The value of personalized approaches to improve pharmacotherapy in renal disease

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THE VALUE OF PERSONALIZED APPROACHES TO IMPROVE PHARMACOTHERAPY IN RENAL DISEASE

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Chapter 1

General introduction

HEALTH MATTERS IN RENAL DISEASE

The kidneys are two bean-shaped organs located in the retroperitoneum, near the back of the body and just below the ribcage. Two of their key functions are the filtration of blood by excreting waste products, and the excretion and reabsorption of important solutes. By the latter, the kidneys serve essential homeostatic functions, including the regulation of the electrolyte, acid-base and volume balance and maintaining an adequate blood pressure.

Diseases of the kidneys, renal diseases, are major causes of disability and death in the world. A decreased filtration functionality of the kidneys leads to debilitating comorbidities, including cardiovascular diseases, anaemia and bone mineral disorders.[1] Progressive renal function loss may result in kidney failure, or end-stage renal disease (ESRD). Due to the scarceness of kidneys available for transplantation, many patients with ESRD rely on dialysis as artificial replacement of their lost kidney function. The technique of dialysis was developed in 1943 by Dr. Willem Kolff (1911–2009), a Dutch physician. Doctor Kolff's work saved countless of lives,[2] but unfortunately mortality in ESRD is still unacceptably high. Around one in five ESRD patients will die within one year after initiating dialysis therapy [3] – a disease fatality rate that is one of the worst in the industrialized world. Moreover, the quality of life of ESRD patients is disheartening. The health utility (an individual's preference for health-related outcomes, commonly known as a persons' quality of life) of ESRD is valued at little over half the utility of perfect health.[4] Indeed, the quality of life of ESRD patients is one of the worst of all chronic conditions, comparable only to uncontrolled heart failure, post-stroke handicaps and severe lung emphysema.[5] Lastly, it is important to realize that health-care costs for ESRD patients pose a large burden on the scarce resources allocated to health-care systems, both in The Netherlands and globally.[6,7]

Considering the above, two goals should be prioritized in clinical treatment regimens for patients with renal disease: delaying and preferably altogether preventing the onset of ESRD,[1] and prolonging survival for patients with ESRD.[8] Personalized approaches to reach these goals are increasing in importance.[9] The defining characteristic of personalized approaches is that they utilize individual patient characteristics to predict disease events, such as ESRD onset or adverse drug events, or response to therapy. It contrasts with standard approaches in which medical decisions are often based on average treatment effects observed in clinical trials. Personalized medicine is an accepted approach and widely regarded as an important tool to improve therapy effectiveness as well as ensure optimal resource allocation of dialysis treatments and the scarce organs available for renal transplantation.[10]

Most commonly associated with personalized medicine, patients' genetic determinants to disease and treatment response may be taken into account when exploring novel treatment strategies and drug development programs. Genetic screen-and-treat programs currently are uncommon in nephrology.[11] However, in an era of increasing importance of personalised medicine such strategies are getting increasing interest.[12] Non-genetic strategies to monitor and optimize pharmacotherapy on a personalized level also remain important. By looking

at specific patient characteristics, information may be gathered that can be used to achieve treatment responses that outperform average responses found in clinical trials. Data from both randomized clinical trials (RCTs) and observational studies may be used in this respect.[13] Indeed, the clinical effectiveness of pharmaceuticals is influenced by many parameters that may be under-studied in RCTs, such as therapy compliance, adverse drug reactions and patients' dietary habits. To this end, observational data from patient registries and prescription databases may serve as invaluable "living textbooks" envisioned over 40 years ago.[14]

Pharmacotherapy in renal disease

No therapies currently exist to reverse the course of chronic renal diseases.[15] Present treatments aim to slow renal disease progression and mitigate its many complications.[1,8] Considering the very poor prognosis of renal patients, improvements are needed aimed to improve long term outcomes, taking into account the balance between costs, clinical benefits and adverse effects. Two examples are given here, the treatment of high blood pressure and the lowering of high serum phosphate. Both examples are addressed later in this thesis in more detail.

High blood pressure is an important risk factor for renal disease. Before the 1950s, no effective drugs were available to control hypertension.[16] Even then, lifestyle suggestions were remarkably similar to modern advice: lowering salt and fat intake and smoking cessation (actually, smoking *reduction* was in some cases recommended).[17] The long-known wisdom that salt raises blood pressure led to the development of diuretics in the late 1950s; diuretics increase the urinary excretion of water and salt from the body, thereby reducing blood pressure. The connection between salt and blood pressure led to the discovery of another class of antihypertensives, albeit through more exotic observations. In the low salt environments of the Amazon rainforest, indigenous tribes such as the Yanomami hunter-gatherers need extreme hormonal adjustments to conserve salt and maintain adequate blood pressure levels.[18] These hormonal adjustments may create haemodynamic vulnerabilities when encountering another inhabitant of the Amazon rainforest, the Brazilian pit viper (*bothrops jararaca*). A bite from this venomous snake causes a dramatic and often fatal loss of blood pressure. Scientists discovered in the 1960s that the venom contains a natural inhibitor of the renin-angiotensin-aldosterone-system (RAAS),[16,19] which plays a key role in regulating blood pressure. One thing leading to another, by studying snake venom, ACE inhibitors (which similarly inhibit the RAAS) were developed in the 1970s. Landmark RCTs later demonstrated that ACE inhibitors not only lower blood pressure but are also renoprotective.[20-23] In fact, its renoprotective properties were found to be stronger than that of other antihypertensive drug classes. Currently ACE inhibitors and other RAAS intervening drugs are a cornerstone in the treatment of renal disease.[24]

Whereas hypertension is a common *risk factor* for renal disease, a common *consequence* is the accumulation of waste products. For example, patients with reduced kidney function are unable to filter and secrete adequate amounts of serum phosphate, leading to hyperphosphatemia.[25]

This electrolyte disturbance may lead to bone mineral disorders, cardiovascular disease and worsening of kidney function (indeed forming a vicious circle).[26-28] Ever since the 1970s the pharmacotherapeutic goal has been to prevent phosphate absorption from food by binding phosphate in the gastrointestinal tract.[29] Early treatments unfortunately backfired when aluminium containing phosphate binders were found to cause serious adverse events.[30] Today, most phosphate binders contain calcium instead of aluminium. Newer developments are non-calcium phosphate binders such as sevelamer and lanthanum carbonate.[31]

Genetic approaches to improve pharmacotherapy

Notwithstanding the advances made in the treatment of renal diseases since the 1950s, the quest for optimal pharmacotherapy is far from over. Highlighting one such quest is the *Renal Genome Network* (ReGeNet), a European network of researchers in nephrology and genetics with the overall aim of generating and translating novel insights from genomic and genetic studies to the clinical benefit of the individual renal patient.[32] The first project of ReGeNet was the *GENomic stratEgies for treatment and prevention of Cardiovascular death in Uraemia and end-stage REnal disease* (GENECURE) project. Within GENECURE, a joint infrastructure for collaborative genetic studies in renal populations was developed. Specific genes and polymorphisms were studied relevant to the natural course of renal diseases, response to treatment and the development of novel treatments.

The progression rate and response to therapy in renal diseases are at least indirectly influenced by genetic factors.[33] One case study of how genetic studies may lead to novel insights for pharmacotherapy in renal patients involves the CC-chemokine receptor 5 (CCR5) gene. The CCR5 gene codes for the CCR5 receptor, a receptor for proinflammatory chemokines involved in cardiovascular disease. A genetic variation, the CCR5Δ32 mutation, leads to deficiency of the receptor.[34] Observational genetic studies, supported by GENECURE, found that the CCR5Δ32 polymorphism attenuated the association between renal inflammation and mortality.[35,36] This exciting observation led to the hypothesis that in an analogous manner, pharmacological blockade of the CCR5 receptor would be of specific benefit to the inflamed dialysis patient. Observational genetic studies can be considered a type of natural, lifelong, clinical trial, with genetically different groups being randomized at conception; a concept known as Mendelian randomization.[37,38] While the Mendelian observation alone may justify a clinical trial,[37,39] important barriers have to be considered. Designing, conducting and analyzing RCTs is time-consuming and sometimes prohibitively expensive. Pharmacoeconomic analyses *prior* to RCTs may help in deciding whether it is clinically and financially worthwhile to pursue further clinical investigations. Thus far, these formal health economic analyses have been lacking.

Non-genetic approaches to improve pharmacotherapy

The efficacy of ACE inhibitors treatment is very heterogeneous and dependent not only on genetic[40,41] but also environmental factors such as therapy compliance[42,43] and dietary habits.[44,45] These interindividually varying non-genetic factors deserve further study in order to optimize personalized pharmacotherapy in renal patients.[46,47]

Observational studies found that increased dietary sodium intake increases proteinuria and accelerates renal disease progression.[48] Furthermore, experimental studies consistently report potentiation of ACE inhibitor efficacy by restriction of sodium excess.[44,49-52] However, no study so far evaluated the association of salt intake on hard renal outcomes in subjects on RAAS intervening drugs. Such studies are necessary to initiate and stimulate dietary intervention programs aimed to optimize dietary habits for the individual renal patient.

ACE inhibitors are associated with a bothersome dry cough in 5 to 20% of all patients.[46,47] This adverse drug effect may adversely affect treatment adherence and quality of life,[53] and is possibly even related to potentially fatal angioedema.[46] Rational therapy for patients experiencing ACE inhibitor induced dry cough is to substitute by angiotensin-II receptor blockers.[54] For this, a correct and timely recognition of the adverse event is required. There are reasons to suspect that this can be improved upon in clinical practice;[55] the area requires further study.

Common drug treatment for hyperphosphatemia consists of calcium-based phosphate binders, mainly calcium carbonate and calcium acetate.[31] Although effective, inexpensive and generally well-tolerated, their use has been controversial because of the risk for hypercalcemia.[56] This can be thought of as substituting one abnormally elevated element (phosphate) for the other (calcium). In renal patients hypercalcemia is also associated with increased mortality, due to vascular calcification and cardiovascular disease.[26,57] Non-calcium phosphate binders, such as sevelamer and lanthanum carbonate, do not pose added risk for hypercalcemia. These newer alternatives are more expensive than calcium binders however and their place in the pharmacotherapeutic chain, especially as first-line treatment, has been disputed.[58,59] This underscores the need for formal health technology assessments assessing their value for specific patient subgroups based on individual treatment response, for example as second-line treatment.

Value in pharmacotherapy in renal disease

Value is a concept defined in terms of monetary worth as well as intrinsic desirability. For example, it is valuable to delay the onset of dialysis: not only because of the large economic burden on health-care systems but also because of the increased mortality and reduced quality of life. Health economics and specifically pharmacoeconomics are concerned with these values by assessing the clinical impact for the patient and the financial impact for society. In doing so, pharmacoeconomic analyses require valid methodologies and structured guidelines.[60,61] After demonstrating the clinical effectiveness of ACE inhibitors in renal disease, health economists were quick to point out its economic benefits.[62,63] These analyses were mainly driven by the

large cost-savings resulting from delaying dialysis care, which costs many thousands of euros per year. Indeed, ACE inhibitors in chronic kidney disease is one of the few treatments that health economist classify as a *dominating strategy*, generating both cost-saving and clinical benefits compared to placebo.[61] Paradoxically, it has been proposed that for patients with ESRD, the *opposite* is true: the more effective a treatment is in prolonging survival of ESRD patients, the less cost-effective it might be, again due to the extraordinary high costs of dialysis care.[64] Other methodological factors that need to be taken into account when performing health economic analyses in the field of nephrology are an adequate time horizon, which differs between predialysis and dialysis patients[26,27]; the costs of dialysis care, which is dependent on country[65]; and the quality of life of patients with renal diseases.[4]

Research aims of this thesis

Part I of this thesis focuses on the value of genetic approaches to improve pharmacotherapy in renal disease. This part of the thesis was supported by GENECURE, a European infrastructure for collaborative genetic studies in renal populations. Firstly, it is widely accepted that pharmacoeconomic analyses should adhere to valid methodologies and guidelines.[60,61] It is unclear however if cost-effectiveness *analyses* of pharmacogenetic screening programs indeed follow these guidelines or whether specific guidelines should be developed. In this respect, **chapter 2** describes a comprehensive literature review of pharmacoeconomic analyses in this field. The knowledge and caveats derived from this review should provide valuable tools for health economists planning to perform further analyses. **Chapter 3** describes a pharmacoeconomic analysis of a screen-and-treat program based on the ACE insertion/deletion (I/D) polymorphism. This common polymorphism influences ACE inhibitor effectiveness.[40,41] **Chapter 4** describes a cost-effectiveness analysis of a novel treatment in renal disease. This chapter utilizes the genetic concept of Mendelian randomization to study the value of pharmacological CCR5 antagonists for dialysis patients.

Part II of this thesis focuses on the value of non-genetic personalized approaches to improve the pharmacotherapy of renal patients, such as prescribing strategies, adverse drug effects and dietary intake. **Chapter 5** focuses on phosphate binders, specifically on a treatment strategy consisting of first-line treatment with cheap, calcium-based binders and second-line treatment with non-calcium binders. The final three chapters focus on the cornerstone of pharmacotherapy in renal diseases: RAAS intervention. **Chapter 6** describes a comparative drug-utility study of patients using ACE inhibitors or ARBs, looking at therapy compliance, persistence and drug switching behaviour. **Chapter 7** explores a common, but easily overlooked adverse drug effect of ACE inhibitors, dry cough. This bothersome and potentially harmful side effect [46,53] is absent in other RAAS intervening agents such as angiotensin II blockers (ARBs). **Chapter 8** describes a post-hoc analysis of one of the landmark trials that demonstrated the renoprotective efficacy of ACE inhibitors in the 1990s, the Ramipril Efficacy In Nephropathy (REIN) trial. In this study the

influence of patients' dietary habits on the effectiveness of ACE inhibitors is assessed, bringing to mind one of the early personalized lifestyle suggestions given before pharmacotherapeutic options for renal diseases were available: lowering salt intake.

Finally, the results of this thesis are summarized and discussed in the discussion section. Here, the findings of the thesis are translated into final conclusions and recommendations, including some future perspectives.

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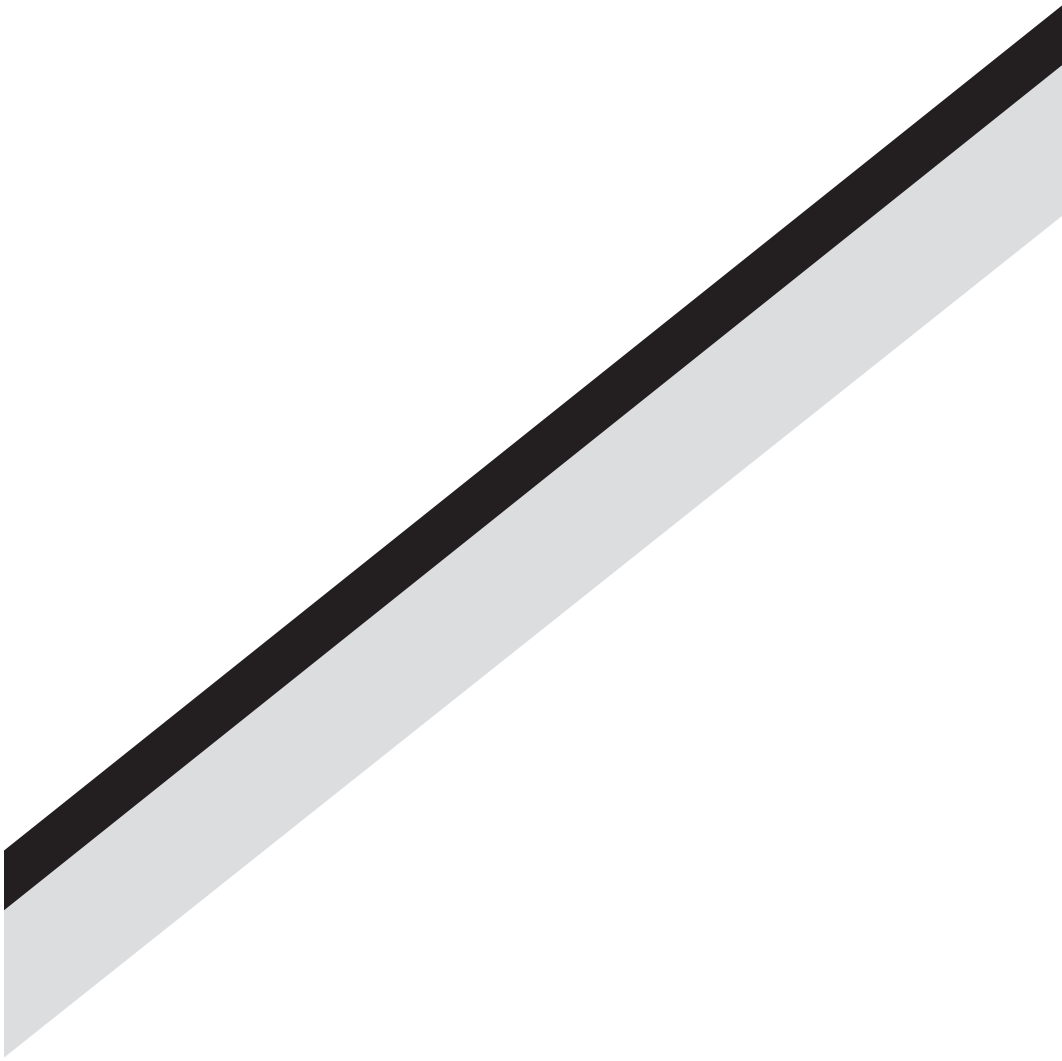

Part I

Genetic approaches to improve pharmacotherapy in renal disease

Chapter 2

Pharmacoeconomic evaluations of pharmacogenetic and -genomic screening programs – a systematic review on content and adherence to guidelines

Stefan Vegter, Cornelis Boersma, Mark Rozenbaum, Bob Wilffert, Gerjan Navis, Maarten J Postma

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ABSTRACT

Background: The fields of pharmacogenetics and pharmacogenomics have become important practical tools for progress goals in medical and pharmaceutical research and development. As more screening tests are being developed, with some already used in clinical practice, consideration of cost-effectiveness implications is important. The aim of this study was to perform a systematic review on content and adherence to guidelines, of recent pharmacoeconomic analyses performed in the field of pharmacogenetics and -genomics.

Methods: Economic analyses performed for screening strategies of genetic variations, which were evidence-based and assumed to be associated with drug efficacy or safety, were included in the review. The 20 included papers cover a variety of health-care issues, including screening tests on Cytochrome P450 (CYP) enzyme genes, Thiopurine s-Methyltransferase (TMPT) and Angiotensin-Converting Enzyme Insertion Deletion (ACE I/D) polymorphisms.

Results: Most economic analyses reported that genetic screening was cost-effective and often even clearly dominated existing non-screening strategies. However, we found a lack of standardization regarding aspects such as the perspective of the analysis, factors included in the sensitivity analysis and the applied discount rates. In particular, an important limitation of several studies relates to the failure to provide a sufficient evidence-based rationale for an association between genotype and phenotype.

Conclusions: Future economic analyses should be conducted using correct methods, by adhering to guidelines and including extensive sensitivity analyses. Most important, genetic screening strategies should be based on good evidence-based rationales. For these goals, we provide a list of recommendations for good pharmacoeconomic practice deemed useful in the fields of pharmacogenetics and -genomics regardless of country and origin of the economic analysis.

INTRODUCTION

The fields of pharmacogenetics and pharmacogenomics have become important practical tools for progress goals in medical and pharmaceutical research and development. Strictly, pharmacogenetics studies the influence of inheritable variations (often single nucleotide polymorphisms or SNPs) on drug response or metabolism, while pharmacogenomics focuses on a wide range of genes in this aspect; both terms are however used interchangeably. In practice, pharmacogenetic or pharmacogenomic screening prior to initiation of medical treatment programs currently offers one of the most promising implications of both research areas.[1,2] Insight into genetic variations can enhance the prediction of response to a drug and the risk for a patient to experience an adverse event. With this information, individual treatment modalities can be developed with optimal effectiveness and minimal adverse events.[1] Several screening tests are already used in clinical practice.[3]

In the Netherlands, as in all developed countries, health-care expenditures pose a large burden to society, with expenditures of almost 10% of GNP (including a share within health-care for drugs at 11%).[4] Controlling drug expenditures is generally seen as an important aspect in controlling health-care costs. Therefore, as from January 2005, full reimbursement of newly registered drugs requires a cost-effectiveness analysis in The Netherlands. Such a role of pharmacoeconomics can also be found in other EU-countries, the US, Canada and Australia. Next to this, cost-effectiveness of other health-care interventions – including screening strategies – is increasingly considered by health-care authorities.

Several reviews have already been published on the pharmacoeconomics of pharmacogenetic and -genomic screening strategies.[5-7] The aim of this study was to perform an updated systematic review on content and of adherence to guidelines on "good pharmacoeconomic practice", with a specific focus on pharmacogenetic and –genomic screening strategies. Ultimate conclusions drawn from this review will be summarized within a formal checklist including several recommendations for future economic analyses.

METHODS

Literature searches were performed using PubMed, Embase and Web of Science up until December 2007. We combined pharmacoeconomic with pharmacogenetic and –genomic terms in UK and US English. Pharmacoeconomic terms included "cost-effectiveness", "cost-utility", "cost-benefit", "cost-minimisation", "pharmaco-economics" and their thesauri variants. Pharmacogenetic terms used were "pharmaco-genetics", "pharmaco-genomics", "genotyping" and their thesauri variants. We included studies if they met the following requirements: (i) peer-reviewed published articles (abstracts or posters were excluded because these could not provide us with sufficient information for extensive reviewing); (ii) economic analysis on a genetic or genomic screening method; and (iii) the genetic or genomic variations were evidenced or at least assumed to influence drug efficacy or -safety. We excluded studies that focused on screening

tests for diagnostic purposes rather than treatment, such as genetic screening of HER2 status for diagnosis of infiltrating breast cancer and genetic screening for diagnosis of cystic fibrosis.[8] Studies on the genotyping of viral genomes such as Hepatitis,[9] or HIV,[10] were also excluded as no human DNA is screened in the process. Still, the study by Hughes *et al* on HIV infected patients was included as it focuses on human DNA, in order to prevent hypersensitivity reactions to the antiviral agent Abacavir.[11] Finally, we only included studies published from the year 2000 onwards, to ensure that both local and international guidelines had at least the potential of being followed.[12] On a large scale, pharmacoeconomic guidelines have become available locally and internationally during the last decennium.

The studies found (285, 904 and 211 in PubMed, Embase and Web of Science, respectively) were independently screened by two reviewers. Reviews, editorials and other non-original research articles were excluded; the remaining studies (156, 439 and 144 in PubMed, Embase and Web of Science, respectively) were screened on title and/or abstract for the mentioned inclusion criteria. No major disagreements between reviewers occurred and 20 papers were included by consensus. All 20 studies could be located using PubMed, 18 using Embase and 19 using Web of Science. Nearly all (18 out of 20) of the studies were not previously covered by a prior systematic review of Phillips and Van Bebber.[7] This seemed largely due to their rather strict inclusion criteria for economic analyses, leading to the exclusion of at least five studies we did include in our review.

Using a standardised extraction form, the following information was extracted from the included studies: (i) health-care issue, (ii) type of economic analysis; and (iii) outcome of the economic analyses. Adherence to guidelines for pharmacoeconomic research was assessed for all economic analyses. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has collected and arranged several country specific pharmacoeconomic guidelines (accessible via http://www.ispor.org). The following four guidelines were analysed as they were deemed both most important and rather universally applicable for the analyses: (i) the requirement for an extensive sensitivity analysis, including information on screening test sensitivity and specificity; (ii) the adequacy of the time-horizon and discounting; (iii) the perspective applied; and (iv) the inclusion of a systematic review of all the evidence. We mainly focused on consensus on these guidelines among countries rather than on variations in specific details.

RESULTS

Categorisation of studies

The studies included in this review focus on specific disease areas and include one or more interacting genes for their analysis. The effects of patients genotype on drugs efficacy or toxicity was generally based on a referenced meta-analysis or on the authors' own literature searches. In some cases the authors had previously performed an association study and based their assumptions on those findings. All studies were retrospective analyses instead of prospective

analyses, in which a clinical trial would be combined with the gathering of economic data. The general approach of selected economic analyses was always the explicit hypothesis of an alternative treatment having certain advantages, by knowing the patients genotype compared with the current treatment given the absence of such genetic information.

Although only few economic analyses have been performed in the field of pharmacogenetics and -genomics, those found cover a variety of issues. These can be divided in two principally distinct areas: pharmacokinetics, the science which studies the route of a drug substance in a patient's body, by absorption (gastro-intestinal tract, skin, etc.), distribution (tissues), metabolism (biotransformation) and excretion (via which route and how fast); and pharmacodynamics, studying the mechanisms of drug action, mainly involving drug efficacy and drug tolerance. The papers are summarized below divided according to these categories; however it should be noted that the associations between genotype and response described were those found or proposed by the authors of the analyses, not by us. The evidence for these associations can sometimes be scarce (see section Systematic review on evidence).

Pharmacokinetic effects of genotypes

Most studies in this review analysed the pharmacokinetic effects of genetic variants, or polymorphisms. The most common type of allele is referred to as the 'wild type allele', while its variants are known as 'mutant alleles'. Mutant alleles encoding for metabolic enzymes can cause structural changes in these enzymes resulting in less active enzymes or changes in gene expression potentially inflicting changes in drug metabolism. This could result in adverse effects caused by increased blood levels of the drug or less efficacy in case of prodrugs such as codeine. Another type of genetic variance is the duplication of alleles, which often results in an increase in metabolic enzymes and thereby decreased drug efficacy or increased drug efficacy in case of prodrugs. Also genetic variants of drug-transporters, such as the G-protein (e.g. in the blood-brain-barrier) can affect the availability of drugs at the site of action.

Cytochrome P450 2C9 [13,14]

The cytochrome P450 2C9 (CYP2C9) enzyme is the main metabolising enzyme of several drugs, including coumarin derivates. Coumarins, such as acenocoumarol and warfarin, are anticoagulants used for the treatment and prevention of thromboembolic events. Patients homozygous for CYP2C9*2 or CYP2C9*3 alleles are slow metabolisers for these drugs. The prevalence has been mentioned at 36%,[13,14] 44% for patient with initial INR>2.5.[13] Slow metabolisation leads to accumulation of the anticoagulant, leading to an increased risk of (fatal) bleeding events. To prevent this, current treatment strategies involve individual monitoring of patients bleeding time (measured as the International Normalized Ratio, INR) and adjustment of drug dosage according to the patient's INR values. Genotyping can a priori identify patients at risk, with the advantage of lowering coumarin dosage beforehand with intensified INR monitoring.

Cytochrome P450 2C19 [15-17]

The cytochrome P450 2C19 (CYP2C19) enzyme mediates the metabolism of many drugs, including proton pump inhibitors (PPIs). Standard therapy of duodenal ulcer due to a *Helicobacter pylori* infection consists of a PPI in combination with one or several antibiotics (also known as eradication therapy). Patients homozygous for CYP2C19*2 or CYP2C19*3 alleles are slow metabolizers of PPIs; these patients have a higher probability successfully eradicating *Helicobacter pylori*. In fast metabolizers on the other hand, treatment is less effective, even potentially resulting in complications such as (re)bleeding. The prevalence of fast metabolizers used in the analyses largely depended on ethnicity, ranging from 35 to 45% for Asians and from 67 to 79% for Caucasians.[15-17] By means of genotyping, these patients can be identified before treatment initiation and be prescribed an altered PPI dosage or alternative acid suppressant treatment independent of CYP2C19 metabolism.

Cytochrome P450 2D6 [18]

The cytochrome P450 2D6 (CYP2D6) enzyme is involved in the metabolism of several drugs prescribed in psychiatry, including tricyclic antidepressants (TCA), monoamine oxidase (MAO) inhibitors, selective serotonin re-uptake inhibitors (SSRI), venlafaxine, and several antipsychotics. Four classifications are commonly applied based on the metabolizing activity of the enzyme: poor metabolizers (PM); intermediate metabolizers (IM); extensive metabolizers (EM); and ultra-rapid metabolizers (UM), the last of which is caused by duplicated alleles. The authors found that the UM group compared to the PM group was associated with a decreased risk of adverse drug events. Costs of treatment of patients in the extreme PM and UM classes were higher compared to costs of treatment in patients classified as IM and EM. Authors reported a prevalence of patients in PM and UM of 12 and 3%, respectively.[18] Either screening of enzyme activity or direct genotyping of CYP2D6 alleles can identify patients at risk for adverse events, possibly resulting in an altered dosage of the CYP2D6 mediated drug.

Thiopurine s-Methyltransferase (TPMT) [19-25]

The Thiopurine s-Methyltransferase (TPMT) enzyme mediates the hepatic metabolism of thiopurine drugs. Identification of the TPMT genotype can be used to predict differences in the activity of the TPMT enzyme, also differentiating between fast, intermediate and slow metabolizers. Thiopurine drugs, such as 6-mercaptopurine (6-MP) and its prodrug azathioprine (AZA), are immunomodulating agents used for treatment and maintenance therapy of several diseases, such as rheumatoid arthritis, systemic lupus erythematosus,[20,21] inflammatory bowel - and Crohn's disease,[19,22,24] bullous pemphigoid (a dermatological condition)[23] and acute lymphoblastic leukemia.[25] In patients with decreased TPMT activity, thiopurine drugs can accumulate in the body which can possibly lead to life threatening leucopenia. Patients with decreased TPMT activity should therefore receive a lower dosage of the thiopurine drug. Current treatment strategy, of thiopurine drugs, consists of frequent monitoring by means of a white-

blood cell count. In contrast, screening of the TPMT gene can be used to determine the optimal dosage beforehand. The prevalence of patients with decreased TPMT activity caused by gene polymorphisms was estimated at approximately 11,3% by all authors.[19-25]

Methylenetetrahydrofolate reductase (MTHFR) [26]

Methotrexate (MTX) is the most commonly prescribed antirheumatic drug for patients with rheumatoid arthritis. Polymorphisms of the Methylenetetrahydrofolate reductase (MTHFR) gene influence patients MTX levels, which can lead to various adverse drug events, possibly resulting in drug discontinuation in as much as 30% of the patients. Patients with MTHFR polymorphisms can be identified using genotyping and can subsequently be prescribed lower dosages of MTX, to lower the risk of adverse drug events. The Japanese study of Kim et al identified polymorphisms in 65,3% of the study population.[26] The authors do state that ethnic differences are considerable, and so their results are not immediately transferable to other –for example, European - settings.

Pharmacodynamic effects of genotypes

Besides influencing the activity of metabolizing enzymes, genetic polymorphisms can cause variations in receptors or the related second messenger systems, leading to pharmacodynamic changes in drug efficacy or tolerability.

Multiple genes involved in the efficacy of Clozapine [27]

Clozapine is currently third choice antipsychotic drug in the USA for treatment of schizophrenia and only prescribed if first or second choices are not tolerated or do not result in a considerable treatment success. Several neurotransmitter-receptor related genes have been found to be associated with the efficacy of Clozapine. A test based on six of these polymorphisms correctly predicted the drug response rate in 77% of all cases.[28] Genetic screening can identify patients with a high success rate of Clozapine treatment. According to Perlis et al, Clozapine should be considered as drug of first choice for these patients.[27]

Alpha-adducin [29]

Patients with the alpha-adducin gene Gly460Trp variant show an increased rate of renal tubular sodium reabsorption. Hypertensive patients with this polymorphism are at increased risk of cardiovascular events. Thiazide diuretics are often regarded drug of first choice for hypertensive patients, although many patients are treated with other antihypertensive drugs. Caucasians with the alpha-adducin polymorphism not treated with diuretics show a 50% increase in risk of myocardial infarction compared to patients who do use diuretics. In particular, Meckley et al estimated a prevalence of patients with the genetic variant at 37%.[29] Genotyping can identify these patients, in whom subsequently treatment switching to or initiation of thiazide diuretics may be encouraged.

Angiotensin-Converting Enzyme Insertion Deletion (ACE I/D) [30,31]

Two authors performed economic analyses on genotyping of the Angiotensin-Converting Enzyme (ACE) gene. Maitland van der Zee et al analysed the effect of the ACE gene insertion deletion polymorphism (ACE I/D) on the efficacy of HMG-CoA reductase inhibitors (statins). These drugs are commonly prescribed for the prevention of coronary events in patients with hypercholesterolemia. According to Maitland van der Zee et al, statins are not effective in lowering the risk of coronary events in patients with the ACE DD genotype, but are effective in patients with the ACE ID or ACE II genotype.[31] Genetic screening for the ACE I/D polymorphism can identify DD carrier patients who can subsequently be prescribed alternative cholesterol-lowering drugs, such as fibrates, nicotinic acid derivates or bile acid sequestrants. The economic analysis of Costa-Scharplatz et al focused on ACE inhibitor treatment efficacy in patients with chronic nephropathies. Results from their meta-analysis,[32,33] indicated that patients with the ACE DD or ACE ID genotype are expected to sufficiently respond to ACE inhibitor treatment, while patients with ACE II genotype will not respond sufficiently.[30] The authors therefore suggest a treatment strategy including identification of patients with the ACE II genotype followed by prescribing Angiotensin II inhibitor treatment, for which no association between ACE I/D genotype and drug efficacy was assumed. The percentage of patients with the ACE DD genotype used by Maitland van der zee was 27%, the percentage of patients with the ACE II genotype used by Costa-Scharplatz was 18%.[30,31]

Human Leukocyte Antigen (HLA) [11]

The antiviral agent Abacavir is often used in combination with other antiviral drugs in highly active anti-retroviral therapy (HAART) of patients infected with Human Immunodeficiency Virus-1 (HIV-1). Patients with the Human Leukocyte Antigen (HLA) B*5701 polymorphism have an increased risk of developing hypersensitivity reaction to Abacavir, which can lead to life threatening hypotension. Genotyping gives the opportunity to identify patients at risk of developing hypersensitivity. These patients can be prescribed other antiviral drugs. Hughes et al did not specifically state a percentage of patients with the polymorphism, but this could be calculated from the paper at approximately 16%.[11]

Mitochondrial 12S rRNA gene [34]

Aminoglycosides are antibiotics effective against Gram-negative bacteria which are often used to treat respiratory infections. These drugs, however, may cause severe renal as well as ototoxic side-effects. Several polymorphisms in the mitochondrial 12S rRNA gene were shown to be associated with aminoglycoside induced hearing loss, most commonly as a result of the A1555G polymorphism. Genotyping may help identify patients at risk for hearing loss even though aminoglycoside antibiotic levels are well within the therapeutic range. These patients can be prescribed antibiotics of the quinolone type, which are not influenced by this polymorphism.

The study of Veenstra et al specifically focused on patient with cystic fibrosis as these have a high risk of Gram-negative bacterial infections. The prevalence of the A1555G variation used for base case analysis was 0.086%.[34]

Outcomes

As shown in Table 1, most studies report that genetic screening is cost effective; in many cases even dominating the non-screening comparator strategy. This can be explained by the fact that patient groups under consideration have a high risk of a severe outcome, such as leucopenia, or the treatment itself involves high costs, such as HIV-treatment. In those cases, a screening strategy obviously poses an attractive option with high probabilities of being cost effective or cost saving, as screening costs are relatively low and only one-off. Only three out of 20 studies concluded a potentially less favourable outcome. The study by Perlis et al on clozapine efficacy in psychiatric patients, found an ICER of USD 47 705 (€36 186) per QALY gained.[27] However, they stated that they used conservative estimates for all relevant parameters, all biasing the end result in favour of the non-screening strategy. Also, Perlis et al mention that the results are still comparable to the cost-effectiveness of many non-genetic medical interventions. Results from the study by Hughes et al on HAART treatment efficacy in patients with HIV vary from dominance to €22 811 per hypersensitivity reaction avoided.[11] This broad range in cost-effectiveness was caused by the exact HAART therapy considered as comparator, as the costs of these therapies vary enormously. A similar broad range was found by Veenstra et al in their evaluation of screening for aminoglycoside-induced hearing loss, stating that the economic impact is largely dependent on uncertain parameters.[34] The authors however, also state that genetic screening is not likely to be cost-effective, largely due to low mutant-allele frequency (estimated at a mere 50 cystic fibrosis patients with the polymorphism *worldwide*) and low test specificity (leading to many false positively tested patients to be prescribed drugs of second choice). Overall, it can be said that most genetic and genomic screening strategies reported by the studies included in this review, have at least the potential of being cost-effective.

Type of economic evaluation

In general, we can distinguish between four types of pharmacoeconomic analyses: cost-minimization analysis (CMA), in which alternative therapies are compared only in terms of costs; cost-benefit analysis (CBA), which also incorporate health effects but these are expressed in monetary units; cost-effectiveness analysis (CEA), describing the health effects in non-monetary terms such as life years gained; and cost-utility analysis (CUA), a generalized type of CEA based on health utility states.[35] Three studies carried out a CMA, it should be noted that these were among the earliest published studies. As genetic screening is performed to enhance therapy efficacy or reduce adverse events, the effects of the screening and non-screening strategies cannot be expected to be the same, which is a requirement for performing CMAs. This explains

the scarceness of CMAs in the field of genetic screening programs, only to be performed as preliminary or pilot analyses. Even for these goals, their use is limited if not inadequate; obviously they are insufficient for ultimate analyses and judgement on economic attractiveness. No studies performed a CBA. Although CBAs have the advantage that results can be compared with CBAs outside of the health-care system, this method is not often used because of the obvious difficulty of translating health effects into monetary terms.

The CEA was the most common used type of economic evaluation (13 out of 20 studies). The types of health effects included for these CEAs differ, as can be seen in Table 1. As a consequence, CEAs for different interventions can often not be compared. In contrast, the outcome of Life Years Gained (LYGs), is suitable for comparison over a wide range of health-care interventions. However, only three studies used this type of health effect, as LYGs cannot always be determined, in particular when the intervention primarily focuses on increasing quality of life rather than prolonging life. Five studies performed a CUA by using Quality Adjusted Life Years (QALYs) as utility/effect measure, a type of economic analysis which can also be used for comparison among different interventions. It should be noted that the "willingness-to-pay" threshold for a QALY varies among countries, in time and can even be disease specific.[36] An explanation for the low number of studies performing a CUA can be found in the difficulties associated with the allocation of valid QALY states to different health conditions.

Adherence to guidelines

Sensitivity Analysis

Economic evaluations, in particular those based on genetic screening, often examine uncommon and/or not (yet) implemented therapeutic strategies with potentially scarce evidence. Therefore, evidence-based data on parameters such as drug efficacy or test sensitivity are often lacking. Sensitivity analyses can be performed to analyse the influence of uncertain factors. Additionally, extensive sensitivity analysis may include a few alternative assumptions on which evidence comes after publication of the model, thus extending the 'expiry date' of the particular published analysis.

All guidelines promote the use of extensive sensitivity analyses, stating that all uncertain parameters should be included. Additionally, most guidelines recommend to perform both univariate (one-way analysis) as well as multivariate (two- or multi-way analysis) analyses. Parameters included in a multivariate analysis should be carefully selected to avoid interpretation problems, as the number of possible variations increases with the number of parameters added.[37] A practical way to overcome this problem is the use of scenarios, in which several factors are set to reflect a specific situation, such as the best-case and worst-case scenarios. Some guidelines recommend the use of probabilistic sensitivity analysis. This type of sensitivity analysis is characterized by the use of probability distributions for the included parameters, as alternative for a predetermined uncertainty range.[37,38] Probabilistic sensitivity analysis is generally considered to be superior over

other types of sensitivity analyses for uncertainty of estimated parameters. Hughes et al, Costa-Scharplatz et al and Meckley et al performed such full probabilistic sensitivity analyses.[11,29,30] Five of the 20 studies included in this review did not include a sensitivity analysis (table 2). Among those were all three studies performing a CMA.[15,18,23] The remaining two studies by Winter et al and Furuta et al, did calculate 95% confidence intervals around the point estimate of the economic outcome based on original patient data.[16,24]

Exact parameters included in the sensitivity analyses vary among the studies that included sensitivity analyses (see table 2). Parameters included for a sensitivity analysis, with major impact on the cost-effectiveness outcome, comprise cost and health effect parameters of treatment of the disease or adverse event under consideration. The cost of the genetic screening test is another important parameter, although often neglected. Variability in the price of a genetic test depends on the commercial availability and whether the test will be performed rarely or on a regular basis. Also, the genotype distribution was often found to have a strong influence on the cost-effectiveness outcome, however also this parameter was often neglected in sensitivity analyses performed within studies included in this review. Specific attention is required for genotype distributions as this will directly influence the number of patients that potentially benefit from the genetic screening procedure. In an author reply to the study of Hughes et al (Abacavir hypersensitivity) it was mentioned that HLA-B*5701 prevalence differs considerably among different demographic groups, witch complicates extrapolation of results based on Caucasians only.[39] Inclusion of genotype distribution in sensitivity analyses allows better extrapolation of results to other populations and especially different ethnicities. Furthermore, information on properties (sensitivity and specificity) of the genetic screening tests resulted to be highly important. This aspect is discussed in more detail below.

Considering the influential parameters mentioned above, a hypothetical cost-effective screening strategy can be defined as follows: (i) the test is utilized in a health-care setting involving high treatment costs and/or severe adverse events; (ii) said test is relatively cheap; (iii) a high percentage of people are carrier of the potentially deleterious polymorphism; and (iv) test characteristics on specificity and sensitivity are excellent.

Sensitivity and specificity of the genetic test

Genetic screening is performed using a genetic test, often based on polymerase chain reaction (PCR). These tests are rapid, widely available, not influenced by exogenous factors and have relatively low costs. The sensitivity and specificity of a test determines its predictive value and thereby largely its economic value. Sensitivity reflects the percentage of positive cases correctly identified by the test. Specificity measures the same for negative test results (percentage of negative test results in a negative population). Although most guidelines do not explicitly state that test parameters should be considered in economic analyses, this could be considered a logical component of the systematic review for evidence and should also be included in a

sensitivity analysis. Unfortunately, test characteristic were not often included in sensitivity analyses, as table 2 shows.

Several PCR tests for TPMT genotyping were developed and validated. According to a study by Yates et al, sensitivity and specificity was found to be 96% and 100%, respectively.[40] The study of Roberts et al estimated the sensitivity of a PCR test for TPMT genotyping at 90%.[41] These figures were used by most authors on TPMT activity.[20-22,24,25] Hughes et al (Abacavir hypersensitivity), Perlis et al (Clozapine response), and Veenstra et al (Aminoglycosides tolerability) also included test parameters, derived from the development process.[11,27,34] However, several studies assumed a sensitivity and specificity of 100% for the analysed genetic tests, without giving exact references.[13-19,23,31] In some cases a rationale exists for omitting information on specificity and sensitivity. For example, Meckley et al used probability data of a patient screening positive for the polymorphism based on literature references, therefore screening test characteristics were not specifically included in their analysis.[29] Kim et al stated that other studies indicated that the test used was nearly 100% accurate.[26] Also on this subject matter, care should be taken to provide good evidence-based data on test characteristics. As an example, Perlis et al [27] performed an economic analysis using sensitivity data on a genetic test developed by Arranz et al.[28] This test correctly predicted response rate in 77% of all cases. However, these results have been disputed by later publications by Arranz et al.[42]

Time-horizon and discounting

All guidelines for pharmacoeconomic evaluations state that the length of analysis should be long enough to capture all the differential effects of compared interventions (screening versus non-screening strategy). Most studies that analysed pharmacokinetic effects of genetic variations, apply a time-horizon of 12 months (see table 3). A lifelong model is generally not needed in these cases as pharmacokinetic effects (e.g. adverse events) often appear relatively soon after initiation of the treatment. In contrast, studies analysing pharmacodynamic effects often adopted a lifelong time-horizon, because the effects are generally on long-term outcomes (e.g. all-cause mortality). Studies with a time-horizon of over a year should apply discounting to correct for the time prevalence people experience in relation to gains and losses.[38] Different country specific guidelines are not unanimous on the percentages that should be applied for discounting. For example, guidelines from Canada, Spain, and New Zealand recommend equal discounting rates for costs and effects at 3%, 6%, and 10%, respectively, whereas the updated Dutch guidelines suggest differential discounting at 4% for costs and 1.5% for health (previously 4% for both) (accessible via http://www.ispor.org/). Next to country specific guidelines, several influential standard works with other recommendations for discount rates exist (e.g. Gold et al [43]). All studies with a time-horizon of over one year discounted costs and health effects, as can be seen in table 3. Most used a base case value of 3% for both costs and effects, referring to Gold et al.[43] As shown in table 3, all these studies used multiple discount rates as part of their sensitivity

analysis, following guideline recommendations. Also, the type of economic analysis appeared to be related to the time-horizon of the study. Most studies conducting a CUA or a CEA with LYG as effect measure generally adopted a lifelong model. Other studies conducted a CEA based on other clinical outcomes using a 12 month time-horizon. The three CMA studies included in this review did not explicitly apply a timeframe.

Study perspective

Most guidelines recommend to adopt the societal perspective, some however state that the preferred perspective depends on the nature and aim of the study. Adopting a societal perspective is often not possible due to the absence of valid estimates of indirect costs. It can be argued that for a first economic interpretation of genetic screening interventions a societal perspective is not necessarily recommended, due to uncertainties regarding possible practical implications. However, for full understanding of the economic impact, indirect costs are ideally considered before final decisions on implementations of screening strategies are made.

Except for one study, all studies included for this review adopted a third-party perspective for their economic analysis. Four studies mentioned that the societal or payers perspective was applied, but this seems not the case or does not become clear from the paper in which only direct medical costs were mentioned.[21,22,27,29] Only the most recent study of Veenstra et al, did adopt a societal perspective for their analysis.[34]

Systematic review for evidence

The relation between a patients genotype and treatment response is part of the so-called genotype-phenotype association. A persons' genotype is fixed and can easily be measured with good reliability, whereas a persons' phenotype not only depends on the genotype but also environmental factors, which can change over time with potential confounding of a clear association. Even when environmental factors are not involved, a sound systematic review for evidence for the association has to be provided. An important part of economic analyses is to model the influence of uncertainty on the cost-effectiveness of treatment strategies and requires therefore evidence-based data on these strategies. A systematic review on such evidence is recommended by all guidelines, some explicitly state that meta-analysis should be performed. However, not all associations from the studies included in this review, can be considered evidence-based in this context.

Some studies do not perform a meta-analysis but merely use small individual studies to base their assumptions on. For example, Marra et al based their assumptions on one small (n=33) clinical study.[20] On the other hand, Winter et al, Priest et al and Akker-van der Marle et al (all on TPMT screening) used data on the association between genotype and clinical outcomes based on several literature findings.[22,24,25] In particular, given the fast developments in genetic research, further studies continue to shed new light on associations between genotypes

and clinical outcomes. For example, You et al in 2004 used data on a presumed association between CYP2C9 polymorphisms and thromboembolic events, whereas Schalekamp et al did not find an association in 2006.[13,14] In fact, we often encountered that economic analyses were based on assumptions differing from or even contradicting other literature studies. The decision model found in the study of Costa-Scharplatz et al was based on the assumption that ACE inhibitor treatment will not be effective in patients with ACE II genotype.[30,31] However, several studies have published no such association. The study population in the analysis of Costa-Scharplatz et al consisted of non-diabetic patients with chronic nephropathy but the authors implied a generalized association for both diabetic and non-diabetic patients; while the assumed genotype-phenotype association is possibly not valid or even opposite for diabetic nephropathy patients.[44] The study by Meckley et al resulted in an authors' reply by Gerhard et al, stressing that the assumed association was not found in other studies and suggesting to be reserved when evaluating economic consequences of such unreplicated associations.[45] Another important issue in this context is the percentage of individuals with the specific polymorphisms under consideration. For example, Veenstra et al base their assumptions on the prevalence of A1555G polymorphism on a study by Tang et al.[46] Within this study 1.161 individuals were screened and one person was found to be carrier of the mutation. Tang et al clearly stated the need for additional large-population studies to more accurately determine the prevalence of this polymorphism.

Table 1: Primary author, year of publication, gene targeted, drug involved, type of economic evaluation, nominator (in original currency and recalculated €'s) and denominator (health effect)

Primary author, year	Gene	Drug	Type	Nominator [e]	Denominator
You, 2004 [14]	CYP 2C9	Coumarin	CEA	USD 5 778 (€7 326)	Bleeding event averted
Schalekamp, 2006 [13]	CYP 2C9	Coumarin	CEA	€4 233 / €2 210 [a]	Bleeding event averted
Desta, 2002 [15]	CYP 2C19	PPI	CMA	Favourable [b]	-
Lehman, 2003 [17]	CYP 2C19	PPI	CEA	Dominant	Ulcer prevented
Furuta, 2007 [16]	CYP 2C19	PPI	CEA	Dominant	Successful eradication
Chou, 2000 [18]	CYP 2D6	Antipsychotics	CMA	- **	-
Marra, 2002 [20]	TPMT	AZA	CEA	Dominant	Adverse event avoided
Oh, 2003 [21]	TPMT	AZA	CEA	Dominant	Serious adverse event
Winter, 2004 [24]	TPMT	AZA	CEA	£487 / £951 [c]	LYG
Dubinsky, 2005 [19]	TPMT	AZA	CEA	Dominant	Time to response
Priest, 2006 [22]	TPMT	AZA	CUA	Dominant	QALY gained
Tavadia, 2000 [23]	TPMT	AZA	CMA	Favourable [b]	-
Akker-Marle, 2006 [25]	TPMT	6-MP	CEA	€4 800	LYG
Perlis, 2005 [27]	Multiple	Clozapine	CUA	USD 47 705 (€36 186)	QALY gained
Meckley, 2006 [29]	α-adducin	Thiazide	CUA	Dominant	QALY gained
Maitland-Zee, 2004 [31]	ACE I/D	Statins	CEA/CUA	Dominant	LYG and QALY gained
Costa-Scharplatz, 2007 [30]	ACE I/D	ACEi	CEA	Dominant	Life Years free of ESRD
Kim, 2006 [26]	MTHFR	MTX	CEA	Dominant	Dropping out
Hughes, 2004 [11]	HLA	Abacavir	CEA	Dominant to €22 811 [d]	Hypersensitivity avoided
Veenstra, 2007 [34]	A1555G	Aminoglycosides	CUA	USD 79.343 (€59.759)	QALY gained

CYP: Cytochrome P450 enzyme; TPMT: Thiopurine s-Methyltransferase; ACE I/D: Angiotensin-Converting Enzyme Insertion Deletion; MTHFR: Methylenetetrahydrofolate reductase; HLA: Human Leukocyte Antigen; A1555G: mitochondrial 12S rRNA gene variation A1555G; PPI: proton pump inhibitors; AZA: Azathioprine; 6-MP: 6-mercaptopurine; ACEi: ACE inhibitors; MTX: Methotrexate; ESRD: End Stage Renal Disease; CEA: cost-effectiveness analysis; CMA: cost-minimization analysis; CUA: cost-utility analysis; QALY: Quality Adjusted Life Year; LYG: Life Year Gained

[a] Schalekamp et al analysed two strategies, genotyping all patients and genotyping patients with initial INR >2.5 only, respectively.[13]

[b] In CMAs no ICERs of ICURs are calculated. Desta et al and Tavadia et al calculated lower total costs for screening than for not screening.[15,23]

[c] Winter et al analysed two patient cohorts, consisting of 30 year old patients and 60 year old patients, respectively.[24]

[d] Hughes et al found that cost-effectiveness strongly depended on the choice of the specific HAART treatment.[11]

[e] All costs are were recalculated to Euros for easy comparison, using exchange rates from the year of publication of the study, using data from the European Central Bank, accessible via http://www.ecb.int/.

Table 2: Factors included in sensitivity analysis and type of sensitivity analysis performed

Main author, year	Factors included in sensitivity Analysis					Type of SA
	Treatment cost	Screening costs	Health effects	Genotype prevalence	Test parameters [a]	
You, 2004 [14]	+	+	+	+	-	Multi
Schalekamp, 2006 [13]	+	+	+	+	-	Multi
Desta, 2002 [15]	not performed					
Lehman, 2003 [17]	-	-	+	+	-	Uni
Furuta, 2007 [16]	not performed [b]					
Chou, 2000 [18]	not performed					
Marra, 2002 [20]	+	-	+	-	+	Uni
Oh, 2003 [21]	+	+	+	+	-	Uni
Winter, 2004 [24]	not performed [b]					
Dubinsky, 2005 [19]	+	-	+	-	-	Multi
Priest, 2006 [22]	+	-	+	-	-	Uni
Tavadia, 2000 [23]	not performed					
Akker-Marle, 2006 [25]	+	+	+	-	+	Multi
Perlis, 2005 [27]	+	+	+	-	+	Uni
Meckley, 2006 [29]	+	+	+	+	-	Multi / Prob
Maitland-Zee, 2004 [31]	-	+	+	-	-	Uni
Costa-Scharplatz, 2007 [30]	+	+	+	+	-	Prob
Kim, 2006 [26]	+	+	+	+	-	Uni
Hughes, 2004 [11]	+	-	+	+	+	Uni / Prob
Veenstra, 2007 [34]	+	+	+	+	+	Uni / Multi

Health effects: the health effects influenced by the screening strategy; SA: sensitivity analysis; Uni: Univariate analysis, Multi: Multivariate analysis, Prob: probabilistic sensitivity analysis

[a] Test parameters were defined as sensitivity and specificity of the genetic screening test.

[b] Winter et al and Futura et al did calculate 95% confidence intervals for cost-effectiveness based on original patient data.[16,24]

Table 3: Time-horizon and discounting percentages applied in the studies reviewed

Main author, year	Time-horizon	Discounting
You, 2004 [14]	12 months	-
Schalekamp, 2006 [13]	12 months	-
Desta, 2002 [15]	-	-
Lehman, 2003 [17]	12 months	-
Furuta, 2007 [16]	<1 month	-
Chou, 2000 [18]	12 months	-
Marra, 2002 [20]	6 months	-
Oh, 2003 [21]	12 months	-
Winter, 2004 [24]	12 months	0%, 1.5%
Dubinsky, 2005 [19]	12 months	-
Priest, 2006 [22]	12 months	-
Tavadia, 2000 [23]	-	-
Akker-Marle, 2006 [25]	Life	0%, 3%
Perlis, 2005 [27]	Life	0%, 3%, 5%
Meckley, 2006 [29]	Life	0%, 3%, 5%
Maitland-Zee, 2004 [31]	Life	0%, 5%
Costa-Scharplatz, 2007 [30]	3 years	0%, 4%
Kim, 2006 [26]	12 months	-
Hughes, 2004 [11]	6 months	-
Veenstra, 2007 [34]	Life	0%, 3%, 5%

Checklist

Based on our systematic review and pharmacoeconomic guidelines, we developed several points of importance for performing pharmacoeconomic analyses on pharmacogenetic and -genomic interventions. We feel that these recommendations should apply regardless of country of origin and should therefore all be considered carefully (see checklist in box 1).

1) Disease or adverse event under study

Generally, a disease that poses a high risk of severe adverse events or presents high treatment costs has a high probability to result in favourable cost-effectiveness outcomes for genetic screening programs. The economic impact and severity of the disease and/or adverse events studied should therefore be assessed in detail.

2) Association between genotype and phenotype

The association between genotype and phenotype must be determined using peer-reviewed studies; studies with large cohorts and meta-analyses are preferred. Studies with new insights or

conflicting results should also be presented. Though case-control studies are suitable for 'simple' gene-disease associations, a better ascertainment can be achieved with cohort studies or randomised clinical trials (RCTs), especially when environmental factors are likely to be involved. Special care should be taken in respect to allele frequencies. A high percentage of people with the genetic polymorphism under consideration indicate a high probability of a cost-effective screening test. These percentages however often differ between different (ethnic) populations.

3) Selection of treatment modalities

Based on a systematic review for evidence, a treatment modality can be developed based on certain advantages provided by knowing the patients genotype and its effects on and advantages over the current treatment strategies. This genetic treatment strategy can then be compared with the current practice treatment strategy (often in the form of an analytical decision model).

4) Type of economic analysis

The type of analysis should be chosen based on the aim of the study and available data. A cost-utility analysis is preferred, but sometimes not practicable. Formal cost-effectiveness analyses are a good second option, especially when using LYG as outcome measurement.

5) Study perspective

Costs of the screening test, medication and of all relevant events, such as adverse drug reactions, should be carefully assessed. A third-party payer perspective is sufficient, as a societal perspective may provide difficulties in the field of pharmacogenetics and pharmacogenomics. However, if possible, a societal perspective should be ideally used.

6) Time-horizon and discounting

The time-horizon of an analysis should be sufficient in capturing all the differential costs and effects between the screening and non-screening strategy. For studies analysing pharmacokinetic effects of certain polymorphisms one year will often be sufficient. For analysing pharmacodynamic effects, or when LYG or QALYs gained are the outcome measurement, a lifetime model would be favoured. Costs and health effects should be discounted with time-horizons exceeding one year. Discounting rates used in the base-case analysis should be based on country specific guidelines or recommendations in standard works. Different discount rates should be included in a formal sensitivity analysis.

7) Sensitivity analysis

A sensitivity analysis should always be performed. Parameters to be included are dependent on the aim of the study, but the following should always be considered: treatment costs, screening costs, health effects influenced by the screening strategy and the genotype distribution among the patient population. Additionally, test characteristics (sensitivity and specificity) should also be included in the sensitivity analysis.

Box 1: Points of importance for performing pharmacoeconomic analysis on pharmacogenetic and -genomic interventions

Points of importance	Comments
1: disease under study	Determine relevance and economic impact of the disease and/or adverse events under study.
2: association genotype - phenotype	Use peer-reviewed studies, preferably meta-analysis and large cohort studies; mention studies with providing new insights or conflicting results; take note of allele frequencies; and test characteristics on sensitivity and specificity.
3: treatment modalities	Assess the current treatment(s), relevant adverse events and drug efficacy; and determine an alternative treatment based on the advantage of knowing a patients genotype in advance.
4: type of economic analysis	Preferably perform a cost-utility analysis or cost-effectiveness analysis.
5: study perspective	A societal perspectives is preferred.
6: time-horizon and discounting	The time-horizon should be long enough to include all costs and effects, discounting rates should be guideline-based and be included in the sensitivity analysis.
7: sensitivity analysis	Include uncertainty around variables included, especially on treatment costs and effects, screening costs, genotype distribution and test parameters on sensitivity and specificity.

DISCUSSION

This paper reviewed economic analyses in the field of pharmacogenetics and –genomics from the year 2000 up until 2007. Both are fast growing disciplines with numerous tests being developed, expecting to result in an increasing need for sound economic analyses in the future. This expectation is supported by the fact that within the studies (searched from the year 2000 onwards), 14 out of 20 studies were performed in 2004 or later. Most analyses found genetic screening to be cost-effective, often even dominating existing non-screening strategies.

Studies included in this review were analysed on specific guidelines for: (i) performing sensitivity analyses, including information on sensitivity and specificity of the screening test; (ii) time-horizon and discounting; (iii) the perspective applied; and (iv) a systematic review of all existing evidence for the genotype-phenotype association and the rationale for a pharmacogenetic-based intervention strategy. These guidelines were selected as they are rather universal among the different countries although details may differ; sensitivity analysis is commonly used to deal with several uncertainties and thus 'prolongs the expiry date' of an individual analysis; results are generally highly dependent on the time-horizon chosen; and discount rate, study perspective and a systematic review for evidence are clear quality aspects for conducting economic studies from pharmacoeconomic guidelines. Our results underpin the importance of these elements in pharmacogenetics and pharmacogenomics. From sensitivity analyses it was shown that the following parameters influenced the cost-effectiveness outcome most: (i) costs and health effects of the treatment or adverse event in question; (ii) cost of the genetic screening test; (iii) genotype distribution; and (iv) test characteristics on specificity and sensitivity.

The level of consistency among the selected economic analyses was generally poor. Such an opinion was also expressed by Phillips and van Bebber in 2004 based on their literature review.[7] Though there have been several publications on standardised methods of how to conduct an economic analysis, we found studies lacking adherence to specific aspects. Among these were adequate mentioning of the study perspective (e.g. mentioning a societal perspective when a third-party payer perspective was actually adopted); the discounting rates applied; and the large variability in parameters included for the sensitivity analyses. We note here that country specific guidelines are not always consistent and therefore partly causing these inconsistencies found. While standard works, such as published by Gold et al,[43] may succeed in improving the level of consistency among analyses, it should also be noted that differences among country specific guidelines often exist due to various reasons including different health-care systems. These differences between countries limit the extrapolating of study results to other countries or health-care systems.

Pharmacogenetic tests are in many ways similar to phenotype-based tests. However, several factors are unique from a cost-effectiveness perspective, most notably considering the fact that a persons' genotype does not always accurately predicts his or hers phenotype, or actual response to the drug treatment. Firstly, providing good estimates on test characteristics on sensitivity and specificity therefore is important, yet however often ignored. Another important limitation found relates to the failure to provide a sufficiently evidence based rationale for the association between genotype and drug effectiveness or toxicity. This correspondingly limits the interpretation of the cost-effectiveness outcomes. Associations should be determined using peer-reviewed studies and data from studies with large cohorts, and meta-analyses are preferred. It is also needed to present the whole scope of results including studies which provide new insights or conflicting results.

Emphases on both the quality of the economic analyses as well as on the technologies of the pharmacogenetic tests are important to insure sound economic evaluations in this field. However, the judgment hereof depends largely on the specific stage in the development process. The requirements for qualitative economic analyses in this field will grow with growing number of evidence-based genetic screening strategies.

Future expectations

Gene association data used for economic analyses considering for this review were generally determined using case-control studies. This type of study design is relatively cheap and effective at ascertaining the direct association between genes and disease.[47] However, genetic studies have shown that gene associations often involve environmental factors in pharmacogenetics and – genomics.[48] Especially when environmental factors are thought to be involved, cohort studies are preferred over case-control studies.[47] Furthermore, to reliably ascertain the effectiveness of a screening method, randomised clinical trials (RCTs) are ideal.[49] Only one study

included in this review was found to use clinical data from a RCT.[16] Furthermore, no RCT on genetic screening strategies has yet been performed with attached pharmacoeconomic goals. These type of prospective studies eliminate many uncertain factors due to randomisation and direct costs allocation and are therefore far more robust than other study designs.[50]

There are notable niches in the fields in which economic analyses have been performed. Not meant to be comprehensive, we provide some examples for which no (full) cost-effectiveness or cost-utility analyses have yet been performed. These include genetic screening of CYP2D6 genotype, the enzyme is involved in the metabolism of many antidepressant and antipsychotic drugs,[18,51] as well as tamoxifen metabolism in breast cancer.[52] Genetic screening of the CYP2C9 genotype in patients with diabetes type II prior to treatment with sulfonylurea seems promising as well,[53,54] no economic studies have yet been performed however. Another important example relates to dihydropyrimidine dehydrogenase (DPB) polymorphisms, that are associated with toxicity for 5-fluorouracil (5-FU) chemotherapy.[55] Other fields of interest were pointed out in a review by Dervieux and Bala:[5] epidermal growth factor receptor mutations to predict response to gefitinib treatment;[56] and vitamin K epoxide reductase genotype to predict response to warfarin treatment,[57] which can be extended to acenocoumarol;[58,59] and phenprocoumon.[60] A recent publication of Ingelman-Sundberg lists seven potentially useful pharmacogenetic screening interventions.[61]

CONCLUSION

Economic evaluations on pharmacogenetic and -genomic treatment strategies are presenting important opportunities for scientific research. In these fields, cost-effectiveness information may relevantly underpin rational decision making from an economic point of view. Even though only few pharmacoeconomic analyses have been performed so far, most screening strategies seem to be both innovative and cost-effective. Future analyses, however should comprise correct methods on good pharmacoeconomic practice for conducting economic analyses. These include adhering to guidelines, such as performing extensive sensitivity analyses. Most importantly, economic analyses within pharmacogenetics and –genomics should be based on evidence-based data. Future adherence to these recommendations and guidelines will results in sound cost-effectiveness analyses for promising pharmacogenetic and pharmacogenomic interventions.

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Chapter 3

Cost-effectiveness of ACE inhibitor therapy to prevent dialysis in nondiabetic nephropathy: influence of the ACE insertion/deletion polymorphism

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ABSTRACT

Introduction: End-stage renal disease is associated with high health-care costs and low quality of life compared with Chronic Kidney Disease. The renoprotective effectiveness of angiotensin-converting enzyme inhibitors (ACEi) is largely determined by the ACE insertion/deletion (I/D) polymorphism. We determined the cost-effectiveness of ACEi therapy in nondiabetic nephropathy for the ACE II/ID and for the ACE DD genotype separately. Furthermore, we considered a selective screen-and-treat strategy in which patients are prescribed alternative, more effective, therapy based on their ACE (I/D) polymorphism.

Methods: Time-dependent Markov models were constructed; cohorts of 1000 patients were followed for 10 years. Data were mainly gathered from the Ramipril Efficacy In Nephropathy trial. Both univariate and probabilistic sensitivity analyses were performed.

Results: ACEi therapy dominated placebo in both the ACE II/ID group (€15 826, and 0.091 quality-adjusted life years gained per patient) and the ACE DD group (€105 104 and 0.553 quality-adjusted life years gained). Sensitivity analyses showed 30.2% probability of ACEi being not cost-effective in the ACE II/ID group, against an almost 100% probability of cost-effectiveness in the ACE DD group. A selective screen-and-treat strategy should incorporate an alternative therapy for patients with the ACE II/ID genotype with an at least 9.1% increase in survival time compared with ACEi therapy to be cost-effective. Sensitivity analyses show that higher effectiveness and lower costs of the alternative therapy improve the cost-effectiveness of a screening strategy.

Conclusions: ACEi therapy is a cost-saving treatment compared with placebo in nondiabetic nephropathy, irrespectively of ACE (I/D) genotype. However, ACEi therapy saved more costs and more health gains were achieved in the ACE DD genotype than in the ACE II/ID genotype. An alternative treatment featuring a modest increase in effectiveness compared with ACEi therapy for patients with the ACE II/ID genotype can be incorporated in a cost-effective or even cost-saving screen-and-treat strategy.

INTRODUCTION

Chronic Kidney Disease (CKD) is characterized by a decline in renal function, which may ultimately lead to End Stage Renal Disease (ESRD). Diabetes Mellitus (DM) is one of the leading causes of CKD and subsequent ESRD. The European Renal Association - European Dialysis and Transplant Association reported that in Europe, prevalence of ESRD caused by DM type 1 or DM type 2 rose from 51.5 to 94.8 per million between 1992 and 2000.[1] The prevalence of ESRD of nondiabetic origin rose from 455.8 to 607.2 per million in the same time period.[1] In the Netherlands 3 095 patients suffered from ESRD of nondiabetic origin in 2008.[2]

Medical treatment modalities for ESRD patients include haemodialysis, peritoneal dialysis and renal transplantation; with haemodialysis being the most and renal transplantation the least common modality.[2] Several studies have assessed the quality of life (QoL) of ESRD patients, invariably showing a considerably lower QoL in ESRD patients compared with CKD patients.[3] Costs of ESRD treatment modalities are high, with a share of the national expenditures in European countries ranging from 0.7% in the UK to 1.8% in Belgium (1.5% in France, 1.6% in Italy).[4] Therefore, to delay or prevent the onset of ESRD is an important clinical goal.

ACEi efficacy and influence of the ACE (I/D) polymorphism

The renoprotective efficacy of angiotensin-converting enzyme inhibitors (ACEi) is undisputed. ACEi have been shown to delay the onset of ESRD in diabetic as well as nondiabetic nephropathy.[5,6] However, individual differences in therapy response are large.[7] An important factor influencing ACEi efficacy is a polymorphism located in the ACE gene. This polymorphism was first described by Rigat *et al* in 1990, and is based on the presence (insertion, I) or absence (deletion, D) of a 287 base pair element in intron 16 of the ACE gene.[8] A recent review presented an overview of the main studies evaluating the relationship between the ACE genotype and response to ACEi in nondiabetic renal disease.[9] The Ramipril Efficacy In Nephropathy (REIN) trial was the largest trial in terms of patient numbers and duration, and crucially was the only study that has used a hard endpoint - namely ESRD.[5] Patients with the ACE DD genotype showed increased susceptibility for ACEi therapy.[10,11] The finding that the ACE (I/D) polymorphism influences treatment efficacy in nondiabetic nephropathy has boosted research efforts for a treatment with increased effectiveness for patients with the ACE II or ID genotype. Such a treatment, incorporated in a selective screen-and-treat strategy, would have a high probability of being cost-effective or even cost-saving, as the ACE II/ID genotype is common and the costs and disease burden associated with ESRD are high.[12,13]

Study objectives

The importance of pharmacoeconomics for decision making is increasing in all fields of healthcare, in particular regarding drug treatments. In that context it is useful to know the cost-effectiveness of ACEi therapy for the separate ACE (I/D) genotypes. Citing a checklist from our group on performing pharmacoeconomic analyses on pharmacogenetic screening

interventions, an important starting point of such analyses is a comprehensive review of the evidence for the assumed association between genotype and phenotype.[12] No selective screen-and-treat strategy in nondiabetic nephropathy based on the ACE (I/D) polymorphism existed at the time, nor were studies found with conclusive evidence for such a strategy. Therefore, our first study objective was to understand the magnitude of difference in cost-effectiveness of ACEi therapy in association with the ACE genotype. In particular, we determined the cost-effectiveness of ACEi therapy versus non-renin-angiotensin system acting antihypertensive drugs in nondiabetic nephropathy separately for those with the ACE DD genotype and those with the ACE II/ID genotype. Our second study objective was to estimate cost-effectiveness of a selective screen-and-treat strategy involving an alternative treatment modality. By employing a threshold analysis, we determined the increase in effectiveness an alternative treatment would require compared with the existing ACEi treatment in order to justify a screen-and-treat strategy, taking into account expected additional costs and health effects. This analysis should provide valuable information to researchers considering new treatment modalities for nondiabetic nephropathy and to decision makers considering research budgets for such research.

METHODS

Data

Data from the Ramipril Efficacy In Nephropathy (REIN) trial were used for this economic analysis. The REIN trial was a randomized controlled trial in nondiabetic nephropathy aimed at determining the efficacy of the ACEi ramipril compared with placebo, at the same level of blood pressure control.[5] The REIN investigators found that the ACE (I/D) polymorphism was a strong predictor of ACEi efficacy; progression to ESRD was considerably and significantly reduced in ACEi- compared with placebo treated patients with the ACE DD genotype (36% in placebo *vs.* 14% in ACEi), while a much smaller reduction was found in those with the ACE II or ID genotype (23% in placebo *vs.* 21% in ACEi).[10,11]

Models

Time-dependent Markov models were constructed with three health-states: CKD, ESRD and death. Cohorts of 1 000 patients entered the model and were followed for a time period of 10 years, and the health states were determined on monthly cycles. Given this short cycle time in the Markov model, no half-cycle correction was used. Patients were not allowed to recover from ESRD by re-entering the CKD state.

Cost-effectiveness analysis of ACEi therapy

For the first study objective, the cost-effectiveness of ACEi therapy was determined as compared with placebo therapy. Cost-effectiveness was determined for patients with the ACE II/ID and with the ACE DD genotype separately.

Threshold analysis for the selective screen-and-treat strategy

For our second study objective, we compared a selective screen-and-treat strategy with the absence of screening. For this goal the Markov model was embedded in a decision-tree analytical framework (figure 1). In the non-screening strategy, all patients received ACEi therapy. In the screening strategy the ACE (I/D) genotype of all patients was screened; those with the ACE DD genotype received ACEi therapy while those with the ACE II/ID genotype received an alternative renoprotective treatment. Because no preferred treatment over ACEi for patients with ACE II/ID genotype currently exists, no prespecified effectiveness for this treatment was assumed. Instead, a threshold analysis was performed in which the effectiveness of the alternative treatment was varied. The increase in effectiveness of the alternative treatment compared with ACEi therapy needed for a screen-and-treat strategy to become cost-effective was determined.

Model parameters

Five parametric survival distributions (Weibull, exponential, lognormal, log logistic and Gaussian) were fitted on the REIN data by maximizing the likelihood ratio (LR); the Akaike information criterion (AIC, lower value indicates better fit) was calculated for each distribution.[14] The effectiveness of ACEi compared with placebo in our model was based on the parameters of the best fitting distribution.

Mortality rates of patients with CKD were calculated using data from the REIN and a similar trial in nondiabetic nephropathy, REIN-2.[15] In these trials nine deaths occurred over a cumulative follow-up of 1 700 patient-years, resulting in an annual mortality rate of 0.53% per year.[5,15] Patients in the REIN trial were followed until ESRD development or death;[5] therefore no data on ESRD mortality were available. Mortality rates of ESRD patients were instead derived from the Dutch End-Stage Renal Disease Registry (RENINE), using data from 1998 to 2008.[2] No differences in mortality rates between the ACE polymorphisms or treatment arms were assumed.

ACE (I/D) polymorphism prevalences were derived from several clinical trials in nondiabetic nephropathy,[10,11,16-20] all described in a systematic review by Ruggenenti, *et al*.[9] Quality of Life estimates were obtained by examining a recently published systematic review,[3] in which one study was reported with QoL estimates for CKD and ESRD based on community preferences, using the Health Utilities Index (HUI)-3.[21] In economic evaluations, community or societal preferences are preferred over patient preferences.[22]

A third-party payer perspective for the cost estimates was adopted. Costs of ESRD were based on a weighted average of Dutch cost estimates for active hemodialysis, passive hemodialysis and peritoneal dialysis, adjusted for inflation to 2008 values.[23] Costs of Ramipril treatment were based on 2008 Dutch prices,[24] including 6% value-added tax and a three-monthly pharmacists' prescription fee of €6,10. In the REIN trial, ACEi therapy was compared with placebo treatment; both treatment arms received similar additional blood pressure lowering drugs and healthcare services.[5] Associated healthcare costs were equal in both groups and therefore not included in our analysis. The costs of an alternative treatment modality in the screening strategy were

based on Dutch prices for the new renin inhibitor Aliskiren,[24] to reflect costs for a new treatment modality; these costs were varied in sensitivity analyses. The price of a genetic screening test for the ACE (I/D) polymorphism was based on polymerase chain reaction and included staff costs.[25] Costs and health effects were discounted at 3% per annum, following recommendations by Gold *et al*,[22] and Drummond *et al*.[26] An overview of all parameters is shown in table 1.

Sensitivity analysis

Univariate and probabilistic sensitivity analyses were performed for both the cost-effectiveness analysis and the threshold analysis. In the univariate sensitivity analyses, all model parameters were varied by 25% in order to determine the main cost and effect drivers in our model. Discount rates were varied based on Dutch guidelines for pharmacoeconomic research recommending differential discounting for costs and health effects, at 4% and 1.5%, respectively.[27,28] Results of the univariate sensitivity analysis are presented in a tornado diagram.[29] In the probabilistic sensitivity analyses, triangular distributions were used for all cost parameters; Beta distributions for ACE (I/D) genotype prevalence and QoL estimates; and Poisson distributions for mortality probabilities. Variation in ACEi effectiveness was captured by non-parametric bootstrapping, in which a random sample of the same size as the original data is drawn with replacement. This procedure is performed a large number of times. Bootstrapping is used to estimate the true distribution of a sample regardless of the distribution of the original data.[29] The probabilistic sensitivity analysis was run 10 000 times.

Statistics

Fitting and bootstrapping of the REIN data was performed in the statistical package R, version 2.5.1.[30] The models and sensitivity analyses were constructed in Microsoft Office Excel 2003.

Figure 1: Decision tree model and Markov model; M represent the start of the Markov model, in which patients were followed for a time period of 10 years and allowed to move from one state to another per month. ACEi: angiotensin-converting enzyme inhibitor; CKD: chronic kidney disease; ESRD: end-stage renal disease.

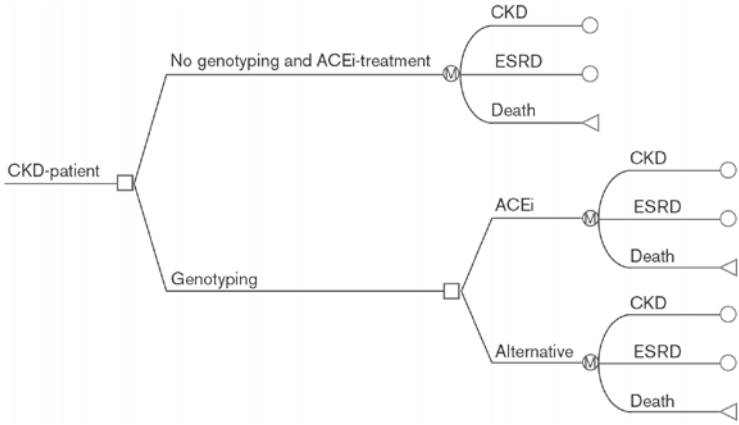

Table 1: Parameters used in the analyses

Variable	Baseline	Univariate sensitivity range	Probabilistic distribution	Reference
Genotype prevalences				
ACE DD prevalence	32.87%	24.65% - 41.08%	Beta	10,11,16-20
Costs				
Dialysis (per year)	€72 354	€54 265 - €90 443	Triangular	23
ACEi therapy (per month)	€3.03	€2.27 - €3.79	Triangular	24
Alternative therapy (per month)	€23.67	€17.75 - €29.59	Triangular	24
Genetic screening test	€50.00	€37.50 - €62.50	Triangular	25
Health effects				
QoL Chronic kidney disease	0.67	0.50 – 0.84	Beta	21
QoL Dialysis	0.54	0.41 – 0.68	Beta	21
Annual mortality rate – CKD	0.53%	0.40% - 0.66%	Poisson	5,15
Annual mortality rate – ESRD	9.95%	7.46% - 12.44%	Poisson	1
ACEi effectiveness in ACE II / ID (days)[a]	15.3	11.5 – 19.1	Bootstrapping	11
ACEi effectiveness in ACE DD (days)[a]	106.1	79.6 – 132.6	Bootstrapping	11
Effectiveness of alternative treatment in screening strategy (days) [b]	Varied in the threshold analysis			

Ranges for univariate sensitivity analysis were ± 25% for all parameters. ACEi: angiotensin-converting enzyme inhibitor; CKD: chronic kidney disease; ESRD: end-stage renal disease; QoL: Quality of life

[a] Effectiveness of ACEi therapy was defined as prolongation of median time to ESRD compared with placebo.

[b] Effectiveness of the alternative treatment was defined as increase in effectiveness compared with ACEi therapy.

RESULTS

Five parametric distributions (Weibull, exponential, lognormal, loglogistic and Gaussian) were fitted on the REIN data. AIC values and visual assessment showed that the lognormal distribution provided the best fit for both genotype groups and both treatment arms. This distribution was therefore selected for use in the Markov model.

Cost-effectiveness of ACEi therapy

In the baseline analysis (table 2), ACEi therapy dominated placebo in both genotype groups, i.e. resulted in clinical benefits as well as cost-savings. In the 10-year timeframe, cost-savings for a patient with the ACE II/ID genotype was €15 826 and €105 104 for a patient with the ACE DD genotype. Overall ACEi therapy resulted in cost-savings of €45 198. QALY's gained per patient were 0.091 for a patient with the ACE II/ID genotype and 0.553 for ACE DD. Overall, ACEi therapy gained 0.243 QALY's per patient in the 10-year timeframe.

Univariate sensitivity analysis showed that dialysis costs and ACEi effectiveness had the largest influence on the cost-savings of ACEi therapy in both genotype groups (figure 2a). The main drivers of health gains were QoL of CKD and ESRD patients, followed by ACEi effectiveness (figure 2b). Probabilistic sensitivity analysis (figure 3; table 2) showed that in the ACE II/ID genotype, ACEi therapy has a 30.2% probability of resulting in an unfavourable outcome (no health benefits or cost-effectiveness of more than €20 000 /QALY). In the ACE DD genotype however, there was only a 0.2% probability of an unfavourable cost-effectiveness outcome.

Table 2: Cost-effectiveness at baseline and probabilistic sensitivity analysis

Cost-effectiveness of ACEi therapy				
	ACEi therapy		Placebo	
	Costs	QALYs	Costs	QALYs
All patients	€115 826	5.130	€160 789	4.887
ACE II/ID genotype	€125 786	5.078	€141 612	4.988
ACE DD genotype	€94 860	5.235	€199 963	4.682
	ΔCosts	ΔQALYs	Costs/QALY	Probability CE (%) [a]
All patients	-€45 168	0.242	Dominance	97.6
ACE II/ID genotype	-€15 826	0.091	Dominance	69.8
ACE DD genotype	-€105 104	0.553	Dominance	99.8

Cost-effectiveness of selective screen-and-treat strategy				
	Screening strategy		Non screening	
	Costs	QALYs	Costs	QALYs
No change in effectiveness change	-€44 221	0.243	-€45 198	0.243
9.1% increase in effectiveness[†]	-€45 102	0.248	-€45 198	0.243
+25% increase in effectiveness[†]	-€46 606	0.256	-€45 198	0.243
	ΔCosts	ΔQALYs	Costs/QALY	Probability CE (%) [a]
No change in effectiveness change	€977	0.000	Dominated	0
9.1% increase in effectiveness [b]	€96	0.005	€19 477	72.3
+25% increase in effectiveness [b]	-€1 408	0.013	Dominance	89.8

The term *dominance* denotes that a strategy saves costs as well as QALYs compared with its comparator strategy (which is then said to being *dominated*). ACEi: angiotensin-converting enzyme inhibitor; QALY: quality-adjusted life year; CE: Cost-Effectiveness

[a] The probability of cost-effectiveness was determined in the probabilistic sensitivity analysis.

[b] Effectiveness of the alternative treatment was defined as increase in effectiveness compared with ACEi therapy, which was defined as prolongation of median time to ESRD compared with placebo.

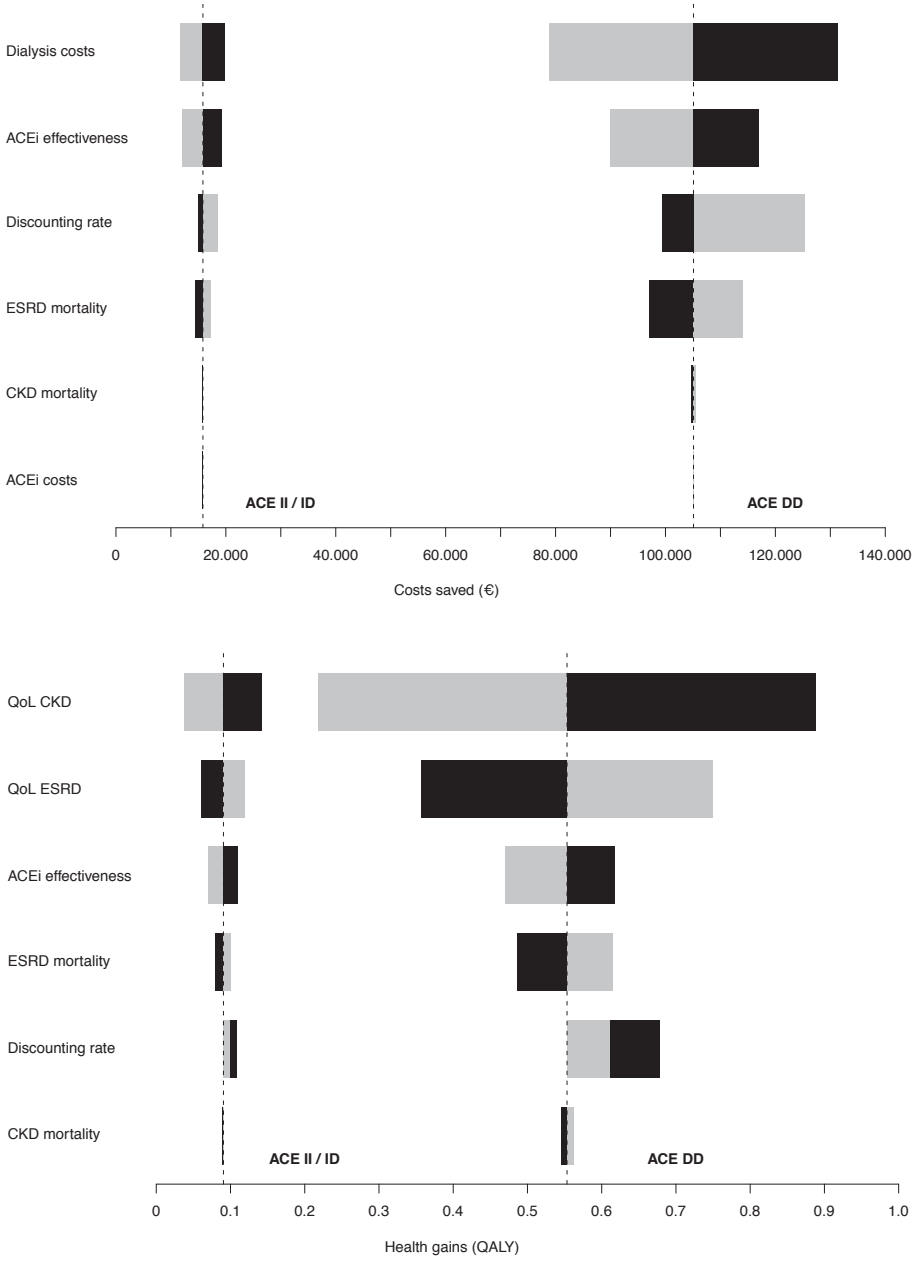

Figure 2: Univariate sensitivity analysis for net cost-savings and health gains of angiotensin-converting enzyme inhibitor (ACEi) therapy; the dashed line represents the baseline analysis. Black bars denote influence of the high end of the sensitivity range and grey bars denote influence of the low end for cost and health gains, respectively. Discounting rate was varied to 0% for both costs and health gains on the low end and 4% and 1.5% on the high end for costs and health gains, respectively. CKD: chronic kidney disease; ESRD: end-stage renal disease; QALY: quality-adjusted life year; QoL: Quality of life

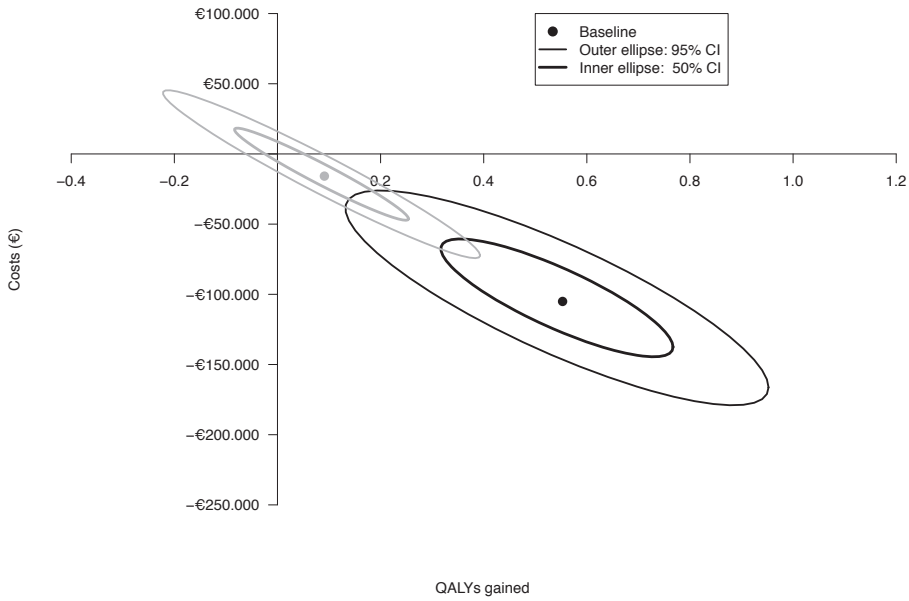

Figure 3: Cost-effectiveness plane for angiotensin-converting enzyme inhibitor (ACEi) treatment in nondiabetic nephropathy for patients with the ACE II/ID genotype (grey ellipse) and ACE DD genotype (black ellipse); baseline analysis; 95 and 50% confidence intervals (CIs) are shown. QALYs: quality-adjusted life years.

Threshold analysis for the selective screen-and-treat strategy

A selective screen-and-treat strategy was based on the decision-tree analytical framework and Markov model (figure 1). The effectiveness of the alternative treatment for ACE II/ID patients in the screening arm of this strategy was varied in a threshold analysis. Results are presented in table 2. This analysis showed that an alternative treatment should increase effectiveness compared with ACEi therapy by 9.1% for a screening strategy to be cost-effective compared with a non-screening strategy. Probabilistic sensitivity analysis showed that the chance of cost-effectiveness under this assumption is 72.3%. With an increase in effectiveness of the alternative treatment of 25% a screening strategy would save €1 408 and 0.013 QALY per patient, thus resulting in a dominating strategy compared with non-screening. The chance of cost-effectiveness under this assumption was 89.8%. When no increase in effectiveness of the alternative treatment was assumed, a screening strategy would generate extra costs and no health gains, thus causing the screening strategy to be dominated by the non-screening strategy.

Univariate sensitivity analyses showed that the costs of dialysis and of the alternative therapy were the most influential factors on the variability of the cost-effectiveness estimates. Two-way analyses were performed for these two variables and the effectiveness of the alternative treatment (figure 4 and 5). Lower costs of dialysis and higher costs of the alternative treatment decreases the cost-effectiveness of a screening strategy.

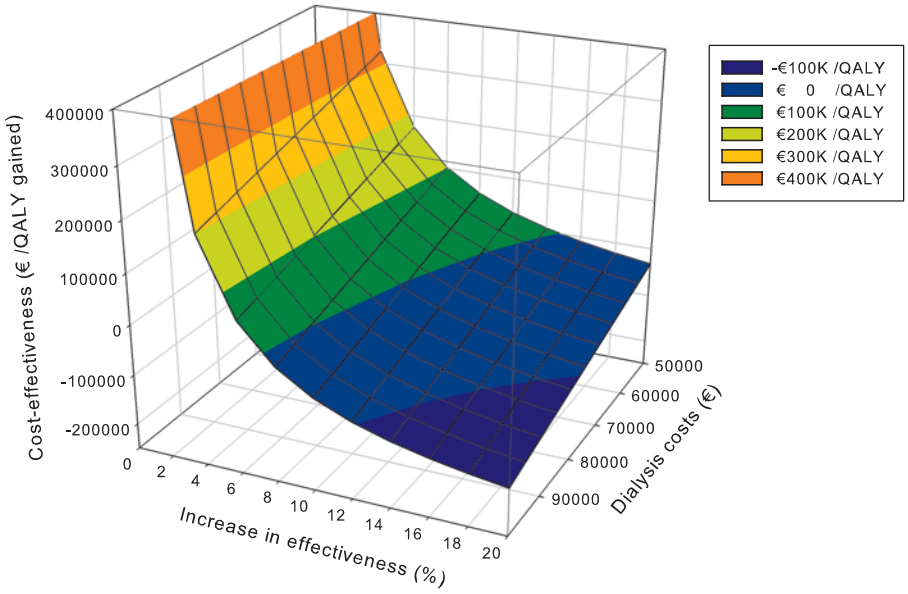

Figure 4: Two-way sensitivity analysis on the cost-effectiveness of a selective screen-and-treat strategy: dialysis costs and effectiveness of the alternative treatment modality. Negative cost-effectiveness values denote cost-savings and health gains. QALY: quality-adjusted life year.

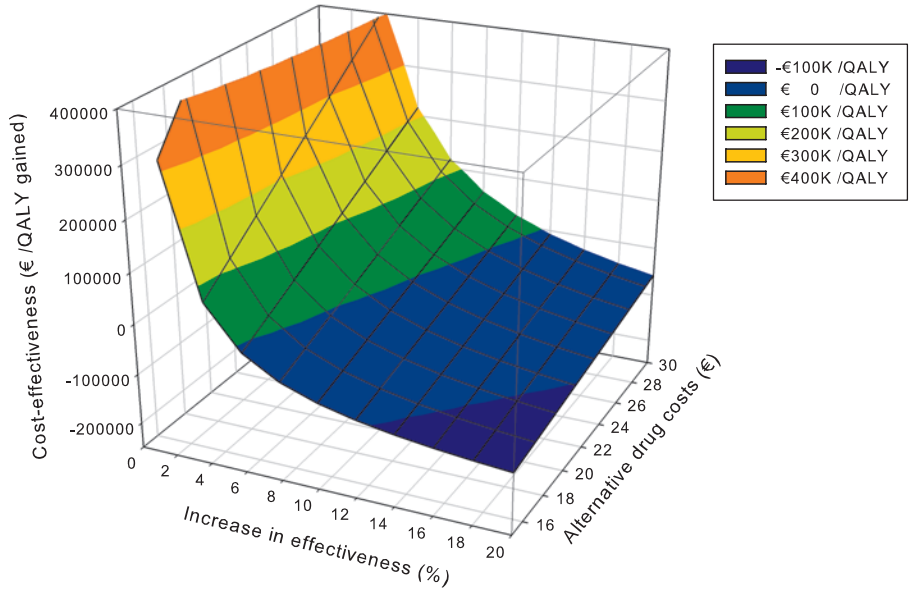

Figure 5: Two-way sensitivity analysis on the cost-effectiveness of a selective screen-and-treat strategy: costs and effectiveness of the alternative treatment modality. Negative cost-effectiveness values denote cost-savings and health gains. QALY: quality-adjusted life year.

DISCUSSION

This study showed that ACEi therapy is a cost-saving treatment modality to prevent ESRD in nondiabetic nephropathy irrespectively of ACE genotype, based on the Caucasian population of the REIN trial. However, while ACEi is cost-saving for all patients, there are considerable differences in cost-effectiveness in the different ACE (I/D) genotypes. ACEi therapy compared with placebo reduced more costs and more QALY's were gained in the ACE DD group than in the ACE II/ID group. In addition, in the ACE II/ID genotype there was a 30.2% probability of ACEi therapy resulting in an unfavourable cost-effectiveness outcome, while the chance of ACEi therapy being cost-effective or even cost-saving in the ACE DD genotype was almost 100%. Although separate analyses for the different polymorphisms have not been performed before, the finding that ACEi therapy is a cost-effective treatment in nondiabetic nephropathy has been reported in other studies. Van Hout *et al* analyzed ACEi cost-effectiveness based on the ACE Inhibition in the Progressive Renal Insufficiency (AIPRI) trial, and found ACEi therapy to save $28 014 per patient, using a time frame of ten years (in 1996 US$, equivalent to €30 272 in 2008 price levels).[31] Ruggenenti *et al* performed a cost-effectiveness analysis based on the REIN trial and found ACEi therapy to save between $16 605 and $23 894 per lifetime (in 2000 US$, equivalent to €20 887 and €30 056 in 2008 price levels).[32] Schädlich *et al* reported cost-savings between 76 700 and 81 900 deutschmarks per patient year of chronic dialysis avoided, using a time frame of one to three years (1999 DEM, equivalent to €51 168 and €54 637 in 2008 EUR).[33] Our model demonstrated cost-savings of ACEi therapy compared with placebo of €45 198 per patient using a ten year time-frame (ACE II/ID and ACE DD combined). Overall cost-savings per patient year of chronic dialysis avoided were €60 597. The larger cost-savings in our study compared with previous studies can be explained by lower discounting rates and higher costs of dialysis assumed in our model compared with the other studies.

The main limitation of this study is the assumption of an association between the ACE (I/D) polymorphism and ACEi therapy response, which is still disputed. In fact, several studies reported that the D allele is associated with ACEi therapy resistance,[16,19] contrary to our model assumptions. The trial used for our analyses was the only trial evaluating a hard endpoint, namely ESRD. A recent analysis in one of the contradicting trials,[19] showed that the preintervention rate of renal function loss (measured as creatinine clearance) was significantly higher in the ACE DD group compared with the other genotype groups.[34] Taking this preintervention rate into account, ACEi therapy did in fact benefit patients with the ACE DD genotype but not those with ACE II or ID genotype.[34] Therefore, while the REIN trial was the largest trial on the subject, other studies seem to confirm the findings. However, environmental factors should also be considered when determining the association between ACE genotype and ACEi response. ACEi therapy response is also dependent on sodium status, with more effective response on low sodium excretion in the ACE DD genotype.[17]

We employed a third-party perspective for our cost estimates as opposed to a societal perspective. While many guidelines recommend adoption of a societal perspective, for a first assessment of the cost-effectiveness of genetic screening interventions there are limitations in performing this in this case due to a lack of data in developmental stages and data being based on efficacy as opposed to real-life effectiveness.[12] In addition, the third party focus is often of prime interest to payer decision makers. However, for full understanding of the economic impact, indirect costs should be considered before final decisions on implementations of screening strategies are made.[12]

The models and parameters used in this economic analysis have been kept as relevant and transparent as possible. However, as in all economic analyses, several assumptions and estimates were made. Sensitivity analyses showed that mortality rates had a minor influence of the cost-effectiveness of the treatment modalities. Mortality rates in CKD were estimated from data obtained from the REIN and REIN-2 study combined. Mortality rates in ESRD were assumed to be similar in both ACE genotype groups. There is evidence that mortality is higher in dialysis patients with the ACE DD genotype,[35] however no information on ACEi therapy versus other antihypertensive drugs was reported. The most influential factor in sensitivity analyses was the cost of dialysis. When higher dialysis costs were assumed, ACEi therapy became more cost-effective in both ACE genotypes. Cost-effectiveness of the selective screen-and-treat strategy also increased with higher dialysis costs, but was also dependent on the assumed effectiveness and costs of the alternative treatment; these factors should therefore be taken into account when developing an alternative treatment to be employed in a selective screen-and-treat strategy.

CONCLUSION

The ACE (I/D) polymorphism is a large determinant of response to ACEi therapy not only in terms of health outcomes but also of cost-effectiveness. This study showed that ACEi therapy compared with placebo reduces costs and improves QALYs more in the ACE DD group than in the ACE II/ID group, although ACEi treatment remains cost-saving in both genotypes. A selective screen-and-treat strategy based on a treatment modality which produces a modest increase in effectiveness in patients with the ACE II/ID genotype can result in large cost-savings and clinical benefits. Unfortunately, clinical evidence for such a selective screen-and-treat strategy has been scarce and no such strategy has yet been implemented in clinical practice. Prior to this, ACEi therapy should be given to nondiabetic nephropathy patients irrespectively of ACE genotype. The large potential cost-savings and clinical benefits associated with a selective screen-and-treat strategy should ensure that studies and trials in this field remain appealing for both researchers and decision makers.

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Chapter 4

Using a genetic, observational study as a strategy to estimate the potential cost-effectiveness of pharmacological CCR5 blockade in dialysis patients

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ABSTRACT

Introduction: Randomized clinical trials are expensive and time consuming. Therefore, strategies are needed to prioritize tracks for drug development. Genetic association studies may provide such a strategy by considering the differences between genotypes as a proxy for a natural, lifelong, randomized at conception, clinical trial. Previously an association with better survival was found in dialysis patients with systemic inflammation carrying a deletion variant of the CC-chemokine receptor 5 (CCR5). We hypothesized that in an analogous manner, pharmacological CCR5 blockade could protect against inflammation-driven mortality and estimated if such a treatment would be cost-effective.

Methods: A genetic screen-and-treat strategy was modelled using a decision-analytic Markov model, in which patients were screened for the CCR5 deletion 32 polymorphism and those with the wild type and systemic inflammation were treated with pharmacological CCR5 blockers. Kidney transplantation and mortality rates were calculated using patient level data. Extensive sensitivity analyses were performed.

Results: The cost-effectiveness of the genetic screen-and-treat strategy was €18 557 per life-year gained and €21 896 per quality-adjusted life years gained. Concordance between the genetic association and pharmacological effectiveness was a main driver of cost-effectiveness. Sensitivity analyses showed that even a modest effectiveness of pharmacological CCR5 blockade would result in a treatment strategy that is good value for money.

Conclusions: Pharmacological blockade of the CCR5 receptor in inflamed dialysis patients can be incorporated in a potentially cost-effective screen-and-treat program. These findings provide formal rationale for clinical studies. This study illustrates the potential of genetic association studies for drug development, as a source of Mendelian randomized evidence from an observational setting.

INTRODUCTION

Pharmacological interventions that are of benefit in nondialysis populations have thus far been disappointing in dialysis patients, underscoring the need for novel intervention strategies, specifically targeted at the dialysis population.[1,2] However, development of novel pharmacological approaches followed by randomized clinical trials is expensive and time consuming, providing an immense obstacle to the development and introduction of innovative approaches in patient care. Research and development costs for a single approved cardiovascular drug can reach hundreds of millions of dollars, with most costs accrued in phase II and III trials.[3] Therefore, alternative strategies are urgently needed to facilitate the multi-faceted process from drug development to introduction in clinical practice. Observational studies using genetic variants might provide such a strategy.[4] Given the random assignment of alleles in gamete formation, genetic variants can be considered to mimic the randomization process of randomized clinical trials. Data obtained through genetic association studies could therefore be considered a type of natural, lifelong, clinical trial, with genetically different groups being randomized at conception, hereby limiting confounding. This approach is known as Mendelian randomization.[5,6]

One of the main driving forces in the accelerated atherosclerosis in end stage renal disease (ESRD) patients is chronic inflammation.[7] This population might therefore benefit from alternative therapies directed against the chronic inflammatory response. In this inflammatory process chemokines and chemokine receptors play an important role.[8-10] One of the chemokine receptors involved is the CC-chemokine 5 receptor (CCR5). Animal data show that pharmacologic intervention in the CCR5 chemokine pathway reduces atherosclerosis.[11-13] The relevance of these findings for humans is supported by genetic association studies on the CCR5 deletion 32 (CCR5Δ32) polymorphism, leading to functional CCR5 deficiency.[14] These studies show that CCR5Δ32 is associated with better outcome in different populations.[15-18] Previously, we found that CCR5Δ32 was associated with protection against mortality in Dutch cohort of dialysis patients characterized by inflammation and replicated these findings a in Swedish cohort .[19] Taken together, these data suggest that intervention targeting inflammation, in particular targeting the CCR5, may have the potential to improve prognosis in ESRD.[20] Interestingly, pharmacological blockade of CCR5 is feasible in human as it is applied in clinical practice for treatment of HIV infection, which increases the feasibility of development of CCR5 blockade as a treatment strategy for protection against inflammation-driven atherosclerosis in ESRD [21].

In line with the above, genetic association data on long term outcome in patients with versus without CCR5Δ32 can be considered as a virtual long term randomized intervention study on pharmacological blockade of the CCR5 receptor providing a fast and cheap simulation set-up for a real-life clinical trial (see figure 1). Systematic reviews have shown that pharmacogenetic screen-and-treat programs show great potential for developing cost-effective treatment modalities.[22,23] In the current analysis, we use these concepts to estimate the potential cost-effectiveness of CCR5Δ32 screening and pharmacological CCR5 blockade in dialysis patients, from the perspective of the Dutch health-care system.

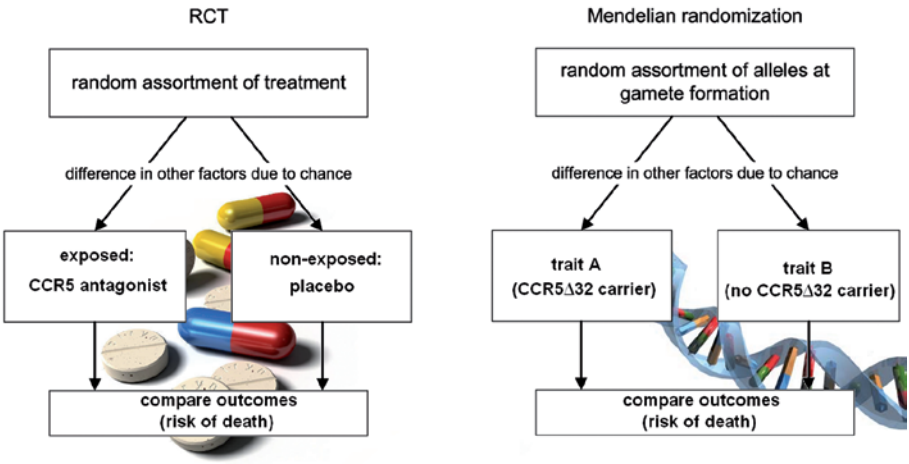

Figure 1: Mendelian Randomization studies use genetic information to simulate the potential effectiveness of pharmacotherapeutic interventions, akin to a RCT.[6]

METHODS

Patients

For the present study we used data from our previously published study on the effect of the CCR5Δ32 polymorphism on inflammation associated mortality in dialysis patients. This study was part of the NEtherlands COoperative Study on the Adequacy of Dialysis (NECOSAD), a multicenter prospective follow-up study comprising incident (new and consecutive) ESRD patients from 38 Dutch dialysis centers included between July 1998 and December 2001. Detailed descriptions of the study design and results have been published previously.[19]

Eligibility criteria for inclusion in the NECOSAD cohort were 18 years or older and no previous renal replacement therapy. All patients gave informed consent and all local medical ethics committees gave their approval. Patients were evaluated at 3 and 6 months after start of dialysis and every 6 months thereafter until death or date of censoring. Censoring involved transfer to a non-participating dialysis center, withdrawal from the study or end of the follow-up period in June 2007. Patients receiving a kidney transplant were not censored; data on their survival were obtained from the Dutch renal registry (RENINE).

Data collection and clinical definitions

High sensitivity CRP (hsCRP) was measured by means of particle-enhanced immunonephelometry using a standard CardioPhase hsCRP for BNII (Dade Behring Holding GmbH, Liederbach, Germany; detection limit 0.1 mg/l, precision 0.1 mg/l).[24] Systemic inflammation was defined as hsCRP concentrations above 10 mg/l. This cut-off point has been used in ESRD patients and has been

validated with regard to the prediction of survival of ESRD patients [25]. Also it was demonstrated that a single measurement of elevated CRP levels was associated with a similar predictive power on mortality as repeated CRP measurements.[26] CCR5 genotypes were determined with a PCR-based allelic discrimination assay using primers (Life Technologies) and allele-specific probes (PE Biosystems) as described previously.[27]

Patients were divided in 4 groups based on their CCR5**Δ**32 genotype and hsCRP level: CCR5 ins/ins with low hsCRP (≤10 mg/l), CCR5 ins/ins with high hsCRP (>10 mg/l), CCR5**Δ**32 with low hsCRP (≤10 mg/l) and CCR5**Δ**32 with high hsCRP level (>10 mg/l). Patients homo- or heterozygous for the deletion-allele were clustered since the presence of one minor allele has been associated with reduced receptor function.[14] Causes of death were classified according to the codes of the European Renal Association – European Dialysis and Transplantation Association (ERA-EDTA).[28] The following codes were used to classify cardiovascular mortality: myocardial ischemia and infarction; cardiac failure, fluid overload and pulmonary oedema; cardiac arrest; cerebro-vascular accident; haemorrhage from ruptured vascular aneurysm; mesenteric infarction; hyperkalaemia; hypokalaemia; cause of death uncertain or unknown.

Analytical approach

We modelled the potential cost-effectiveness of CCR5Δ32 screening and pharmacological CCR5 blockade using a decision-analytic Markov model (Figure 2). Markovian modelling is a commonly used technique in decision analyses to handle the complexity of multiple interconnective possible consequences.[29] The health states in our Markov model were hemodialysis (HD), peritoneal dialysis (PD), renal transplantation (Tx) and death. Cohorts of 1000 patients entered the model in the HD or PD health-state and were followed for a time period of 10 years. Clinical data were used to model transition probabilities; patients could receive a kidney transplant, experience renal graft failure and return to dialysis or die. The number of patients in each health state was determined by monthly cycles throughout the entire follow up period.[30]

Effectiveness of pharmacological CCR5 blockade

Transition probabilities for kidney transplantation and mortality were calculated using the patient level NECOSAD data.[19] Kidney transplantation and mortality rates were calculated for the four patient groups. Because of small numbers the rate of renal transplant failure was calculated for all four groups combined. Pharmacological CCR5 blockade was assumed to mimic the effects of the Δ32 polymorphism in subjects with high inflammation status, thus improving patient survival in the patient group with the CCR5 ins/ins genotype and systemic inflammation up to the level of the patient group with the CCR5Δ32 polymorphism and systemic inflammation. In particular, the relative risk (RR) for pharmacological CCR5 blockade in the inflamed group was calculated using clinical data as 0.61 for all-cause mortality, 0.41 for cardiovascular mortality and 0.80 for non-cardiovascular mortality. While the main focus of the current analysis was

on mortality, we also calculated, based on clinical data, that pharmacological CCR5 blockade improved the probability of renal transplantation (RR=2.41). To reflect our main focus on mortality we performed a separate analysis without modelling an effect on the probability of renal transplantation.

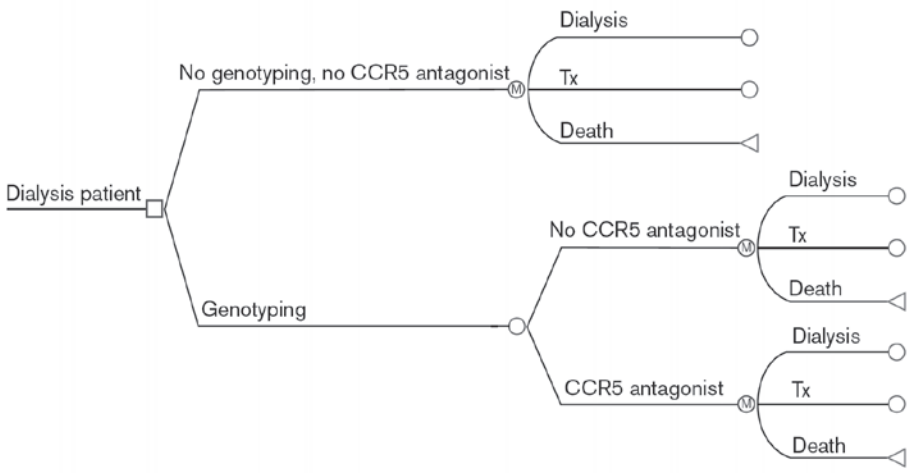

Figure 2: Decision tree and Markov model (M). Transition probabilities of the Markov model are shown in table 2. Tx: renal transplantation

Utilities

Health-related quality of life (QoL) of patients on haemodialysis (HD) and peritoneal dialysis (PD) were obtained by interviewing patients participating in the NECOSAD study, detailed inclusion criteria and methods are described elsewhere.[31] QoL of patients in the Dutch NECOSAD study were assessed with the EQ-5D instrument, which were applied to data from a UK population sample to obtain community based preference data.[32] No QoL-assessment of transplanted patients was performed in NECOSAD patients; these utilities were obtained from a Swedish study [33]. With QoL measurements, cost-effectiveness estimations can be made in terms of costs per Quality-adjusted Life-years (QALY) gained. A commonly cited implicit thresholds for treatments that are deemed good value for money is €50 000 per QALY in The Netherlands.[34]

Costs

A third-party health-care payer perspective was adopted for cost estimates. Health-care costs were classified into two categories: related costs and unrelated future costs.[35]

Related costs comprise costs directly related to the strategy under consideration. The cost of the genetic screening test for the CCR5Δ32 polymorphism was based on polymerase chain reaction and included staff costs.[36] The price of hsCRP screening was based on Dutch laboratory prices. Drug costs of pharmacological CCR5 blockade were based on Dutch prices of the CCR5

antagonist Maraviroc 300 mg (Celsentri) once daily,[37] including 6% value-added tax and a three-monthly pharmacists' prescription fee of €6,00. Costs of cardiovascular mortality were based on national Dutch life tables and health-care expenditures adjusted for comorbidities.[38] Costs of non-cardiovascular death and of transplantation graft failure were derived from a study with data from Dutch registries on renal diseases.[39]

Unrelated future costs comprised costs that are independent of current spending, apart from the effects of that spending on survival.[40,41] In particular, as dialysis and renal transplantation care are not a direct consequence of CCR5 blockade but of the preexisting condition of end-stage renal disease; these costs were consistently classified as unrelated future costs. The costs of dialysis and renal transplantation were based on data on volumes of recourse use, including consultations, hospitalisations and laboratory services and use of medication obtained from the NECOSAD study.[31]

In line with current pharmacoeconomic guidelines, unrelated future costs were not included.[35,42] However, to determine the influence of unrelated future costs, these costs were included in a separate analysis. All costs were updated to 2009 values.

Discounting rates

Costs were discounted at 4% per annum and health effects at 1.5% per annum, following Dutch guidelines for pharmacoeconomic research.[43]

Sensitivity analyses

Univariate and probabilistic sensitivity analyses and a threshold analysis were performed. In the univariate sensitivity analysis, all model parameters were varied by 25% in order to determine the main cost and effect drivers in our model. Discount rates were varied to 0% and 3% per annum based on recommendations by Gold *et al* and Drummond *et al*.[44] The probabilistic sensitivity analysis was performed according to standard methods,[29] using 10 000 iterations and included all model parameters, except therapy costs and effectiveness of pharmacological CCR5 blockade which were explored in a threshold analysis. Gamma distributions were assumed for costs and beta distributions for utilities.[29] In the absence of data on standard deviations for costs, we assumed 25% of the mean. Uncertainty in mortality and transplantation rates was captured by nonparametric bootstrapping of the NECOSAD data, using 10 000 iterations.[45] As equivalence between genetic effects and associated pharmacologic effectiveness is not a given fact,[46] a threshold analysis was performed to determine the combined influence of drug effectiveness and treatment costs of pharmacological CCR5 blockade on the cost-effectiveness of the screen-and-treat strategy. The pharmacoeconomic model and sensitivity analyses were constructed using the statistical package R, version 2.5.1 (R Foundation, Vienna, Austria). A graph of the threshold analysis was constructed using Sigmaplot, version 10.0 (SYSTAT Software Inc., Chicago, Illinois, USA).

RESULTS

Study population

The study population used for modeling consisted of 413 patients. The CCR5 ins32/del32 polymorphism was distributed as follows: ins/ins: 333 (80.6%); ins/del: 73 (17.7%) and del/del: 7 (1.7%). The genotype distribution did not deviate significantly from Hardy-Weinberg equilibrium (p=0.21). Baseline characteristics are shown in Table 1. The patient characteristics for the different genotype groups were similar at the start of dialysis, except antihypertensive medication use. Patients homo- or heterozygous for the deletion allele used more antihypertensive medications (p=0.01). From the 413 patients included, 225 (55%) had the CCR5 ins/ins genotype and low hsCRP levels, 108 (26%) the CCR5 ins/ins genotype and high hsCRP levels, 55 (13%) the CCR5Δ32 polymorphism and low hsCRP levels and 25 (6%) the CCR5Δ32 polymorphism and high hsCRP levels.

Mortality and transplantation rates

Annual transition probabilities without CCR5 antagonist therapy are shown in Table 2. The probability of renal transplantation was lower in the patient group with CCR5 ins/ins genotype and systemic inflammation compared to the three other patient groups. Cardiovascular and non-cardiovascular mortality was higher in the patient group with CCR5 ins/ins genotype and systemic inflammation compared to the other patient groups. In the Markov model, pharmacological CCR5 blockade in this patient group improved survival and the probability of renal transplantation up to the level of patients with the CCR5Δ32 polymorphism and systemic inflammation (Table 2).

Table 1: Baseline characteristics

	N = 413
Sex: males	253 (61.3)
Age (years)	62 (50-71)
Caucasian	379 (91.8)
Haemodialysis	277 (67.1)
Peritoneal dialysis	136 (32.9)
Primary kidney disease	
Diabetes mellitus	75 (18.2)
Glomerulonephritis	48 (11.6)
Renal vascular disease	76 (18.4)
Other	214 (51.8)
Cardiovascular disease	144 (34.9)
Diabetes mellitus	105 (25.4)

Table 1 (Continued)

	N = 413
Smoking	
Never	120 (29.2)
Former	194 (47.2)
Current	97 (23.6)
DBP (mmHg)	83 (12.8)
SBP (mmHg)	150 (25.4)
Antihypertensive medication	356 (86.2)
Lipid-lowering medication	121 (29.3)
hsCRP (mg/l)	5.1 (1.9-13.7)
hsCRP > 10 (mg/l)	133 (32.2)
Cholesterol (mmol/l)	5.0 (1.3)
Albumin (g/l)	32.5 (6.9)
Hemoglobin (g/dl)	11.0 (1.4)
GFR (ml/min)	4.2 (3.1)
Kt/V/week	2.3 (0.9)

CRP : C-reactive protein; DBP : diastolic blood pressure; GFR : glomerular filtration rate ; hsCRP : high-sensitivity CRP ; SBP : systolic blood pressure.

Table 2: Annual transition probabilities (95% CI) in the four CCR5Δ32 polymorphism and inflammation status groups without treatment with pharmacological CCR5 blockade.[19]

	CCR5 ins/ins, no inflammation (n=225)	CCR5 ins/ins, Inflammation [a] (n=108)	CCR5Δ32, no inflammation (n=55)	CCR5Δ32, Inflammation (n=25)
Transplantation	10.9 (8.9-13.4)	5.1 (3.0-8.4)	11.2 (7.4-16.8)	11.8 (6.4-21.5)
Transplantation graft failure	2.2 (1.2-4.0)	2.2 (1.2-4.0)	2.2 (1.2-4.0)	2.2 (1.2-4.0)
Cardiovascular mortality	4.3 (3.2-5.7)	9.5 (6.8-13.1)	4.1 (2.3-7.4)	4.0 (1.5-10.3)
Noncardiovascular mortality	4.4 (3.3-5.8)	9.7 (7.0-13.4)	4.5 (2.6-7.8)	7.8 (4.0-15.1)

CCR5: CC-chemokine receptor 5; CCR5Δ32: CC-chemokine receptor 5 deletion 32; CI: confidence interval.
[a] In the genotyping strategy of the economic model, patients with the CCR5 insertion/insertion and high inflammation status received CCR5 antagonists; thereby increasing transplantation rates and reducing mortality rates up to the level of patients with the CCR5Δ32 polymorphism and high inflammation status.

Table 3: Parameters used in the analyses

Variable	Baseline value ± SD	Reference
Costs		
Discounting rate for costs	4%	43,47
Related costs[a]		
Genetic screening test	€50 ± 13	36
CRP screening test	€21 ± 5	
Drug costs Maraviroc (per year)	€5 057 ± 1,264	37
Transplantation graft failure	€4 581 ± 1,145	39
Cause of death		
Myocardial ischemia and infarction	€2 448 ± 612	38
Cardiac failure/ fluid overload/ pulmonary oedema	€4 529 ± 1,132	38
Cardiac arrest	€2 448 ± 612	38
Cerebrovascular accident	€5 753 ± 1,438	38
Mesenteric infarction	€3 550 ± 888	38
Hyperkalaemia	€1 224 ± 306	38
Cause unknown or cause uncertain[b]	€3 469 ± 867	38
Noncardiovascular mortality	€2 316 ± 579	39
Unrelated future costs[a]		
ESRD care costs		
Hemodialysis year 1	€84 825 ± 21,206	31
Hemodialysis later years	€80 482 ± 20,121	31
Peritoneal dialysis year 1	€65 706 ± 16,427	31
Peritoneal dialysis later years	€60 985 ± 15,246	31
Transplantation year 1	€52 199 ± 13,049	31
Transplantation later years	€10 440 ± 2,610	31
Health effects		
Discounting rate for health effects	1.5%	43,47
Quality of Life		
Hemodialysis	0.71 ± 0.275	31
Peritoneal dialysis	0.75 ± 0.256	31
Transplantation	0.86 ± 0.133	33
Mortality and transplantation probabilities	See table 1	19
Therapy effectiveness (relative risk)		
All-cause mortality	0.61	19
Cardiovascular mortality	0.41	19
Noncardiovascular mortality	0.80	19
Renal transplantation	2.41	19

ESRD: end-stage renal disease; SD: standard deviation

[a] In the absence of data on standard deviations for costs, we assumed 25% of the mean.

[b] Weighted average of all cardiovascular mortality causes.

Cost-effectiveness

Parameters used for the analyses are shown in Table 3. Screening for the CCR5Δ32 polymorphism and treating patients with the CCR5 ins/ins genotype and systemic inflammation with pharmacological CCR5 blockade resulted in an average of 0.36 life years and 0.31 QALYs gained at an expense of €8 482 per patient compared to €1 863 per patient in the nonscreening cohort (Table 4). Therefore, the incremental cost-effectiveness ratio (ICER) of the screen-and-treat strategy compared to not screening was €18 557 per life-year gained (LYG) and €21 896 per QALY gained. Results were similar without the model assumption that pharmacological CCR5 blockade improved patients' probability of renal transplantation, €18 494 per LYG and €24 642 per QALY gained.

As described, the unrelated future costs of dialysis and transplantation care due to improved survival were not included. The aforementioned increased survival of 0.36 life years in the genetically screened cohort indeed required considerable dialysis costs. These costs were only partly offset by a shift towards less costly renal transplantation care in these patients. In total, additional unrelated future costs were €6 720 per patient in the screening cohort. When these costs are included, the cost-effectiveness of the selective screen-and-treat strategy rose considerably to €37 400 per LYG and €44 127 per QALY gained, thus doubling the ICERs for these scenarios.

Table 4: Cost-effectiveness in the base-case analysis

	Costs	Life years	QALY
Comparators			
Standard care	€1 863	5.71	4.36
Screen-and-treat strategy	€8 482	6.07	4.67
Screen-and-treat strategy (no Tx effect)	€8 460	6.07	4.63
Cost-effectiveness		Cost per LYG	Cost per QALY gained
Screen-and-treat strategy		€18 557	€21 896
Screen-and-treat strategy (no Tx effect)		€18 494	€24 642

QALY: quality-adjusted life year; Tx: renal transplantation

Sensitivity & threshold analyses

Results of the probabilistic sensitivity analysis are shown in Figure 3, demonstrating the uncertainty around the cost-effectiveness estimates of the screen-and-treat strategy. The increase in cost-effectiveness as well as the uncertainty around these estimates due to including unrelated future costs is evident. In Figure 3, the solid dot denotes the base-case outcome (using the most likely parameter estimates) while the inner and outer ellipses denote the 50% and 90% probability intervals, respectively, around this base-case estimate.

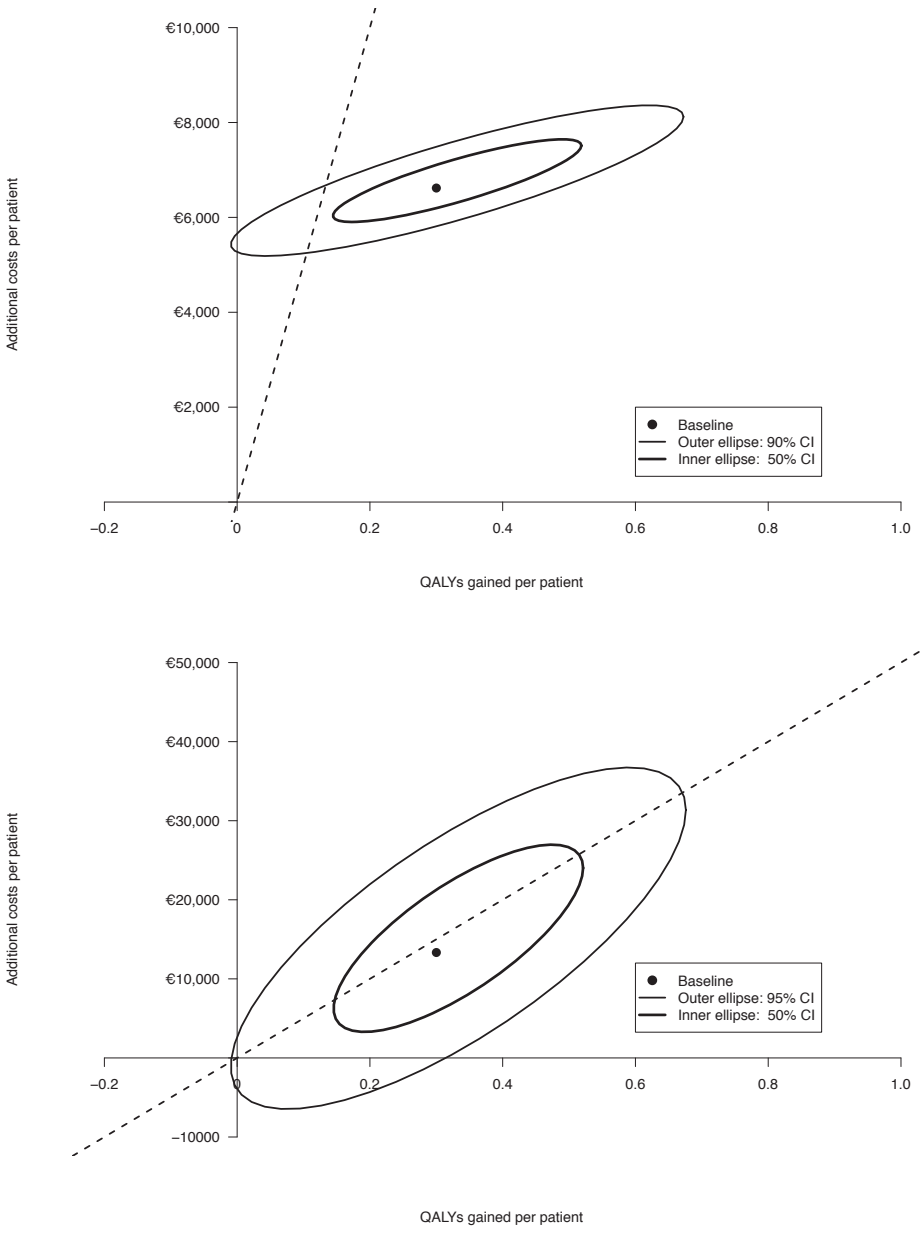

Figure 3: Cost-effectiveness of the screen-and-treat strategy. Top figure: excluding unrelated future costs (end-stage renal disease care costs). Bottom figure: including unrelated future costs. Dotted line denotes the willingness to pay threshold for one quality-adjusted life year at €50 000.[34] CI: confidence interval; QALY: quality-adjusted life year.

Univariate sensitivity analyses showed that the main drivers of the cost-effectiveness of the screen-and-treat strategy were the costs of pharmacological CCR5 blockade and the effectiveness of pharmacological CCR5 blockers to reduce mortality. The cost-effectiveness was relatively insensitive to plausible variations of the other parameters. These two main parameters were further explored in a threshold analysis, shown in Figure 4. The red line in this figure denotes the base-case assumptions for drug effectiveness and treatment costs. With decreasing therapy costs and increasing therapy effectiveness, cost-effectiveness of the screen-and-treat strategy improved. With the costs of pharmacological CCR5 blockade at the base-case level of €5 057 per year or €421 per month, a RR for all-cause mortality of 0.82 or lower would cause the cost-effectiveness of the screen-and-treat strategy to be €50 000 or less per QALY gained. If the costs of CCR5 blockers drop, even a modest effectiveness in reducing inflammation-driven mortality would result in a treatment strategy that is good value for money.

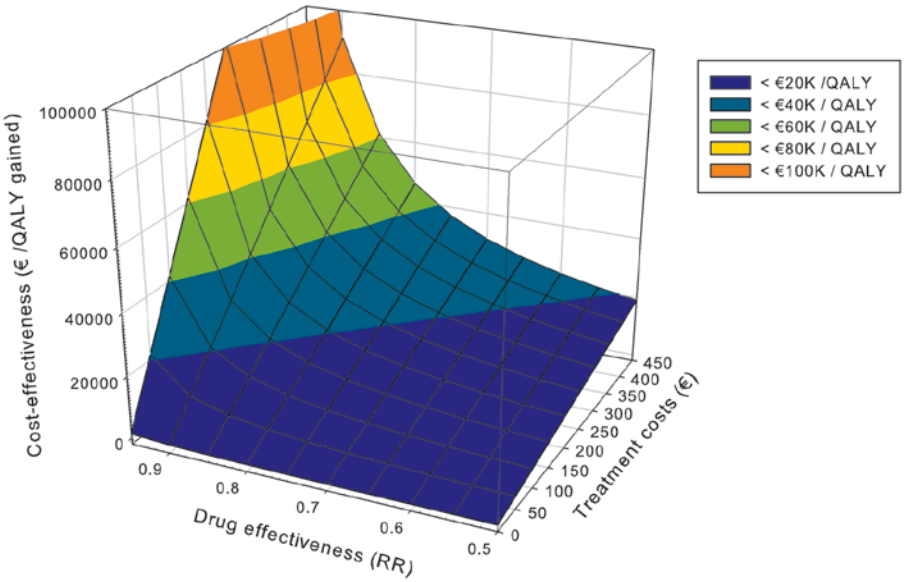

Figure 4: Threshold analysis on the influence of CCR5 blocking therapy costs and effectiveness on the cost-effectiveness of a screen-and-treat strategy. QALY: quality-adjusted life year; RR: relative risk.

DISCUSSION

Our study analyzed the potential cost-effectiveness of screening for the CCR5Δ32 polymorphism and selectively treating dialysis patients with the CCR5 ins/ins genotype and systemic inflammation with pharmacological CCR5 blockers. It was shown that such a strategy could be incorporated in a potentially cost-effective genetic screen-and-treat program.

Observational studies in which a genetic polymorphism is associated with a well-characterized functional phenotype can be considered as a type of clinical trial, with randomization at conception, referred to as Mendelian randomization.[4-6] Following this approach, we investigated the presumption that in an analogous manner, pharmacological CCR5 blockade could lead to better survival in ESRD patients and estimated the cost-effectiveness of a genetic screen-and-treat strategy based on this strategy. We used data from a genetic association study in ESRD patients. In this study an association with better survival was found in incident dialysis patients with systemic inflammation carrying the CCR5Δ32 genotype, which was replicated in a Swedish ESRD cohort, hereby showing the robustness of these findings. Moreover, since the number of patients in the CCR5**Δ**32 groups was small, we did in the previous study an analysis on the two cohorts combined, leading to the same results.[19] The presence of the CCR5Δ32 polymorphism, leading to a less functional receptor,[14] was used as a naturalistic form of pharmacologically blocking the CC-chemokine 5 receptor. This approach was used recently in Cholesterol Ester Transfer Protein (CETP) inhibition, identifying alleles which lead to reduced CETP levels and activity.[48] Other cost-effectiveness assessments of potential pharmacologic interventions have previously been performed, for example in cardiovascular disease and polypill therapy.[49] Considering the ACCE (analytic validity, clinical validity, clinical utility and ethical, legal and social issues) model framework for enhancing the evaluation of genetic tests, our study adds to the second C by providing cost-effectiveness data that supports clinical utility.[50,51]

A long-standing controversy in health-economics is whether unrelated future costs should be included in cost-effectiveness analyses.[40,41,52,53] Dialysis treatment is expensive and associated with a high cost per QALY gained.[31,54] As dialysis is required lifelong, the cost-effectiveness of therapies in ESRD patients have been said to be driven more by dialysis costs than by the costs and benefits of the intervention under consideration itself.[55] Our analysis confirms these earlier findings and underscores the relevance of the debate by calculating that inclusion of dialysis and renal transplant care costs doubles the incremental cost-effectiveness ratio of the screen-and-treat strategy. Several studies in ESRD patients did not include the future costs of ESRD-care,[56-58] while others analysed therapies both with and without future costs.[59-61] By excluding ESRD-costs in the main analysis but including them in a separate analysis our results can be widely compared. The cost-effectiveness with inclusion of future ESRD-costs were comparable to other studies focusing on systemic anticoagulation,[61] hyperphosphatemia,[60] secondary hyperparathyroidism,[59] and anemia.[62]

In addition to adherence to guidelines for pharmacoeconomic research as possible within the constraints of novel pharmacogenetic screening programs,[22] the present study had two major

strengths: 1. the analyses considered hard end points, mortality and renal transplantation; 2. most primary data used in the pharmacoeconomic analysis, such as costs, quality of life estimates and efficacy data, were derived from a single prospectively followed dialysis cohort (NECOSAD). These strengths enhanced the clinical relevance and analytical robustness of the study findings. Although cost data used in our study were specific for the Netherlands, chronic kidney disease (CKD) care costs such as dialysis costs have been reported to fall within a narrow range despite considerable variation in country of study, methodology and imputed costs.[54] Country specific variations in drug costs and discounting rates have been accounted for in sensitivity analyses.

An important aspect of our study is the notion that equivalence between genetic effects and associated pharmacologic effectiveness is not a given fact. For example, a discordance has been described between the genetic effect of familial hypercholesterolemia and the effectiveness of statin treatment on cardiovascular mortality.[46] The explanation for this discrepancy lies in the fact that genetic factors, as opposed to pharmacologic interventions, cause life-long differences in risk factors.[46] Genetic factors are also not affected by traditional sources of uncertainty in clinical effectiveness, such as therapy compliance. Indeed, sensitivity analyses showed that the cost-effectiveness was highly influenced by the concordance between the genetic association and pharmacological effectiveness. Still, while the true effectiveness of pharmacological CCR5 blockade in ESRD patients on mortality is not (yet) known, this study, in particular the threshold analysis, provides valuable information for future clinical trials in this field. In this context, the threshold analysis showed that even modest pharmacological effectiveness would result in a treatment strategy that is good value for money. A similar approach has recently been taken in analysing the potential cost-effectiveness of alternative treatments for CKD patients resistant to ACE inhibitors due to ACE (I/D) polymorphisms.[36] Finally, the robustness of the cost-effectiveness estimate depends on whether or not pharmacologically blocking CCR5 is safe in ESRD patients. However, treating HIV-infected ESRD patients with a CCR5 antagonist seemed safe and no dose adjustments were necessary.[63] The next research step could be conducting an observational cohort study in HIV-infected ESRD patients, to compare cardiovascular morbidity or mortality or surrogate endpoints such as intima media thickness, among users and non-users of CCR5 blocker therapy.

CONCLUSION

In conclusion, we evaluated the potential cost-effectiveness of pharmacologically blocking the CCR5 receptor in inflamed dialysis patient with the CCR5 ins/ins genotype, and found it to be similar to existing treatment modalities for dialysis patients. Recently CCR5 blockade has indeed become feasible in humans. Our data suggest that, from an economic point of view, it would be worthwhile to study whether pharmacological blockade of CCR5 has therapeutic and economic benefits in dialysis patients with persistent inflammation. Our study is an illustration of the potential of genetic studies in drug-development programs, as a new source of Mendelian randomized evidence from an observational setting.

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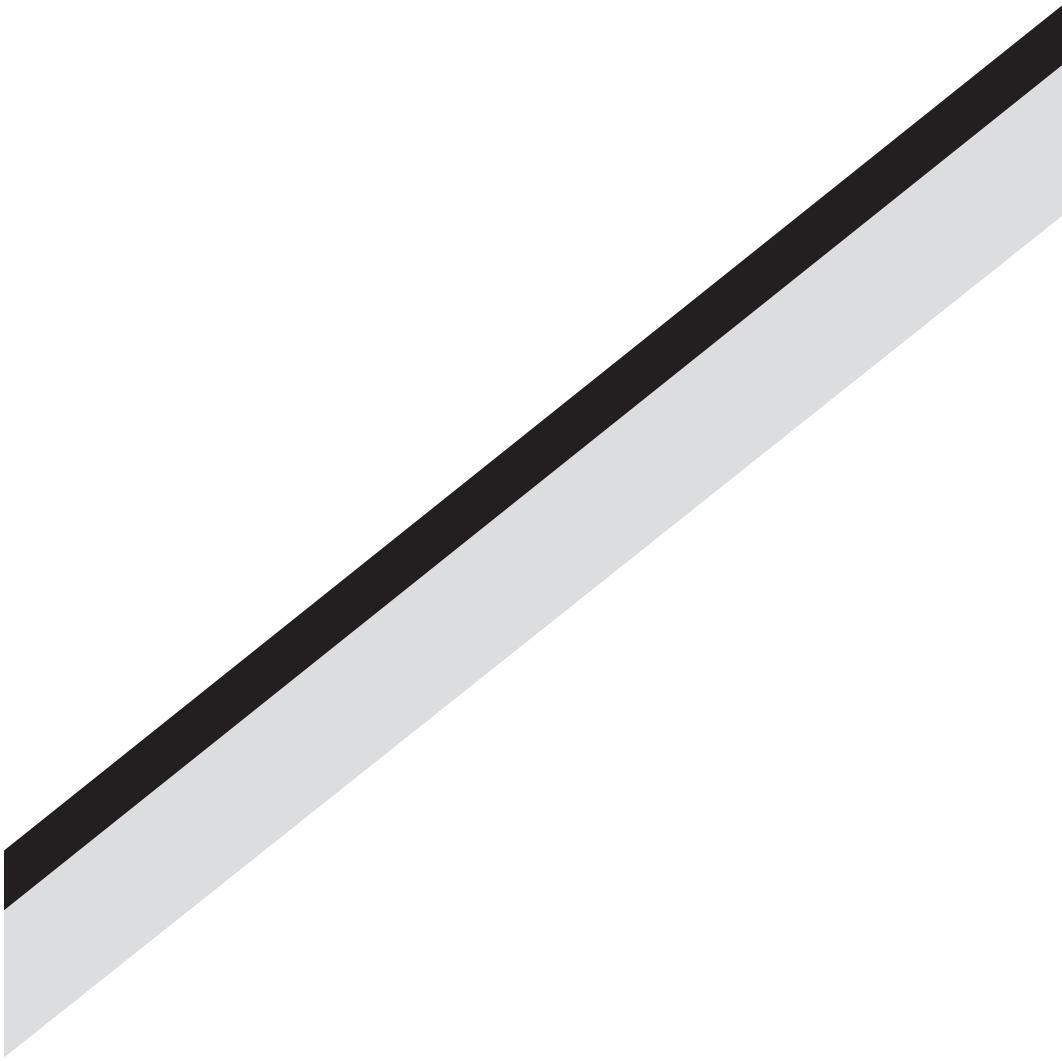

Part II

Non-genetic approaches to improve pharmacotherapy in renal disease

Chapter 5

Cost-effectiveness of lanthanum carbonate in the treatment of hyperphosphatemia in chronic kidney disease before and during dialysis

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ABSTRACT

Objectives: Hyperphosphatemia is a common and harmful condition in patients with chronic kidney disease (CKD). We determined the cost-effectiveness of the non-calcium based phosphate binder lanthanum carbonate (LC) as second-line treatment of hyperphosphatemia after therapy failure with calcium-based binders (CB).

Methods: Two CKD populations were modelled: 1) predialysis CKD patients, and 2) incident dialysis patients. Patients not responding to CB with serum phosphate (SP) level >5.5mg/dl received a trial with LC. Patients not responding to LC (SP >4.6mg/dl) returned to CB treatment. Patient-level data were obtained from clinical trials in predialysis and dialysis. Time-dependent, life-long Markov models (discounting at 3.5% annually) were developed, using a UK National Health Service perspective.

Results: The health gains with second line LC treatment compared to CB treatment were 44 and 56 quality-adjusted life-years (QALYs) for the predialysis and incident dialysis populations, respectively. Second-line LC was a cost-saving strategy in the predialysis population, caused by cost-savings of delayed CKD progression. Second-line LC was cost-effective at £6 900 (90% Probability Interval: £5 800 - £8 300) per QALY gained in the dialysis population. Results were robust to plausible variations in other model parameters; inclusion of future unrelated dialysis costs had a large influence on cost-effectiveness estimates.

Conclusions: Second-line treatment with lanthanum carbonate is associated with considerable clinical benefits and good value-for-money in CKD, irrespective of dialysis status. These results support K/DOQI guidelines to treat CKD patients with hyperphosphatemia irrespective of dialysis status.

INTRODUCTION

Hyperphosphatemia is an electrolyte disturbance characterised by an excess of serum phosphorous in the blood. It is a common and harmful condition in patients with chronic kidney disease (CKD), irrespective of dialysis status.[1] CKD is a continuous process [2] and deregulation of serum phosphate (SP) levels can occur at any point in this process.[3] Increased phosphate levels are independently associated with increased morbidity and mortality in CKD patients on dialysis [4-6] and predialysis across different CKD stages.[7-9] Treatment guidelines issued by the Kidney Disease Outcomes Quality Initiative (K/DOQI) recommend that serum phosphate levels are maintained between 2.7 and 4.6 mg/dl in predialysis patients and between 3.5 and 5.5 mg/dl in dialysis patients.[10] Unfortunately, less than half of the patients actually achieve and sustain these targets.[11]

Current first line drug treatment of hyperphosphatemia in the UK as in other countries, in combination with dietary restrictions,[10] consists of calcium based phosphate binders (CB), in particular calcium carbonate and calcium acetate.[12] When calcium agents are ineffective or inadequate, a strategy of dose escalation may be inappropriate due to increased risk for hypercalcemia,[13] which is linked to increased mortality.[5,14] K/DOQI guidelines recommend that total daily intake of calcium, from food and drug treatments, should not exceed 2000 mg.[10]

Lanthanum carbonate (LC) is a non-calcium based phosphate binding agent licensed for hyperphosphatemic dialysis patients [15,16] and recently also for CKD patients not yet on dialysis.[17,18] Treatment with LC after therapy failure with calcium carbonate treatment (i.e. second line LC treatment) was found to constitute good value-for-money in dialysis patients.[19] The cost-effectiveness of LC in predialysis patients, however, has not been assessed. The goal of the present study was to determine the cost-effectiveness of second line LC treatment of hyperphosphatemia in CKD patients before and after dialysis initiation, from a UK National Health Service perspective.

METHODS

Cost-effectiveness analysis

The cost-effectiveness of second line LC treatment was assessed for two CKD populations: 1) a predialysis CKD population, and 2) an incident dialysis population. Incremental cost-effectiveness ratios (ICERs) were calculated as cost per life year gained and cost per Quality Adjusted Life Year (QALY) gained. In addition, the Net monetary benefit of LC over the comparator at a decision-maker willingness-to-pay threshold of £30,000 per QALY was evaluated.[20] Outcomes were rounded to the nearest £100. The SP level upon which LC treatment is indicated for use is >5.5 mg/dl;[21] the target SP level is ≤4.6 mg/dl for predialysis patients and ≤5.5 mg/dl for dialysis patients.[10] Choice of therapy initiation and evaluation of treatment response was modelled according to these guidelines, shown in Figure 1. Second line LC treatment was considered for non-responders to calcium based binders with SP levels exceeding 5.5 mg/dl. Response to LC

was evaluated within an 8-week drug trial period; patients not achieving target SP levels during this drug trial were switched back to calcium agents.

Economic Model

A decision analytical structure was developed and linked to a time-dependent Markov model.[22] Markovian modelling is a commonly used technique in decision analyses to handle the complexity of multiple interconnective possible long-term consequences. The health states were "predialysis", "dialysis" and "death"; dialysis patients were not allowed to return to a predialysis state. The number of patients in each health state was determined by yearly cycles; a half-cycle correction was applied in order to account for the fact that events may occur at any point during the year. For the cost-effectiveness analysis irrespective of dialysis status, the model was populated with cohorts of 1000 simulated predialysis patients; for the analysis in dialysis patients, cohorts of 1000 incident dialysis patients were used. An overview of all model parameters is shown in Table 1. The model structure and parameter assumptions were discussed with two UK clinical experts who were consulted for this study.

Drug efficacy

Patient level data were obtained from two randomized clinical trials, one in predialysis patients (n=56 treated with LC),[17] and one in dialysis patients (n=123 treated with LC and n=257 treated with CB).[23] Because of the relatively limited data available for predialysis patients, the base case drug efficacy for predialysis patients was based on pooled data of predialysis and dialysis patients. Only data from dialysis patients with comparable baseline SP levels as predialysis patients, however, were used to calculate drug efficacy in predialysis. The assumption that the efficacy of drug intervention in dialysis patients with comparable SP levels to predialysis patients is transferable was verified as reasonable and appropriate by the clinical experts consulted for this study. Long-term response to LC was modelled using patient level data [23] with a previously reported method [19] and was assumed to be the same for predialysis and dialysis patients.

Clinical efficacy and adverse events

Mortality rates according to patients' SP level were derived from epidemiological studies in 3490 predialysis patients [8] and 40,538 dialysis patients.[5] Baseline expected survival was estimated using long-term observational data for almost 28 000 predialysis patients [24] and over 66 000 dialysis patients [25]. CKD progression rates were based on data for 4231 CKD stage 4 patients.[26] The baseline survival and CKD progression rates were adjusted for patients' average SP levels before applying SP specific relative risks.[19] In the trials used for this analysis, vomiting was significantly increased in LC compared to CB in predialysis patients (4.0%) [17] and dialysis patients (7.2%).[23] Duration of vomiting was estimated to be 7 days;[19] during this period patients were assumed to be prescribed an antiemetic drug (domperidone, 40 mg daily).

Costs and utilities

A third-party payer (UK National Health Service) perspective was adopted for cost estimates. Drug doses of lanthanum carbonate and calcium agents were based on the mean actual daily dosage from the trials in predialysis patients [17,27] and dialysis patients.[23] Drug costs were based on the British National Formulary (BNF).[28] The costs of dialysis were based on a weighted average [29] of UK cost estimates for hemodialysis and peritoneal dialysis.[30] Dialysis costs in added life years as a consequence of the more effective phosphate binder strategy were classified as 'unrelated future costs', because prolonged dialysis care is exclusively related to the extended life of treated patients and not directly to the choice of phosphate binder.[31,32] Following previous pharmacoeconomic analyses, these future unrelated dialysis costs were excluded from the base case analysis but included in sensitivity analysis. All costs were updated to 2009 values. Quality of life (QoL) estimates were identified using a recent systematic review.[33] Using a weighted average of studies identified in this review, a QoL utility of 0.71 was used for predialysis patient and 0.61 for dialysis patients.[34,35] A utility decrement of 0.14 was assumed for a vomiting episode, derived from a published study.[36]

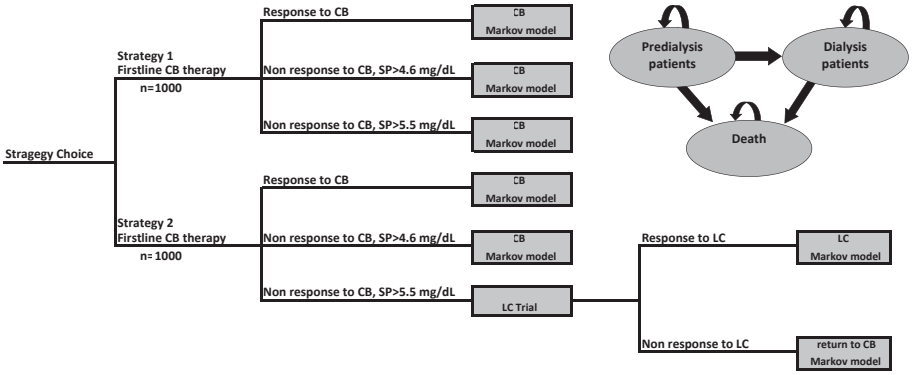

Figure 1: Decision analytical structure and Markov model (top right corner)

Table 1: Model parameters

	Predialysis value (95% CI)		Dialysis value (95% CI)		PSA	Ref
Clinical pathways						
Treatment initiation (mg/dl)	>5.5		>5.5			21
Target level (mg/dl)	<4.6		<5.5			10
Drug efficacy						
First line response rate to CB	45.6%	(40.5-50.9)	62.2%	(59.0-65.4)	Binomial	23,27
Second line response rate to LC	18.8%	(16.0-21.6)	44.6%	(40.0-48.5)	Binomial	17,23
Long-term response to LC	λ = 0.55 γ = 0.92	(0.46-0.65) (0.78-1.05)	λ = 0.55 γ = 0.92	(0.46-0.65) (0.78-1.05)	Weibull	17,23
Mortality and CKD progression						
Baseline yearly mortality	5.6%	(5.2-5.9)	λ = 0.21 γ = 0.87	(0.15-0.26) (0.76-0.99)	Normal / Weibull	24,25
RR of mortality by SP level						
<2.5 mg/dl:	0.95	(0.69-1.32)	1.00	(0.96-1.24)		
2.5-3.0 mg/dl:	1.00	(1.00-1.00)	"	"		
3.0-3.5 mg/dl:	1.15	(0.95-1.39)	1.00	(0.93-1.07)		
3.5-4.0 mg/dl:	1.32	(1.09-1.61)	"	"		
4.0-4.5 mg/dl:	1.34	(1.05-1.71)	1.00	(1.00-1.00)		
4.5-5.0 mg/dl:	1.83	(1.33-2.51)	"	"	Normal	5,8
5.0-5.5 mg/dl:	1.90	(1.30-2.79)	1.07	(1.01-1.14)		
5.5-6.0 mg/dl:	"	"	"	"		
6.0-7.0 mg/dl:	"	"	1.25	(1.17-1.34)		
7.0-8.0 mg/dl:	"	"	1.43	(1.31-1.54)		
8.0-9.0 mg/dl:	"	"	1.67	(1.51-1.86)		
>9.0 mg/dl:	"	"	2.02	(1.76-2.27)		
Baseline yearly CKD progression	14.3%	(13.6-15.0)	NA		Poisson	26
RR CKD progression (mg/dl)	1.19	(1.10-1.29)	NA		Normal	26
Quality of Life						
Quality of life	0.71	(0.69-0.73)	0.61	(0.57-0.65)	Beta	34,35
Utility decrement vomiting	0.14	(0.08-0.20)	0.14	(0.08-0.20)	Beta	36
Adverse events						
Increase of vomiting for LC	4.0%	(3.0-5.0)	7.2%	(5.4-9.0)	Triangular	17,23
Duration of vomiting	7 days	(5.3-8.8)	7 days	(5.3-8.8)	Triangular	19
Drug costs						
Yearly drug price of LC	£1 198	(1 047-1 347)	£1 540	(1 454-1 625)	Lognormal	28
8-week LC trial	£177	(153-200)	£224	(212-235)	Lognormal	28
Yearly drug price of CC	£56	(29-83)	£85	(77-96)	Lognormal	28
Yearly drug price of CA	£40	(21-60)	NA		Lognormal	28
Dialysis costs [a]	NA		£34 100	(28 120-42 230)	Lognormal	30
Discounting rate	3.5%		3.5%			15

CI: confidence interval; PSA: probabilistic sensitivity analysis; RR: relative risk; LC: lanthanum carbonate; CB: calcium binders; CC: calcium carbonate; CA: calcium acetate; CKD: chronic kidney disease; SP: serum phosphate; NA: Not applicable

[a] Weighted by prevalence of dialysis modalities (hemodialysis: 24.4%, home hemodialysis: 1.1%, satellite hemodialysis: 18.6%, ambulatory peritoneal dialysis: 3.8%, continuous ambulatory peritoneal dialysis: 5.2%).[29]

Sensitivity Analysis

Parameter uncertainty was handled by performing probabilistic sensitivity analysis (PSA).[22] In the probabilistic sensitivity analysis (PSA), joint parameter uncertainty was handled by specifying a probability distribution for each of the parameters,[22] shown in Table 1. For parameters based on patient level data as well as literature review, probability distributions as suggested by health-economic guidebooks were used.[37] No probability distribution could be adopted for adverse event rates; therefore a triangular distribution was used. To explore the sensitivity of the results to uncertainty in individual parameters, scenario analyses were performed using alternative literature sources and variations in structural pathway decisions. In one scenario, future unrelated dialysis costs were included.

Time horizon and discounting

A lifelong model was adopted, following all patients until death or a maximum follow-up of 40 years, with shorter time horizons explored in sensitivity analysis. Costs and health effects were discounted at an annual rate of 3.5% in line with standard UK guidance.[15]

Statistics and software

Baseline characteristics were compared using student's t-test or chi-square test, where appropriate. A P-value of <0.05 was considered statistically significant. The cost-effectiveness model was developed and built in Excel; the PSA to calculate 90% probability intervals (90% PI) was performed with the Excel add-on @RISK. Statistical tests and graphs were produced using the statistical program R.

RESULTS

Baseline characteristics

Age, gender and baseline SP were similar between LC and CB treated patients, both for predialysis and dialysis patients. Age and baseline SP did not differ significantly between the predialysis patients and the subset of SP-matched dialysis patients used for pooling; there were however slightly more females in the predialysis population (50% *versus* 36%, P=0.04).

Drug efficacy

In predialysis patients, first line response rate to calcium based phosphate binders was 45.6%. Hence, in the simulated cohort of 1000 CKD predialysis patients, 544 (54.4%) patients did not achieve SP targets with first line CB treatment. In the LC strategy, 230 out of these 544 non-responders had a SP level >5.5 mg/dl and therefore received an 8-week trial of LC treatment. Of these, 43 (18.8%) showed therapy response to LC, the remaining 187 patients returned to CB treatment. Upon entering the dialysis health state, the target SP treatment level recommended by international guidelines changed from ≤4.6 mg/dl for predialysis patients to ≤5.5 mg/dl in

the dialysis population [10]. Because of this change in target SP level, more patients treated with LC were classified as therapy responders. An incremental 79 patients responded to second line LC treatment compared to CB after reaching dialysis.

In the population of incident dialysis patients, first line CB response rate was 62.2%. Thus, in the 1000 incident dialysis patient cohort, 378 (37.8%) patients did not achieve SP targets with first line CB treatment. In the LC strategy, 168 (44.4%) showed therapy response to LC, the remaining 210 patients returned to CB treatment. The total number of therapy responders in the two CKD populations is presented in Table 2.

Health outcomes

Median survival of predialysis patients predicted by our model was 6.5 years median survival of incident dialysis patients was 3.5 years. The increase in therapy response with second line LC treatment resulted in additional life years and QALYs in both CKD populations (Table 2). In predialysis patients, 21.3 (15.4-28.2) additional dialysis-free years were gained with second line LC treatment due to delayed CKD progression. The total clinical benefit of second line LC treatment was 44.1 (33.4-54.2) QALY's in the predialysis population and 55.8 (42.6-72.3) QALY's in the dialysis population.

Cost-effectiveness

For the predialysis patient population, second line LC treatment was a dominating strategy compared to only CB treatment (i.e. second line LC resulted in cost-savings as well as clinical benefits). Because SP levels influenced CKD progression in the model, improved SP control with second line LC treatment resulted in considerable prevention and delay of end stage renal disease. Indeed, the cost-savings in predialysis patients were mainly due to prevented or delayed dialysis-care costs. The net monetary benefit for a willingness to pay of £30 000 per QALY gained was £1 700 (90% PI: 1 200-2 200). For the incident dialysis patient population, the cost-effectiveness was £6 900 per QALY (90% PI: £5 500 - £8 800 per QALY), with a net monetary benefit of £1 300 (90% PI: 900-1 700), shown in Table 2.

Sensitivity analyses

The results were robust to plausible variations in model parameters, both in the predialysis population (Fig. 2) and in the dialysis population (Fig. 3). Using alternative discounting rates or literature sources for CKD progression [38,39] or varying the frequency of adverse events did not influence the cost-effectiveness outcome. Using an alternative source for dialysis mortality [4] increased the ICER in the dialysis population to £22 300 per QALY. Of note, not using pooled data for drug efficacy in predialysis patients (i.e. using data of predialysis patients only) had no considerable influence on the cost-effectiveness for LC in this population with an ICER of £1 500 per QALY (90% PI: 900-2 300), Figure 2. Including unrelated future dialysis costs, however, had a

large influence on LC cost-effectiveness. When unrelated future dialysis costs were included, the ICER increased to £48 600 per QALY gained in the predialysis population and £63 000 per QALY gained in the dialysis population.

Table 2: Cost-effectiveness of second line LC treatment in predialysis and dialysis

	Predialysis Value (90% PI)	Dialysis Value (90% PI)
Therapy response		
Additional LC responders in predialysis	43 (34-53)	NA
Additional LC responders in dialysis	79 (69-89)	168 (151-185)
Total additional LC responders	122 (109-135)	168 (151-185)
Health effects		
Life years gained	69.4 (53.6-85.9)	91.9 (70.7-117.8)
Dialysis free years gained	21.3 (15.4-28.2)	NA
QALYs gained	44.1 (34.1-54.2)	55.8 (42.6-72.3)
Costs		
Additional drug costs	£387 (333-451)	£386 (338-446)
Dialysis costs	-£726 (-1020 - -509)	NA
Total costs	-£339 (-634 - -129)	£386 (338-446)
Cost-effectiveness		
Cost per LY gained (£)	Dominating	£4 200 (3 400 - 5 300)
Cost per QALY gained (£)	Dominating	£6 900 (5 500 - 8 800)
Net monetary benefit [a]	£1 700 (1 200 - 2 200)	£1 300 (900 - 1 700)

PI: probability interval; LC: lanthanum carbonate; LY: life year; QALY: quality-adjusted life year; NA: not applicable
[a] At a threshold willingness-to-pay of £30,000 per quality-adjusted life year

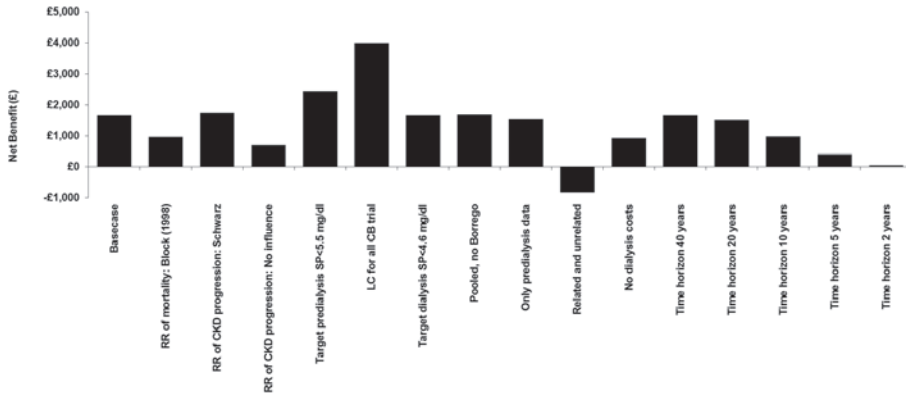

Figure 2: Sensitivity analysis in predialysis

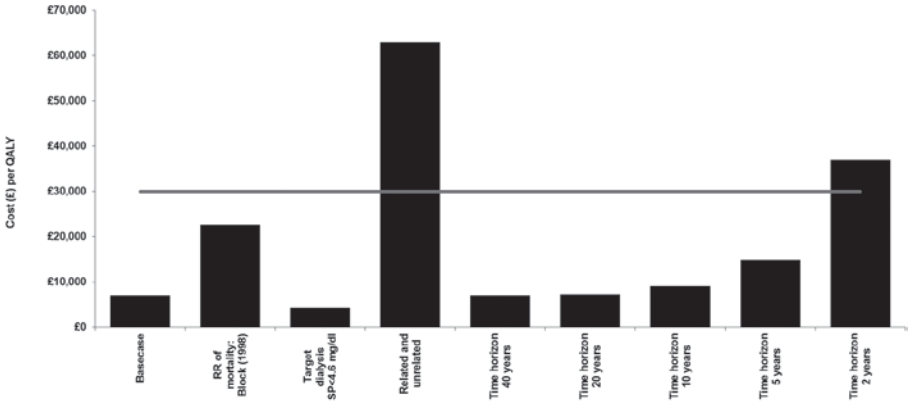

Figure 3: Sensitivity analysis in dialysis
* Line denotes threshold willingness-to-pay of £30,000 per QALY

DISCUSSION

While the efficacy of calcium and non-calcium based phosphate binders is similar in a treat to target setting,[40,41] calcium agents are cheaper and often prescribed as first line therapy. Non calcium based phosphate binders, such as lanthanum carbonate and sevelamer, may be prescribed after therapy failure or other contraindication for calcium agents. Our model demonstrated that second line use of LC was cost-effectiveness irrespective of dialysis status. In a 1000 predialysis patient cohort, a total of 70 life years and 44 QALYs were gained by second line LC use, as well as 21 dialysis free years. In addition, cost savings of £339 per patient were seen, resulting in second line LC use *dominating* the comparator strategy. In the 1000 incident dialysis patient cohort, a total of 92 life years and 56 QALYs were gained by second line LC use and the ICER was £6 900 per QALY, within the acceptable UK thresholds of cost-effective treatments.

One of the main cost-effectiveness drivers in our model was the rate of CKD progression in predialysis patients. Dialysis costs are high and therefore delaying dialysis initiation can lead to large cost-savings. Indeed, earlier studies have found that treatments that delay CKD progression are cost-saving.[42,43] Improved SP control with second line LC treatment [26,38,39] resulted in considerable prevention and delay of end stage renal disease. By monetizing these clinical benefits, our model predicted overall cost-savings for second line LC treatment, despite the higher drug costs of LC compared to calcium agents. In our model, median survival of predialysis and dialysis patients was 6.5 and 3.5 years, respectively. The external validity of our model is supported by observational data of 335 Canadian CKD predialysis patients (median survival of 6.4 years) [44] and over 3000 Scottish incident dialysis patients (median survival of 3.2 years).[45]

The results were robust to plausible variations in model parameters, including discounting rate and data sources for CKD progression and mortality. Unrelated future dialysis costs, however, had a large influence on the ICER. Unrelated future costs were excluded from the base case

analysis. The inclusion or exclusion of unrelated future costs is the topic of a longstanding and as-of-yet unresolved discussion;[31,32] in fact dialysis has been center-stage in this discussion.[46,47] Our results add to this discussion by demonstrating, in sensitivity analysis, that positive cost-effectiveness outcomes were largely dependent on the exclusion of future unrelated costs.

This study, to the best of our knowledge, is the first analysing the cost-effectiveness of phosphate binders in CKD patients before dialysis initiation. A previous cost-effectiveness analysis in dialysis patients reported an ICER of second line LC of £25 000 per QALY.[19] The previous analysis used data from a 1998 observational study of Block, et al. [4] In contrast, our model used a larger (40 538 *vs.* 6 407 patients), more recent (2004 vs. 1998) and longer follow-up (2.0 years versus 1.5 years) study by the same authors.[5] Several other model parameters were updated as well, including drug costs and QoL estimates.

Our model suffered from some limitations. Data on LC and CB efficacy were derived from 56 and 28 predialysis patients, respectively.[17,27] Although a lack of data in predialysis also applies to other non-calcium phosphate binders,[48] we tried to overcome this limitation by pooling predialysis patients with a subset of dialysis patients. Dialysis patients with SP level comparable to predialysis patients were selected for pooling in order to reduce heterogeneity. Indeed, population characteristics between the two populations were found to be similar. Furthermore, sensitivity analysis showed that results were similar when dialysis patients were excluded from the pooled dataset. Therefore, the use of pooled efficacy data enhanced the robustness of our results without biasing the cost-effectiveness outcome. Another limitation of our study was that in the predialysis population, the majority of LC treated patients were phosphate binder naïve,[17] thereby not accurately modelling second line LC treatment.

Several conservative model assumptions were made for this analysis. Patients treated with non-calcium based binders experience less hypercalcemic events compared to CB treated patients.[49] Hypercalcemia has been linked to increased mortality in dialysis [5,14] and predialysis;[50,51] a causal link between binder choice and mortality however has not confirmed in a recent meta-analysis [49]. Therefore, we conservatively did not model any influence of hypercalcemic events in our analysis. LC reduces pill burden compared to calcium agents, which has been associated with higher quality of life and patient preference [52,53] and improved drug compliance.[53] Quantitatively useful data for model inclusion of these parameters were not available; therefore we conservatively did not model any influence of pill burden on quality of life or drug efficacy. Finally, lowering SP reduces the risk of bone disease and non-fatal cardiovascular events, reflected by a decrease in hospitalizations.[5,54] This was not included in the model due to a lack of available data.

CONCLUSION

In conclusion, the use of lanthanum carbonate as second line treatment for hyperphosphatemia after first line use of calcium based phosphate binders, results in considerable health benefits and is cost-effective, using a UK National Health Service perspective, irrespective of dialysis

status. The results of this study strengthen K/DOQI recommendations to treat CKD patients with elevated serum phosphate levels irrespective of dialysis status.[10] Furthermore, our results suggest that second line treatment of lanthanum carbonate after therapy failure with calcium based phosphate binders may be considered in CKD patients irrespective of dialysis status.

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Chapter 6

Compliance, Persistence and Switching Patterns of ACE Inhibitors and ARBs

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ABSTRACT

Objective: To investigate compliance, persistence, and switching patterns for angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).

Methods: Drug-utilization analysis using a large prescription database. Prescription data for more than 50,000 incident users of ACE inhibitors or ARBs were collected, cumulating close to 200,000 patient-years of medication use. Incidence, drug dosage, 1-year compliance, long-term persistence, and switching patterns were analyzed. The specific drugs investigated were captopril, enalapril, lisinopril, perindopril, ramipril, and fosinopril (ACE inhibitors), and losartan, valsartan, irbesartan, candesartan, and olmesartan (ARBs). Results were adjusted for age, sex, starting date, and comorbidities.

Results: The 1-year compliance (88.3% vs 88.3%, P = .996) and 3-year persistence (81.9% vs 82.4%, P = .197) rates were similar between ACE inhibitors and ARBs. Users of ACE inhibitors more often switched therapy (24.2% vs 13.1%, P <.001), primarily to an ARB. Variations in compliance, persistence, and switching behavior were detected between specific ACE inhibitors, but not between specific ARBs.

Conclusions: Although residual confounding and indication bias cannot be ruled out, this study showed that compliance, persistence, and switching behavior varied between specific ACE inhibitors but not between specific ARBs. These results support prescribing of cheap generic ARBs as opposed to expensive ARBs. Apart from factors leading to therapy switches, compliance and persistence were similar between ACE inhibitors and ARBs.

INTRODUCTION

Antihypertensives are a cornerstone in the prevention and treatment of cardiovascular and renal diseases.[1] Agents that inhibit the renin-angiotensin-system (RAS), which include angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are especially important. RAS inhibitors have demonstrated efficacy for intermediate parameters such as blood pressure and proteinuria, but also for cardiovascular mortality and end-stage renal disease (ESRD).[2-6]

ACE inhibitors are widely used as first-choice RAS inhibitor, due to long experience and low costs compared to ARBs. These advantages are decreasing however due to present and upcoming patent expirations of ARBs. Furthermore, ARBs are associated with placebo-like tolerability [7,8] which may improve therapy compliance and persistence. On a group level, ARBs are sometimes proposed to be superior to ACEi.[9] However, comparative studies often fail to demonstrate clinically relevant differences between ACEi and ARBs and guidelines commonly suggest they are equivalent for nearly all indications.[10]

Complicating these matters is the debate surrounding the comparative effectiveness of *specific* ACE inhibitors and ARBs.[11,12] For the specific drugs there is no conclusive evidence on differences in drug efficacy and tolerability. A recent meta-analysis of 32 placebo-controlled trials suggested that all ACE inhibitors have similar efficacy to reduce mortality in congestive heart failure.[13] Results from observational studies on the other hand are conflicting on the existence of a class effect.[14,15] Similarly, recent reviews were unable to draw conclusions on the comparative efficacy of specific ARBs.[12,16] Real-life drug-utilization patterns can supplement evidence from clinical trials.[11,17] Firstly, drug compliance and persistence are recognized markers of drug efficacy and tolerability.[18] Secondly, therapy switches are signs of unsatisfactory treatment response and unacceptable adverse effects.[19,20] The objective of our study was to investigate drug compliance, persistence and switching patterns of RAS inhibiting agents in newly treated patients.

METHODS

Database

Prescription data between 1999 and 2010 were retrieved from the IADB.nl database, which holds a representative sample of the Dutch population of over 500,000 individuals. Each prescription record contains basic patient characteristics and information on drug, dosage, prescriber (general practitioner [GP] or specialist hospital doctors) and dispensing date. The IADB.nl prescription database has been validated for drug-utilization studies,[21,22] and has previously been used for such studies.[23,24] Due to high patient-pharmacy commitment in the Netherlands,[25] complete medication histories of individuals could be retrieved or constructed through linking pharmacy registries. Drugs were systematically classified using the Anatomical Therapeutic Chemical (ATC) Classification System of the World Health Organization (WHO) [26]. In the Netherlands, health care insurance is semi-privatized. Risks for insurance companies are regulated by a national

equalization pool. Risks for the public are minimized by the obliged purchase of coverage and by government-mandated acceptance for basic insurance plans. The medications included in these analyses are all fully reimbursed without restriction.

Patient population and drugs

Incident users of RAS inhibitors (ATC 'C09') older than 18 years were included. The following drugs were investigated: Captopril, Enalapril, Lisinopril, Perindopril, Ramipril, Fosinopril (ACE inhibitors); and Losartan, Valsartan, Irbesartan, Candesartan, and Olmesartan (ARBs). Fixed-dose combinations with diuretics were also included. Combined, these drugs constituted 96% of all RAS inhibitors in the database. Comorbidities were recorded by proxy of comedication, prescribed before or at maximum half a year after initiating RAS inhibiting therapy. Diabetes Mellitus (DM) therapy was identified by prescription of glucose lowering drugs (ATC 'A10').[27] Dyslipidemia therapy was identified by prescription of lipid lowering drugs (ATC 'C10').[27] Ischemic heart disease (IHD) therapy was identified by prescription of either nitrates (ATC 'C01DA') or platelet aggregation inhibitors (ATC 'B01AC').[28] Heart failure (HF) therapy was identified by prescription of either digoxin (ATC 'C01AA05') or loop diuretics (ATC 'C03C').[29] Chronic Obstructive Pulmonary Disease (COPD) therapy was identified by incident use of adrenergic inhalants (ATC 'R03A') or anticholinergic inhalants (ATC 'R03BB') in patients aged 55 years or older.[30] Incident use of COPD therapy was defined as the first use of an inhaler while being known in the database for at least one year. Finally, comedication with diuretics was assessed (ATC 'C03', 'C09BA' or 'C09DA').

Drug-utilization patterns

Drug-utilization patterns were investigated: incidence, dosage, one-year compliance, long-term persistence and switching behavior. The drug that was most commonly prescribed within its class was used as reference drug (Enalapril for the ACE inhibitors and Losartan for the ARBs).

Incidence and dosage

Incidence was defined as the first drug used after being present in the database for at least one year.[23,24] Because up-titration is common and necessary to achieve optimal blood pressure control,[31] the dosage was measured six months after drug initiation. The dosage was expressed in defined daily doses (DDD), one DDD is the mean dose per day for a drug used for its main indication in adults.[32]

Compliance

Drug compliance (synonym: adherence) is defined as "the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen".[33] A common method is the Proportion of days covered (PDC), calculated as the number of days the patient had access to the drug divided by the number of days in a specified time period.[34] This time period was

one year, starting at therapy initiation. Based on empirical studies to predict hospitalizations for hypertension and congestive heart failure,[35] a threshold of 80% was used to dichotomize between compliant and non-compliant patients. Patients who discontinued therapy or switched to a different drug were excluded, as this was analyzed in separate analyses. Differences in compliance were analyzed compared to the reference drug, adjusting for age, gender, year of initiating therapy and comorbidities.

Persistence

Whereas drug compliance refers to treatment *intensity*, drug persistence focuses on treatment *duration*. Drug persistence is defined as "the duration of time from initiation to discontinuation of therapy".[33] Persistence was measured using the Refill-sequence method. The time between the first prescription and the point at which an unacceptable prescription gap occurs was measured.[36] The length of this unacceptable gap or 'grace period' was 90 days.[36,37] In case of overlapping prescriptions, the second prescription was shifted forwards to account for drug stockpiling.[38] Patients were censored when lost to follow up or when switching therapy, as switching was analyzed separately. Differences in persistence were analyzed compared to the reference drug, adjusting for age, gender, year of initiating therapy and comorbidities.

Switching

A switch was defined as a RAS inhibiting agent permanently substituting the initial drug therapy.[39] Specific analysis was performed for switches from an ACE inhibitor to an ARB, which can be related to adverse events, in particular angioedema and dry cough.[8,24] Differences in switching patterns were analyzed compared to the reference drug, adjusting for age, gender, year of initiating therapy and comorbidities.

Statistics

All continuous variables are presented as mean ± standard deviation, unless noted otherwise. Differences in compliance were tested using Logistic regression. Differences in persistence and switching patterns were plotted using Kaplan-Meier plots and tested using the Log-rank test and Cox Proportional Hazard (Cox PH) analysis. All statistical analyses were performed using R, version 2.5.1 (the GNU Project, www.r-project.org/).

RESULTS

Prescription data of 53,000 incident users of ACE inhibitors and angiotensin receptor blockers (ARBs) were collected. A total of 51,181 patients initiated therapy on the predefined drugs. These patients cumulated close to 200,000 patient-years of medication use. Baseline characteristics of these patients are shown in Table 1. The type of medical prescriber was similar for users of ACEi and ARBs (percentage of general practitioner (66.5% *versus* 66.9%, P=0.465). ACE inhibitor

users were older than ARB users (63.2±14.1 *versus* 61.5±13.7) and more often male (48.8% *versus* 42.8%), both P<0.001. Comorbidities were more common in users of ACE inhibitors compared with ARB users, including DM (19.8% vs 14.5%), dyslipidemia (38.3% vs 30.6%), IHD (40.7% vs 30.3%), HF (21.6% vs 14.3%), and COPD (3.8% vs 3.0%); users of ACE inhibitors also were more likely to comedicate with diuretics (57.6% vs 55.5%) (all P <.001). Patient characteristics varied among users of different ACE inhibitors (Table 1), while users of different ARBs were largely similar.

Incidence and dosage

The most frequent prescribed ACE inhibitor was Enalapril (37.2%) and the most frequent prescribed ARB was Losartan (34.5%); these drugs were used as reference drugs. The median prescribed dosage corresponded to the DDD (Table 1, Figure 1). The two exceptions were Captopril, which was prescribed below the DDD of 50 mg in 65% of all patients, and Ramipril, which was prescribed above the DDD of 2.5 mg in 70% of patients.

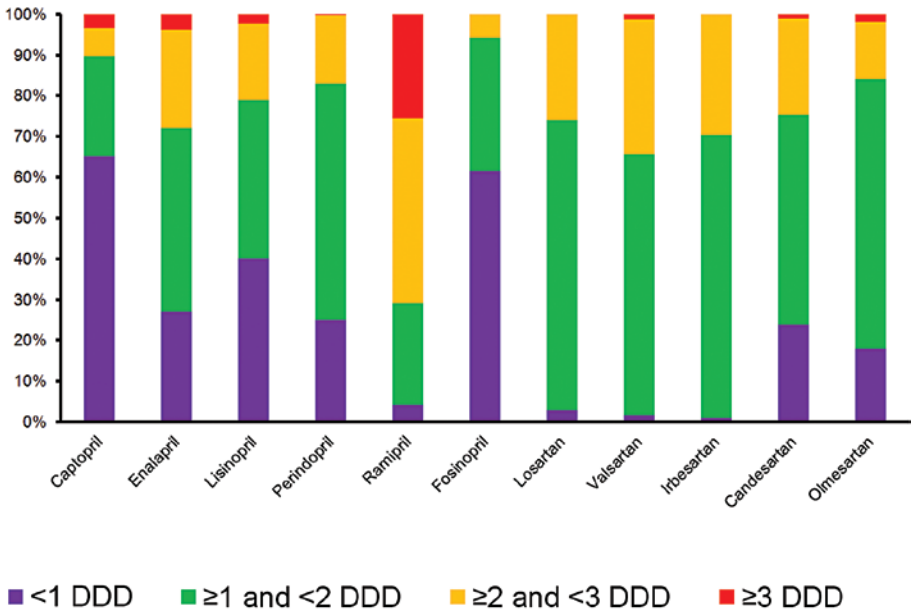

Figure 1: Drug Dosage Measured in Defined Daily Doses

DDD indicates defined daily dose.

Table 1: Baseline characteristics of patients initiating RAS inhibiting therapy

	N	Dosage	Age (years)	Gender (%m)
All	51181		62.9±14.0	47.6
ACE inhibitors	40555		63.2±14.1	48.8
Enalapril	15083	10 mg	62.2±14.3	44.3
Lisinopril	12103	10 mg	63.0±14.0	49.4
Perindopril	7569	4 mg	63.7±13.7	54.5
Ramipril	3608	5 mg	65.7±13.6	53.8
Fosinopril	1257	10 mg	65.6±13.6	52.3
Captopril	935	25 mg	66.0±14.7	43.9
ARB's overall	10626		61.5±13.7	42.8
Losartan	3667	50 mg	61.6±14.2	42.1
Irbesartan	3514	150 mg	61.8±13.2	42.7
Candesartan	1676	8 mg	61.0±14.1	43.1
Valsartan	1662	80 mg	61.4±13.4	44.8
Olmesartan	107	20 mg	59.5±13.7	38.3

	Comorbidities					
	DM (%)	Dyslipidemia (%)	IHD (%)	HF (%)	COPD (%)	Diuretics (%)
All	18.7	36.7	38.5	20.1	3.6	57.1
ACE inhibitors	19.8	38.3	40.7	21.6	3.8	57.6
Enalapril	22.1	28.8	26.7	15.9	3.3	59.9
Lisinopril	19.9	36.7	39.3	21.3	3.6	58.1
Perindopril	14.9	55.3	60.5	23.3	4.3	52.7
Ramipril	19.9	52.7	60.6	34.5	5.4	53.2
Fosinopril	18.1	32.7	43.7	34.2	4.0	59.9
Captopril	21.6	25.3	44.1	38.1	3.7	67.0
ARB's overall	14.5	30.6	30.3	14.3	3.0	55.5
Losartan	15.6	27.0	29.4	14.1	3.3	57.5
Irbesartan	16.1	34.4	33.0	14.3	3.0	56.7
Candesartan	10.8	27.6	27.9	14.5	2.7	47.9
Valsartan	12.3	33.0	29.1	14.1	2.5	56.0
Olmesartan	18.7	36.4	24.3	16.8	0.9	54.2

Compliance

After excluding 24,805 patients who discontinued or switched treatment, 20,236 ACE inhibitor and 6,140 ARB users were analyzed for one-year compliance. By design, none of these patients had switched or permanently discontinued RAS therapy. Higher patient age and comedication for dyslipidemia increased the chance of being compliant (9.4% and 25.6% over 10 years, respectively, P <.001), while comedication for COPD and later year of initiating therapy decreased the chance of being compliant (-24.3% per year [P = .005] and -1.5% per year [P = .035], respectively). The compliance of ACE inhibitor and ARB users was 88.3% (P=0.996) for both classes. There was variation in compliance between the specific molecules (Table 2), both without and with adjustment for age, gender, year of initiating therapy and comorbidities. Compliance among users of Ramipril (90.4%, P=0.05) and Fosinopril (91.6%, P=0.017) was higher compared to Enalapril (87.9%). Within the ARB group, users of Candesartan were found to be significantly less compliant compared to Losartan (86.1% *versus* 88.8%, P=0.027).

Persistence

Persistence is presented in Table 2 and Figure 2. Higher patient age (hazard ratio [HR] = 0.91 per 10 years, P<.001), later year of initiating therapy (HR = 0.71 per year, P <.001), comedication for IHD (HR = 0.90, P = .001), and comedication for HF (HR = 0.75, P <.001) increased the chance of being persistent, while comedication for dyslipidemia (HR= 1.24, P <.001), comedication for COPD (HR = 1.26, P =.001), or use of diuretics (HR = 1.15, P <.001) decreased the chance of being persistent. After three years of treatment, persistence on ACE inhibitors and ARBs was not significantly different both without and with adjustment possible confounders (81.9% *versus* 82.4%, P=0.197). Between the different ACE inhibitors, persistence differed significantly (overall P<0.001). Enalapril users showed the lowest persistence rate after three years, namely 80.8%, which was significantly lower compared to other ACE inhibitors. Users of Ramipril and Fosinopril showed the highest persistence, 85.8% and 83.4% respectively (P<0.001 and P=0.047 *versus* Enalapril, respectively). In contrast, there were no significant differences in persistence among ARB users (overall P=0.073). The use of different grace periods, such as 60 days or 120 days, did not change the relative order of persistence.

Switching

Users of ACE inhibitors switched drugs more than ARB users. After three years of therapy, 24.2% of ACE inhibitor users had switched therapy, compared to 13.1% for ARB users (P<0.001). This difference in switching rates was not dependent on the year of starting therapy or any other possible confounders. Compared to Enalapril, users Perindopril switched less often, while users of Captopril switched significantly more. Most ACE inhibitor switchers started using an ARB (75.0%). Users of Perindopril and Captopril switched significantly less often to an ARB compared to Enalapril. Users of Candesartan switched less often to another RAS inhibitor compared to Losartan.

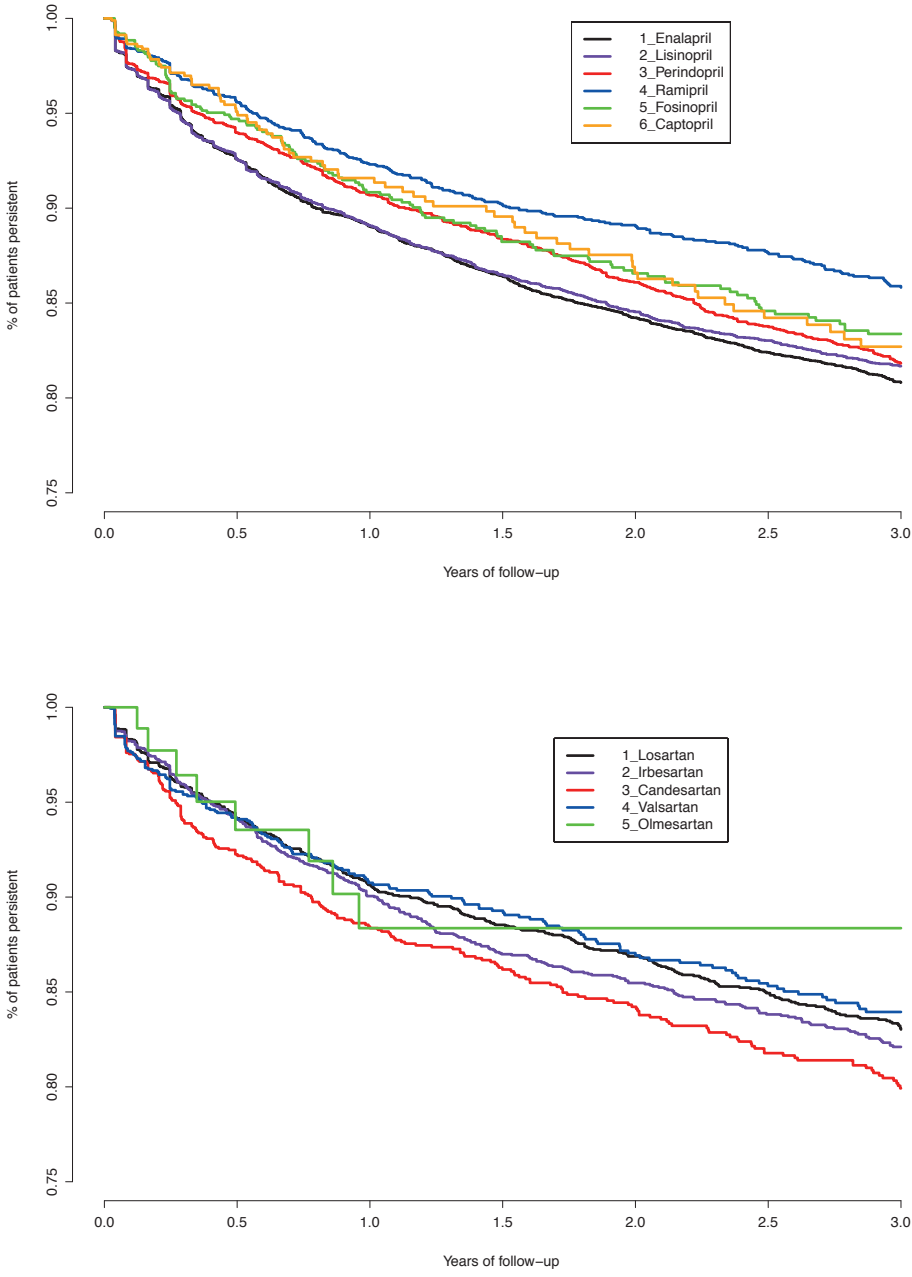

Figure 2: Persistence Rates for ACE inhibitors (top panel) and ARBs (bottom panel)

Table 2: One-year Compliance, Three-Year Persistence and Switching Rates

	Compliance (%)	Persistence (%)	Switch rate (%)	Switch rate to ARB (%)
All	88.3	82.0	21.9	
ACE inhibitors	88.3	81.9	24.2	18.4
Enalapril [a]	87.9	80.8	25.8	19.4
Lisinopril	88.2	81.7 [b]	23.0 [b]	18.9
Perindopril	87.8	81.8 [b]	20.0 [b]	16.2 [b]
Ramipril	90.4 [b]	85.8 [b]	24.3	17.5
Fosinopril	91.6 [b]	83.4 [b]	27.8	18.9
Captopril	87.1	82.7 [b]	38.6 [b]	13.0 [b]
ARB's overall	88.3	82.4	13.1	
Losartan [a]	88.8	83.0	14.0	
Irbesartan	89.0	82.1	12.7	
Candesartan	86.1 [b]	80.0	11.1 [b]	
Valsartan	88.2	83.9	13.7	
Olmesartan	89.4	82.7	21.3	

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; RAS, renin-angiotensin system.
[a] Reference drug within the drug class.
[b] $P<0.05$ versus the reference drug.

DISCUSSION

In the present study we analyzed drug utility patterns of RAS inhibitors. Apart from therapy switches, compliance and persistence were similar between ACE inhibitors and ARBs. On the drug level, several differences between the ACE inhibitors were detected. Ramipril and Fosinopril users showed higher compliance and persistence rates than the other ACE inhibitors, possibly indicative for more favorable drug tolerability profiles. Users of ARBs on the other hand were similar in terms of compliance, persistence and switching behavior.

The most frequently prescribed RAS inhibitors were Enalapril and Losartan. These drugs are among the first marketed members in their classes, underlining the emphasis that is placed on prescribing experience in The Netherlands. The prescribed dosage often corresponded to the DDD. As an exception, Ramipril was often prescribed at a higher dose, 5 mg/day, compared to the DDD of 2.5 mg. Clinical trial data in cardiovascular [5] and renal disease [6] also showed that Ramipril is often prescribed at doses above 2.5 mg/day.

A novel finding of our study is that, apart from factors leading to therapy switches, compliance and persistence were similar between ACE inhibitors and ARBs. These results at first glance seem to disagree with previous studies, including one in 15,000 hypertensive patients that reported superior persistence with ARBs.[9] However, in our study, patients were censored at the time of

switching. No such censoring was used in other studies and as a consequence, these studies failed to detect the similarity in compliance and persistence between drug classes. Indeed, our results showed that switching was more frequent in ACE inhibitors compared to ARBs, in agreement with previous studies.[9] Reasons for the difference in switching patterns between ACE inhibitors and ARBs at the class level deserve careful attention. One possible explanation is the well-known existence of ACE inhibitor specific adverse events, such as angioedema and dry cough [8,24] and the placebo-like tolerability of ARBs.[7,8] A large meta-analysis of randomized controlled trials with ACE inhibitors and ARBs found only minor differences in discontinuation rates due to adverse drug events,[40] however real-life observational studies have found discontinuation rates due to ACE inhibitor adverse events to be as high as 19%.[41] Another possible explanation is strong marketing of the newer ARBs, although year of therapy initiation was not an influential confounder in the analyses. Prescription sales of antihypertensive drugs has been shown to be correlated with marketing efforts of pharmaceutical companies.[42] Regardless of the reasons for switching, long-term persistence can be negatively influenced by switching therapy;[43] this should be a topic for further research.

There was variation in drug-utilization patterns between the specific ACE inhibitors. The average prescribed dosage of Captopril was below the DDD and did not increase over time. Captopril users often switched to a different ACE inhibitor. Together, these findings suggest that patients and physicians prefer to switch drugs rather than increasing the pill burden of Captopril. This is in accordance with evidence that once-daily antihypertensive dosing regimens are associated with superior compliance.[44] Users of ramipril and fosinopril showed high rates of compliance and persistence, which might indicate favorable drug tolerability profiles compared with other ACE inhibitors. These results are in accordance with previously published data analyzing compliance and persistence in over 6,000 ACE inhibitor users, that also found highest compliance and persistence for Ramipril and lowest for Enalapril.[45] In contrast to ACE inhibitors, the specific ARBs had very similar patterns of drug utilization. Candesartan users were less compliant and switched less often compared to other ARBs. The difference in compliance was small however (86.1% *versus* 88.8%) and previous studies have found no differences in adverse event rates between ARBs across the approved dosage ranges.[16] A confounding effect of indication bias or residual confounding therefore cannot be ruled out. Our results support a recent cost-effectiveness analysis in recommending generic cheaper ARBs over more expensive branded ARBs, as the differences in efficacy are small.[46] Our study showed that differences in compliance, persistence, and switching behavior between ARBs are also small, thereby providing even less reason to prescribe expensive ARBs.

Our study has several limitations. Firstly, our analysis used prescription data and does not necessarily reflect actual drug use. Validation studies however showed good correlation between prescription claims and actual drug use.[47] Secondly, indication of prescribing was not registered in our database. Although we adjusted the results for several comorbidities by

proxy of comediation, the possibility of residual confounding, influence of treatment history (such as chronic kidney disease) or indication bias remains. In addition, some comorbidities are associated with underprescribing, such as cholesterol lowering therapy.[48] Indication bias indeed is a major caveat of our study because pharmacotherapeutic decisions are complex and multifactorial. Although the differences between ACE inhibitors found in our study are supported by literature and are indicative of differences in drug tolerability profiles, there is no proven causality. For the same reason, frequency of medication administration (e.g. once-daily, twice-daily) could not be analyzed due to indication bias. Temporal confounding, for example through publication of new trial evidence, might have influenced drug-utility patterns. These effects have been described previously, for example for non-antihypertensive medications after discovery of serious side effects.[49] We adjusted for year of therapy initiation in our study; this did not influence results. Finally, our study was an analysis of a Dutch prescription database and results therefore are not necessarily generalizable to other countries due to differences in reimbursement policies, socioeconomic levels and ethnicity. Still, the real-life drug-utilization patterns of our study should provide valuable data to supplement evidence from clinical trials.[11]

CONCLUSION

In conclusion, although residual confounding and indication bias cannot be ruled out, this study showed that compliance, persistence, and switching behavior varied among users of different ACE inhibitors, but not among users of different ARBs. In terms of drug-utilization characteristics there appears to be no reason for prescribing more expensive branded ARBs as compared to cheaper generic ARBs. Apart from factors leading to therapy switches, compliance and persistence were similar between users of ACE inhibitors and ARBs.

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Chapter 7

Misdiagnosis and mistreatment of a common side-effect: angiotensin-converting enzyme inhibitor-induced cough

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ABSTRACT

Aims: Angiotensin converting enzyme inhibitors (ACEi) are frequently prescribed for various cardiovascular and renal diseases. A common side-effect of these drugs is a persistent dry cough. Physicians who fail to recognise a dry cough to be ACEi related may attempt to treat it with antitussive agents, instead of recommended ACEi substitution. Prescription behaviour in the general population considering treatment of the side-effect with antitussive agents has not been studied before.

Methods: Drug dispensing data between 2000 and 2007 were retrieved from the IADB.nl database. A prescription sequence symmetry analysis was used to determine whether antitussive agents were prescribed more often following ACEi initiation than the other way around. A logistic regression model was fitted to determine predictors.

Results: We identified 27 446 incident users of ACEi therapy. One thousand and fifty-four patients were incident users of both ACEi and antitussives within a half-year time span. There was an excess of patients being prescribed antitussive agents after ACEi initiation (703 *vs.* 351), adjusted sequence ratio 2.2 [confidence interval (CI) 1.9, 2.4). Female patients were more likely to be prescribed antitussive agents following ACEi therapy initiation, odds ratio 1.4 (CI 1.1, 1.9), age and co-medications were not significant predictors.

Conclusions: There was a significant and clinically relevant excess of patients receiving antitussives after ACEi initiation. The results suggest that cough as a side-effect of ACEi is not recognized as being ACEi related or is symptomatically treated with antitussive agents instead of ACEi substitution. The estimated frequency of antitussive treatment of ACEi-induced dry cough is 15%.

INTRODUCTION

Angiotensin-converting enzyme inhibitors (ACEi) can be prescribed for various cardiovascular and renal diseases. Cardiovascular indications for ACEi therapy include hypertension and prevention of myocardial infarction, stroke and heart failure.[1] In chronic kidney disease, ACEi are renoprotective in both diabetic,[2] as well as non-diabetic patients.[3,4] Unfortunately, a well-documented side-effect of ACEi is a persistent dry cough, the frequency of which ranges from 5-20%.[5,6] The side-effect usually develops within a few weeks after ACEi initiation; is not dose-dependent and is more common in women.[5,7,8] The persistent and troublesome nature of the cough often warrants discontinuation of the ACEi, after which the side-effect will usually abate within a few days.[9,10] Substitution of the ACEi with alternative agents, preferably angiotensin II antagonists, is recommended.[9,11]

Despite the fact that ACEi associated cough is well documented, some studies have noted a delay in the correct diagnosis of the side-effect[12], possibly related to poor knowledge on the side-effect and the recommended course of action.[13] In patients with congestive heart failure the side-effect might be overlooked because it may be ascribed to pulmonary congestion.[5] Patients in whom a dry cough is not recognized to be ACEi related, which can often easily be determined by means of a dechallange test,[14] might be subjected to extensive and unnecessary evaluations, diagnostic tests, and consultations. Physicians may attempt to treat the cough with antitussive agents,[5,12] such as noscapine or codeine. Prescribing antitussive agents for ACEi induced dry cough instead of ACEi treatment substitution constitutes irrational pharmacotherapy.[5,12,15]

In the present study we analysed whether there is an excess of antitussive treatments following ACEi initiation. Such prescription behaviour would indicate that ACEi induced cough is either not recognized or, arguably irrationally, treated with antitussive agents by physicians and pharmacists. The influence of patient characteristics on this irrational prescription behaviour was determined.

METHODS

Drug dispensing data at the individual level were retrieved from the IADB.nl database, which holds prescription records of approximately 500 000 individuals. In the IADB.nl database, each prescription record contains basic patient characteristics (anonymous identifier, gender and date of birth) and information on drug name, anatomical therapeutical chemical (ATC) code, dosage, and dispensing date (www.IADB.nl).[16,17] The use of over the counter (OTC) drugs and in-hospital prescriptions are not included. Due to high patient commitment to their pharmacy in The Netherlands,[18] complete medication histories of individuals could be retrieved. Data between January 2000 and December 2006 were used for the analyses.

All incident users of both ACEi (ATC codes 'C09A'; 'C09B') and antitussive agents (ATC codes 'R05D') were identified. Incidence was defined as not having been prescribed the drug in question for at least one year while being known in the database for that period. A prescription sequence

symmetry analysis was used to determine whether antitussive agents were prescribed more often following ACEi initiation than the other way around.[19] To this end, incident users of both treatments with a half-year timespan of each other were selected for analysis. The number of individuals starting ACEi first and antitussive agents second, divided by the number of individuals starting antitussive agents first and ACEi second, is called the sequence rate. This sequence rate is an estimate of the incidence rate ratio of antitussives prescribing in ACEi exposed *vs.* non-exposed person time.[19,20] The calculated sequence rate should be adjusted for time trends in use of the study drugs, because if a drug is prescribed with increasing incidence there will be a non-specific excess of that drug being prescribed last. The rationale, advantages and limitations of the prescription sequence analysis and the adjustment for time trends in drug use, are discussed in detail elsewhere.[19,20]

A multivariate logistic regression model was fitted on the data to determine predictors of being prescribed antitussive agents following ACEi therapy initiation. Specifically, we focused on age; sex; comorbidity obstructive airway disease (by proxy of ATC codes 'R03'); comorbidity diabetes mellitus (by proxy of ATC codes 'A10'); and co-medication of angiotensin II antagonists (ATC codes 'C09C' and 'C09D'); β-blockers (ATC codes 'C07'); calcium channel antagonists (ATC codes 'C08'); and diuretics (ATC codes 'C03'). Co-medication was defined as having been prescribed a minimum of three prescriptions for the drug(s) in question within a time interval of one year. The model was also adjusted for the date of ACEi prescription. Statistical analyses were performed using SPSS, version 15.0 (SPSS Inc. Chicago, IL, USA).

RESULTS

We identified 27 446 incident users of ACEi therapy. Of these, 1082 patients were selected who were incident users of antitussive agents before or after a half-year timespan of ACEi initiation. 28 patients (2.6%) started both therapies on the same day and were excluded from the analysis. In the remaining group of 1054 patients, the mean age at ACEi initiation was 65.3 (SD 13.9) years; 61.3% were female. 11.6% had recorded use of medication for obstructive airway diseases; 18.8% for diabetes mellitus.

Of the 1054 patients, 703 started ACEi therapy first and antitussive agents second against 351 patients who started antitussive therapy first, yielding a sequence ratio of 2.0 [95% confidence interval (CI) 1.8, 2.3]. Adjusted for incidence trends in drug use the sequence ratio was 2.2 (95% CI 1.9, 2.4).

Multivariate logistic regression analysis (table 1) showed that females were more likely to be prescribed antitussive agents following ACEi therapy initiation, while age and co-medications were not significant predictors.

Table 1: Predicting factors for receiving antitussive agents following angiotensin-converting enzyme inhibitor (ACEi) initiation over the opposite prescription order, total study population of 1054

Variable	n (%)	Odds ratio	95% confidence interval
Date of ACEi prescription (per month)		1.00	(0.99, 1.00)
Age (per year)		1.00	(0.99, 1.01)
Female gender	646 (61.3)	1.45	(1.11, 1.90)
Recorded use of co-medication			
Obstructive airway disease	122 (11.6)	1.18	(0.78, 1.80)
Diabetes mellitus	198 (18.8)	1.40	(0.99, 1.98)
Angiotensin II antagonists	23 (2.2)	0.93	(0.39, 2.26)
β-blockers	358 (34.0)	1.01	(0.76, 1.33)
Calcium channel antagonists	110 (10.4)	1.52	(0.96, 2.42)
Diuretics	298 (28.3)	0.84	(0.63, 1.14)

ACEi: angiotensin-converting enzyme inhibitors

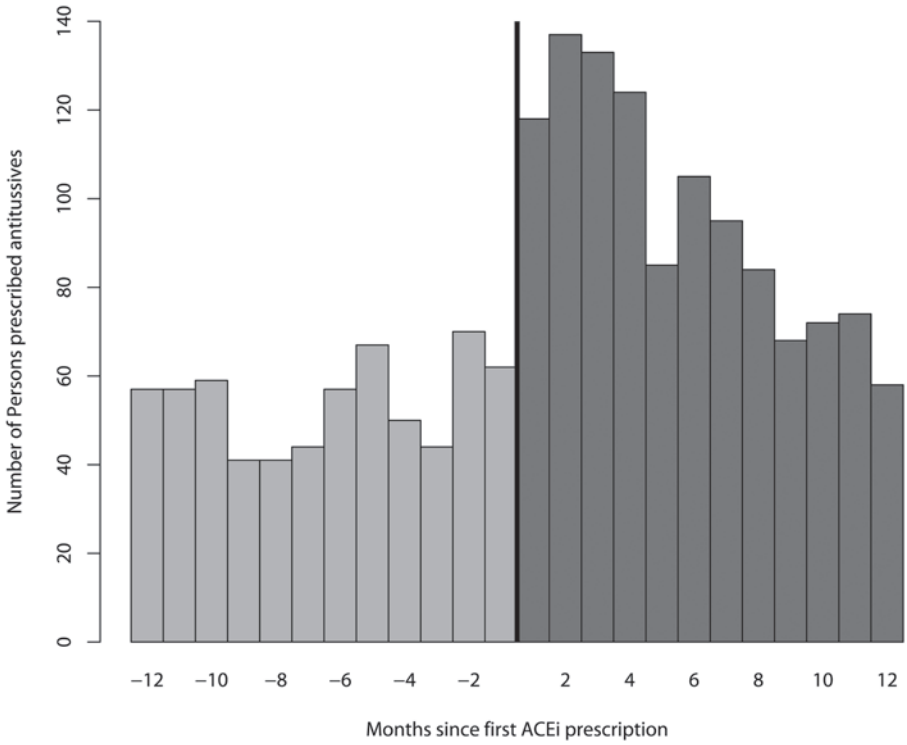

Figure 1: Prescription asymmetry of first antitussive prescription within 1 year before or after angiotensin-converting enzyme inhibitor (ACEi) initiation (n=1802)

DISCUSSION

Although ACEi-induced dry cough is a well-documented side-effect, prescription behaviour in the general population considering treatment of the side-effect with antitussive agents has not been studied before. Prescribing antitussive agents for ACEi-induced cough instead of ACEi treatment substitution constitutes irrational pharmacotherapy, because of avoidable polypharmacy,[15] low evidence of effectiveness of the antitussives,[5,12] and exposure to side-effects of the antitussive agents, which include drowsiness and nausea.

Our data identified 27 446 incident users of ACEi therapy; 2745 of those can be expected to have developed an ACEi induced dry cough, assuming a frequency of 10%.[6] The prescription symmetry analysis revealed a crude excess of 703-351 = 352 patients with the prescription order ACEi–antitussive. Adjusting for incidence trends in use of the study drugs resulted in an excess of 376 patients; which can be considered an estimate of the number of antitussive treatments attributable to ACEi-induced cough.[19] Therefore, the estimated frequency of antitussive treatment of the side-effect within half a year of ACEi initiation is 376 / 2745 = 15.2%. It should be noted that this estimate is inversely related to the assumed prevalence of ACEi-induced cough.

Multivariate logistic regression analysis confirmed that women are more likely to develop an ACEi-induced cough.[5,7,8] Age and comorbidities were not found to influence the prescription order, confirming earlier studies in which no other predictive factors for ACEi-induced dry cough other than gender were identified.[5] Albeit non-significantly, recorded use of co-medication for diabetes mellitus and calcium channel antagonists showed an increased OR for the prescription order ACEi–antitussive agent. Possibly, physicians are unwilling or hesitant to substitute ACEi therapy in these frail patient groups because of the cardiovascular- and renoprotective properties of ACEi.

Possibly, the physicians in our study did recognise the dry cough as an ACEi-induced side-effect and discontinued or substituted ACEi therapy, but also prescribed an antitussive agent for symptomatic treatment. ACEi-induced cough is often not susceptible to antitussive treatment.[5,12] However, we performed a second analysis in which we excluded patients who, after the first antitussive prescription, did not receive new ACEi prescriptions; results were similar, adjusted sequence ratio 1.7 (95% CI 1.4, 1.9). Therefore, antitussive agents are prescribed for ACEi-induced cough while the ACEi treatment is continued.

In our analysis incident users of ACEi and antitussive agents within a half-year timespan were included. To test the validity of this time span, an exploratory analysis with a one year timespan was performed. The prescription asymmetry of first antitussive prescription before and after ACEi initiation is shown in figure 1. Most of the excess of antitussives are prescribed within half a year of ACEi initiation, validating the half-year timespan chosen in our analysis.

CONCLUSION

We found a significant and clinically relevant excess of patients receiving antitussive agents following the first half-year after ACEi initiation. This prescription sequence asymmetry suggest that the dry cough is either not recognized as being ACEi-related or symptomatically treated with antitussive agents instead of the pharmacotherapeutically more rational ACEi substitution with other agents such as angiotensin II antagonists. The estimated frequency of antitussive treatment of the ACEi-induced dry cough is 15%.

ACKNOWLEDGEMENTS

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Chapter 8

Sodium intake, ACE inhibition and progression to ESRD

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ABSTRACT

Introduction: High sodium intake limits antihypertensive and antiproteinuric effects of angiotensin-converting-enzyme inhibitors (ACEi) in patients with chronic kidney disease (CKD).

Methods: This observational, post-hoc analysis of the Ramipril Efficacy In Nephropathy (REIN) and REIN-2 trials, evaluated the association of sodium intake with proteinuria and progression to end-stage renal disease (ESRD) in 500 non-diabetic CKD patients on standardized ramipril therapy (5mg/day) and monitored by serial 24-hour urinary sodium and creatinine measurements. Patients were categorized to low (LSD), medium (MSD) or high (HSD) sodium diet according to average follow-up 24-hour urinary sodium/creatinine excretion <100, ≥100 and <200, or ≥200 mEq/g, respectively. Time-dependent Cox models were used. During a follow-up of over 4.25-years, ninety-two individuals (18.4%) developed ESRD.

Results: Among 111, 336 and 53 patients on LSD, MSD or HSD, the ESRD incidence was 6.1 (95% CI 3.8-9.7); 7.9 (6.1-10.2); and 18.2 (11.3-29.3) per 100 patients-years, respectively (P<0.001). The antiproteinuric effect of ACE inhibition was blunted in HSD patients, whereas blood pressure was similar among groups. 100 mEq/g increase in urinary sodium/creatinine excretion was associated with 1.61-fold (1.15-2.24) increase in ESRD incidence [1.38 (0.95-2.00) after adjusting for baseline proteinuria]. The association was independent from blood pressure, but was lost after adjustment for changes in proteinuria.

Conclusions: Thus, in non-diabetic CKD, high sodium intake (more than 14 grams of salt daily) appears to blunt the antiproteinuric effect of ACE inhibitor therapy which, independent of blood pressure control, is associated with less effective protection against progression to ESRD. Restricting sodium intake may be important to optimize renoprotection in this population.

INTRODUCTION

Increased urinary protein excretion is a major determinant of progressive renal function loss in subjects with chronic kidney disease (CKD). Studies in diabetic and non-diabetic CKD, showed that renoprotective treatments limit GFR decline and progression to ESRD to the extent they lower proteinuria, independent of blood pressure (BP) control.[1-4] These findings imply that urinary proteins should be reduced as far as possible, ideally to less than 1 g per day.[5]

Inhibitors of the renin-angiotensin-system (RAS), such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), are the antihypertensive drugs that most effectively reduce urinary proteins and slow GFR decline in subjects with CKD.[1-3,6] The efficacy of treatment, however, is heterogeneous and dependent on inborn[7] and environmental[8-12] factors. Data in experimental diabetes,[13,14] adriamycin nephrosis,[15] uninephrectomized rats or in Munich Wistar rats with spontaneously reduced nephron numbers,[16] uniformly show that expansion of sodium pool, with glomerular hyperfiltration and activation of the renal RAS induced by enhanced sodium intake, all contribute to blunt the BP and proteinuria lowering effect of RAS inhibitors.[17] Consistently, observational studies in humans found that increased dietary sodium intake increases proteinuria and accelerates renal disease progression.[18] However, no study so far evaluated the associations between salt intake, proteinuria, and renal disease progression in subjects on RAS inhibiting treatment. Hence, in this study we evaluated the association of sodium intake with proteinuria and progression to ESRD in five-hundred subjects with CKD retrieved from REIN[1-3] and REIN-2[19] trials who were on stable ramipril therapy. Our working hypothesis was that blunted antiproteinuric effect of RAS inhibition therapy in patients with high salt intake might translate into less effective protection against progression to ESRD. This hypothesis was based on experimental and human evidence discussed above and arose before expectation of outcome data in our patient population.

METHODS

Patients

Of the 177 patients with proteinuric CKD included between 1992 and 1995 in the REIN trial[1-3] and randomized to ramipril therapy and 335 patients included between 1999 and 2003 in the REIN-2 trial all treated with ramipril[19] but not already included in the REIN trial, 500 (97.7%) had at least one measurement of 24-h urinary sodium excretion and were considered in the present analysis. Both trials included subjects aged 18-70 years with CKD and persistent proteinuria (urinary protein excretion ≥1 g/24-h for at least three months without urinary tract infection or overt heart failure). Full study characteristics and inclusion and exclusion criteria are detailed elsewhere.[1-3,19] The primary outcome analysed in both studies was incidence of doubling of serum creatinine or ESRD. Subjects from both studies were recommended a low-sodium diet and a daily protein intake of about 0.8 g/kg. No change to diet was introduced during the observation period. Thus, all 500 patients included in the present study fulfilled the same selection criteria, had the same

recommended diet and were on stable ACE inhibitor therapy with ramipril at the same daily dose (5 mg). One-hundred-seventy-two patients from the placebo arm of the REIN study who fulfilled the same selection criteria and had been managed according to the same treatment and monitoring guidelines**,** but had not received RAS inhibitor therapy served as controls. Patients in the REIN and REIN-2 trials provided written informed consent to study participation according to the Declaration of Helsinki guidelines. The study protocols were approved by the ethics committee and institutional review board of each of the participating centers.

Measurements

The exposure of interest, daily sodium intake, was estimated by measuring 24-hour urinary sodium excretion. To correct for body size and possible collection errors, urinary sodium excretion was normalized to urinary creatinine excretion by calculating the sodium/creatinine ratio from 24-h urine samples (SC-ratio, mEq/g).[20] Urinary urea and protein excretion were normalized to urinary creatinine excretion, as well. BP was measured at randomization and every 3 months thereafter. Creatinine clearance, 24-h urinary protein, sodium and urea excretion were measured at randomization, at three and six months after randomization, and every six months thereafter. Baseline data were taken when all subjects had completed the six-week wash-out period from previous ACE inhibitor therapy, that is, at randomization for patients from REIN and at the inclusion visit for those from REIN-2. Thus all baseline data were without ACE inhibition and all outcome data were with ramipril (5 mg/day) therapy.

Statistical analyses

As described in previous similar studies,[11,18] we identified patients with low- (LSD), medium- (MSD), or high sodium diet (HSD) based on urinary sodium/creatinine excretion averaged throughout the study less than 100 mEq/g, between 100 mEq/g and 200 mEq/g, and greater than 200 mEq/g (these cut-off levels of 100 mEq/g and 200 mEq/g approximated 125 and 250 mEq per day, equivalent to 7 and 14 grams of salt per day, respectively). Consistency of sodium intake was assessed using the Stuart-Maxwell test. Differences in baseline characteristics were determined using Wilcoxon Rank-sum test and Fisher Exact test, as appropriate. Differences in ESRD incidence rates were tested using the Chi-square test. Differences in short-term changes in proteinuria (percent values[6,10]) and BP (absolute values) were tested with Wilcoxon rank-sum tests; subsequent changes were analysed using a joint modeling approach incorporating survival outcomes[21] to account for survivor bias. Antihypertensive comedication was described; Fisher exact test and McNemar's test were performed for comparisons among groups and time periods, respectively. Survival curves were drawn using the Kaplan-Meier method; the log-rank test was used to assess differences in survival among groups and Cox Proportional Hazards analysis was used to calculate hazard rates. Non-linearity was tested by plotting the Martingale-residuals.

To reduce within-person data variability and reliably quantify individual sodium exposure, sodium intake was also modeled continuously using time-dependent Cox models, with cumulative average of urinary sodium/creatinine excretion as independent variable.[22,23] The hazard ratio for ESRD was determined per 100 mEq/g increase in SC-ratio. Potential confounders included in the Cox models were gender, age, baseline mean arterial BP, use of antihypertensive co-medication at baseline, 24-h urinary urea excretion during follow-up, creatinine clearance at baseline, and log-transformed 24-h proteinuria at baseline. For exploratory purposes, we adjusted for changes in mean BP and antihypertensive co-medication during follow up, and log-transformed 24-h proteinuria during follow-up in separate Cox models.

Correlations between urinary sodium excretion and proteinuria or BP at baseline and during follow up were analysed using linear regression; at least two measurements per patient were required.

Urinary sodium and urea excretion at the last visit were not considered to avoid an undesirable adjustment for sequelae,[22] related to an anorectic decrease in nutritional intake just prior to start of dialysis in patients progressing to ESRD.[24] All analyses were also performed using non-normalized sodium excretion as independent variable and the two sodium metrics were compared through Bayesian information criteria.[25]

All statistical analyses were performed using R, version 2.5.1. All data are presented as mean±standard deviation unless indicated otherwise. A P value of less than 0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics

The 500 included subjects had a mean of 5.4±2.8 urinary sodium and creatinine measurements over a follow-up of 26.2±15.6 months. Twenty-six patients (5.2%) had only one measurement. Their baseline characteristics were similar to those of subjects with more measurements (data not shown). Mean urinary sodium and sodium/creatinine excretion at baseline were 177.6±72.3 mEq/24h and 139.0±54.9 mEq/g, respectively. Based on their average urinary sodium/creatinine excretion during the observation period, 111, 336 and 53 patients were categorized in the LSD, MSD and HSD group, respectively (Table 1). Sodium intake was a relatively fixed trait since patient distribution to the three sodium intake groups did not change significantly when only baseline urinary sodium/creatinine measurements were considered (P=0.442). There were more males in the LSD than in the MSD and HSD groups and primary glomerular diseases were more frequent in the LSD than in the MSD group. Body-mass index, BP and creatinine clearance at baseline were similar among groups, whereas urinary protein/creatinine and urea/creatinine excretion were significantly lower in the LSD and MSD groups than in the HSD group.

Table 1: Baseline characteristics based on sodium diet groups

	Sodium diet group		
	LSD (n=111)	MSD (n=336)	HSD (n=53)
Demography			
Men (n [%])	100 (90.1%)	251 (74.7%) *	30 (56.6%) *†
Age (mean [SD], years)	52.0 (14.5)	51.2 (14.8)	56.2 (15.3) †
Body-surface area (mean [SD], m2)	1.81 (0.39)	1.82 (0.24)	1.78 (0.19) *
Body-mass index (mean [SD], kg/m2)	25.8 (3.8)	26.3 (4.7)	26.1 (5.1)
Renal disease			
Glomerular (n [%])	68 (61.8%)	161 (47.9%) *	26 (49.1%)
Interstitial, polycystic (n [%])	3 (2.7%)	13 (3.9%)	3 (5.7%)
Other, unknown (n [%])	40 (36.0%)	162 (48.2%) *	24 (45.3%)
Blood pressure			
Systolic blood pressure (mean [SD], mmHg)	142.4 (15.5)	144.5 (18.5)	146.2 (18.8)
Diastolic blood pressure (mean [SD], mm Hg)	89.3 (10.1)	88.8 (11.0)	89.0 (9.1)
Mean arterial pressure (mean [SD], mm Hg)	107.0 (10.4)	107.3 (12.2)	108.0 (10.7)
Renal parameters			
Creatinine clearance (mean [SD], ml/min)	43.8 (18.6)	43.6 (19.7)	40.1 (22.3)
Urinary creatinine excretion (mean [SD], g/day)	1.4 (0.3)	1.3 (0.4)	1.1 (0.4) *†
Urinary protein excretion (median [IQR], g/day)	3.0 (2.7)	2.8 (2.4)	3.1 (2.4)
Urinary protein/creatinine excretion (median [IQR], g/g)	2.0 (2.2)	2.1 (1.9)	2.6 (2.3) *†
Urinary urea excretion (mean [SD], mmol/day)	19.6 (11.2)	19.9 (7.6)	18.2 (7.3)
Urinary urea/creatinine excretion (mean [SD], mmol/g)	14.4 (8.5)	15.3 (4.9)	17.4 (6.7) *
Urinary sodium excretion (mean [SD], mEq/day)	121.5 (59.6)	185.2 (61.8) *	242.7 (82.7) *†
Urinary sodium/creatinine excretion (mean [SD], mEq/g)	87.8 (38.2)	140.1 (31.9) *	236.5 (64.8) *†

* P<0.05 versus LSD; † P<0.05 versus MSD

Sodium diet groups

Of the 92 subjects (18.4%) who progressed to ESRD, 18 (16.2%) were in the LSD group, 57 (17.0%) and 17 (32.1%) in the MSD and HSD group, respectively (P<0.001, Figure 1). The ESRD incidence rate per 100 patient-years was 6.1 (95% confidence interval 3.8 to 9.7) in the LSD group; 7.9 (6.1 to 10.2) in the MSD group, and 18.2 (11.3 to 29.3) in the HSD group. Patients in the HSD group had a 3.3 (1.7 to 6.4) fold and 2.4 (1.4 to 4.1) fold excess risk of progressing to ESRD compared to patients in the LSD (P<0.001) or MSD (P=0.002) groups, respectively. MSD compared to LSD patients had a non-significant 1.4 (0.8 to 2.4) fold excess risk of progressing to ESRD. Data did not change appreciably when the 26 patients with only one measurement of urinary sodium/creatinine ratio were not considered in the analyses.

Urinary protein/creatinine excretion decreased after three months of treatment (Figure 2, left panel) by 31% (P<0.001), 25% (P<0.001) and 20% (P=0.036) vs baseline in the LSD, MSD and

HSD groups, respectively. Thus, the antiproteinuric efficacy of RAS inhibition was significantly higher in LSD patients compared to MSD (P=0.031) and HSD (P=0.034). Consistently, there was a significant trend to less proteinuria reduction for increasing salt intake (P=0.012). After these initial changes, proteinuria declined further during follow up at a rate of 0.66% (0.00 to 1.29%) per month (P=0.039). However, whereas in LSD and MSD groups proteinuria reduction was sustained throughout the whole observation period, in the HSD group the antiproteinuric effect of RAS inhibition waned over time and urinary protein excretion tended to increase towards baseline values (Figure 2, left panel). Unlike proteinuria, BP was similar in the three groups (Figure 2, right panel) at baseline, shortly after RAS initiation and on subsequent follow up. Concomitant use of BP lowering medications was similar among groups at baseline, whereas on follow-up there were fewer patients on diuretic therapy in the LSD than in the MSD or HSD groups (Table 2).

As observed in the 500 subjects on ramipril therapy, also in the cohort of 172 controls on non-RAS inhibitor therapy subjects in the HSD group tended to have more proteinuria at baseline and on follow up than those in the LSD and MSD group, respectively. In controls, however, there were no appreciable differences in follow-up changes in proteinuria among salt intake groups. Again, BP was similar among groups throughout the whole observation period (Figure 3, Left and Right panel, respectively).

Table 2: Concomitant antihypertensive treatments at baseline and throughout follow-up in patient groups categorized as having been on a low- (LSD), middle- (MSD) or high sodium diet (HSD).

	Baseline			Follow-up		
	LSD	MSD	HSD	LSD	MSD	HSD
Alpha-adrenergic agents	33 (29.7%)	92 (27.4%)	12 (22.6%)	31 (27.9%)	68 (20.2%)†	7 (13.2%)
Beta blockers	24 (21.6%)	81 (24.1%)	14 (26.4%)	29 (26.1%)	78 (23.2%)	13 (24.5%)
Calcium channel antagonists[a]	25 (22.5%)	92 (27.4%)	20 (37.7%)	63 (56.8%)†	184 (54.8%)†	30 (56.6%)†
Diuretics	40 (36.0%)	132 (39.3%)	23 (43.4%)	35 (31.5%)	154 (45.8%)†*	25 (47.2%)*

[a] Note that patients in the intensified blood pressure control arm of the REIN-2 (which was achieved with felodipine) were for the present study classified as receiving calcium channel antagonists as concomitant treatment

* P<0.05 versus LSD in the same time period

† P<0.05 versus Baseline use in the same diet group

Sodium excretion as a continuum

A 100 mEq/g increase in urinary sodium/creatinine ratio was associated with a 1.61-fold (95% confidence interval 1.15 to 2.24) increase in ESRD occurrence. This association was independent of age, gender, underlying renal disease, previous inclusion in REIN or REIN-2, and baseline BP. The significance of the association, however, was partially lost [HR=1.38 (0.95-2.00)] after adjusting for baseline proteinuria (Table 3).

In the multivariable model adjusted for age, gender, BP, creatinine clearance, and concomitant antihypertensive treatment at baseline and 24-hour urea excretion throughout the whole study period, 100 mEq/g increase in urinary sodium/creatinine ratio was associated with 1.67-fold (1.07 to 2.60) excess risk of progression to ESRD (Table 3). Exploratory analyses showed

that the association was independent of changes in BP and antihypertensive co-medication on follow-up. Conversely, the significance of the association [HR=1.14 (0.72-1.80)] was fully lost after adjustment for baseline and follow up 24 hour urinary protein excretion, (Table 3). Similar findings were obtained when urinary sodium/creatinine excretion was considered as a continuous variable (Figure 4). With this approach unadjusted analyses showed a strong association between urinary sodium excretion and progression to ESRD (Model 1, Figure 4). The significance of the association was attenuated when analyses were adjusted for baseline proteinuria (Model 2) and was fully lost when adjustments included changes in proteinuria during the follow-up (Model 3).

Although similar findings were obtained when urinary sodium excretion was not normalized for concomitant urinary creatinine excretion (Table 3), the creatinine normalized model provided a better fit according to the Bayesian information criteria (BIC=1012 versus 1016 for the non-normalized model, using the same patients and measurements in both models).

Relationships between sodium, proteinuria and ESRD

Urinary sodium/creatinine excretion was significantly and positively correlated with urinary protein/creatinine excretion at baseline (R=0.134, P=0.013) and on follow up (R=0.182, P<0.001), whereas no correlation was found with BP at baseline (R=0.005, P=0.927) or during follow up (R=0.031, P=0.556). In turn, urinary protein/creatinine ratio at baseline [HR=1.30 (1.19 to 1.41)] and on follow up, [HR=1.38 (1.30 to 1.47)] predicted ESRD progression, independent of gender, age, creatinine clearance and BP.

Table 3: Time-dependent Cox model, hazard ratios per 100 mEq/d of urinary sodium excretion and per 100 mEq/g of urinary sodium/creatinine excretion

	Urinary sodium excretion		Urinary sodium /creatinine excretion	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Unadjusted:	1.35 (0.96-1.89)	0.089	1.61 (1.15-2.24)	0.005
Univariable adjusted				
Age	1.35 (0.96-1.90)	0.082	1.60 (1.14-2.24)	0.006
Gender	1.33 (0.95-1.88)	0.099	1.77 (1.26-2.50)	0.001
REIN / REIN 2 cohort	1.37 (0.97-1.93)	0.074	1.77 (1.28-2.54)	0.001
Diagnosis	1.34 (0.95-1.88)	0.094	1.61 (1.15-2.25)	0.005
Blood pressure	1.35 (0.95-1.91)	0.096	1.69 (1.19-2.40)	0.003
Proteinuria	1.11 (0.77-1.60)	0.592	1.38 (0.95-2.00)	0.086
Multivariable adjusted [a]				
Without proteinuria	1.67 (1.16-2.39)	0.006	1.67 (1.07-2.60)	0.025
Including proteinuria	1.36 (0.89-2.06)	0.150	1.37 (0.84-2.22)	0.202
Adjusted for changes during follow-up (time-dependent)				
Blood pressure	1.67 (1.16-2.42)	0.006	1.59 (1.01-2.50)	0.047
Proteinuria	1.28 (0.86-1.92)	0.223	1.14 (0.72-1.80)	0.573

[a] The multivariable model was adjusted for age, sex, mean arterial blood pressure at baseline, antihypertensive comedication at baseline, urinary urea excretion during follow-up, and baseline creatinine clearance

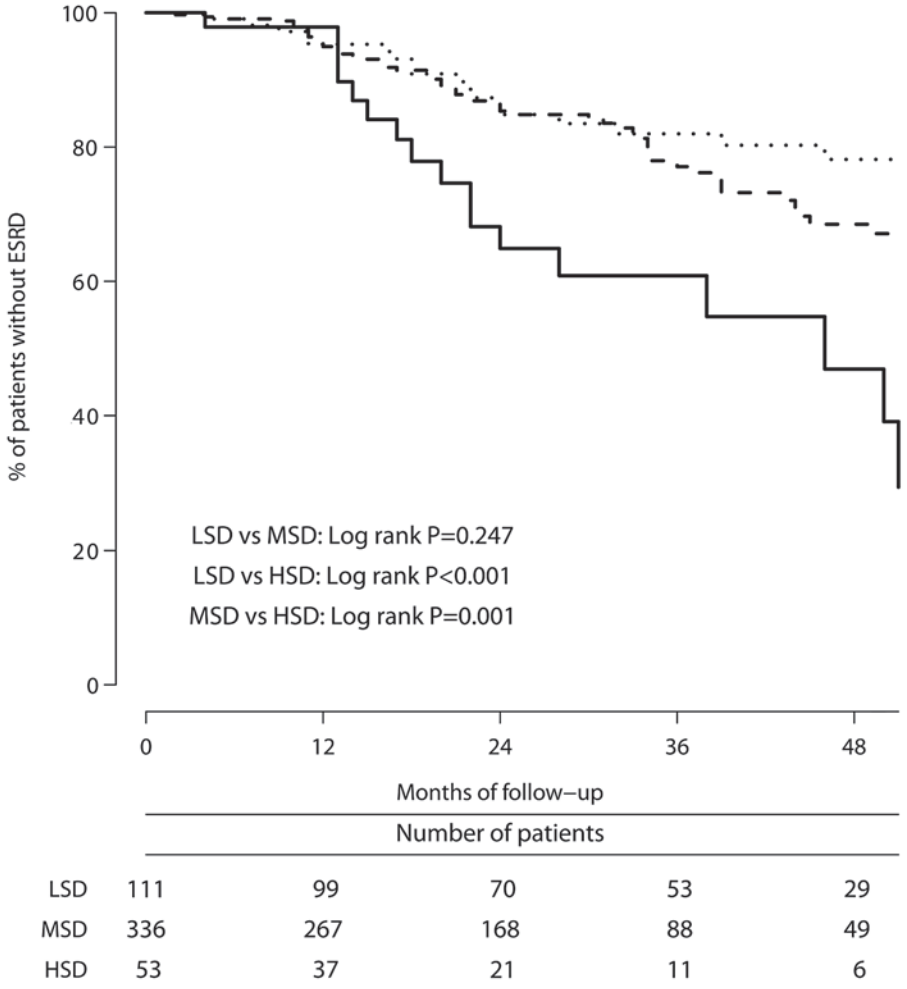


Figure 1: Kaplan-Meier ESRD survival curves in patients categorized in low- (LSD, dotted line), middle- (MSD, broken line) or high sodium diet (HSD, continuous line) groups according to their urinary sodium/creatinine ratio on follow-up

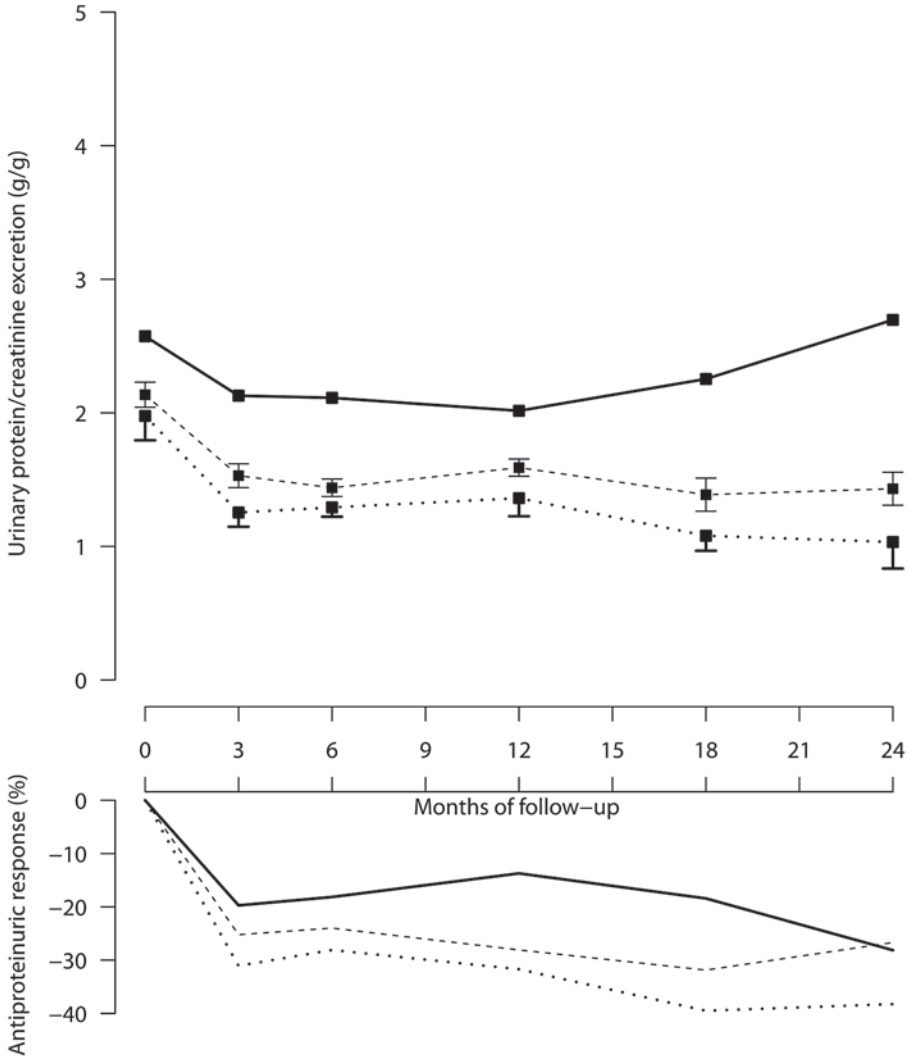
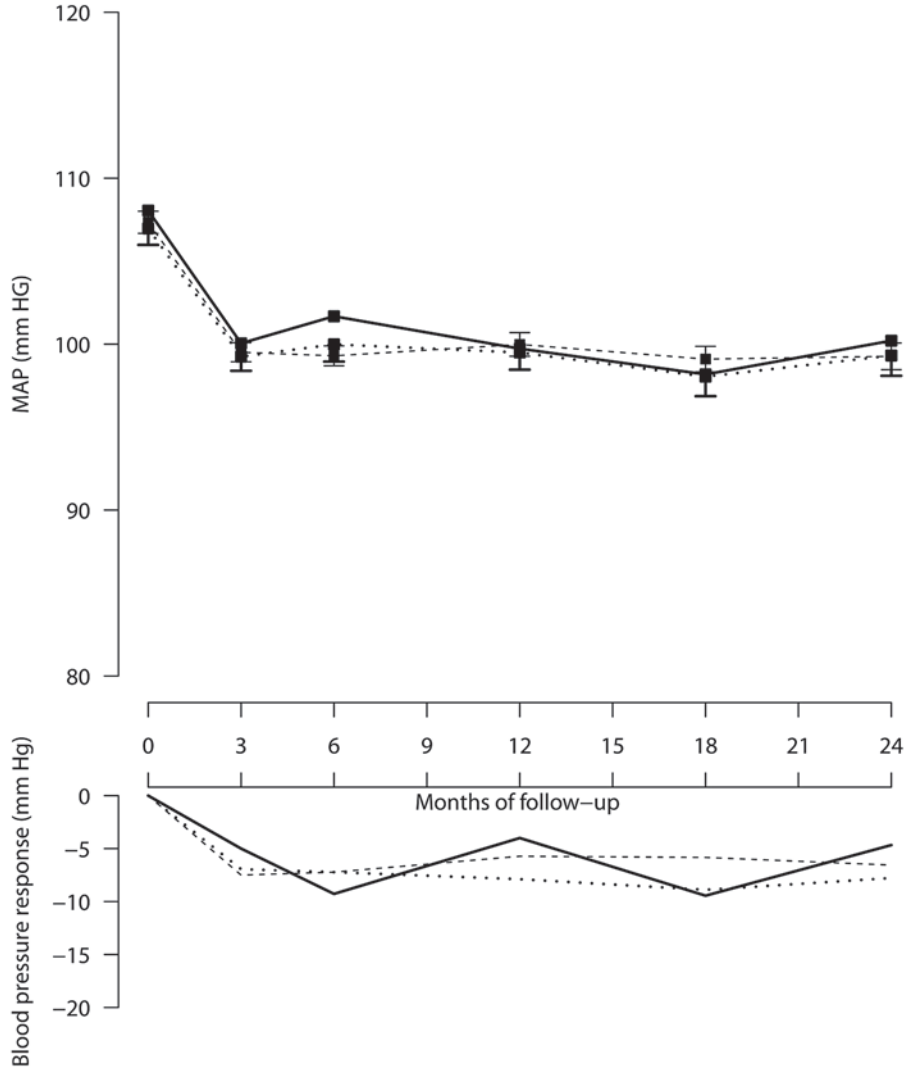


Figure 2A: Twenty-four hour urinary protein/creatinine excretion during follow-up (median and SE of the Median; median change from baseline, left panel); and mean BP during follow-up (mean and SEM; median change from baseline, right panel) in 500 patients on ramipril therapy categorized in low- (LSD, dotted lines), middle- (MSD, broken lines) or high sodium diet (HSD, continuous lines) groups according to their urinary sodium/creatinine ratio on follow-up.


120
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100
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MAP (mm HG)
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3
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Months of follow–up
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Blood pressure response (mm Hg)

Figure 2B

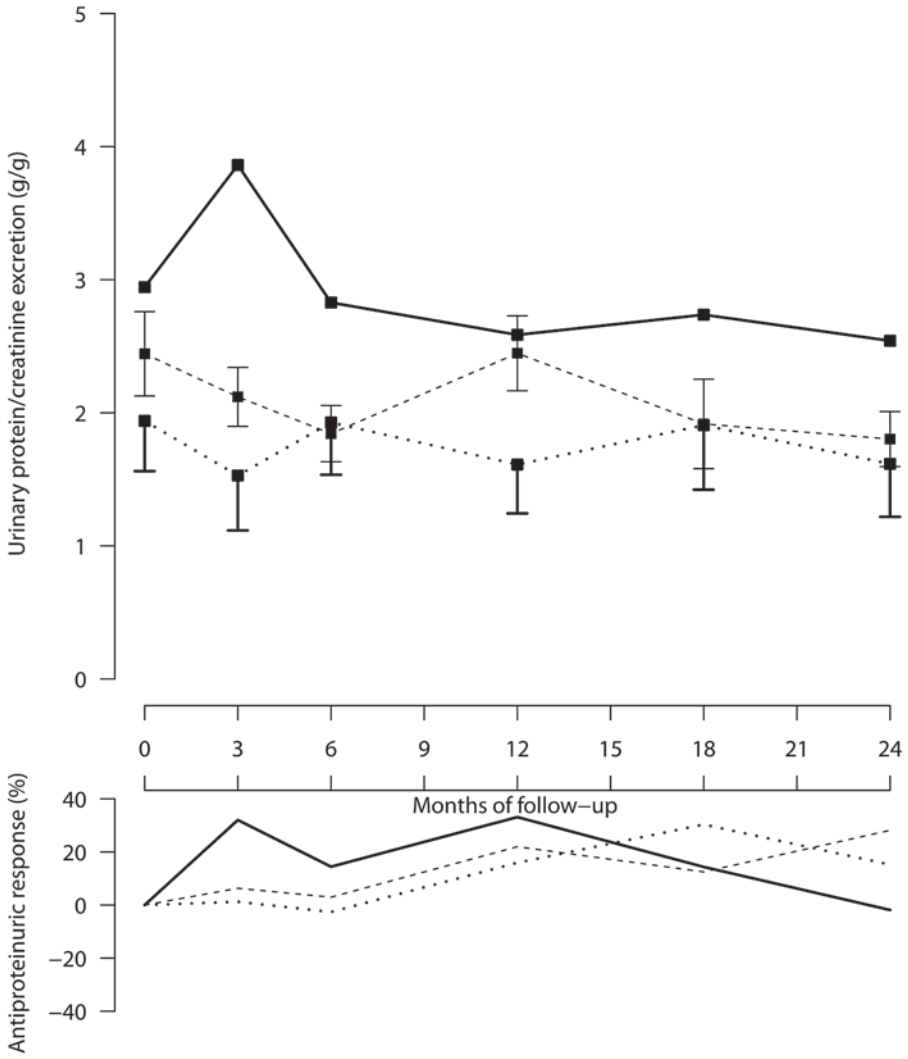
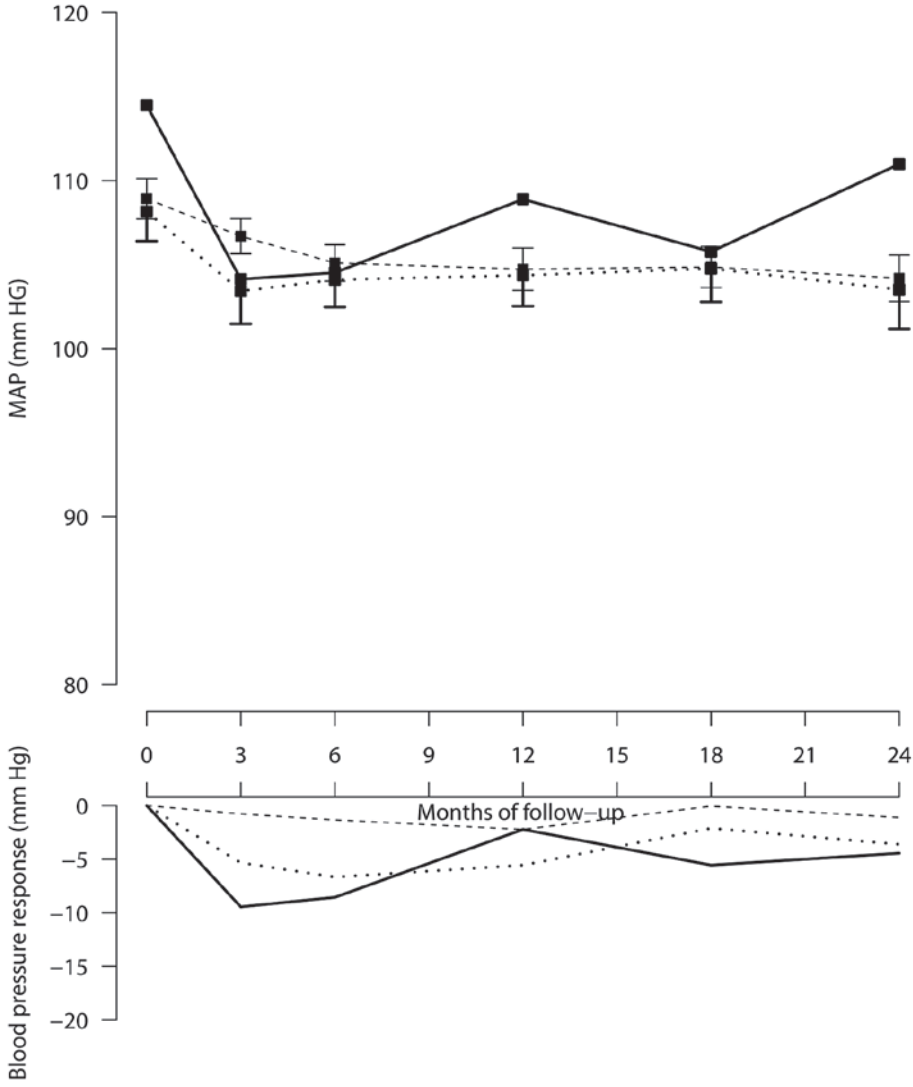


Figure 3A: Twenty-four hour urinary protein/creatinine excretion during follow-up (median and SE of the Median; median change from baseline, left panel); and mean BP during follow-up (mean and SEM; median change from baseline, right panel) in 172 controls on non-RAS inhibitor therapy categorized in low- (LSD, dotted lines), middle- (MSD, broken lines) or high sodium diet (HSD, continuous lines) groups according to their urinary sodium/creatinine ratio on follow-up.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Months of follow–up
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Blood pressure response (mm Hg)

Figure 3B

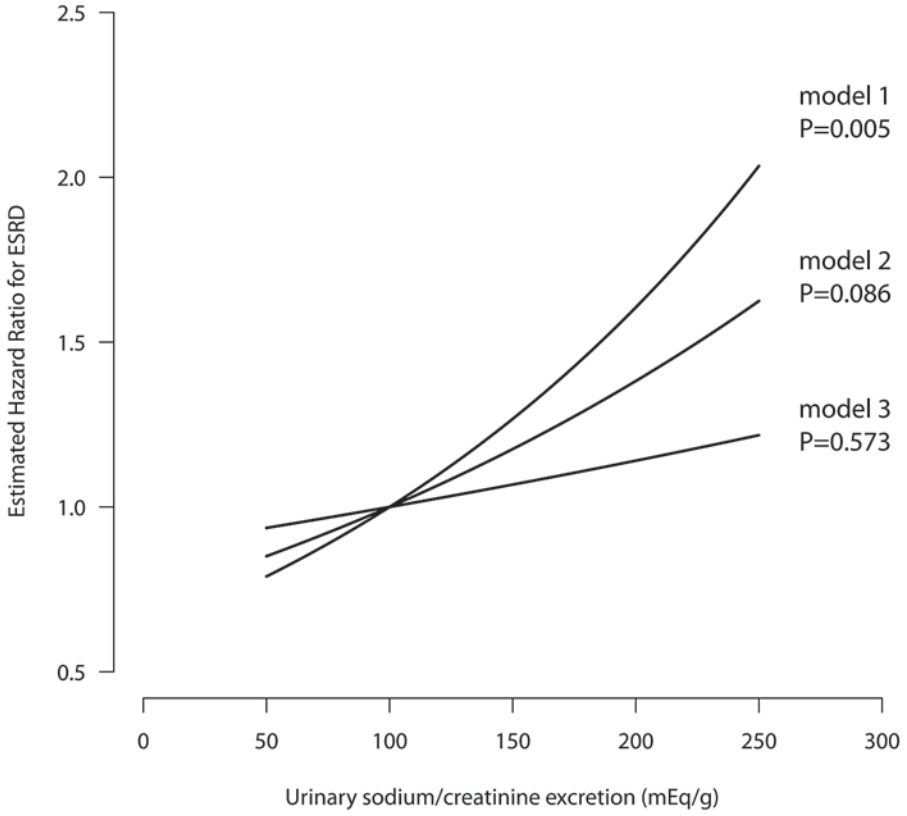

Figure 4: Association between urinary sodium/creatinine excretion on a continuous scale and ESRD for the unadjusted Cox PH model (model 1), adjusted for baseline proteinuria (model 2) and adjusted for changes in proteinuria during follow-up (model 3). The dotted line shows the baseline HR of 1 for patients with a urinary sodium/creatinine excretion of 100 mEq/g.

DISCUSSION

Two are the key findings of our present study: 1. In humans with non-diabetic CKD on ACE inhibitor therapy high salt intake is associated with increased risk of progression to ESRD, 2. The excess risk associated with increased salt exposure appears to be mediated by blunted antiproteinuric effect of ACE inhibitor therapy in this population. Among five-hundred subjects, those who had a urinary sodium excretion exceeding 200 mEq per gram of urinary creatinine had a 2.4 and 3.3 fold higher incidence of ESRD compared to those with a urinary sodium/creatinine excretion between 100 and 200 mEq/g or less than 100 mEq/g, respectively. Despite a similar blood pressure control, urinary proteins decreased more in patients in the low and middle salt intake group than in those in the high salt intake group. Even more important,

in the high salt intake group the antiproteinuric effect of ramipril therapy waned over time and urinary protein excretion tended to increase towards baseline values. These findings are consistent with well-established evidence that the renoprotective effect of ACE inhibitors or ARBs is largely explained by their effect of reducing urinary proteins,[1-4] an effect that is limited or even blunted by excess sodium intake.[8-12] Increased sodium exposure could also explain the "escape phenomenon" observed in previous studies and why it was more frequent in subjects who were not on concomitant diuretic therapy.[26-29]

On average, one-hundred mEq increase in daily sodium excretion per gram of creatinine (equivalent to an incremental intake of 125 mEq of sodium or seven grams of salt) increased the risk of ESRD by 61 percent. This excess risk was independent of age, gender, underlying renal disease, creatinine clearance at inclusion, as well as protein intake and BP control throughout the observation period, but was not significant anymore when the analyses were adjusted for 24-hour urinary protein excretion at inclusion and on follow up. On the other hand, urinary sodium excretion was positively correlated with baseline and follow up proteinuria that, in turn, independently predicted the risk of ESRD progression. Although the number of events and of patients was too small to formally test the possibility of a significant interaction between urinary sodium excretion, proteinuria and risk of progression to ESRD, the above findings converge to indicate that the association between salt intake and outcome was largely mediated by the effects of salt exposure on proteinuria. Finding that high sodium intake was associated with more proteinuria already at inclusion was consistent with previous data showing that daily sodium intake exceeding 200 mEq enhanced proteinuria in subjects not on RAS inhibitor therapy.[18] Thus, our data suggest that subjects with high salt intake had more proteinuria at inclusion because of the association of sodium overload with urinary proteins.[8-11,30-34] This interpretation is consistent with evidence that also among the 172 controls on non-RAS inhibitor therapy proteinuria was more severe in patients with high salt intake despite patient characteristics and BP control were similar among salt intake groups.

Finding that BP control was independent of daily sodium intake can be explained by the fact that antihypertensive therapy was titrated to pre-defined BP targets. Indeed, subjects with more sodium intake more frequently required combined treatment with a diuretic - first line therapy in both REIN and REIN-2 studies.[1-3,19] Addressing why the antiproteinuric and renoprotective effect of ACE inhibitor therapy in subjects with high sodium intake was not restored by concomitant diuretic therapy was beyond the purposes of the present study. A reasonable speculation is that sodium overload was not fully corrected by diuretic therapy. Of note, sodium overload increases ACE activity in renal and vascular tissues, which enhances vascular conversion of angiotensin-I to angiotensin-II and blunts the effects of ACE inhibition in rats and humans with high sodium intake.[35] Independent of BP control, enhanced intrarenal ACE activity has been associated with accelerated renal damage in several experimental models of chronic renal disease[36] and might explain at least part of the excess proteinuria and renal risk associated with high sodium intake observed in our present study.

Average sodium intake approximated 10 grams per day, more than two folds the intake recommended by current guidelines for renal patients.[37] This is of concern since our data show that even a small increase in salt intake is associated with an incremental risk of ESRD. A daily salt intake exceeding 14 grams (equivalent to more than 200 mEq per gram of creatinine) was associated with an ESRD rate of 18.2% per 100 patient-years, compared to 7.9% in subjects with less salt intake. Previous studies consistently showed the benefits of low sodium diet on BP and proteinuria, but provided no information on the harmful consequences of huge salt intake on hard clinical end points.[8-11] These novel findings are relevant to health care providers since prevention strategies aimed to avoid extreme excess in sodium intake - even without dietary restrictions that might affect patient compliance[38] - would be extremely important to substantially limit the risk of renal disease progression in clinical practice.

Monitoring salt intake

We categorized our patients according to three ranges of sodium intake that were defined on the basis of cut-off levels similar to those used in previous studies.[10,11,18,39] At variance with previous studies that used a single baseline measurement of urinary salt excretion or the average of the measurements on follow-up,[40] in our time-dependent Cox model we used, for the first time in this clinical setting, a cumulative average of sodium excretion. This is a gold standard approach to model the relationship between longitudinally measured covariates and a given event[22] that has been extensively applied in cardiovascular studies to assess the risk of events associated with the consumption of certain foods or nutrients. This approach allowed to reduce within-person data variability and more reliably quantify long-term sodium exposure.[41] In this patient cohort, sodium intake was a relatively fixed trait and few patients appreciably changed their dietary sodium intake during follow up. Normalizing urinary sodium excretion to concomitant creatinine excretion allowed to account for erroneous urine collections, but also resulted in an excess of females and older patients in the high sodium group that was likely explained by the reduced urinary creatinine excretion in these two populations. Since sodium and protein intake are often correlated we also adjusted the Cox-model for urinary urea excretion, as a marker of dietary protein intake. Thus, the association between urinary sodium excretion and ESRD reflected a genuine predictive value of sodium intake unaffected by a confounding effect of concomitant protein intake.

Strengths and Limitations

In addition to the use of gold-standard measures to monitor salt intake, the present study had two major strengths: 1. analyses considered a hard end point such as ESRD; 2. data were obtained from a large and homogenous population prospectively followed and treated according to standardized guidelines in the setting of controlled clinical studies. This enhanced the clinical relevance of the study findings and limited the confounding effect of random fluctuations due

to heterogeneous patient characteristics and treatments. This enhanced the reliability of the analysis and the robustness of the findings, despite the relatively small number of patients and events. The findings were further strengthened by evidence that a similar association between sodium exposure and outcomes was observed when urinary sodium excretion was considered as a categorical or a continuous variable. Moreover, finding that average sodium excretion in our study population was similar to that reported in other observational studies in renal patients[42] or in general population samples[43] enhanced the generalizability of the results. The major limitation of the present study is that this was a post-hoc analysis of trials originally designed for other purposes. Due to the observational nature of our study, a direct causal relationship between higher salt intake and worse outcome while on ACE inhibitor therapy cannot be definitely proven. Such an association, however, was not appreciable in controls on non-RAS inhibitor therapy. Independent of the above, the pathogenic role of excess sodium exposure could be definitely addressed by intervention trials prospectively testing the association of diets with different salt intake on renal disease progression.

CONCLUSIONS

Our present observational analysis suggests that in CKD patients on ACE inhibitor therapy, high sodium intake is associated with accelerated progression to ESRD, mediated by increased proteinuria but independent of underlying renal disease, BP control and urea excretion, taken as a marker of dietary protein intake. Avoiding excess sodium exposure may be important to slow renal disease progression and limitations in salt intake are expected to achieve major clinical benefits in this population that will largely offset the small inconveniences of minimal dietary restrictions. Optimal salt intake to optimize renoprotection in the setting of a multimodal approach titrated to urinary proteins and other determinants of renal disease progression[5] needs to be identified in the setting of prospective clinical trials.

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Chapter 9

General Discussion

Partly adapted from:
Postma MJ, Boersma C, Vandijck D, Vegter S, Le HH, Annemans L

Expert Review of Pharmacoeconomics & Outcomes Research. 2011 Aug;11(4):367-9

DISCUSSION

The value of personalized medicine for renal patients

Renal diseases and its comorbidities are debilitating, increase mortality and put a large burden on societies' health-care budgets. A common consequence of progressive renal function loss is end-stage renal disease (ESRD), with a disheartening quality of life, high treatment costs and a fatality rate that is one of the worst among many diseases in the industrialized world. Main goals in nephrology care currently are, and will be in the future, to delay and preferably altogether prevent the onset of ESRD and its complications, and to improve survival for patients with ESRD. Strategies to improve long term outcomes will have to take into account the balance between costs, clinical benefits and adverse effects.

Personalized approaches to improve pharmacotherapy for renal patients are increasing in importance and are under constant development. Determining a patients' genetic makeup in order to predict or optimize therapeutic response has become the approach most commonly associated with personalized medicine. However, also non-genetic approaches in which individual patient characteristics influence disease progression, therapy response or adverse drug effects, may be considered. In renal disease as well as other medical fields, personalizing medicine provides new challenges for assessing it's clinical and health economic value.[1] This thesis deals with epidemiological and health economic issues relating to genetic and non-genetic approaches to improve pharmacotherapy for patients with renal diseases. This chapter summarizes and discusses the main results, findings and ideas as described in the previous chapters, including some future perspectives.

PRINCIPLE FINDINGS AND FUTURE PERSPECTIVES

PART I: GENETIC APPROACHES TO IMPROVE PHARMACOTHERAPY

Part I of this thesis focused on the value of genetic approaches to improve pharmacotherapy for the renal patient. **Chapter 2** described a literature review presenting an overview of pharmacoeconomic analyses in the field of pharmacogenetics and –genomics. The aim was to gain more insight in the different pharmacogenetic programs under health economic evaluation; as well as the level of adherence to current pharmacoeconomic guidelines. Using a systematic literature search, 20 studies were assessed covering among others Cytochrome P450 (CYP) 2C9 polymorphisms, Thiopurine s-Methyltransferase (TMPT) polymorphisms and the Angiotensin-Converting Enzyme Insertion/Deletion (ACE I/D) polymorphism. It was noticed that no studies had been performed in the field of renal diseases. Most studies reported that genetic screening was cost-effective or even cost-saving. This important finding underscores the large potential value of pharmacogenetic screen-and-treat programs. More disappointing was the lack of standardization regarding methodological aspects such as the economic perspective and sensitivity analyses. In particular, one important limitation was the failure of many studies to

provide a sufficient evidence-based rationale for the modelled association between genotype and phenotype. Chapter 2 concluded that the field of pharmacogenetics is promising (both from clinical and health economic viewpoints) but also still under development. To assist in future health economic evaluations, the review provided a checklist of items that should always be taken into account regardless of the clinical field of the analysis. This set of recommendations has been used for the EU HIScreenDiag-project.[2]

WORK RELATED TO CHAPTER 2

In 2010, our group, assisted by a pharmacy student of the University of Groningen, performed an update of the literature.[3] This update included over 40 economic studies, over twice the number of studies included in our 2008 review.[4] The quality of the economic analyses had improved over time; we noticed increased use of cost-utility analyses (the most solid type of health-economic analysis), longer time windows and more extensive sensitivity analyses. Interestingly, most studies were still conducted by academia or hospitals without commercial funding. This supports the thesis that currently, the main focus lies in increasing awareness of genetic testing rather than influencing treatment- and reimbursement policies. Thus, the challenge of future research is to actively involve actual decision making and reimbursement of genetic test strategies.

Chapter 3 used the caveats and recommendations from chapter 2 to perform a pharmacoeconomic analysis using pharmacogenetic data. The analysis focused on a common polymorphism that influences ACE inhibitor effectiveness in nondiabetic renal disease: the ACE insertion/deletion (I/D) polymorphism. In these patients, patients with the ACE DD polymorphism show a markedly better response to ACE inhibitor treatment. The economic evaluation showed that overall, ACEi therapy is a cost-saving treatment compared with placebo in nondiabetic nephropathy. This is in accordance with earlier studies,[5,6] and is driven mainly by the delay in progression towards expensive dialysis care costs. The influence of the ACE (I/D) genotype on cost-effectiveness outcomes was substantial; ACE inhibitor treatment saved more costs and more health gains were achieved in those with the ACE DD genotype than in those with the ACE II/ID genotype. Indeed the analyses estimated a considerable chance that ACE inhibitor therapy is not (cost-) effective in patients with the ACE II/ID genotype. This study justifies further clinical research into drugs that are not (or less) influenced by the ACE I/D polymorphism. In chapter 3 we also assessed a potential pharmacogenetic screening program. It was found that an alternative treatment featuring even a modest increase in effectiveness compared with ACEi therapy for patients with the ACE II/ID genotype can be incorporated in a cost-effective screen-and-treat strategy. Thus, this study demonstrated that the large potential value of pharmacogenetic screen-and-treat programs, as noted in chapter 1, also applies to the field of nephrology.

Chapter 4 describes another cost-effectiveness analysis based on genetic information in renal disease. This study focused on a previously observed association with better survival in dialysis patients with systemic inflammation carrying a deletion variant of the CC-chemokine receptor 5 (CCR5).[7] Following the concept of Mendelian randomization it was hypothesized that in an analogous manner, pharmacological CCR5 blockade protects against inflammation-driven mortality. Based on this assumption, the analysis in chapter 4 estimated that pharmacological blockade of the CCR5 receptor in inflamed dialysis patients can indeed be incorporated in a potential cost-effective screen-and-treat program. Similar to other health-economic works,[4,8] this study provides a formal rationale for clinical research, and thus helps in prioritizing research goals. Thus, the study illustrates the potential of cost-effectiveness assessments alongside genetic association studies from an observational setting for drug development programs.

PART II: NON-GENETIC APPROACHES TO IMPROVE PHARMACOTHERAPY

Part II focused on non-genetic personalized approaches for renal patients. The health economic value of phosphate binders was explored in **chapter 5**. Non-calcium phosphate binders have advantages in that they do not lead to hypercalcemia and may be effective in patients not (adequately) responding to calcium binders. These newer drugs are more expensive however, which advocates against their first-line use.[9,10] For the first time in a cohort comprised of predialysis and dialysis patients, we reported the cost-effectiveness of non-calcium based phosphate binders as second-line treatment, for specific patients. Such a treatment strategy was found to be *dominating*, i.e. leading to lower costs as well as clinical benefits. This health technology assessment aims to assists rational pharmacotherapy in renal disease based on personalized information, i.e. an individuals' treatment response.

WORK RELATED TO CHAPTER 5

A recent study of our group, assisted by pharmacy students of the University of Groningen, explored phosphate binders use of dialysis patients (identified by proxy of erythropoietin comedication).[11] Surprisingly, the study found that despite a lack of health economic rationale, non-calcium phosphate binders were increasingly used as first-line treatment. This trend is shown in figure 1. In 2009, first-line use of sevelamer was over 60% of total phosphate binder use. This finding demonstrates and cautions against a discrepancy between health technology assessments and drug prescription behaviour in clinical practice; it also emphasises that pharmacoeconomics deserves a prominent role in clinical treatment guidelines.

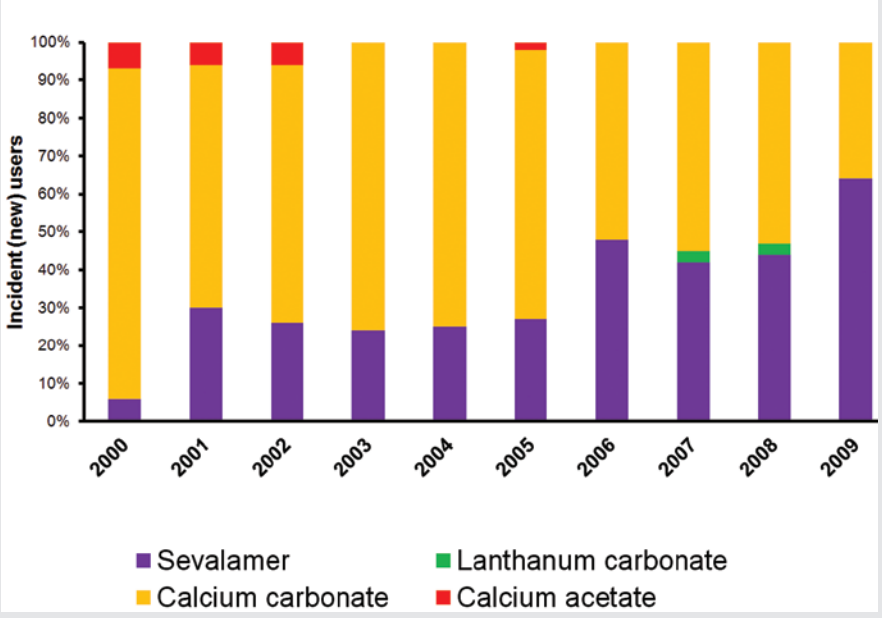

Figure 1: First-line use of phosphate binders in dialysis patients from 2000-2009

Chapter 6 reported an investigation of drug utilization patterns of ACE inhibitors and ARBs, using the IADB.nl prescription database. We analyzed data of over 50,000 incident users of ACE inhibitors or ARBs. Remarkably, compliance and persistence were similar between users of ACE inhibitors and ARBs despite their often assumed differences in tolerability. On the other hand, users of ACE inhibitors more often switched therapy, primarily to an ARB. Another finding was that drug utilization patterns were very similar between different ARB molecules. This finding supports the prescription of cheap, generic ARBs as opposed to ARBs that are still under patent. Due to the limitations of our prescription database IADB.nl,[16,17] we were not able to limit this analysis to renal patients only. Further research should be directed as to whether differences exist between patient subgroups.

Chapter 7 explored a common, but easily overlooked adverse drug effect of ACE inhibitors, dry cough. This study followed on the premise that physicians who fail to recognise this adverse drug effect may attempt to treat it with antitussive agents instead of substituting other RAAS intervening agents. Using for the first time in the IADB.nl database a prescription asymmetry analysis,[12] we found an excess of patients being prescribed antitussive agents within half a year of initiating ACE inhibitor therapy. The estimated frequency of antitussive treatment of ACE inhibitor induced dry cough was 15%. This study showed that major improvements in pharmacotherapy need not always come from complex pharmacogenetic or pharmacoeconomic considerations, but can also be achieved by simply following well-known pharmacotherapeutic rationales, applied to and paying close attention to the individual renal patient. This study also underscores the need for high quality pharmacotherapeutic knowledge. Fortunately, The Netherlands has a well-developed system of pharmacotherapy audit meetings (PTAMs), in which prescription behaviour is regularly discussed and analyzed. High quality PTAMs have been found to improve rational pharmacotherapy.[13] We previously suggested that PTAMs are a possible explanation for the high agreement between antihypertensive drug choices and guidelines in the Netherlands.[14] PTAMs and similar systems should be continued and developed in order to continuously optimize pharmacotherapy for renal patients.

WORK RELATED TO CHAPTER 7

We followed up our research on ACE inhibitors and dry cough together with a group of pharmacy students of the University of Groningen. The aim of this follow-up study was to investigate the role of ACE inhibitor induced cough on therapy compliance and persistence with ACE inhibitors. This research is currently ongoing. Preliminary results indicate that ACE inhibitor treated patients in which the adverse drug effect of dry cough is not recognized, indeed show lower compliance compared to patients without this adverse effect (compliance: 78.2% versus 84.1%, P=0.039). This further strengthens the thesis that timely recognition and correct treatment of adverse drug effects may be a cheap and effective personalized approach to improve therapy effectiveness in renal patients.[15]

Chapter 8 described a post-hoc analysis of the Ramipril Efficacy In Nephropathy (REIN) and REIN-2 trials. This analysis draws back on the early personalized lifestyle suggestions given before pharmacotherapeutic options were available in renal disease: restriction of dietary salt intake. It is well-known that high sodium intake limits antihypertensive and antiproteinuric effects of angiotensin-converting-enzyme inhibitors (ACEi) in renal patients, as well as in hypertension, in short-term studies. The impact of sodium intake on the long term outcome of ACEi treatment, however, is unknown. We evaluated the effect of sodium intake on proteinuria and progression to end-stage renal disease (ESRD) in 500 non-diabetic renal patients on ACE inhibitor therapy during a follow-up of over 4.25-years. This study was the first to assess the impact of sodium intake on hard clinical endpoints in renal disease. The main finding was that high sodium intake (more than 14 grams of salt daily) blunted the antiproteinuric effect of ACE inhibitor therapy which, independent of blood pressure control, was associated with less effective protection against progression to ESRD. These results require confirmation from prospective intervention studies. These should also focus on the potential benefits of even further reductions in sodium intake; the study strongly suggests that even a modest restriction of sodium intake can optimize renoprotection and substantially improve long term renal outcome.

GENERAL DISCUSSION

The need to produce, judge and disseminate the value of pharmacotherapy has seen an upsurge in the last decade. Indeed, health technology assessments (HTAs) have become a prerequisite before widespread clinical use of pharmacotherapies in Western countries can be considered. HTAs use evidence-based medicine techniques and provide a toolkit comprising of criteria, standards, procedures and guidance for use in practice.[18] Even more, HTAs informs or advices reimbursement decisions in several Western countries.[19] Health technology assessments have proven to be very useful in analyzing new pharmacotherapies at the population level. In particular, the HTA process defines the procedures and requirements that provide the suppliers of the technologies with clear-cut pathways to market access and reimbursement. Indeed, in many Western economies the pathways for manufacturers to get new drugs to market are fairly straightforward, with clear steps and decision criteria centered around clinical information, such as epidemiology, burden of disease, and the effectiveness and safety of therapy.[20] Furthermore, guidelines for cost–effectiveness analyses provide methodological standards.[21,22]

Personalized approaches to improve pharmacotherapy are increasing in importance but provide new challenges for HTAs.[1] In contrast with non-personalized approaches, there is an absence of implemented procedures, criteria and standards in assessing personalized medicine. Thus, compared with manufacturers of innovative drugs, manufacturers of innovative testing technologies or other personalized approaches are faced with higher uncertainties and vagueness with regards to assessing clinical and health economic benefits. Several difficulties for HTA of personalized medicine can be identified. Assessment of epidemiology and burden of disease may suffer from the inherent limited clinical evidence. Furthermore, information on therapy effectiveness and safety are almost exclusively based on population level data, often inferred from efficacy and toxicity evidence from randomized controlled trials. A related issue is the desire of HTA bodies to measure effects in 'hard' end points for morbidity and mortality rather than intermediate end points, such as biomarkers and subclinical or asymptomatic disease. Finally, HTAs require additional information not only on the effectiveness and safety of the pharmaceutical, but also on the costs and predictive power of the diagnostic or testing element.

Given the general lack of the HTA-approach in personalized medicine, the question arises whether standard HTA methodology, guidelines and criteria would be applicable at all. We argue that this set of tools, in principle, indeed seems adequate. Firstly, difficulties related to limited data also exist in other fields, such as orphan diseases. It should be noted, however, that in The Netherlands (but not in some other countries such as Scotland) orphan drug developers can be exempted from providing a full pharmacoeconomic evaluation.[23] This, together with other incentives, aims to stimulate the development of orphan drugs – an approach that may be extended to personalized medicine. Secondly, although cost–effectiveness estimates, sensitivity analyses and budget impact predictions can be expected to differ between personalized and

conventional HTAs, this is no reason to adopt different HTA criteria. Instead, it calls for careful assessment of these differences. Thirdly, when only intermediate end points are available, it is well-accepted to use models to extrapolate to relevant clinical measures. Lastly, we noted that many aspects of HTAs were in fact common between non-personalized and personalized medicine, for example discounting issues, choice of comparator and measurement of quality-adjusted life years.[4,8]

Some specific aspects of HTA of personalized medicine should be considered; slight revisions in guidelines and criteria may be appropriate compared with population-based innovative drugs' assessments. This mainly applies to the field of pharmacogenetic screening programs (although it may be extended to other personalized approaches as well). For example, potential negative effects resulting from false-positive outcomes of testing warrant consideration, including quality-adjusted life-years impacts. Moreover, ethical aspects may not be in line with economic arguments seeking optimal sensitivity, specificity and cost combinations. Notably, the level of economic evidence may differ from what is generally experienced in population-based medicine; thus stressing the need to include all evidence including potentially conflicting results from case-control and observational settings into the economic analysis. Given genetic variability, the question as to whether the patients in the studies on the testing and diagnostic technologies are representative of the target groups for personalized medicine is one of utmost importance, and specific studies may be required to ensure representativeness. Furthermore, and fully in line with efficacy/effectiveness issues rather than clinical validity, the test should show a high clinical utility in practice, translating into an acceptable cost–effectiveness that is robust in extensive sensitivity analysis regarding uncertainty in test characteristics such as accuracy and predictive value.

The caveats and recommendations described above have been incorporated in a checklist of items that should always be taken into account in the assessment of pharmacogenetic screening programs.[4] This set of recommendations have been used for the EU HIScreenDiag-project.[2]

In general, we conclude that economic guidelines developed for population-based medicine as a set of standards are also adequate for evaluating personalized medicine technologies, although slight changes and specific foci should be made to optimize applicability in testing strategies. If specific points listed are taken up in the coming years and further applications are undertaken along these lines, HTAs in personalized medicine may highly benefit from the abundance of experience that has been gathered with HTA of population-based medicine.

The value of sodium restriction in renal patients

The potential health economic value of reducing dietary sodium intake in renal populations is worth discussing. A recent literature review identified studies that assessed the health economic value of interventions to reduce sodium intake on the population-wide level.[24] The location of the interventions and the method used to achieve sodium reductions varied, the conclusion though was the same for all studies: population-wide interventions for salt reduction are very cost-effective. The body of evidence on the value of sodium reduction in (diseased) subgroups, especially renal populations, however is scarcer and deserves further attention.[25] The cost-effectiveness of nutritional counselling has been studied for patients with hypertension[26]; obesity and ischaemic heart disease[27]; previous myocardial infarction[28]; and indeed chronic kidney disease.[29] This last study did not study the effect of sodium reduction but of low-protein diets. Thus, there is a need for health economic evaluations of sodium intervention programs in renal populations, which are known to be more salt-sensitive than the general population.[30]

As discussed in the previous chapter, HTAs of personalized medicine approaches often have to deal with difficulties related to scarceness of data and uncertainty of effects. In this respect, an evaluation of the value of sodium restriction in renal patients should have considerable advantages. Firstly, the body of evidence supporting the thesis that high dietary sodium intake is a determinant of therapy resistance to blockade of the renin–angiotensin–aldosterone system (RAAS) is large, growing and unambiguous.[30] Secondly, the analyses presented in chapter 7 support that the deleterious effects of high dietary sodium intake are not only expressed in short-term studies on intermediate endpoints,[31-35] but indeed affect hard renal endpoints. Thirdly, the test characteristics of this personalized approach are favorable; sodium intake can be measured accurately by analysis of 24 hour urinary sodium excretion, preferably normalized to 24 hour urinary creatinine excretion.[36] If 24 hour urinary collections prove in clinical practice to be too cumbersome or not feasible, regular assessment using spot urine samples provides a fast, cheap and accurate alternative to predict 24 hour sodium excretion.[37] Finally, the costs and economic benefits of a dietary intervention program are favorable. Dialysis care costs are around €70,000 per annum;[38] an amount that justifies the allocation of specialized dieticians for renal patients. Specialized dietary assistance might indeed prove to be necessary because compliance to dietary recommendations has been reported to be low in renal patients.[39]

Pharmacoeconomics, end-of-the-pipeline and first step research

Health economics is often regarded "end-of-the-pipeline" research, meaning that after years of drug development and clinical testing, assessing the cost-effectiveness is the last step in determining its clinical value. In that sense, chapters 3 and 4 followed an unconventional rationale. In both chapters, *hypothetical* drug treatment strategies were evaluated.

In chapter 3, a drug treatment was evaluated that was assumed to be less dependent on the ACE genotype. Angiotensin-II receptor blockers are thought to be less influenced by the ACE (I/D) gene - and have even been modelled as such in health technology assessments.[40] However this assumption is far from certain. This caveat has been voiced in the checklist provided in chapter 2, which recommended that the association between genotype and phenotype must be carefully described.

In chapter 4 the study rationale was also unconventional – and demonstrative of new applications of health economics. Using genetic information the hypothesis was made that pharmacological blockade of the CCR5 receptor would confer clinical benefits to dialysis patients. Interestingly, CCR5 receptor antagonists are currently used in therapies for HIV infection. It should be noted that although the health economic evaluation *suggests* good value for money of CCR5 receptor antagonists, this is not a guarantee. Indeed, equivalence between genetic effects (of the CCR5 polymorphism) and associated pharmacologic effectiveness (of CCR5 antagonists) is not a given fact. For example, a discordance has previously been described between the genetic effect of familial hypercholesterolemia and the associated effectiveness of statins on cardiovascular mortality.[41] An explanation for this discrepancy lies in the fact that genetic factors, as opposed to pharmacologic interventions, cause life-long differences in risk factors.[41] Genetic factors are also not affected by traditional sources of variability in effectiveness, such as therapy compliance. Still, while the true effectiveness of pharmacological CCR5 blockade in dialysis patients is not (yet) known, this study provides valuable information for future clinical trials. Clinical trials are time consuming and expensive, prohibiting the evaluation of every interesting hypothesis. The results of chapter 4 provided a formal rationale to design and conduct clinical studies.

Chapters 3 and 4 show that health economics is not only "end-of-the-pipeline" research; it may also serve as a first step for clinical studies on novel pharmacotherapeutic options.

The health economic paradox of future dialysis costs

Chapters 3, 4 and 5 identified a fundamental issue in health economic analyses that warrants discussion, namely the inclusion of dialysis care costs in health technology assessments in ESRD patients. The cost-effectiveness of dialysis can roughly be estimated by assuming 1) a health-related quality of life of 0.60 for dialysis patients [42]; 2) yearly costs of dialysis of €70,000 [38]; and 3) a negligible life-expectancy of ESRD patients without dialysis care. The incremental cost-effectiveness ratio of dialysis than is 70,000 / 0.6 ≈ 120,000 euro per QALY. This ICER exceeds thresholds that society is generally assumed to be willing to pay for medical interventions. Nonetheless, dialysis treatment *is* provided around the world wherever health care budgets allow,[43,44] including in countries that normally uphold strict cost-effectiveness thresholds such as the United Kingdom and Canada. The phenomenon in which society will spare no costs in order to prevent individuals from certain death is called the "Rule of Rescue".[45] This Rule also applies to some other medical treatments (e.g. chemotherapy, with ICERs up to the millions of euros) and non-medical interventions (e.g. search-and-rescue operations at sea).[45] Treatments that do not prevent *certain* death but reduce the *probability* of death generally do not fall under the Rule of Rescue.

In health technology assessments of treatments that prolong the life expectancy of dialysis patients, dialysis costs are categorized as unrelated future costs. Unrelated future costs are defined as '*costs that are independent [of a treatment], apart from the effects [of that treatment] on survival*'.[46,47] Thus, a treatment that prolongs the life of a dialysis patients will cause an increase in dialysis costs which are classified as unrelated costs, because the need for dialysis was already present (and remains unaffected by) this life-prolonging treatment. From a purely theoretical point of view, it can be argued that including unrelated future costs is valid and excluding them will lead to inconsistencies in calculations.[48] Nonetheless, this issue is a long-standing controversy in health economics.[46,47,49,50] This issue seems to be of particular relevance in renal disease.[51] By demonstrating the enormous impact of dialysis costs on cost-effectiveness outcomes, this thesis intends to contribute to strong scientifically-based methodologies to address this controversy.

Work related to future dialysis costs

Our group, assisted by pharmacy students of the University of Groningen, further explored the impact of dialysis care costs on the cost-effectiveness of phosphate binders.[52] Second-line treatment with non-calcium binders prolongs the life of dialysis patients. The main finding of the study was that irrespective of the costs of the therapy (even free of charge!); the costs of dialysis care; or the cost-effectiveness threshold used, second-line treatment was never cost-effective when dialysis care costs were included. This study demonstrates an important discrepancy between optimizing pharmacotherapy and optimizing pharmacoeconomics. On the one hand, inclusion of future dialysis costs has its methodological merits as it ensures a consistent analysis of both costs and effects. On the other hand, treatments that prolong life will bear the economic burden of prolonged dialysis care and as a result can never achieve cost-effectiveness. This is an important issue that decision makers should be aware of.

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SUMMARY

Renal diseases decrease patients' life expectancy and quality of life and strain health-care budgets. In the quest to improve pharmacotherapy, personalized approaches tailored for individual patients are increasing in importance.

Work presented in this thesis includes a checklist for health technology assessment of genetic screen-and-treat strategies; and explored two such strategies in renal medicine. It was found that the ACE (I/D) polymorphism influences the (cost-)effectiveness of ACE inhibitors in non-diabetic renal disease. The second genetic strategy involved a polymorphism coding for the CCR5 receptor, the genetic deficiency of which is associated with improved survival in dialysis patients. A modelling study in this study suggested that pharmacologic blockade of the CCR5 receptor has similar potential for clinical and economic benefits.

This thesis also deals with non-genetic approaches to improve pharmacotherapy. Firstly, optimal prescribing strategies may result in economic benefits, as studied in this thesis for specific phosphate binders (lanthanum carbonate) used as second-line therapy. Evidence was also presented favouring cheap RAAS intervening drugs, as no difference in therapy compliance was found between cheap and more expensive drugs. Secondly, pharmacotherapy can be improved by correctly diagnosing and treating adverse side effects, as studied in this thesis for ACE inhibitor induced cough. Thirdly, therapy effectiveness of ACE inhibitors can be improved for patients eating too much salt; lower salt intake was associated with decreased renal disease progression.

In conclusion, personalized approaches to improve pharmacotherapy in renal disease may improve the individual patients' health and quality of life, and may also decrease the economic disease burden for society.

SAMENVATTING

Nierziekten verlagen de levensverwachting en kwaliteit van leven en zijn erg duur. Om de farmacotherapie te verbeteren worden *personalized approaches,* behandelingen toegespitst op de individuele patiënt, steeds belangrijker.

Het werk in dit proefschrift bevat een checklist voor doelmatigheids-onderzoek van genetische strategieën; tevens werden twee genetische strategieën voor nierpatiënten onderzocht. Uit het eerste onderzoek bleek dat het ACE-(I/D)-polymorfisme de (kosten-)effectiviteit van ACE remmers bij niet-diabetische nierziekte beïnvloedt. Het tweede onderzoek richtte zich op een polymorfisme voor de CCR5 receptor; een genetisch defect van deze receptor is geassocieerd met een verbeterde overleving bij dialyse patiënten. Een model beschreven in dit proefschrift suggereert dat farmacologische blokkade van de receptor óók klinische en economische voordelen kan bieden.

Dit proefschrift beschrijft ook niet-genetische strategieën om de farmacotherapie te verbeteren. Ten eerste, juiste keuzen in voorschrijven kan economische voordelen bieden, zoals blijkt uit onderzoek naar het voorschrijven van specifieke fosfaatbinders (lanthaancarbonaat) als tweedelijns therapie. Dit proefschrift onderschrijft voorschrijven van goedkope RAAS interveniërende geneesmiddelen, aangezien er geen verschil in therapietrouw werd gevonden tussen dure en goedkope middelen. Ten tweede, farmacotherapie kan verbeterd worden door nauwkeurig te letten op bijwerkingen, zoals in dit proefschrift onderzocht werd voor de bijwerking prikkelhoest bij ACE remmers. Ten derde, farmacotherapie bij nierziekten kan verbeterd worden door een hoge zoutinname te vermijden. De effectiviteit van ACE remmers bleek namelijk groter bij minder zoutinname.

Er kan geconcludeerd worden dat *personalized approaches* veel potentie bieden bij nierziekten. Ze kunnen niet alleen de zorg voor individuele patiënten verbeteren maar ook grote economische voordelen bieden voor de samenleving als geheel.

LIST OF PUBLICATIONS

Publications supporting thesis

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CURRICULUM VITAE

Stefan Vegter was born in Drachten, municipality Smallingerland, province Fryslân, The Netherlands, on 20th august 1984. After finishing high school in Leeuwarden, he started his studies of Pharmacy at the University of Groningen in 2002. During his studies he worked as a part-time research assistant at the department of PharmacoEpidemiology and PharmacoEconomics (PE^2) in 2006. His research project dealt with the pharmacoeconomics of pharmacogenetic screening and -intervention programs. This project later evolved into a main topic of his PhD program. Stefan Vegter received his Masters' and pharmacists' degrees from the University of Groningen in 2009.

In 2008, Stefan Vegter started his PhD program at the University Medical Centre Groningen and the University of Groningen at the Department of Pharmacoepidemiology and Pharmacoeconomics; his promotores were Prof. Dr. M.J. Postma (pharmacoeconomics) and Prof. Dr. G.J. Navis (nephrology). The recurring theme in his PhD research was the quest to improve pharmacotherapy in renal disease by personalized approaches, both genetic- and non-genetic. Stefan Vegter was a member of the health-economics working group for the internationally renowned GENECURE project. The projected date of obtaining his PhD degree is March 2012.

Stefan has interests and ample experience in pharmacoepidemiology and pharmacoeconomics, and has worked on several multi-national projects. During his PhD research, Vegter authored or co-authored over a dozen scientific publications and gave podium or poster presentations at internationally renowned congresses, including the American Society of Nephrology (ASN) and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) congress. Stefan occasionally gives lectures on pharmacoeconomic and pharmacoepidemiologic topics to pharmacy students at the University of Groningen.

Currently, Stefan Vegter holds a part-time position at the University of Groningen, studying the value of pharmaceutical care in community pharmacies. Stefan Vegter owns a consultancy company, *Vegter Health Economic Research*, which performs evidence-based health economics and outcomes research for pharmaceutical companies in The Netherlands, the UK, and other countries, often in close collaboration with other consultancy companies.