CHAPTER-8

Summary and General Discussion
CHAPTER EIGHT

The first objective of this thesis was to explore the pharmaco-epidemiological aspects of screening on albuminuria in the general population. For this purpose, baseline clinical data and 4.2 years follow-up data of the PREVEND cohort study were used. This clinical data were linked to the electronic pharmacy data from the Inter-Action Data-Base (IADB) which contains the drug-dispensing data from community pharmacies \[1\]. Firstly, we investigated the effect of a population-based screening (as a determining factor) on the drug use. Secondly, we studied the risk-benefit of specific drugs on cardio-renal risk factors (outcome of drug usage). In this respect we evaluated the long-term effect of statins and hormonal contraceptives on progression or regression of urinary albumin excretion and renal function.

The second objective of this thesis was to explore the pharmaco-economic aspects of a population-based screening on albuminuria. Firstly, we studied the quality requirements for such an analysis through investigating the national pharmaco-economic guidelines; in particular, we reviewed peer-reviewed Dutch health-economic studies with respect to adherence to pharmaco-economic guidelines. Next, and applying these guidelines we used the data of the PREVEND Intervention Trial and extrapolated the results of this RCT into a lifetime analysis by using models for the cost-effectiveness of screening on microalbuminuria. We investigated whether it is economically worthwhile to implement screening for albuminuria in the general population.

Screening for cardio-renal risk factors: the determinant of drug use

A population based screening is only effective if treatment will be started following the identification of subjects without treatment whereas treatment would be appropriate \[2\]. In the PREVEND study, a letter intervention was applied with the goal to obtain a higher proportion of patients receiving treatment. The letter contained the result of screening: actual blood pressure and cholesterol level as well as the presence of an abnormal plasma glucose and UAE. The letter was sent to both the participant and her/his general practitioner (GP). The letter advised the GP on initiating, either a blood pressure (BPLD) and/or lipid lowering drug (LLD).

In chapter 2, we evaluated the effect of this letter intervention on prescribing of BPLD and/or LLD. A year after screening, our therapeutic advice was followed in about one of three subjects with hypertension and one of four subjects with hyperlipidemia. We found that the GP’s decision to follow our advice was influenced by the level of the risk factor itself, but not by the presence of other cardiovascular risk factors.
Another aspect of a population-based screening program is that it might be possible that some participants experience harm [3-4]. The assumption is that the benefits of early diagnosis in asymptomatic individuals will outweigh any possible ‘side-effect’ associated with screening, diagnosis and treatment. Some argue against a screening because such programs may result in medicalisation. However, little is known yet about negative consequences of a screening program for cardiovascular and renal risk factors in early prevention.

In chapter 3, we studied the effect of population-based screening for cardio-renal risk factors on drug prescribing. We found that incidence of prescribed drugs, either related or un-related to the screening purpose, was not different between those who participated and those who did not participate in the PREVEND screening. Thus, our data showed that a screening program to improve cardiovascular and renal conditions does not lead to higher drug use in the screened population compared with the unscreened population. This study also showed that a targeted screening, that is screening in a cohort that is likely to be at higher risk, enhances appropriate drug use; i.e. drug use increases in the drug classes expected and not overall.

Cardio-renal risks factors: the outcome of drug use

Many drugs are found to be related to urinary albumin excretion (UAE). In the second section of the pharmacoepidemiological part of this thesis, two drug classes were investigated in this respect; hormonal contraceptives (HC) and lipid lowering drugs (statins). In chapter 5, we considered in detail the impact of long-term use of HC on changes in blood pressure (BP), UAE and glomerular filtration rate (GFR). We found that the start of HC was associated with worsening of BP, UAE and GFR. Our data also showed that cessation of HC resulted in an improvement of those outcomes. With respect to the generation of HC, our data suggest that third generation agents might be more harmful than second generation HC. These data suggest that long-term HC use may worsen cardiovascular and renal conditions, but stopping HC restores such conditions.

In chapter 4 we investigated the effect of statins on UAE and GFR, using the data from the randomised controlled trial PREVEND-IT and the observational PREVEND cohort. In the PREVEND-IT we found no effect after 4 year treatment of 40 mg pravastatin on UAE. In contrast, our observational PREVEND cohort study of 3440 subjects showed that statins induced a rise in UAE, especially when used in higher dose and for longer duration. From both studies, we could not confirm that
statins are associated with better GFR preservation. On the other hand we also did not find a negative effect on GFR.

Screening for albuminuria: the pharmaco-economic aspect

It has been shown that albuminuria may predict cardiovascular disease and renal function outcome in subjects with diabetes [5-7] or hypertension [8-13] as well as in the general population [14-20]. Therefore, micro-albuminuria might be an easy detectable marker for vascular dysfunction. In that respect, screening on albuminuria may be a useful tool to identify subjects at risk for CVD and/or progressive renal failure [21-22].

However, before screening programs can be implemented, cost effectiveness of the program needs to be established. In chapter 7, we estimated the cost-effectiveness of screening on albuminuria and subsequent treatment with fosinopril of subjects with UAE > 15 mg/d for early prevention of cardiovascular and renal morbidity and mortality. The data from PREVEND-IT, a double blind RCT using a 2x2 factorial design was extrapolated into a lifetime analysis. The estimated costs of screening were derived from the PREVEND observational study. Our study was designed as far as possible according to the Dutch guidelines for pharmacoeconomic research (chapter 6); for that purpose, pharmacoeconomic guidelines were investigated in detail by comparing them with published health-economic studies.

Our estimation of the cost-effectiveness ratio (CER) from the Dutch health care perspective was €16,700/life year gained (LYG). With maximum acceptable cost-effectiveness willingness to pay for the Netherlands of €20,000/LYG, our point estimate would be considered cost-effective. Stochastic analysis indicated an estimated 60% probability of this screening and treatment being cost-effective. Limiting the screening and treatment to subjects over 60 years old and subjects with UAE > 50 mg/d improves cost-effectiveness. Because this study was based on the non-significant trend toward fewer CV events with fosinopril in PREVEND-IT, the result of this study should be interpreted as a hypothesis-generating study and these findings need confirmation in a larger multi-center study. In this study, we as expected had no case of end stage renal disease (ESRD) during the 4 years follow-up, thus the endpoints of PREVEND-IT were only for cardiovascular events in the end. We also did not include follow-up costs of the events; its inclusion would have enhanced cost-effectiveness further.
Pharmacoepidemiologic and pharmacoeconomics: the aspect of drug use

All studies in this thesis provide insight into aspects of drug use and drug prescribing. Combining clinical data of the PREVEND observational cohort and the PREVEND-Intervention Trial with drug-dispensing data of IADB has resulted in a dataset which allows us to do drug utilization research and pharmacoepidemiologic and pharmaco-economic studies. Below, we review the chapters in this thesis with regard to the availability of this unique set of drug use data.

Firstly, we focused on determinants of the drug use. We investigated whether a population-based screening (as a determinant) could influence drug prescription (chapter 3). We demonstrated that a screening program itself does not lead to more drug prescribing, neither in the screening-related nor in the screening-unrelated drugs. Comparing the patterns of drug use of the screened enriched population, an screened random sample and an un-screened population increased our understanding how and when drugs are prescribed in these different groups. We estimated the number of patients exposed to drugs within a given time period. Such estimates gave us insight in the prevalence of drug use at the time of the initial screening as well as on the incidence of use of drugs in selected time periods.

Drug utilization research may enable us to assess whether an intervention undertaken to improve drug use by giving a treatment recommendation to the general practitioner has the desired impact on drug prescribing. In chapter 2, we have shown that an intervention, such as a letter recommendation, significantly changed prescribers’ attitude to make a therapeutic decision for their patient. We have shown that the subjects/patients characteristics (e.g. demographic parameters, cardio-renal risk factors and comorbidity) are also playing a role in profiles and trends in drug use.

Pharmacoepidemiology focuses on the benefits and adverse-effects of drugs in the general population. The driving force behind this development was a growing awareness that health outcomes of drug use in the rigorous setting of randomized clinical trials is not necessarily the same as health outcome of drug use in everyday practice. The clinical trials often have limited samples of carefully selected patients. Moreover, drug utilization research also provides insight into the efficiency of drug use, i.e. whether a certain drug therapy provides relevant health gains. Drug utilization research can thus help to set priorities for the rational allocation of health care budgets. Therefore for the second aspect of drug use, we focused on health outcome (benefits and side-effects) and economic consequences of drug use (chapter 4, 5 and 7). In these chapters, we assessed the potential effects of a specific drug (as an exposure factor) on cardio-renal outcomes such as changes
in blood pressure, UAE and GFR. Economic consequences including cost/benefit of treatment were estimated using the data from a clinical trial (chapter-7), using state-of-the-art pharmacoeconomic methods.

Thirdly, we provided detailed information on patterns of drug use, particularly for those drug related to cardio-renal outcomes, as we were interested in the differences between the effects of current versus former users. Such descriptions are most meaningful when they are part of a continuous evaluation system, i.e. when the patterns are followed over time and trends in drug use can be described, enabling us to specify the differences between those who have stopped, started or continuously used a medication (chapter 4 and 5).

Fourthly, we could assess the quality of drug use. Quality indicators of drug use that are included in our analysis involve type of regimens, drug dosage and period of drug exposure. In this thesis, these indicators are used to determine the difference between type of regimen, drug dosage and period of exposure on renal outcomes such as UAE and GFR.

**Methodological consideration: experiences and challenges**

**Study design, confounding and propensity score in observational study**

An important aspect of our studies is that we were able to provide a data from a prospective observational cohort study with long term follow-up (4.2 years for the clinical data of PREVEND and 6.5 years of pharmacy data of IADB). Observational studies always raise concerns about biases in some that may account for or contribute to the findings. In observational studies, patients and their physicians select treatment on the basis of clinical need or preference, which can result in differences in clinical outcomes solely because of differences between those who do and do not receive treatment (indication bias). In contrast, random assignments in an RCT guarantees that patient characteristics, both known and unknown, will be the same in the treatment groups. However, knowledge derived from RCT’s cannot always be translated directly to daily clinical practice. Patients that are included in an RCT frequently are not the ones that clinicians encounter in their office. This is especially true for nephrology, as in many of the important cardiovascular trials studying the effect of antihypertensives, statins, or anticoagulants patients with chronic kidney disease are excluded. In other words, the observational study provides information about treatment in the population in daily practice, and differs from the situation in clinical trials [23-24].

An alternative way of dealing with confounding by indication caused by non-randomized assignment of treatments in cohort studies, is the use of
propensity scores, a method developed by Rosenbaum and Rubin [25-26]. The propensity score of an individual is defined as the conditional probability of being treated given the individual’s co-variates. However, this technique can not adjust for residual un-measured covariates, but can aid in understanding determinants of drug use and lead to improved estimates of drug effects [27].

**Internal and external validity** - All studies in the pharmacoepidemiology part of this thesis are based on electronic-drug-dispensing data from community pharmacies. We used the computerised pharmacy database (from IADB) that provides valid and reliable information on drug use. Previous studies have demonstrated that dispensing data from Dutch pharmacies offer an accurate picture of the use of prescription drugs outside the hospital [28-29]. However, one limitation is that pharmacy data do not have information about indication of the drug.

Use of large computerised databases and record linkage has become increasingly important in pharmacoepidemiology research. The greatest advantages of using routinely collected data are minimisation of study costs and time required to complete a study, considerations that are particularly relevant for longitudinal studies such as in this thesis. The advantage of using databases also includes the possibility of obtaining large sample sizes and reduces the risk for recall bias, which is a significant problem in interviews and questionnaire methods. Another advantage of using pharmacy data is the detailed information regarding drug use (duration, dose, and drug classes) during the whole study period. We also were able to compare the drug use between subjects in the PREVEND cohort with drug use in the general population (from IADB).

**Clinical impact and future research**

A screening programme on microalbuminuria could also help to detect subjects with undiagnosed diabetes, hypertension and hyperlipidemia. Our study showed that one third of the hypertensive subjects were not yet known to have hypertension and one third of those with hypertension were not adequately treated. Comparable data were found for hyperlipidemia. Furthermore, we found that the likelihood to use blood pressure or lipid lowering drugs increased when higher values of blood pressure or cholesterol level were found. Unfortunately, the presence of concomitant risk factors did not influence the prescribing behaviour. This aspect was further studied in chapter-3. After a long period of follow-up, we could not find any medicalization effect in our screened population compared to a
non-screened population. We could thus not confirm that screening for cardio-renal risk factors leads to more drug prescribing and might therefore be harmful for the population. Interestingly, we also showed that a screening is in fact only effective in improving drug use, when it is limited to those with a higher risk, such as in a cohort enriched for albuminuria.

Another point addressed in this thesis refers to the relation between use of a specific drug and the change in albuminuria and renal function over time. Firstly, we should pay attention to our finding that statins are associated with a rise in albuminuria in our observational study. Although this finding was not confirmed in our PREVEND IT clinical trial, this finding requires further attention. Fortunately, statins were not associated with a fall in GFR. Secondly, we found that hormonal contraceptives independently were associated with a worsening of blood pressure, albuminuria and renal function, but our data also showed that stopping may result in correction of these effects. Even though our data are limited to subjects with only modest renal damage, we do think these data are of interest for clinicians as also early renal damage is associated with an impaired renal and vascular prognosis. Because statins and hormonal contraceptives are widely used in the general population our results may be of public health importance and need confirmation in other studies.

Can we implement a screening program for albuminuria in daily practice? The evidence showed that a screening program with subsequent treatment for those with an elevated albuminuria improved CV morbidity and mortality. Our data suggest that screening of albuminuria and subsequent treatment with an ACE inhibitor appeared to be cost effective in our population. The costs needed to gain one life year were € 16,700. The costs were even lower when we limited the analysis to subjects with an UAE > 50 mg/d and an age over 50 or 60 year. This study is based on a single screening for microalbuminuria of the general population. Further studies are needed to evaluate whether re-screening at some later time offers additional benefit. A Markov Model should be developed to simulate a periodic screening procedure in the general population inclusive long-term beneficial effects on renal damage.

The PREVEND cohort and IADB form a unique set of data. Presently, third screening of the PREVEND subjects has been completed and data on cardiovascular and renal morbidity and mortality are available and pharmacy data have been collected until the end of 2005. These long-term follow-up (approximately 10 years) makes it possible to provide longitudinal analyses on cardiovascular and renal disease progression in relation to drug use.
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