Things change: The early identification of patients with an unfavourable prognosis

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Chapter 1

General introduction
and outline of this thesis

BACKGROUND

Chronic medical conditions are highly prevalent affecting approximately 3.4 billion people worldwide.[1] These chronic conditions, not only pose a considerable burden of disease on patients and their families, with potentially severe limitations on daily life, but they also come with substantial costs on society and healthcare systems through work absence and potentially long lasting clinical care.[2,3] A chronic medical condition is defined as a health state or disease of long duration (≥ 3 months) with persistent effects and slow progression over time. The most common chronic medical conditions are cardiovascular diseases, chronic respiratory diseases, diabetes and mental disorders. These four conditions account for over 50% of the total prevalence of all chronic medical conditions. Other common medical conditions include chronic kidney disease, osteoporosis, arthritis and oral health problems.[4,5]

Management of chronic medical conditions is generally focused on enhancing functional status, minimizing distressing symptoms, secondary prevention and enhancing quality of life; obtaining and/or maintaining a controlled disease condition is another important goal and treatment should be adjusted if necessary based on clinical status of the patient.[6,7] However, initiated (ineffective) treatment does not always improve health outcomes in the long-term e.g. over a period of two years, resulting in subgroups of patients that may continue treatment without clear benefit and an uncontrolled disease condition; this may pose a risk of side effects and unnecessary costs for society. Non-optimal treatment is associated with higher healthcare utilization and costs, including more hospital admissions, unscheduled doctor visits and use of emergency services.[8-10]

In this thesis we explored four chronic medical conditions, namely: depressive disorders, anxiety disorders, hypertension and asthma with the aim to improve identification of patients with an unfavourable prognosis of chronic disease, early in their treatment course, which may facilitate proactive approaches to improve clinical outcomes.

UNFAVOURABLE PROGNOSIS IN CHRONIC CONDITIONS

Most costs in healthcare are spend on a relatively small subgroup of patient with long-term healthcare utilization without clear treatment benefit, but at risk of potential side effects.[8,11] As the recommended treatment may be helpful for many patients with a specific chronic condition, for others it may not. The lack of clear treatment benefit in patients with an uncontrolled disease condition can be attributed to various treatment

aspects e.g. treatment compliance, type of treatment and/or drugs or the mutual trust between clinician and patient.[12] Selecting a most appropriate treatment, based on patient characteristics such as demographics and clinical symptoms alongside relevant clinical guidance, can not only improve patients' wellbeing, but increase the efficiency of healthcare utilization.[13]

Depressive and anxiety disorders are the most common mental disorders, with an estimated prevalence of respectively 298 and 273 million people worldwide, and compared to other mental disorders (e.g. personality- and somatoform disorders) associated with the most disability days per year and the highest economic burden.[14,15] Approximately 20% of the patients with a depressive disorder is not in remission after two years of treatment, for anxiety disorders this is over 50%.[16-18]

Hypertension, or elevated blood pressure, is one of the most prominent risk factors of cardiovascular morbidity and mortality.[19] Worldwide, over one billion people have hypertension.[20] For the majority of patients, over 75%, control of blood pressure remains suboptimal, and therefore these patients remain at increased risk of, for example strokes and coronary heart disease.[19,21]

Asthma is a common non-communicable chronic respiratory disease, and affects at least 235 million people worldwide of which 50-60% not controlled.[22] Uncontrolled asthma patients are at increased risk of visiting an emergency department due to severe exacerbations, hospitalization, or even death.[9,23]

EARLY IDENTIFICATION OF PATIENTS WITH AN UNFAVORBALE PROGNOSIS

Information on early treatment response may allow greater accuracy in predicting an (un)favourable prognosis to guide decision making.[24-25]

Most prognostic models to study treatment effects include only (baseline) patient characteristics, where prognostic models considering and including early treatment response are less studied, or less commonly known. While patient characteristics provide the opportunity to explore the associations with treatment outcome and selecting the most appropriate treatment (precision medicine), the use of early treatment response has the capacity to inform on treatment progress, and to guide decisions to reconsider treatment. For example, no or minimal treatment response after the first few months of

treatment could be an indicator to reconsider treatment approach.

In depressive and anxiety disorders, variables commonly associated with prolonged treatment duration are: housing situation, family history, age, level of education, symptom severity and co-morbid disorders.[16,17] In addition, several studies on specific (drug) treatments, have found that response to treatment within two to eight weeks may be an indicator of further recovery.[26-30]

Most prognostic models concerning uncontrolled hypertension include a single measurement of (self-monitored) blood pressure. Additional predictive variables that have been identified include patient characteristics such as smoking status, treatment adherence, age, level of education, sex, ethnicity and body mass index (BMI).[31,32] Despite the frequently mentioned advantages of monitoring blood pressure, only limited data is published to support the use of multiple measurements in prognostic models.[33]

Uncontrolled asthma is commonly associated with smoking, lower socioeconomic status, poor medication adherence, comorbidities and race.[7,34-37] Additionally, several studies of long-term outcomes suggest that whether asthma control will be achieved may already be judged at a three month review.[38,39]

OVERVIEW OF THIS THESIS

The aim of this thesis is to study the potential of identifying patients with an unfavourable prognosis of chronic disease, early in their treatment course, which may facilitate proactive approaches to improve clinical outcomes. To achieve this goal, we tried to develop easy to use prediction models enabling clinicians to identify patients with an increased risk of an unfavourable prognosis, based on patient characteristics and information on early treatment response.

OUTLINE OF THIS THESIS

In **chapter 2** we described and quantified the impact of treatment duration on mental healthcare utilization in patients with depressive and anxiety disorders. These analyses serve to demonstrate the relevance of early identification of patient with longer treatment course and the potential impact on available resources of longer treatment course could be prevented.

In **chapter 3** we aimed to improve clinical prediction of a prolonged treatment course based on symptoms, and explored the additional predictive value of early treatment response in symptoms, in patients with depressive and anxiety disorders. In **chapter 4** we explored whether we could identify patients with an increased risk of persistent uncontrolled hypertension (systolic blood pressure > 140 mmHg) after approximately three months of treatment, using self-monitored blood pressure measurements. In **chapter 5** we aimed to assess the risk of future adverse outcomes in patients with asthma, such as (severe) exacerbations, fixed airflow limitation and/or side-effect of medication. We considered patient characteristics and clinical variables at baseline, and information on early treatment response as potential predictors.

In **chapter 6** we tried to identify those patients, based on prespecified subgroups on different levels of Fractional exhaled Nitric Oxide (FeNO), who benefit most from FeNO-driven stepped-care asthma management in primary care, compared to conventional symptom-based asthma management.

Finally, in **chapter 7** we summarize the main findings of this thesis and discuss the clinical implications and future perspectives, with a concluding remark.

STUDIES USED IN THIS THESIS

ROM GGZ Rivierduinen: depressive and anxiety disorders

A cohort study with routine outcome monitoring (ROM), collected in routine care by GGZ Rivierduinen, a regional mental healthcare provider in the western part of the Netherlands.[40] Since 2002, all patients referred to GGZ Rivierduinen for treatment of depressive, anxiety and somatoform disorders are routinely assessed with a psychometric test battery. Data on diagnosis and severity of psychiatric symptoms are collected at intake, after treatment is initiated, and subsequently every 3-4 months. ROM includes self-reported and observer-rated measures, as well as generic and disorder-specific questionnaires. Completion of ROM questionnaires is supervised by trained psychiatric research nurses (or psychologists), not involved in treatment. ROM data are primarily used for diagnosis and to inform clinicians and patients about treatment progress. For the current study, we selected patients aged 18-65 years, who were referred to GGZ Rivierduinen between January 2007 and June 2011, with a primary clinical diagnosis of a depressive or anxiety disorder according to the attending physician.

TeleHype: hypertension

Data was obtained from the the TeleHype-study: a trial of TELEmonitoring and self-management support of patients with uncontrolled HYPErtension. A pragmatic randomized controlled trial (RCT) comparing solely usual care to telemonitoring of blood pressure and self-management support via an internet-based service, in addition to usual care. In this cohort patients were aged 18-75 years, with a diagnosis of hypertension; a systolic blood pressure > 140 mmHg or >130 mmHg if diabetes or chronic kidney disease was present. Follow-up was 12 months and patients filled out online questionnaires at approximately three-monthly intervals. We only analyzed data of the telemonitoring strategy with self-monitored blood pressure measurements, as data of the usual care strategy did not contain sufficient information on early treatment response. Blood pressure was measured twice in the morning and twice in the evening. A detailed description of study procedures and participants will be published elsewhere (trial registry: ISRCTN10969896).

ACCURATE: asthma

The Asthma Control Cost-Utility Randomized Trial Evaluation (ACCURATE) is a pragmatic cluster-randomized trial comparing asthma management strategies in primary care, for patients aged 18-50 years, with a diagnosis of asthma and prescribed inhaled corticosteroids.[39,42] Patients' first assessment originated from 87 general practices in the areas of Leiden, Nijmegen and Amsterdam (the Netherlands) in the period from June 2009 until 2010. Clinicians provided treatment according to the principle of stepped-care, based on (inter)national evidence-based treatment guidelines, supported by an internet-based decision support tool. Follow-up was 12 months and patients filled out online questionnaires about demographics, quality of life and clinical information at approximately three-monthly intervals.

SMASHING: asthma

The validation dataset was obtained from another RCT in primary care, aiming at achieving controlled asthma. In this study, 37 general practices in the Leiden and The Hague area participated, and the Outpatient Clinic of the Department of Pulmonology at the Leiden University Medical Centre; recruited September 2005 to September 2006.[38]

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