribing indicators were used to assess the occurrence and nature of DDIs, such as the number
feasible to perform a prescription-sequence analysis using pharmacy data in the nursing home setting. Although the constipating effects of certain drugs should be taken into account, this may not necessarily explain the high rate of laxative use found in the nursing homes we studied. Effects of dietary factors and physical activity on laxative use needs further investigation. The studies discussed above were carried out to identify problem areas in drug prescribing in the elderly, especially those residing in nursing homes. Results of these studies may help to identify patients at increased risk of drug-related problems.

**How to identify patients at risk?**

To enable the identification of patients at risk of drug-related problems, more information than pharmacy data alone is needed. Clinical data and information from prescribers can provide insight into clinical outcomes, as well as into any preventive measures that have already been undertaken and how these patients are currently being monitored. One way to identify patients at risk of unwanted pharmacotherapy effects, is to use prescribing indicators to signal potentially suboptimal prescribing. Although many prescribing indicators have been developed and used internationally [9], few of these can be used with pharmacy prescription data and few are specific for drug-related problems common in nursing homes. In a pilot study [10], we found that a set of prescribing indicators developed on the basis of current pharmacotherapy guidelines, could be used to evaluate prescribing practices in nursing homes and to identify patients at risk of potential suboptimal prescribing. However, information from the prescriber on clinical data was needed to identify patients who were actually at risk for drug-related problems. In some cases, deviation from national guidelines and drug formularies may not mean that the patient is treated suboptimally. This discrepancy between potential and actual inappropriate prescribing has been reported earlier [11] and stresses the importance of taking the patient's clinical response and the prescribers' rationale into consideration. Furthermore, it is often difficult to define prescribing indicators that actually reflect potential suboptimal prescribing. Although evidence-based practice guidelines may serve as a basis, these sometimes differ from expert opinions [12]. In nursing home practice, evidence-based guidelines are just beginning to emerge, and the lack of specific nursing home guidelines hampers the development of good prescribing indicators in this setting. In many cases, however, prescribing indicators can be used to signal potentially suboptimal prescribing, as was also found in recent studies [12,13]. Together with clinical data, such as laboratory values or clinical outcomes, the risks for the patient can be adequately perceived and preventive measures taken on both an individual patient and population-based level. In our view, the pharmacological knowledge of the hospi-
tional pharmacist together with the clinical knowledge of the nursing home physician may act synergistically in detecting drug-related problems in the elderly. Also other caregivers, such as nurses, may play an important role in signalling adverse drug effects in clinical nursing home practice.

The ultimate question, however, is whether potentially suboptimal prescribing leads to actual clinical problems [14]. We investigated this with respect to a frequently occurring, potential DDI. The potential DDI between acenocoumarol and NSAIDs constitutes one of the most frequently encountered DDIs in the nursing home study population and to date its clinical relevance remains unknown. The study presented in this thesis found that this interaction led to a clinically relevant outcome in about half of all elderly outpatients exposed, namely the increase of the prothrombin ratio expressed as the international normalised ratio (INR) above the therapeutic window. To be able to identify patients at risk for this drug-drug interaction, several patient characteristics were investigated as potential determinants. One of the determinants we included was genetic polymorphism of cytochrome P450 2C9 (CYP2C9). This enzyme is involved in the metabolism of numerous drugs including acenocoumarol and NSAIDs, such as diclofenac, naproxen and ibuprofen. We hypothesized that patients with a variant allele on CYP2C9 (CYP2C9*2 and CYP2C9*3) would be more likely to experience the increase in prothrombin time due to the DDI. We found that none of the determinants investigated was associated with the occurrence of increase in prothrombin time. However, patients with one of the variant alleles mentioned above, required a lower dose of acenocoumarol than patients who had the wild-type genotype and we are currently investigating this matter in more detail. In the meantime, all patients who are prescribed acenocoumarol and an NSAID simultaneously should be monitored, in view of the increased risk for elevated INR levels.

The studies described above, show the importance of capturing data on drug use as well as data on clinical variables to be able to identify patients at risk for drug-related problems. The following clinical variables should be included:

- Laboratory test values: insight into potassium levels, creatinine levels, INR, glucose levels, cholesterol levels and other parameters is often necessary to identify adverse effects of drug therapy such as decreased renal function as a result of NSAID therapy. These data are often available in clinical chemistry laboratory computer systems, and sometimes in the nursing home computer systems. Hard copies of the laboratory test results are available in the medical chart of the patient. In the near future, results of genotyping may also be available [15].
- Serum drug levels: information on serum drug levels may be needed to determine the clinical relevance of certain drug-drug interactions. These data are routinely stored in hospital pharmacy computer systems.
- Clinical status of the patient: this includes diagnoses, data from the nursing home physicians and medical specialists visits, and clinical outcomes. In Dutch nursing homes, these data are manually recorded in the patients’ medical chart. Sometimes electronic patient records are available.

Quality of life

It could be argued, that together with clinical outcomes such as the frequency of adverse events another issue that needs to be taken into account is the quality of life (QoL) in the frail elderly population. For instance, in clinical practice the impact of side effects from ACE-inhibitors in this population, is higher than in the general population. This may lead to a more adverse risk-benefit balance. The impact of various drug-related problems on this populations’ quality of life, will therefore be different to that in the general population. Measuring QoL, however, is not something that is routinely done in nursing home patients and such data are not readily available. In the elderly, the “Short Form-36” (SF36) is regarded as a suitable, reliable and valid questionnaire and outcome tool [16,17]. However to our knowledge, this questionnaire has been used only in community-dwelling elderly and not in Dutch nursing home residents. A high incidence of non-completion on SF36 questions relating to physical and mental function has been reported [16]. In nursing homes the prevalence of physical and mental disorders among residents is much higher and therefore the SF-36 is possibly not a suitable tool for measuring QoL. It is with these considerations in mind, that we believe that routinely measuring QoL in nursing home patients is probably not one of the first issues to focus on. Instead, QoL should be taken into account when the effects of drug use are evaluated on an individual basis where relevant or when possible.

Future perspectives

Optimal use of clinical and pharmacy data to monitor drug effects

Efforts should be directed towards optimal use of existing clinical, pharmacy and laboratory records. This may lead to several advances in the pharmacotherapeutical care of the frail elderly. First, on the basis of clinical characteristics individual patients could be monitored prospectively regarding potential adverse drug effects and adverse outcomes. Record-linkage of pharmacy and clinical data provides an excellent opportunity to optimally use both sources of information. In the nursing home setting, most relevant information is available. Since not all
clinical information is stored in automated databases, initiatives should be taken to stimulate computerised recording of such information. In our study, we used data from a national nursing home database (SIVIS) to obtain information on clinical diagnoses. Attention should be given to accurate recording of SIVIS diagnoses, as we found several discrepancies between SIVIS data and pharmacy data. For example, it is highly unlikely that an antidiabetic drug is prescribed without a registered indication of diabetes mellitus. Data on INR were collected for investigating the clinical relevance of the potential pharmacokinetic interaction between acenocoumarol and NSAIDs. Such data were not readily available in computerised databases. It has been shown that computerised surveillance of adverse drug reactions (ADRs) is feasible in hospitals [8,18]. Others have suggested that detecting adverse drug reactions would be more effective and less time-consuming if electronic patient records were available [18]. Ideally, all medical information of individual patients should be available on an electronic patient record. Electronic patient records are not usually available in Dutch nursing homes but initiatives are currently being developed to change this. In primary care, an electronic ‘care card’ is being developed, on which all patient related medical information is stored. In this way, health care professionals can gain insight into the patient information needed in order to carry out their professional duties. This is particularly advantageous when patients are admitted from home to hospital and or from nursing home to hospital and vice versa. In this way, optimal seamless care can be provided. An issue that should be considered here, is patient privacy. Information that is not needed for carrying out professional activities should be separated from information that is necessary. This can easily be done once the data is in electronic format. Another advantage of the use of electronically available patient information, is the possibility for monitoring patient outcomes on real-time basis as information on drug use and clinical outcome can stored in the same database. In the meantime, different databases can be record-linked to provide the opportunity of real-time monitoring for drug-related problems. Internationally, it has already been shown that it is feasible to record-link patient-specific information that is stored separately into large databases to monitor and evaluate effects of drug use in large populations (MEMO [9], SAGE [20]).

A second advantage of combining existing clinical, pharmacy and laboratory records, is the possibility to study outcomes of drug use in more detail and to establish reliable risk-benefit analyses of drug use. Outcomes that could be studied are hospital admissions, adverse drug effects and quality of life, although as discussed earlier, measuring the latter is difficult. Relatively little is known about the relationship between drug use and clinically adverse outcomes in nursing homes in the Netherlands. Internationally, many studies have focussed on falls and fractures [6,21-25]. Psychotropic drugs, such as antidepressants and benzodiazepines, have all been associated with an increased risk of falls in nursing home residents. However, other clinical outcomes have been studied less frequently. An example is the association between bowel function and anticholinergic drug use [26]. Quality of life could also be an important outcome when the risks and benefits of drug use in the frail elderly are balanced. While the number of life years gained often plays a decisive role in determining the value of a pharmacotherapeutic intervention, this may not be the case in the frail elderly. The impact of adverse drug effects is much higher in this group, and quality of life could in some cases determine whether or not drug therapy should be started. For example, in the treatment of heart failure, the adverse effects of drug therapies may be more important than the number of life years gained.

Role of the hospital pharmacist

There are various stages at which hospital pharmacists can play a key role in monitoring drug-related problems in frail, elderly people. Firstly, hospital pharmacists have the opportunity to use pharmacy data for drug utilisation research. The studies in this thesis have demonstrated that hospital pharmacy data are a useful tool for studying the use and effects of drugs in the elderly, especially in the nursing home setting. Further use of these data for research should be encouraged, which implies the development of initiatives for anonymous and continual data collection. Special export files [27] would facilitate the building of a database that can be continuously updated with current data from pharmacies. The fact that the number of hospital pharmacies using the same computer system is still increasing in the Netherlands contributes to the building of such a database and further collaboration is needed between hospital pharmacies on this point. In particular, collaboration in the field of nursing home medicine could contribute to the creation of large databases for adequate performance of drug utilisation and safety studies. An important prerequisite is that the prescription data cover a sufficiently long period, preferably several years. Initiatives concerning hospital prescription data arising from the Stichting Farmaceutische Kengetallen (SFK), an organisation that forms part of the Royal Dutch Association for the Advancement of Pharmacy (KNMP), are currently being explored. Secondly, hospital pharmacists can play an important role in initiating and conducting pharmacoepidemiology research in nursing homes. Special interest groups could be formed, to facilitate and carry out research projects related both to drug-related problems and other relevant clinical outcomes in the nursing home. Monitoring of ADR occurrence is also an issue in which hospital pharmacists could play an essential role as they have the tool to gather relevant information from prescribers and patients.

Finally, the studies in this thesis show that use of existing clinical and laboratory data is
important to estimate the clinical relevance of drug-related problems, such as drug-drug interactions. These can be monitored and studied both on an individual and on a population based level. Co-operation with other health care organisations, such as Outpatient Thrombosis Services and Clinical Chemistry Laboratories, can contribute to the optimal use of existing experience and data.

### References