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

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THE EARLY IDENTIFICATION OF PATIENTS AT RISK OF AN UNFAVOURABLE PROGNOSIS

PROEFSCHRIFT

Ter verkrijging van
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in 1989

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Leden Promotiecommissie	Prof. dr. J.G. van der Bom
	Prof. dr. E.H.D. Bel (AMC Amsterdam)
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The work described in this thesis was performed at the department of Clinical Epidemiology, the department of Psychiatry and the department of Biomedical Data Sciences (section Medical Decision Making), Leiden University Medical Centre, Leiden.

I just want to make you proud.

CONTENTS

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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Chapter 2

Mental healthcare utilization for depressive and anxiety disorders: The impact of treatment duration.

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Submitted

ABSTRACT

Objective
To quantify the impact on mental healthcare utilization in relation to treatment duration, in patients with depressive or anxiety disorders.

Design
Cohort study based on administrative data.

Setting
Standard care within a regional mental health care provider.

Participants
Patients (aged ≥ 18) with a diagnosis of a depressive or anxiety disorder and a first face-to-face contact between January 2010 and June 2011; closing date of the study June 2013.

Main Outcome(s) and Measure(s)
Absolute frequency and contact density of face-to-face contacts.

Results
For patients with a depressive disorder, a longer treatment duration (>24 months) (26% of patients) accounted for more than 63% of all face-to-face contacts, and contact density in the initial six months of treatment counted on average 11 more face-to-face contacts. For patients with an anxiety disorder, a longer treatment duration (22% of patients) accounted for more than 55% of all face-to-face contacts; and contact density counted on average 7 more face-to-face contacts in the initial six months of treatment. For both depressive and anxiety disorders, contact density gradually decreased over time on average for all patients with the exception of patients with a treatment duration longer than 24 months.

Conclusions and Relevance
Patients with a longer treatment duration have a high impact on use of mental healthcare resources. For patients with a longer duration of treatment, contact density was already higher in the initial six months of treatment, and density did not decrease over time. Further research to identify patients early in their treatment course and targeted interventions for this group could be promising to improve outcome and reduce costs.

INTRODUCTION

Depressive and anxiety disorders are the most common mental disorders, with an estimated number of respectively 298 and 273 million people, equivalent to approximately 4.1% and 3.7% of the world's population.[1] These highly prevalent disorders are associated with a high burden of disease and high impact on society, translating into substantial direct and indirect costs.[2,3,4] Direct costs are related to treatment and utilization of other healthcare resources, and indirect costs are related to reduced quality of life, decreased productivity, absenteeism, and functional impairment in personal and interpersonal areas of life.[5,6]

Most direct costs for patients with a depressive or an anxiety disorder, are generated by a relatively small group of patients with a high healthcare resource utilization: in psychiatric services 10-30% of patients may account for 50 to 80% of mental healthcare resource utilization.[7] A study focusing on high utilizers of healthcare resources in patients with a depressive disorder demonstrate that the top 10% of the patients may accounted for approximately 50% of all-cause costs.[8] One metanalysis in patients with generalized anxiety disorders found that high utilization of health care resources was partly explained by longer duration of treatment, suggesting that treatment duration is one of the important factors contributing to high utilization of resources.[9]

Detailed quantified knowledge about mental healthcare related costs in these highly prevalent mental disorders can inform healthcare policies and potentially allocation of resources to identified patient groups.[10] The aim of this study was to quantify the utilization of resources in the treatment of depressive and anxiety disorders in a single mental health institution, focusing on absolute number of face-to-face contacts and number of contacts within fixed time periods (density), comparing patients with different lengths of treatment duration.

METHODS

We performed a cohort study based on administrative data of GGZ Rivierduinen, a Regional Mental Health Care Provider (RMHCP) in the Western part of The Netherlands. Patient-identifiable data were removed from the database to secure patients' confidentiality and to comply to Dutch law on research with clinical data. The use of these anonymized data for research has been approved by the Ethical Review Board of Leiden University Medical Centre (LUMC).

Patients

The study was based on administrative data containing information on type and frequency of face-to-face contacts recorded between January 2010 and June 2013. For the current study, we selected consecutive outpatients aged ≥ 18 with an initial face-to-face contact at GGZ Rivierduinen in an 18 months period between January 2010 and June 2011, with a primary clinical diagnosis of a depressive or anxiety disorder according to the attending physician. In the administrative system of GGZ Rivierduinen, the primary clinical diagnosis represents the primary focus of clinical care. The diagnostic classification was based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) andincluded depressive disorders (coded as 296.20 - 296.24, 296.30 - 296.34, 296.90, 300.4 or 311) and anxiety disorders (coded as 300.00, 300.01, 300.02, 300.21-300.23, 300.29, 300.3, 308.3 or 309.81). As we could observe face-to-face contacts until June 2013, we had a minimum of two years of follow-up for each patient. The final sample included 3,814 patients, with a total of 149,059 face-to-face contacts. Data on age and sex was extracted from administrative data of GGZ Rivierduinen.

Study outcome: face-to-face contacts

The dataset included information about all face-to-face patient contacts to the RMHCP. The treatment duration was calculated starting at the first face-to-face contact until either the last contact before the close of treatment, or the closing date of the study. These face-to-face contacts were labelled diagnostic, routine outcome monitoring,[11] pharmacotherapy or psychotherapy sessions. Our primary outcome was the total number of face-to-face contacts per patient. Given that each type of contact contributes to the utilization of resources, we counted all face-to-face contacts, without differentiation between various types of contacts. The secondary outcome was the frequency of face-to-face contacts over time (contact density), defined as the number of face-to-face contacts per 6 months.

Statistical analysis

Analyses were performed separately for patients with a depressive disorder and patients with an anxiety disorder. Baseline age was expressed as mean (standard deviation), and sex as number (percentage). Total treatment duration was calculated for each patient, starting at the first face-to-face contact and ending either at the last face-to-face contact before the close of treatment, or at the closing date of the study. Next, we stratified patients into five subgroups, according to total treatment duration (< 6 months, 6-12 months, 12-18 months, 18-24 months, and > 24 months) and calculated the proportion of the total number of patients in each of the subgroups. To calculate the impact on

resources, we counted the number of face-to-face contacts per subgroup and calculated the proportion of the total number of face-to-face contacts.[12]

To determine contact density of face-to-face contacts, we counted the number of face-to-face contacts in every six-month period of treatment duration, and computed the mean number of face-to-face contacts for each of the subgroups within the consecutive six months' periods. We only considered contact density for patients who were under treatment for the whole respective six months' period. For each of the subgroups, contact density was compared to contact density of the subgroup with a treatment duration longer than 24 months, using independent sample t-test.

Sensitivity analysis

Our final sample included 719 patients (19%) who were still in treatment at the closing date of the study (withdrawn alive). As a consequence, we could not observe ongoing treatment for these patients. To explore the potential impact of this unobserved treatment time, we performed a sensitivity analysis, where we limited the sample to an inclusion period of six months, between January 2010 and June 2010. This reduced the total sample substantially, but increased the minimum observation time from two to three years. Thus, we could approximate the impact of missed observation time to some extent, by repeating the calculations of the proportions of face-to-face contacts in each of the subgroups of treatment duration in this sample.

For analyses, STATA statistical software version 14 (Statacorp, College Station, Texas, USA), and SPSS version 20.0 for Windows (SPSS Inc., Chicago, III, USA) were used.

RESULTS

PATIENT CHARACTERISTICS

In the period from January 2010 until June 2011 3,814 patients started treatment; 2,286 with a primary depressive disorder and 1,528 with a primary anxiety disorder. In patients with a depressive disorder, the mean age was 46.5 years (SD 17.3) and 59.4% was female. In patients with an anxiety disorders, the mean age was 38.4 years (SD 15.9) and 64.1% was female (Table 1).

Number of face-to-face contacts

For depressive disorders, 2,286 patients accounted for a total of 113,459 face-to-face contacts (Table 2). Of these, 600 patients (26.2%) had a treatment duration of 24

months or longer, who accounted for 70,919 (62.5%) of all face-to-face contacts. For 530 patients (23.2%) treatment had not yet ended at the closing date of the study; minimum treatment duration for those patients was at least 24 months or longer.

For anxiety disorders, 1,528 patients accounted for a total of 57,841 face-to-face contacts. Of these, 336 patients (22.0%) had a treatment duration of 24 months or longer, who accounted for 32,207 (54.7%) of all face-to-face contacts. For 289 patients (18.9%) treatment had not yet ended at the closing date of the study.

The disproportionate number of face-to-face contacts in patients with longer treatment duration both in depressive and anxiety disorders is illustrated graphically in Figure 1.

TABLE 1. *Patient characteristics of patients with a depressive disorder (n = 2,286) and anxiety disorders (n = 1,528); stratified per duration of treatment duration.*

	Depressive disorders					
	< 6 months (N = 707)	6-12 months (N = 426)	12-18 months (N = 278)	18-24 months (N = 275)	> 24 months (N = 600)	Total (N = 2,286)
Mean age (SD)	46.7 (17.7)	45.8 (16.3)	45.7 (17.0)	46.0 (17.3)	46.1 (16.2)	46.5 (17.3)
Female sex N (%)	412 (58.3)	260 (61.0)	162 (58.3)	167 (60.7)	357 (59.5)	1,358 (59.4)
	Anxiety disorders					
	< 6 months (N = 495)	6-12 months (N = 326)	12-18 months (N = 222)	18-24 months (N = 149)	> 24 months (N = 336)	Total (N = 1,528)
Mean age (SD)	40.6 (17.0)	37.4 (15.5)	36.2 (15.0)	38.2 (16.5)	37.8 (14.3)	38.4 (15.9)
Female sex N (%)	318 (64.2)	207 (63.5)	141 (63.5)	101 (67.8)	212 (63.1)	979 (64.1)

TABLE 2. *Number of face-to-face contacts. Expressed in the total numbers of face-to-face contacts per subgroup of total treatment duration.*

	Depressive disorders					
	< 6 months (N = 707)	**6-12 months (N = 426)**	**12-18 months (N = 278)**	**18-24 months (N = 275)**	**> 24 months (N = 600)**	**Total (N = 2,286)**
face-to-face contacts	6,069	9,856	9,846	16,769	70,919	113,459
	Anxiety disorders					
	< 6 months (N = 495)	**6-12 months (N = 326)**	**12-18 months (N = 222)**	**18-24 months (N = 149)**	**> 24 months (N = 336)**	**Total (N = 1,528)**
face-to-face contacts	3,522	7,072	7,601	7,439	32,207	57,841

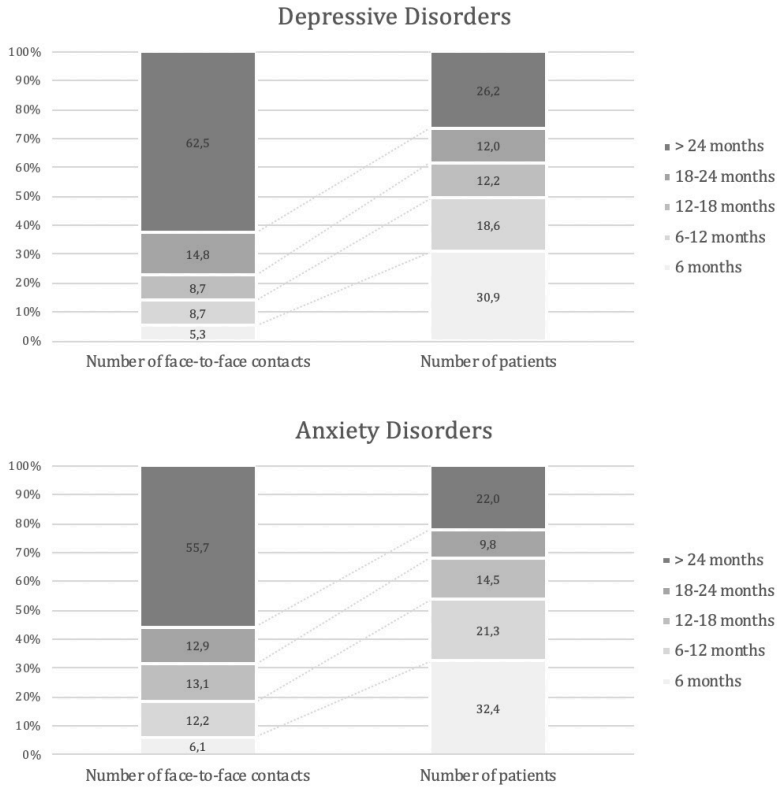

FIGURE 1. *Proportion of healthcare resource utilization in clinical practice.*

Contact density

Contact density, stratified in subgroups of treatment duration is shown in Figure 2. Contact density gradually decreased over time for all treatment durations, except for patients with a treatment duration of 24 months or longer. Table 3 shows the mean difference in contact density, relative to patients with a treatment duration longer than 24 months. For example, for patients with a depressive disorder, the mean difference of 9.1 in the (upper) second column means that patients with a treatment duration of 6-12 months have on average 9.1 (CI95 6.1,11.6) less face-to-face contacts in the first 6 months of treatment, compared to patients with a total treatment duration of 24 months or more. Both for depressive and anxiety disorders, contact density was significantly lower in all six months periods in the subgroups with a treatment duration of less than 18 months as compared to a treatment duration of 24 months or more. For depressive disorders, the difference was significant for the subgroup with total treatment duration of 18-24 months, starting at 6-12 months' time in treatment. For

anxiety disorders, the difference was significant for the subgroup with total treatment duration of 18-24 months, for 12-18 months' time in treatment only.

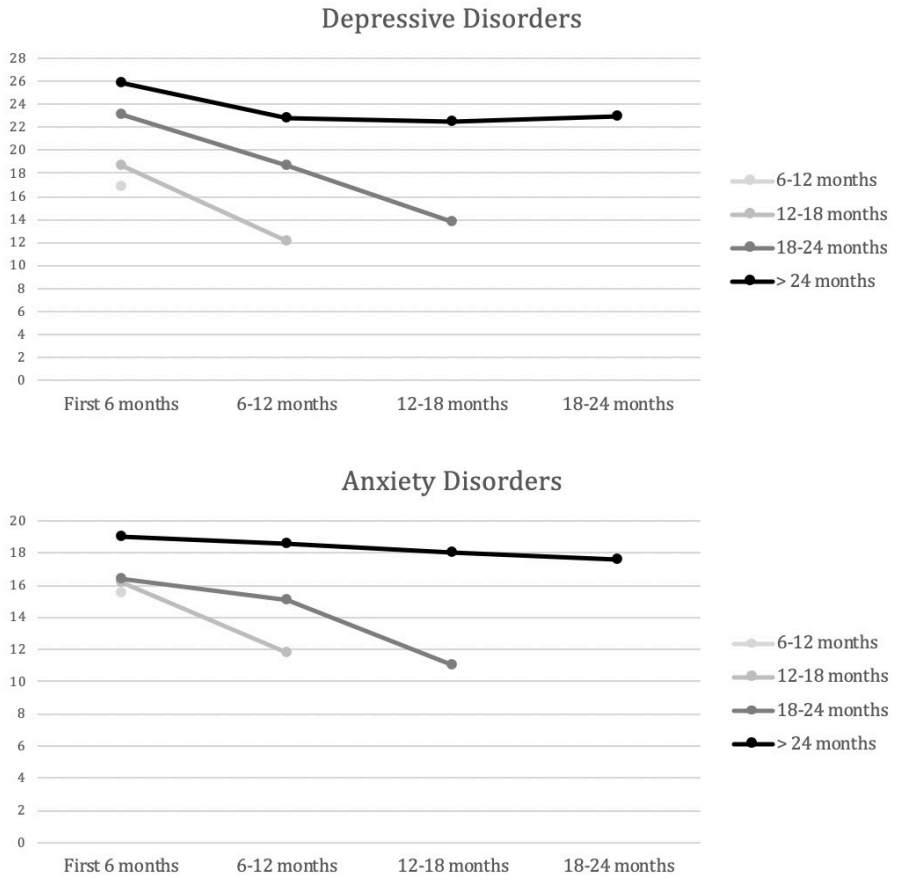

FIGURE 2. *Mean number of face-to-face contacts per patient stratified per six months of total treatment duration. The x-axis represents the period in treatment (e.g. first six months of treatment). The color of the lines shows the total treatment duration.*

Sensitivity analysis

In the first six months of the inclusion period 1,265 patients started treatment, 770 with a primary depressive disorder and 495 with a primary anxiety disorder (*see the online supplement for full details, appendix 1).* The proportion of patients withdrawn alive improved from 23.2% to 17.9% for depressive disorders, and from 18.9% to 17.2% for anxiety disorders; minimum treatment duration for those patients withdrawn alive

in this sensitivity analysis was at least 36 months. The proportion of patients with a treatment duration longer than 24 months in this smaller sample was similar to the total sample: 25.3% and 26.2% for depressive disorders and 23.6 and 22.0% for anxiety disorders, respectively. The proportion of contacts accounted for by patients with treatment duration longer than 24 months increased from 62.5% to 66.9% for depressive disorders and from 54.7% to 58.2% for anxiety disorders.

TABLE 3. *Mean differences (95% confidence interval) in contact density of face-to-face contacts, relative to patients with a treatment duration longer than 24 months.*

DEPRESSIVE DISORDERS

	Time in treatment →					
Total treatment duration ↓	First 6 months	p-value	6-12 months	p-value	12-18 months	p-value
6-12 months	9.1 (6.7,11.6)	< 0.001	-		-	
12-18 months	7.2 (4.5,10.0)	< 0.001	10.6 (8.1,13.0)	< 0.001	-	
18-24 months	2.8 (-0.8,6.4)	0.126	4.0 (0.7,7.4)	0.019	8.7 (6.1,11.4)	< 0.001

ANXIETY DISORDERS

	Time in treatment →					
Total treatment duration ↓	First 6 months	p-value	6-12 months	p-value	12-18 months	p-value
6-12 months	3.5 (1.0,6.0)	0.007	-		-	
12-18 months	2.9 (0.5,5.4)	0.021	6.8 (4.0,9.6)	<0.001	-	
18-24 months	2.7 (-0.5,5.6)	0.102	3.5 (-0.6,7.6)	0.093	7.0 (4.0,10.1)	< 0.001

DISCUSSION

In this cohort of psychiatric outpatients with a depressive or an anxiety disorder, we demonstrate that a limited proportion of patients with treatment duration longer than 24 months utilized a substantial proportion of mental healthcare resources. This was not only due to the longer duration of the treatment, but also due to the contact density per six months. When stratified according to treatment duration, contact density gradually decreased over time for all patients, with the exception of patients with a treatment duration longer than 24 months. Higher health resource utilization is not merely a function of treatment time; it is also due to a higher density of face-to-face contacts over the entire time of treatment.

Our finding of a disproportionate impact on resources by a minority of patients in mental health care has been abundantly demonstrated in previous studies.[7-8,13-16] In a review of 72 studies Kent et al.[7] concluded that in most studies, 10-30% of the patients identified as heavy users, accounted for 50 to 80% of mental healthcare resource utilization. Our

findings specifically confirm these findings for outpatients with depressive or anxiety disorder, which was not unexpected for prolonged duration of treatment. Our findings on contact density, however, have not been reported before. These findings suggest that a prolonged duration of treatment is already foreshadowed in an increased intensity of treatment early in the trajectory. The subsequent lack of tapering of contact density may serve as a further indicator for prolonged duration of treatment and a disproportionate impact on resources. From an earlier study in the same population, we know that longer treatment trajectories were predicted early in treatment by high ratings on the Brief Symptom Inventory, a multidimensional checklist of psychological symptoms. This indicates that these patients most likely have more severe disorders and/or more complexity due to co-morbidity.[10] Additionally, co-morbid personality disorders added to the prediction of longer duration of treatment for depressive disorders and age (>40 year) added to the prediction for anxiety disorders. Higher contact density is likely to be explained to some extent by such factors, especially early on in treatment.[17-21] Still, high contact density in general and the lack of any tapering of density over time could perhaps contribute clinically as additional indicators of prolonged treatment. One study, in an entirely different health domain, suggests that just the awareness by the treatment staff of a potential negative outcome may contribute to improve outcome.[22]

A strength of our study is that it is based on an integral set of administrative data for an entire region in a natural setting, with sufficient information to conduct a minimum of two-year follow-up. Although we cannot be sure that findings will generalize to other settings, our findings of disproportionate utilization of resources by a minority of patients, is clearly in line with previous studies, as mentioned before.

The main limitation of our study is that it involved administrative data only and the data were not collected for the purpose of this study. However, as our data are part of the reimbursement system, that is meticulously monitored, we believe the data do reflect the actual duration and density of treatment.[23,24] Also, from previous studies in GGZ Rivierduinen, we have some insight in the type a treatment that is provided.[25] Depressive disorders are more frequently treated with pharmacotherapy (55%) than psychotherapy (24%), while this is the reverse for anxiety disorders (23% and 59%). For both conditions, the remaining minority is treated with combinations or with other treatments. Guideline adherence in early stages of treatment was good in general, but less so for prolonged trajectories. Unfortunately, however, in depth information about patient characteristics, treatment details and specified outcomes was not available. As a consequence, it remains unclear to what extent the continued and disproportionate treatment effort added value to the outcome of these potentially complex patients.

Further research is clearly implicated. Another limitation is that treatment was still ongoing in our cohort at the closing date of the study. As a consequence, we will have underestimated the treatment effort involved in the longest trajectories. To estimate the potential impact of this unobserved treatment time, we conducted a sensitivity analysis for a shorter inclusion period of six months and thereby a longer follow-up of three years. The proportion of patients with unobserved time decreased from 23.2 to 17.9% for depressive disorders and from 18.9% to 17.2% for anxiety disorders. Apparently, many of the patients withdrawn from observation after two years were still in treatment after three years. This further underlines that the finding as reported should be considered as a minimum estimate for the impact of prolonged treatment on mental health resources.

In conclusion, we confirmed that in psychiatric outpatients the minority of 26% (depressive disorders) and 22% (anxiety disorders) of patients with a treatment duration longer than 24 months utilized more than 63% and 55% of treatment resources respectively. Contact density per six months remained high for these patients over the entire duration of treatment. Further research of the added value of these disproportionate treatment efforts to the outcome of these potentially complex patients is clearly implicated.

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ONLINE SUPPLEMENT. APPENDIX 1.

Our final sample included 719 patients (19%) with a treatment duration of at least 24 months of treatment, who were still in treatment at the end of follow-up (withdrawn alive). Therefore, we performed a sensitivity analysis in order to reduce the number of patients withdrawn alive and thereby increase the number of end-to-end treatment durations. As a sensitivity analysis we shortened the inclusion period by selecting patients with a first face-to-face contact before June 2010 (instead of June 2011) and calculated the proportion of mental healthcare utilization by dividing the total number of face-to-face contacts per stratification period, by the total number of face-to-face contacts.

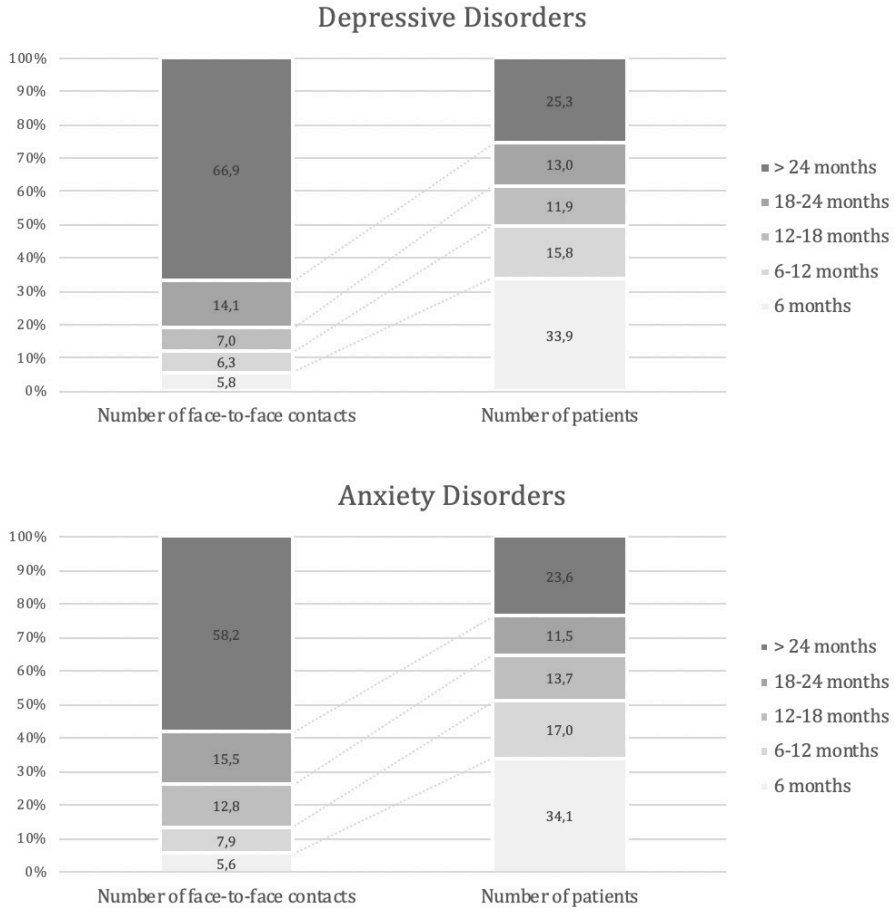

FIGURE 1. *Proportion of healthcare resource utilization in clinical practice.*

Chapter 3

Prediction of prolonged treatment course for depressive and anxiety disorders in an outpatient setting: the Leiden routine outcome monitoring study.

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ABSTRACT

Objective

The aim of this study was to improve clinical identification of patients with a prolonged treatment course for depressive and anxiety disorders early in treatment.

Method

We conducted a cohort study in 1.225 adult patients with a depressive or anxiety disorders in psychiatric specialty care setting between 2007 and 2011, with at least two Brief Symptom Inventory (BSI) assessments within 6 months. With logistic regression, we modelled baseline age, gender, ethnicity, education, marital status, housing situation, employment status, psychiatric comorbidity and both baseline and 1st follow-up BSI scores to predict prolonged treatment course (> 2 years). Based on the regression coefficients, we present an easy to use risk prediction score.

Results

BSI at 1st follow-up proved to be a strong predictor for both depressive and anxiety disorders (OR = 2.17 (CI95% 1.73-2.74); OR = 2.52 (CI95% 1.86-3.23)). The final risk prediction score included BSI 1st follow-up and comorbid axis II disorder for depressive disorder, for anxiety disorders BSI 1st follow-up and age were included. For depressive disorders, for 28% of the patients with the highest scores, the positive predictive value for a prolonged treatment course was60% (sensitivity 0.38, specificity 0.81). For anxiety disorders, for 35% of the patients with the highest scores, the positive predictive value for a prolonged treatment course was 52% (sensitivity 0.55, specificity 0.75).

Conclusions

A high level of symptoms at 2-6 months of follow-up is a strong predictor for prolonged treatment course. This facilitates early identification of patients at risk of a prolonged course of treatment; in a relatively easy way by a self-assessed symptom severity.

INTRODUCTION

Depressive and anxiety disorders are the most common mental disorders (Vos et al. 2012), with an estimated prevalence of respectively 298 and 273 million people worldwide. These disorders are associated with a high burden of disease (Wittchen et al. 2011) and high impact on society (Gustavsson et al. 2011), translating into substantial direct and indirect costs. Direct costs are related to treatment and the use of other health care services, and indirect costs to reduced quality of life, loss of productivity, absenteeism and functional impairment in many other personal and interpersonal areas of life (Donohue & Pincus, 2007; Combs & Markman, 2014).

The course of depressive disorders is variable, with approximately 60% of patients recovering within the first six months after diagnosis and up to 80% within two years (Steinert et al. 2014). Recurrence risk is 15-40% in two years. A persistent course with no major improvement despite treatment over two years or more, has been reported for 5 to 20% of patients, although slow improvements tend to continue over time (Hardeveld et al. 2010; Stegenga et al. 2012; Riihimaki et al. 2014; Steinert et al. 2014). For anxiety disorders the initial course is less favourable, with only 46% of patients recovering within two years and a similar recurrence risk of 15-40%, depending on type of anxiety disorder (Steinert et al. 2005; Penninc et al. 2011; Bruce et al. 2013).

In general, slow and incomplete recovery is associated with longer treatment duration (Riihimaki et al. 2014) and a longer treatment duration is associated with higher healthcare resource utilization (Haller et al. 2014); as for example more (severe) symptoms for patients with a prolonged treatment course, comorbidities, or treatment resistance in patients with a prolonged treatment course (Von Korff et al. 1992, Crown et al. 2002, Richards 2011, Dennehy et al. 2015). The majority of healthcare resources are consumed by a relatively small group of patients with a prolonged treatment course (Rais et al. 2013, Robinson et al. 2016).

Several studies have found that early response to treatment within two to eight weeks partially predicts further recovery (Van et al. 2008; van Calker et al. 2009; Tadic et al. 2010; Kim et al. 2011; Baldwin et al. 2012). Identification of patients with an unfavourable initial course of treatment could provide opportunities to target this subgroup with higher intensity treatment and potentially reduce chronicity early in the course of treatment (Trivedi & Baker, 2001; Lutz et al. 2009; Kendrick et al. 2016). Given that only limited data are published to support this, further research is implicated.

The implementation of Routine Outcome Monitoring (ROM) in mental health care provides an opportunity to study treatment course and symptom change, measured by general symptom inventories, such as the Brief Symptom Inventory (BSI) (Lutz et al. 2009, Katon et al. 2010, de Beurs et al. 2011). In the current study, we aimed to improve the clinical prediction of treatment duration for depressive and anxiety disorders in a routine care outpatient setting, and to identify patients with an unfavourable prognosis early in treatment course. Especially, we aimed to assess the role of the BSI, as an indicator of composite symptom severity, to predict prolonged treatment course and to develop an easy to use prediction model.

METHODS

This is a naturalistic cohort study with routine outcome monitoring (ROM), being collected in routine care by GGZ Rivierduinen, a Regional Mental Health Care Provider in the Western part of The Netherlands.

Since 2002, all patients referred to GGZ Rivierduinen for treatment of mood, 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. A detailed description of ROM can be found elsewhere (de Beurs et al. 2011).

For the purpose of research, patient-identifiable data were removed from the database to secure patients' confidentiality and to comply to Dutch law on research with clinical data. The Medical Ethical Committee of the LUMC approved the general study protocol regarding ROM, in which ROM is considered as an integral part of the treatment process (no written informed consent is required and the use of anonymized data for research is approved). A comprehensive protocol (titled "Psychiatric Academic Registration Leiden database") was used, to safeguard the anonymity of participants and ensure proper handling of the data. None of the participants objected to the anonymized use of their data for scientific purposes.

Patients

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. In the administrative system of GGZ Rivierduinen, the primary clinical diagnosis represents the primary focus of clinical care. The diagnostic classification was based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) and included depressive disorders (coded as 296.20 - 296.24, 296.30 - 296.34, 296.90, 300.4 or 311) and anxiety disorders (coded as 300.00, 300.01, 300.02, 300.21-300.23, 300.29, 300.3, 308.3 or 309.81). Bipolar and cyclothymic disorders were not included. For every patient, only the first treatment episode in the study period was considered. The selection was further restricted to patients with at least two ROM assessments within the first six months of treatment, one at baseline and a second ROM at least eight weeks after treatment initiation. As patients with only one ROM assessment were most likely not treated in the outpatient clinics, and no early treatment response can be assessed with only one assessment. We included only patients who had a continuation of treatment for at least six weeks after the second ROM assessment, continuation of treatment was defined as the absence of administrative termination of care. As the database closed June 2013, we accounted for the problem of right truncation by only including incident patients with a diagnosis up to June 2011. Therefore, each patient had a potential follow-up period of two year. The final sample included 1,225 patients, with minimum treatment duration of 14 weeks as a result of the specified inclusion criteria. See flow chart (figure 1) for details.

Psychiatrists and clinical psychologists or psychotherapists provided outpatient treatment in accordance with national evidence-based guidelines, consisting of pharmacotherapy, psychotherapy, or a combination of both. Psychotherapy for anxiety and depressive disorders, according to national guidelines, is mostly time limited cognitive behavioural therapy or interpersonal therapy. In our naturalistic cohort data, we did not have sufficient detail to accurately capture provision of care for individual patients and these data were not included in the analyses. From previous studies in GGZ Rivierduinen, we know that MDD is more frequently treated with pharmacotherapy than psychotherapy (55% and 24% respectively), while this is the reverse for anxiety disorders (23% and 59%). For both conditions, the remaining minority is treated with combinations or with other treatments. Guideline adherence in general was good (van Fenema et al. 2012). As this is an observational study, we did not in any way influence treatment modalities.

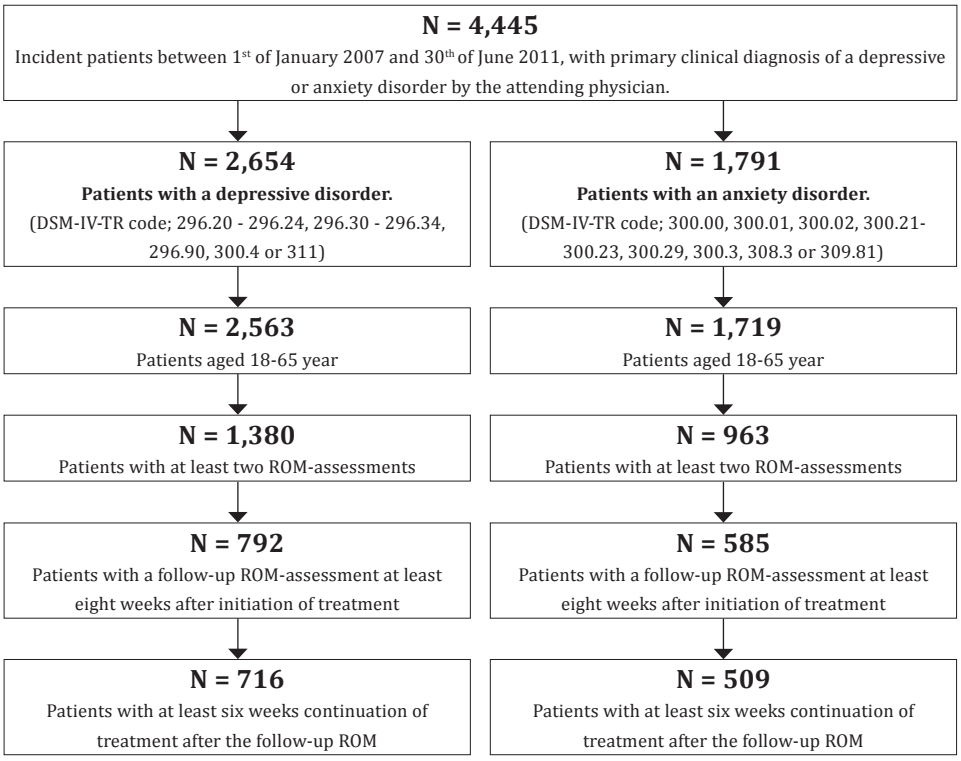

FIGURE 1. *Flowchart of patient selection*[1].

Outcome

The primary outcome of the study was prolonged treatment course. For depressive and anxiety disorders as primary treatment focus, it is common practice in the Netherlands to limit specialist care, as far as possible, to the symptomatic episodes. After an episode is successfully treated, it is common practice to refer patients back to primary care, where pharmacotherapy may be continued. Coverage of primary care is close to 100% in the Netherlands. We defined prolonged treatment course as a consecutive treatment duration of two years or more. For depressive and anxiety disorders, prolonged treatment courses, of two year or more, in general not only indicate difficult stabilization of the patients, but also constitute a high impact on service of costs and are preferably avoided. Treatment duration was defined as time since the first ROM-assessment to the administrative date of termination of care. Reasons for termination care are routinely coded in the administrative system. Around 80% of termination of care was mostly in

1 ROM =Routine Outcome Monitoring

mutual consensus, usually suggesting that treatment goals were obtained. One-sided termination by the patient can be considered as dropout, which amounted to 11%. Other reasons for termination include one-sided by the therapist (6%), moving home (<1%) or death (<1%).

Potential predictor variables

Demographic variables age and gender were obtained from the administrative data at baseline. Data on ethnicity, education, marital status, housing situation, and employment status were based on a ROM self-report questionnaire. Ethnicity was assumed to be Dutch, if both parents were born in the Netherlands. Education was divided into three levels 'low' (no education, primary school until approximately 10th grade), 'medium' (ranging from 11th grade through high school and community college) and 'high' (college undergraduate/graduate and higher). Marital status was categorized as 'married or cohabiting', 'divorced', 'widowed' or 'never in a relationship'. Housing situation was categorized as 'living alone', 'living with a partner without children', 'living without a partner, but with children', 'living with a partner and children, or living with family' and 'other'. Housing situation category 'other' was treated as missing as it contained fewer than 5 patients. For employment status, we distinguished between five categories 'housewife or -man, or retired', 'working', 'unemployed', 'on sick leave' or 'other'. Diagnostic information was extracted from the Dutch so-called Diagnosis-Treatment combination administrative data. Data on DSM-IV-TR diagnosis on Axis I and Axis II, other than the primary diagnosis, were extracted and considered as psychiatric comorbidity.

Ratings of psychiatric symptoms over the past seven days were obtained from the Brief Symptom Inventory (BSI). The BSI is a short form of the Symptom CheckList-90, consisting of 53 items rated on a 5-point Likert scale, and covering nine dimensions: somatization, obsessive-compulsive, internal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. Total BSI score, and scores on subscales, are computed as the sum of item-scores divided by the number of items. Higher scores indicate more severe psychiatric symptoms. The BSI has an acceptable internal consistency (Cronbach's alphas 0.71 to 0.85), and test-retest reliability (0.68 to 0.91) (Derogatis & Melisaratos, 1983). The total score and subscale scores are sensitive indicators of therapy effect (de Beurs et al. 2012). Here, we use the BSI-total score as an indicator of composite symptom severity, capturing not only symptoms of a particular disorder, but also symptoms of any comorbid symptoms. The normal range of the score may vary somewhat between populations. For the population of GGZ Rivierduinen we found in a previous study that 95% of a normal reference group will have BSI-total

score below 0.68, while more than 75% of a treated group will have a rating above this cut-off (Schulte-van Maaren et al. 2012).

General health status was assessed with the Short Form-36 (SF-36). The SF-36 is a 36-item self-report questionnaire that assesses health status in eight domains: physical functioning, social functioning, physical problems, emotional problems, mental health, vitality, bodily pain and general health (Ware & Sherbourne, 1992). For the purpose of this study, we decided to only use the subscale "general health" (Cronbach's alpha 0.70-0.81), based on previous literature (van Noorden et al. 2012).

Statistical analysis

Analyses were performed separately for patients with a primary depressive disorder and patients with a primary anxiety disorder. Baseline characteristics are summarized as number and percentage for categorical variables, or as mean and standard deviation (SD) for continuous variables. We used logistic regression analysis to predict prolonged treatment course, defined as treatment duration of two years or more since the first ROM-assessment. Baseline characteristics that were univariably associated with prolonged treatment course were selected for prognostic modelling. We used backward selection with criteria for variable removal of $p < 0.10$. Model performance was assessed and compared with the area under the receiver operating curve (AUROC) and internally validated with bootstrap resampling (n = 750). Model fit was assessed and compared by measuring Bayesian information criterion (BIC). Three models were compared:

1. Baseline characteristics, excluding baseline BSI (model 1)
2. Baseline characteristics, including baseline BSI (model 2)
3. Baseline characteristics, including baseline BSI plus BSI 1st follow-up (model 3)

Based on the regression coefficients of our final model a risk prediction score was developed as extensively described by Sullivan et al. (2004), in order to facilitate clinical application of the model. The risk prediction score was divided in quartiles and tested for sensitivity and specificity in relation to the outcome of prolonged treatment course (*see the online supplement for more details, appendix 1)*.

Sensitivity analyses

In a sensitivity analysis, we compared the baseline characteristics of our study population with the population of excluded patients who had only one BSI assessment, or a second BSI assessment outside our defined time range of 2-6 months. Furthermore, we analysed the final model 2 (baseline characteristics, including baseline BSI) within

the excluded population, and compared the results with the included population. Last, we performed additional prognostic modelling with BSI-delta (difference between baseline BSI and BSI 1st follow-up); baseline characteristics, including BSI 1st follow-up and BSI-delta.

Statistical calculations were performed using SPSS Version 20.0 for Windows (SPSS Inc., Chicago, III, USA) and R Statistical Software (version 3.2.3).

RESULTS

Patient characteristics

Of 1,225 patients that we included, 716 had a primary depressive disorder and 509 a primary anxiety disorder (table 1). In patients with a depressive disorder, the mean age was 41.2 years (SD 12.7) and 60.9% were female. The mean BSI was 1.38 (SD 0.70) at baseline, and symptoms significantly improved at first follow-up assessment (mean BSI 1.03; SD 0.70), on average 3.7 months after baseline. In patients with an anxiety disorder, the mean age was 35.6 (SD 12.7) and 62.3% were female. The mean BSI was 1.25 (SD 0.79) at baseline, and symptoms significantly improved at first follow-up assessment (mean BSI 0.91; SD 0.72), on average 4.1 months after baseline.

Predictors of prolonged treatment course in depressive disorders

The median treatment duration, given our selection, in depressive disorders was 16.7 months (IQR 8.0-28.1); 42.0% had a prolonged treatment course. In univariable logistic regression, prolonged treatment course was significantly predicted by BSI-baseline (OR 1.51, CI95% 1.22-1.87), BSI 1st follow-up (OR 2.09, CI95% 1.67-2.62), general health status, employment status, and comorbid Axis II disorders (*see the online supplement for more details, appendix 2)*. In multivariable logistic regression analyses model 1 (baseline variables but no BSI), the variables general health status and comorbid Axis II disorder remained in the model after backward selection. After including BSI-baseline (OR 1.37, CI95% 1.17-1.93) in model 2, no baseline variables were removed from the model. The remaining coefficients did not materially change. Adding the BSI 1st follow-up in model 3 yielded an OR of 2.17 (CI95% 1.73-2.74), while BSI-baseline was removed from the model. Model 3 included comorbid Axis II disorder and BSI 1st follow-up.

TABLE 1. *Patient characteristics of patients with a depressive disorder (n = 716) and patients with an anxiety disorders (n = 509). For continuous variables; values are stated as the mean (standard deviation). For categorical variables; values are numbers (percentages)[2].*

	Depressive disorders		Anxiety disorders	
Continuous variables	**Mean**	**SD**	**Mean**	**SD**
BSI baseline	1.38	0.70	1.25	0.79
BSI 1st follow-up	1.03	0.70	0.91	0.72
General health (SF36)	15.00	4.01	13.96	4.04
Age	41.2	12.7	35.6	12.7
Categorical variables	**N**	**%**	**N**	**%**
Female gender	436	60.9	317	62.3
non-Dutch ethnicity*	125	19.1	74	14.5
Employment status*				
Employed	276	42.1	233	49.7
Home	76	11.6	46	9.8
Unemployed	63	9.6	43	9.2
Sick leave	195	29.8	96	20.5
Other	45	6.9	51	10.9
Housing situation*				
Alone	146	22.5	92	19.6
Partner, no children	140	21.5	108	23.1
Partner and children, or with family	311	47.8	248	53.0
No partner, with children	53	8.2	20	4.3
Educational status*				
Low	279	42.6	182	38.8
Medium	261	39.8	197	42.0
High	115	17.6	90	19.2
Comorbid Axis I disorder	185	25.8	172	33.8
Comorbid mood disorder	26	3.6	95	18.7
Comorbid anxiety disorder	80	11.2	53	10.4
Comorbid somatoform disorder	30	4.2	23	4.5
Comorbid Axis II disorder	40	5.6	32	6.3

* Employment status, marital status and educational status was missing for 61 patients with a depressive disorder, and for 40 patients with an anxiety disorder. Housing situation was missing for 66 patients with a depressive disorder, and for 41 patients with an anxiety disorder. Ethnicity was missing for 62 patients with a depressive disorder, and for 40 patients with an anxiety disorder.

Model 3 had the highest internally validated AUROC of 0.65 and lowest BIC, pointing towards its better predictive performance than model 1 or 2 (respectively with an internal AUROC of 0.59 and 60). In medical diagnostic test evaluation, very high AUROCs (0.95 or higher) are desirable. In prediction studies AUROCs of 0.70 or higher would be considered strong effects (Hajian-Tilaki, 2013). Details of all three models are shown in the online supplement, *table 3A of appendix 2*.

2 BSI = Brief Symptom Inventory

Table 2A presents the risk prediction scores corresponding to the final model; higher scores indicate a higher risk of prolonged treatment course. From our final prediction model, we derived an easy to calculate score which ranged from 0 to 6; a score of 5 could not be achieved. For 27% of patients with a risk score of 4-6 points, the positive predictive value of prolonged treatment course was 60%, compared to 36% (1-negative predictive value) for patients with a score of 0-3 points. At this cut-off level sensitivity was 0.38 and specificity 0.81. See table 3A for details.

TABLE 2A. *Risk prediction score for prolonged treatment course (≥ two year) in patients with a depressive disorder; assessed after approximately three months of treatment[3].*

Factor	Points
Comorbid Axis II disorder	
No	0
Yes	2
BSI 1st follow-up	
< 0.53	0
0.53-0.89	1
0.89-1.45	2
> 1.45	4
Total score (range)	**0-6**

TABLE 3A. *Risk prediction score for prolonged treatment course (≥ two year) in patients with a depressive disorder; assessed after approximately three months of treatment.**

Risk prediction score	No prolonged treatment course	Prolonged treatment course	Total
0-3	338	187	525
4-6**	77	114	191

N = 716. * For 28% (N = 191) of patients with the highest scores (4-6), the positive predictive value for a prolonged treatment course was 60% (sensitivity 0.38, specificity 0.81). ** A score of 5 could not be achieved.

Predictors of prolonged treatment course in anxiety disorders

For anxiety disorders, the median treatment duration, given our selection, was 16.6 months (IQR 10.1-28.7); 33.0% had a prolonged treatment course. In univariable analysis, prolonged treatment course was significantly predicted by BSI-baseline (OR 1.94, CI95% 1.46-2.57), BSI 1st follow-up (OR 2.64, CI95% 1.98-3.51), older age, general health status, non-Dutch ethnicity and comorbid Axis I disorder. In multivariable logistic regression analyses model 1 (baseline variables but no BSI), the variables regarding

3 ROM =Routine Outcome Monitoring

general health status, older age, and non-Dutch ethnicity remained in the model after backward selection. After including BSI-baseline (OR of 1.78, CI95% 1.31-2.43) in model 2, general health was removed from the model, with no material change for the other variables. Adding the BSI 1st follow-up in model 3, BSI 1st follow-up yielded an OR of 2.52 (CI95% 1.86-3.23), whereas the baseline BSI assessment and ethnicity were removed from the model. Model 3 included older age and BSI 1st follow-up.

Model 3 had the highest internally validated AUROC of 0.68 and lowest BIC, pointing towards its better predictive performance than model 1 or 2 (respectively with an internal AUROC of 0.60 and 0.63). In medical diagnostic test evaluation, very high AUROCs (0.95 or higher) are desirable. In prediction studies AUROCs of 0.70 or higher would be considered strong effects (Hajian-Tilaki, 2013). Details of all three models are shown in the online supplement, *table 3B of appendix 2*.

Table 2B presents the risk prediction scores corresponding to the final model; higher scores indicate a higher risk of prolonged treatment course. From our final prediction model, we have derived an easy to calculate score which ranged from 0 to 3. For 35% of patients with a risk score of 2-3 points, the positive predictive value of prolonged treatment course was 52%, compared to 23% (1-negative predictive value) for patients with a risk score of 0-1 points. At this cut-off level sensitivity was 0.55 and specificity 0.75. See table 3B for details.

TABLE 2B. *Risk prediction score for prolonged treatment course (≥ two year) in patients with an anxiety disorder; assessed after approximately three months of treatment[3].*

Factor	Points
Age	
≤ 40 year	0
> 40 year	1
BSI 1st follow-up	
< 0.38	0
0.38-0.71	0
0.72-1.34	1
> 1.34	2
Total score (range)	**0-3**

Sensitivity analyses

In sensitivity analyses, baseline characteristics and performance of final model 2 (baseline characteristics, including baseline BSI) were similar for the excluded

patients (data not shown, depressive disorder N =1.183 , anxiety disorders N = 756). Furthermore, the addition of BSI-delta did not change the choice of the final model; BSI-delta did not remain in the model.

TABLE 3B. *Risk prediction score for prolonged treatment course (≥ two year) in patients with an anxiety disorder; assessed after approximately three months of treatment.**

Risk prediction score	No prolonged treatment course	Prolonged treatment course	Total
0-1	256	76	332
2-3	85	92	177

N = 509. * For 35% (N = 177) of patients with the highest scores (2-3), the positive predictive value for a prolonged treatment course was 52% (sensitivity 0.55, specificity 0.75)

DISCUSSION

In this cohort of outpatients with depressive or anxiety disorders, we showed that higher level of symptom severity at 2-6 months is the strongest predictor for prolonged treatment course. Our prediction model showed that patients in highest risk categories had a 60% positive predictive value of prolonged treatment course in patients with depressive disorders, and 52% for patients with anxiety disorders in the highest risk categories.

Our data confirm and contribute to earlier findings. First, we showed that a higher baseline level of symptom severity is independently associated with prolonged treatment course (van Beljouw et al. 2010; Katon et al. 2010; Stegenga et al. 2012), which is in line with many previous studies predicting the course of depressive disorders (Van et al. 2008; Vuorilehto et al. 2009; Lamers et al. 2011; Boschloo et al. 2014; Riihimaki et al. 2014; Gueorguiva et al. 2017) and anxiety disorders (Andreescu et al. 2008; Penninx et al. 2011; Prins et al. 2011; Green et al. 2015; Lamers et al. 2016). Secondly, for prolonged treatment course in patients with a depressive disorder comorbid personality disorders (Beaton & Rao, 2013, Gunderson et al. 2014) was found as independent predictors. In outpatients with anxiety disorders, we found also older age (Boschloo et al. 2014; Penninx et al. 2011) to be independent predictors for prolonged treatment course. Thirdly, in our study, 1st follow-up level of symptom severity had better predictive ability for prolonged treatment course compared to baseline level of symptom severity. Taking 1st follow-up level of symptom severity into account in prediction research was, to our best knowledge, first described by Fennell and Taesdale (Fennell & Taesdale, 1987). Few other studies have used a similar approach (Trivedi & Baker, 2001; Lutz et al. 2009; van Calker et al. 2009; Tadic et al. 2010; Richardson et

al. 2012). The observation that addition of the 1st follow-up assessment outperforms the baseline level of symptom severity, and thereby the rate of change deserves some further elaboration. This finding is consistent with the assumption that patients with high symptom severity at the 1st follow-up were likely to score high at the baseline BSI, or even higher. These might be the patients with poor initial recovery, which in turn might be predictive of poor outcome 2 year later. Patients with a low(er) score at the 1st follow-up could consist of a mix of patients improving from a higher score at baseline or remaining low which heralds' better outcome overall (Richardson et al. 2012). Consistent with these assumptions and our findings, the rate of change, and thereby the baseline assessment no longer added information at the moment of first follow-up. It is the level of symptom severity at the moment of assessment that determines risk of prolonged treatment course of the patient. Note that it is not our conclusion that the baseline assessment is without meaning; at baseline the level of symptom severity still predicts prolonged treatment course, albeit less discriminating. For early identification of patients with a less favourable course of treatment, the second BSI-measurement proves to be the single most informative variable.

Strengths of our study include that it was based on a large naturalistic treatment seeking population in psychiatric specialty care, with few exclusion criteria, contributing optimal external generalizability. Therefore, the external validity of our findings is likely higher than findings in samples from RCTs. Furthermore, structured data were collected with ROM as part of the normal clinical process, which was supervised by specially trained research nurses who were not involved in treatment. Based on our analyses, we could construct an easy to implement risk prediction score, which could be used in routine care.

Our results should be interpreted considering a number of limitations. First, we used the BSI for the assessment of the presence and severity of a broad range of symptoms, which may not be specific enough to fully capture clinical features or subtle changes in all depressive and anxiety disorders. The BSI has proven to be sensitive to treatment effect, but the sensitivity remains slightly behind compared to disorder-specific questionnaires (Lee et al. 2005). Second, information on specific treatment given was not available, thus the particular details of treatment for individual patients could not be taken into account in our analyses. In previous analysis in the population of GGZ Rivierduinen, we have found that treatment broadly followed guidelines, but this cannot be confirmed for individual patients (van der Lem et al. 2011; van Fenema et al. 2012). Third, data were limited to what was clinically available and we had no exhaustive set of predictors. We cannot exclude the possibility that other factors such as patient and/or

family history, childhood trauma, specific co-morbidity (e.g. pervasive developmental disorder), or personality characteristics (e.g. neuroticism) may add to the prediction (Young et al. 2006; Skodol et al. 2010; Lamers et al. 2011; Richards, 2011; Steinert et al. 2014), although in many studies the level of symptom severity outperforms these other variables as well (Spijker et al. 2002; van Beljouw et al. 2010; Stegenga et al. 2012; Boschloo et al. 2014; Riihimaki et al. 2014). The level of symptom severity could reflect to some extent the presence of a multitude of other risk factors, which could support the simplification of risk prediction to single symptom severity scores.

Despite potential limitations, the risk prediction model we developed in this study provides the clinician with an early estimate of prolonged treatment course; patients can easily be classified as having a low or a high predicted risk of poor outcome. This allows for personalized clinical risk profiling relatively early in the course of treatment. Higher risk prediction scores indicate a higher risk of a longer treatment duration, for 28% of the patients within the three highest risk categories, the positive predictive value of prolonged treatment course was 60%: corresponding to an AUROC of 0.65. Although the sensitivity of the score is not very strong the positive predictive value is sufficient to consider patients with a high-risk score for evaluation and monitoring of rational medication switches, add-on psychotherapy, application of social activation and early rehabilitation techniques or interventions to reduce adverse life circumstances. Although not studied here, patients that are initially misclassified, could perhaps be picked up later on, as it seems possible that the predictive value may continue to gain strength over time. Further studies are warranted to see how repeated monitoring could improve prediction. Evidence of effectiveness of such interventions is still needed, but our score at least allows for early risk stratification and for further research in the effectiveness of intensified treatment.

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Chapter 4

The early identification of patients at risk of persistent uncontrolled hypertension, using self-monitored blood pressure.

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ABSTRACT

Background

Early identification of patients with an increased risk of persistent uncontrolled hypertension could provide opportunities for timely adjustment of treatment. To that end, we aimed to develop an easy to use prediction model to identify patients at risk of persistent uncontrolled hypertension.

Methods

We used data of 56 adult with uncontrolled hypertension from a 12-month primary care RCT with three-monthly assessments and self-monitored blood pressure measurements. With logistic regression we modelled the association between level of persistent uncontrolled hypertension risk, patient characteristics, and early treatment response. Persistent uncontrolled hypertension was defined as self-monitored blood pressure of > 135 mmHg at 12 months.

Results

Patients had a mean age of 61.9 (SD 8.3) and 54.4% was female. The mean systolic self-monitored blood pressure was 144.8 (SD 12.4) at baseline. Taking data on early treatment response into account, self-monitored blood pressure after approximately two months, the risk prediction improved (AUROC 0.91) compared to a model containing only baseline self-monitored blood pressure (AUROC = 0.82). The risk prediction includes two easy to obtain predictors, namely; the initial self-monitored blood pressure and the first follow-up self-monitored blood pressure. Other (patient characteristic) predictors did not contribute to the prediction.

Conclusion

We developed an easy to use risk prediction score to identify patients with persistent uncontrolled hypertension after one year of high blood pressure treatment, based on baseline and two month self-monitored blood pressure. It can be used as an online self-management support in order to improve real-time blood pressure.

INTRODUCTION

Worldwide, over one billion people have hypertension.[1] Hypertension is one of the most prominent risk factors of cardiovascular morbidity and mortality.[2] Hypertension is a silent (chronic) condition, therefore, many people will not experience any symptoms. However, raised blood pressure could lead to health issues, including heart attack and stroke. Lowering blood pressure (BP) by lifestyle and drug treatment strategies can substantially reduce premature morbidity and mortality. However, for the majority of patients having hypertension, control of blood pressure remains sub-optimal.[3]

Treatment of hypertension is still mainly based on clinical blood pressure measurements. However, self-monitored blood pressure has several advantages such as a higher frequency of blood pressure measurements, elimination of the white coat effect, low costs and easy application.[4-6] Furthermore, several studies have also shown self-monitored blood pressure is superior to clinical measurements in predicting important end points, including all-cause mortality, progression of chronic kidney disease, and functional decline in the elderly.[7]

To date, most hypertension prognostic models include only one initial self-monitored blood pressure measurement, besides other predictive factors including smoking status, treatment adherence, age, level of education, sex, ethnicity and body mass index (BMI).[8] The performance of a prognostic model might substantially improve by including the early treatment response, as we have recently demonstrated in asthma.[9] More importantly, such a prognostic model including identification of patients with an unfavourable early treatment response potentially allows early identification of those patients with an increased risk of persistent uncontrolled hypertension, thereby providing opportunities for timely adjustment of treatment. Thus far, only limited data is available on repeated blood pressure measurements in a prognostic model and home measurements were not incorporated, even despite the common mentioned advantage of (continuously) self-monitored blood pressure.[8,10,11] We hypothesized that adding an assessment of early treatment response after three months aids in the prediction of persistent uncontrolled hypertension.

Overall, the aim of this study was to develop an easy to use prediction model, in patients currently diagnosed with hypertension, based on patient characteristics and early treatment response assessed by self-monitored blood pressure measurements.

METHODS

Study design

We analysed potential predictive variables of hypertension using primary care data from the TeleHype-study: a trial of TELEmonitoring and self-management support of patients with uncontrolled HYPErtension. The dataset was obtained from a pragmatic randomized control 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. We only analysed 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. Clinicians provided treatment according to usual care, based on (inter)national evidence-based treatment guidelines, supported by an online self-management tool. Patients were asked to monitor blood pressure as often as they wanted, patients were encouraged to do this especially in a 7-day intensified monitoring period. During the 7-day intensified monitoring period patients were asked to monitor blood pressure twice in the morning and twice in the evening over three out of seven consecutive days; according to the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines.[12] A detailed description of study procedures and participants will be published elsewhere (trial registry: ISRCTN10969896).

Study population

In this cohort patients were aged 18-75 years, with a diagnosis of hypertension in general practice; a systolic office blood pressure > 140 mmHg, or if diabetes or chronic kidney disease were present > 130 mmHg. Follow-up was 12 months and patients filled out online questionnaires at approximately three-monthly intervals. We limited our selection to patients with completed self-monitored blood pressure measurements at twelve months.

Potential predictor variables

Demographic and clinical variables that potentially predict future risk were obtained at baseline including age, sex and current smoking status. At baseline, medication adherence was assessed with the Medication Adherence Report Scale (MARS),[13] indirect utilities from the general public were obtained by the EuroQol 5 dimensions (EQ-5D).[14,15] Self-management characteristics are measured using the Partners In Health scale (PIH-NL).[16] At baseline and per three-monthly interval mean self-monitored blood pressure was measured, and health-related quality of life was assessed with the Short Form (SF)-12.[17] The results obtained three months after the baseline visit were used as

measures of early treatment response.

Outcome

Our primary outcome of interest was the presence of self-monitored hypertension after twelve months of treatment. We classified patients as having persistent uncontrolled hypertension based on their mean self-monitored blood pressure of > 135 mmHg at twelve months of follow-up. Mean self-monitored blood pressure was calculated based on twelve self-monitored blood pressure measurements within seven consecutive days, patients were asked to measure their blood pressure four times per day, twice in the morning and twice in the evening. In keeping with international guidelines, the first four measurements were eliminated (the first day of measurements), and the mean self-monitored blood pressure was calculated based on the remaining eight self-monitored blood pressure measurements.[18-21]

Model development

With logistic regression we studied the relation between uncontrolled self-monitored blood pressure (>135 mmHg) at twelve months and baseline characteristics plus the information on early treatment response. Baseline variables that were univariably associated with future risk (p-value < 0.10) were initially selected for multivariable logistic regression and backward selection was performed (p-value < 0.10). Second, we studied the additional contribution of information on early treatment response by adding variables, assessed at three months follow-up, to the first multivariable logistic regression model. Performance of all multivariable models was assessed with the area under the receiver operating curve (AUROC), which we internally validated with 2,000 bootstraps. Based on the regression coefficients of our final model a risk prediction score was developed as extensively described by Sullivan et al. (2004), in order to facilitate clinical application of the model (*online supplement, table S1*).[22] Cut-offs were based on sensitivity and specificity, and clinical perspective, in relation to the outcome of persistent uncontrolled hypertension.

RESULTS

Patient information

We included 56 patients with a diagnosis of hypertension (table 1). Patients had a mean age of 61.9 (SD 8.3) and 54.4% was female. The mean systolic self-monitored blood pressure was 144.8 (SD 12.4) at baseline (first 7-day intensified monitoring period), and blood pressure significantly improved at the second 7-day intensified monitoring

period (mean systolic self-monitored blood pressure 138.8; SD 13.6), on average 2.6 months after baseline.

TABLE 1. *Baseline characteristics (n = 56). For continuous variables; values are stated as the mean (standard deviation). For categorical variables; values are numbers (percentages).*

Continuous variables	
Age years	63.9 (8.4)
Systolic blood pressure (mmHg)	144.8 (12.4)
Diastolic blood pressure (mmHg)	87.0 (9.8)
EQ-5D	0.9 (0.1)
EQ-5D Visual Analogue Scale	76.7 (15.5)
Medication Adherence Report Scale	3.4 (0.5)
SF-12 Physical Health Score	-61.5 (8.1)
SF-12 Mental Health Score	-71.8 (10.7)
PIH-NL Knowledge	26.2 (4.6)
PIH-NL Coping	19.7 (3.5)
PIH-NL Management in symptoms	20.2 (3.3)
PIH-NL Adherence to treatment	14.2 (2.3)
PIH-NL Total	80.3 (11.6)
Categorical variables	
Female sex	30 (53.6)
Current smokers	4 (7.1)

SF-12 = Short Form , EQ-5D = EuroQol 5 dimensions, PIH = Partners In Health

TABLE 2. *Univariable odds ratios (95% confidence interval) and corresponding p-values in the derivation dataset.**

Continuous variables	**Odds ratio (CI95%)**	**p-value**
Age years	1.01 (0.95-1.08)	0.74
Systolic blood pressure (mmHg)	1.08 (1.02-1.16)	0.01
Diastolic blood pressure (mmHg)	0.05 (0.00-93.46)	0.43
EQ-5D	0.98 (0.95-1.02)	0.28
EQ-5D Visual Analogue Scale	0.58 (0.22-1.57)	0.29
Medication Adherence Report Scale	1.08 (1.02-1.16)	0.01
SF-12 Physical Health Score	1.01 (0.94-1.07)	0.88
SF-12 Mental Health Score	1.00 (0.96-1.05)	0.90
PIH-NL Knowledge	0.93 (0.83-1.05)	0.24
PIH-NL Coping	1.02 (0.88-1.19)	0.80
PIH-NL Management in symptoms	0.98 (0.83-1.15)	0.82
PIH-NL Adherence to treatment	0.83 (0.65-1.07)	0.15
PIH-NL Total	0.98 (0.94-1.03)	0.45
Categorical variables		
Female sex	1.12 (0.39-3.21)	0.83
Current smokers	1.30 (0.17-9.97)	0.80

SF-12 = Short Form , EQ-5D = EuroQol 5 dimensions, PIH = Partners In Health

Predictors of uncontrolled self-monitored blood pressure

With univariable logistic regression, uncontrolled self-monitored blood pressure (> 135 mmHg) at twelve months was significantly predicted by systolic and diastolic self-monitored blood pressure at baseline, with respectively an OR of 1.14 (CI95% 1.06-1.24) and an OR of 1.08 (CI95% 1.02-1.16) per mmHg (table 2). Other baseline variables were not univariable associated with persistent uncontrolled hypertension.

Using multivariable logistic regression analysis with the univariably associated baseline variables only systolic self-monitored blood pressure remained in the model after backward selection, therefore resulting in a univariable prediction model, corresponding to an internally validated AUROC of 0.82 (0.71-0.93). Multivariable logistic regression analysis with both systolic self-monitored blood pressure measurements, initial systolic blood pressure and systolic blood pressure after approximately two months, resulted in an internally validated AUROC of 0.91 (0.84-0.98); both measurements remained in the model (OR of 1.09 (1.00-1.19) and an OR of 1.18 (1.05-1.33)). The AUROC of the model with early treatment response differs significantly from the model without early treatment response ($p < 0.05$) (figure 1).

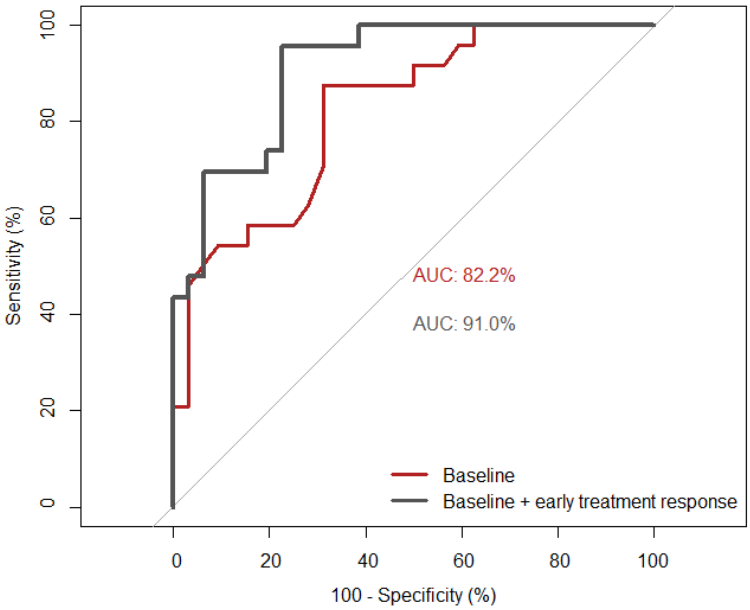

FIGURE 1. *ROC-curves for models with and without early treatment response. The AUROC of the model with early treatment response differs significantly from the model without early treatment response (p = 0.03).*

Figure 2 presents the risk prediction scores corresponding to the final model. From our final prediction model, we derived an easy to calculate score which ranged from -1 to 12. For 57% of patients with a risk score of 5-12 points, the positive predictive value of prolonged treatment course was 65%, compared to 5% (1-negative predictive value) for patients with a score of 0-4 points. At this cut-off level sensitivity was 0.96 and specificity 0.64. For a risk score of 5-12 points either baseline systolic self-monitored blood pressure was ≥ 150 mmHg or after approximately two months of treatment systolic self-monitored blood pressure was ≥ 130 mmHg. See also table 5.

		CURRENT VISIT					
		< 120	120-129	130-139	140-149	150-159	160+
PREVIOUS VISIT (2-3 month before)	< 120	-1	0	2	4	6	8
	120-129	-1	0	2	4	6	8
	130-139	0	1	3	5	7	9
	140-149	1	2	4	6	8	10
	150-159	2	3	5	7	9	11
	160+	3	4	6	8	10	12

FIGURE 2. *The risk prediction score in clinical practice: simplified. The risk prediction score is assessed within two moments of time. Higher scores indicate a higher risk of persistent hypertension (ranging from -1 to 12). For patients with a risk score of 5-12 points, the positive predictive value of persistent hypertension was 65%, compared to 5% (1-negative predictive value) for patients with a score of 0-4 points. At this cut-off level sensitivity was 0.96 and specificity 0.64.*

TABLE 3. *Multivariable odds ratios (95% confidence interval) and corresponding p-values; at baseline (AUROC of 0.82 (CI95% 0.71-0.93)) and after two months of treatment at follow-up (AUROC of 0.91 (CI95% 0.84-0.98).*

	OR (CI 95%)	p-value	OR (CI 95%)	p-value
Systolic blood pressure (mmHg) at baseline	1.14 (1.06-1.24)	0.001	1.09 (1.00-1.19)	0.06
Systolic blood pressure (mmHg) at two months			1.18 (1.05-1.33)	< 0.01
AUROC	**0.82 (0.71-0.93)**		**0.91 (0.84-0.98)**	

TABLE 4. *Construction of the persistent hypertension risk prediction score. The risk prediction score is assessed within two moments of time; first part at baseline (here defined as the previous visit) and after approximately two-three months, here defined as the current visit.*

Factor	Points
Current visit	
Self-monitored systolic blood pressure	
< 120	-1
120-129	0
130-139	2
140-149	4
150-159	6
≥ 160	8
Previous visit	
Self-monitored systolic blood pressure	
< 120	0
120-129	0
130-139	1
140-149	2
150-159	3
≥ 160	4
Total score (range)	**-1 ; 12**

TABLE 5. *The distribution of patients for the risk prediction score of persistent hypertension; assessed after approximately two months of treatment. Higher scores indicate a higher risk of persistent hypertension; high risk scores ranging from 5 to 12.**

Risk prediction score	N patients without persistent hypertension	N patients with persistent hypertension	Total
-1	0	0	0
0	2	0	2
1	2	0	2
2	5	0	5
3	6	0	6
4	6	1	7
5	2	3	5
6	5	5	10
7	1	2	3
8	1	4	5
9	0	2	2
10	1	4	5
11	0	0	0
12	0	2	2

N = 56. * For 57% (N = 32) of patients with the highest scores (5-12), the positive predictive value for persistent hypertension was 65% (sensitivity 0.96, specificity 0.64).

DISCUSSION

In this study we have developed a prediction model that can be used to accurately predict persistent uncontrolled hypertension in primary care. Initial higher self-monitored blood pressure can be used as an estimate, resulting in an AUC of 0.82. The performance of the risk prediction model is improved by adding an assessment of early treatment response (AUC 0.91). Higher self-monitored blood pressure at approximately two months, indicating an unfavourable initial response to treatment is the strongest predictor of persistent uncontrolled hypertension after one year of treatment.

Comparisons with literature

Our study confirms and adds to previous studies. In contrast to other studies, we used self-monitored blood pressure as an outcome. Self-monitored blood pressure, with or without telemonitoring, when used by general practitioners to titrate antihypertensive medication, has been shown to lower systolic blood pressure.[23] With an increased number of general practitioners and many patients using self-monitoring, it could become the cornerstone of hypertension management in primary care, elimination of the white coat effect, low costs and easy application.[4] Increased successful reduction of hypertension in primary care, will benefit the risk of cardiovascular morbidity and mortality.[24]

Our final risk prediction model included two assessments of systolic self-monitored blood pressure as predictors of persistent uncontrolled hypertension, other predictors were outperformed and therefore not included in the final risk prediction model. First, self-monitored systolic blood pressure is the strongest predictor. This adds to other studies, where systolic and/or diastolic blood pressure were included in hypertension risk prediction models.[25-28] Especially our study adds to the previous study of Hozawa et al. (2000) which showed the prognosis of hypertension would be improved by treatment focused on systolic rather than on diastolic self-monitored blood pressure measurements.[29] Second, early treatment response was included in our risk prediction model by the inclusion of multiple assessments of self-monitored blood pressure. Despite the advantages and availability of self-monitored blood pressure measurements over time, early treatment response is not a common measure in risk prediction models. Most risk prediction models include only one assessment of blood pressure.[25-28] However, early treatment response adds an insight that can be acted upon; guiding decisions in the treatment plan. For example, when early treatment response is minimal after approximately two months of treatment, and self-monitored blood pressure is still marked as hypertension, it is quite likely that the patient will still have raised blood pressure after one year of treatment. In contrast to previous

studies we showed that as soon as two months after initiated treatment these patients can be identified, where other studies showed this effect after six months.[23,30] Third, our study showed that initial blood pressure and early treatment response are by far the most important predictors of persistent uncontrolled hypertension, whereas the contribution of additional predictors was limited.[8] Within this study we could not make any statement about family history or physical inactivity because both were not available. However, other variables did not end up in the risk prediction of persistent uncontrolled hypertension and our predictive performance is already very high.

Strengths and weaknesses

Extensive self-monitoring of blood pressure is a strength of our study. Patients monitored blood pressure two times in the morning and two times in the evening, within seven consecutive days and we took the mean, which accounts for variability and measurement errors in blood pressure. Another strength is the implementation of the use of early treatment response as a predictor for future raised blood pressure in routine care. Easy to assess, in contrast to for example risk prediction models including genetic factors.[31] A limitation of our study is the small sample size of this study. Despite this, the effects are internally validated and high (AUC 0.91). Another limitation could be the telemonitoring which was additive to the self-monitored blood pressure, therefore patients awareness of hypertension may be increased, as well as drug compliance.[32] At the same time, telemonitoring could be a strength of our study; the predictive performance of the risk prediction model is high, and the accessibility of telemonitoring and self-monitored blood pressure is easy.[23,33-36]

Clinical implications

The developed risk prediction score provides the clinician, and patients, with a clear estimate of persistent uncontrolled hypertension. Since only self-monitored systolic blood pressure measurements are required, this aids the implementation of this model in clinical practice and empowers the patient, at home. With the inclusion of early treatment response in the model, a review of effectiveness of treatment is included and to our best knowledge not commonly used in clinical practice as a predictor. It is especially meaningful to consider patients without or with minimal decrease of systolic blood pressure (high risk patients) for evaluation and monitoring of rational medication switches, therapy compliance, reduce salt-intake or interventions to reduce adverse life circumstances.

Conclusion

We showed the additional value of systolic blood pressure as early treatment

response in risk prediction of persistent uncontrolled hypertension; increased systolic blood pressure approximately two months after initiation of treatment improves predictive performance compared to initial characteristics only. Successful reduction of hypertension in primary care, especially focussing on patients with minimal or no decrease of systolic blood pressure, may benefit the risk of cardiovascular morbidity and mortality.

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ONLINE SUPPLEMENT APPENDIX 1

TABLE S1. *Based on the regression coefficients of our final model the risk prediction score was developed.*[23]

Variable	Beta	Categories	Reference (W)	Beta * ($W-W_{REF}$)	Points†	Rounded points
Self-monitored systolic blood pressure, baseline	0.083	< 120	120	-0.374	-0.450	0
		120-129	**124.5**$_{REF}$	0.000	0.000	0
		130-139	134.5	0.830	1.000	1
		140-149	144.5	1.660	2.000	2
		150-159	154.5	2.490	3.000	3
		> 160	166	3.445	4.150	4
Self-monitored systolic blood pressure, follow-up	0.169	< 120	120	-0.761	-0.961	-1
		120-129	**124.5**$_{REF}$	0.000	0.000	0
		130-139	134.5	1.690	2.036	2
		140-149	144.5	3.380	4.072	4
		150-159	154.5	5.070	6.108	6
		> 160	166	7.014	8.450	8
Intercept	-35.727					

† Constant B = 0.830

Variable. The remaining variables of the risk prediction model.

Beta. The regression coefficients corresponding to the variables.

Categories. Variables are categorized into meaningful categories.

Reference (W). The reference value for each category was determined; the midpoint of each category. Furthermore, we determined the base category for each variable, for the referent ($_{REF}$) profile.

Beta * ($W-W_{REF}$). We determined how far each category is from the base category in regression units; multiplying the beta by the difference between reference value for the specific category and the reference value for the base category.

Points. In order to compute the risk prediction points, we had to set a constant B for the point system, or the number of regression units that will correspond to one point. We set the constant as the smallest beta (self-monitored systolic blood pressure, baseline) and multiplied it by ten; we multiplied the constant by ten in order to keep the total risk prediction score in a feasible range without loss of accuracy. Points were computed by (*Beta * ($W-W_{REF}$)) / constant B*.

Rounded. Risk prediction points were rounded to the nearest integer.

Chapter 5

Development and validation of personalized prediction to estimate future risk of severe exacerbations and uncontrolled asthma in patients with asthma, using clinical parameters and early treatment response.

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ABSTRACT

Current level of asthma control can be easily assessed by validated instruments, but it is currently difficult to assess individuals' level of future risk. Our objective is to develop, and validate, a risk prediction score for level of future risk, including patient characteristics and information on early treatment response.

We used data of 304 adult patients with asthma from a 12-month primary care randomized controlled trial with 3-monthly assessments. With logistic regression we modeled the association between the level of future risk and patient characteristics including early treatment response. Future risk was defined as Asthma Control Questionnaire (ACQ) score of 1.5 or more at 12 months or the experience of at least 1 exacerbation during the final 6 months. We developed a risk prediction score on the basis of regression coefficients.

Performance of the risk prediction score improved, taking into account data on early treatment response (area under receiver-operating curve [AUROC] = 0.84) compared with a model containing only baseline characteristics (AUROC = 0.78). The score includes 6 easy-to-obtain predictors: sex, ACQ score and exacerbations in the previous year at baseline and at first follow-up, and smoking status and exacerbations in the previous 3 months (indicating early treatment response). External validation yielded an AUROC of 0.77. The risk prediction score classified patients into 3 risk groups: low (absolute risk, 11.7%), intermediate (47.0%), and high (72.7%).

We developed and externally validated a risk prediction score, quantifying both level of current asthma control and the guideline-defined future risk. Patients' individual risk can now be estimated in an easy way, as proposed but not specified, by asthma management guidelines.

INTRODUCTION

According to asthma management guidelines, clinicians should assess the current level of control of asthma symptoms, alongside the level of guideline-defined future risk of adverse outcomes, while taking into account individual patient characteristics. The goal is to obtain and/or maintain controlled asthma, as opposed to partly controlled or uncontrolled asthma, and treatment should be adjusted if necessary.[1,2,3,4] The rationale for this goal is that uncontrolled asthma increases the risk of experiencing asthma exacerbations, has an increased mortality ratio, and is associated with higher health care utilization and costs, including more hospital admissions, unscheduled doctor visits, and use of emergency services.[5,6,7] Despite this, currently 50% to 60% of patients with asthma are not controlled.[8,9]

Although the current level of asthma control can be easily assessed by validated instruments such as the Asthma Control Questionnaire (ACQ),[10] guideline-defined future risk is difficult to assess in clinical practice. In asthma management guidelines, future risk is usually defined as the occurrence of (severe) exacerbations in the (near) future, fixed airflow limitation, and/or side effect of medications.[1,2,3] The main focus has been on identifying which patient characteristics increase the likelihood of experiencing a future exacerbation.[8,11,12] Predictive factors that have been identified include smoking, lower socioeconomic status, poor medication adherence, comorbidities, and race.

The development of fixed airflow limitation is hard to predict, especially at regular structured review visits in primary care. However, it is associated with long-term uncontrolled asthma, which can be monitored.[13] For this reason, guideline-defined future risk should not only involve the occurrence of exacerbations but also incorporate the risk domain of uncontrolled asthma. Specifically predicting the occurrence of side effects might be possible, but it will be highly correlated to medication dosage.[14,15,16] Therefore, reducing the risk of side effects of medications could be accomplished, especially in patients with a low guideline-defined future risk, by safely downtitrating medication. Therefore, we aimed to analyze which patient characteristics predict guideline-defined future risk, defined as a combination of exacerbations and uncontrolled asthma, and create a prediction model on the basis of these outcomes defining patients as having a low, medium, or high risk.

In addition, several studies of long-term outcomes suggest that whether controlled asthma will be achieved may already be judged at a 3-month review.[17,18] Therefore, we believe that adding an assessment of early treatment response after 3 months of

treatment aids in the prediction of guideline-defined future risk.

Overall, the aim of this study was to develop, and externally validate, an easy-to-use prediction model enabling clinicians to identify patients with an increased guideline-defined future risk, based on patient characteristics and early treatment response.

METHODS

Study design

We analyzed potential predictors of guideline-defined future risk, described as level of asthma control and the occurrence of exacerbations, using data from 2 previous studies. The derivation data set was obtained from a pragmatic cluster-randomized controlled trial comparing 3 asthma management strategies in primary care. We analyzed data of only the 2 strategies that aimed at the same treatment goal, controlled asthma. The third strategy aimed at partly controlled asthma, and was therefore excluded. Patients' first assessment originated from 87 general practices in the areas of Leiden, Nijmegen, and Amsterdam from June 2009 until 2010. A detailed description of study procedures and participants of the randomized controlled trial has been published elsewhere.[18,19] The validation data set was obtained from another randomized controlled trial 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 from September 2005 to September 2006.[17] In both studies, 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 (see this article's Online Repository at www.jaci-inpractice.org). To our knowledge, there was no overlap in general practices or patients between both data sets.

Study population

In the derivation cohort, patients were aged 18 to 50 years, with a diagnosis of asthma and prescribed inhaled corticosteroids. Follow-up was 12 months and patients filled out online questionnaires at approximately 3-month intervals. We limited our selection to patients with a complete ACQ score at 12 months, and we excluded patients if no data were available at either baseline, 3 months, or 12-month follow-up. For the validation cohort, the same inclusion criteria and follow-up intervals applied.

Outcome

Our primary outcome of interest was guideline-defined future risk. We classified patients as having an increased level of future risk if patients experienced uncontrolled asthma at 12 months, defined as an ACQ score of greater than or equal to 1.5,[13] or if they experienced at least 1 severe asthma exacerbation during the final 6 months of the trial.

Potential predictors

Demographic and clinical variables that potentially predict guideline-defined future risk were obtained at baseline including age, sex, body mass index, previous smoking, age of asthma onset, level of education, having a pet, symptoms of allergy, allergic rhinitis, and fractional exhaled nitric oxide (Feno) concentration.[1,2,3,12,20] At baseline and every 3 months, current smoking status was updated, lung function was measured by spirometry (prebronchodilator absolute FEV1), the level of asthma control with the 6-item ACQ, and quality of life with the Asthma-related Quality of Life Questionnaire (AQLQ). In addition, current medication usage was assessed by the practice nurse and medication adherence with the Medication Adherence Report Scale (MARS) as a potential predictor. The results obtained 3 months after the baseline visit were used as a measure of early treatment response. A severe asthma exacerbation was defined as a course of oral prednisolone prescribed for worsening asthma for 3 or more days, or an emergency department visit/hospitalization due to asthma.[21] At baseline, the occurrence of at least 1 severe exacerbation over the previous year was assessed. Experiencing an exacerbation within the first 3 months after the baseline visit was also assessed as a potential measure of early treatment response.

Model development

With logistic regression we studied the association between guideline-defined future risk and baseline characteristics plus information on early treatment response. Baseline variables univariably associated with future risk ($P < .10$) were selected for multivariable logistic regression, and then backward selection was performed ($P < .10$). The final selection of variables with comparable predictive properties was based on clinical feasibility. Second, we studied the additional contribution of information on early treatment response by adding variables, assessed at 3 months, to the first model. Performance of all multivariable models was assessed with the area under the receiver-operating curve (AUROC) and for calibration we used the Hosmer-Lemeshow test.[22] The AUROC was internally validated and corrected for optimism using internal bootstrap resampling (2000 bootstrap samples). A correction for optimism is needed because the performance of a model in a derivation data set will be better than the performance of a model in another data set. Based on the regression coefficients

of our final model, a risk prediction score was developed (see Tables E1 and E2 in this article's Online Repository at www.jaci-inpractice.org) and risk categories were established, to facilitate clinical application of the model.[23] Cutoffs were based on absolute risks, as mentioned in previous literature, approximately 10% in the low-risk category and 48% in the high-risk category.[24]

Model external validation

We applied our risk prediction model, obtained from the derivation data set, to the validation data set (n = 195) and calculated the AUROC. Furthermore, we computed the absolute risk for patients, per risk prediction score.

Sensitivity analysis

First, as a sensitivity analysis we compared our results to solely using the ACQ to decide whether and how to adjust treatment, which is proposed as an interpretation of current clinical practice. Second, we performed the same statistical analysis as described, for solely an ACQ score of 1.5 or more or at 12 months as outcome measure, and for solely the experience of at least 1 severe asthma exacerbation during the final 6 months of the trial. As a third sensitivity analysis, we compared results on self-reported questionnaires at baseline (MARS, ACQ, and AQLQ), between participants from this study and people who were excluded.

For analyses, STATA statistical software version 14 (Statacorp, College Station, Texas) and SPSS version 20.0 for Windows (SPSS Inc, Chicago, III) were used.

RESULTS

Baseline characteristics

The derivation data set consisted of 304 patients (Figure 1), of which 83 (27.3%) experienced an event at 12 months, 52 scored above 1.5 on the ACQ, 19 experienced a severe exacerbation, and 12 had both events. Demographic and clinical patient characteristics (Table I) demonstrated a study population with a mean age of 40.2 ± 8.5 years and 69.0% being women. The mean score for the baseline ACQ was 0.93 ± 0.74, and the mean baseline AQLQ score was 5.87 ± 0.88. The validation data set consisted of 195 patients with a mean age of 36.3 ± 8.6 years and 69.0% being women. The baseline ACQ had a mean score of 1.09 ± 0.72, and the mean baseline AQLQ score was 5.77 ± 0.81.

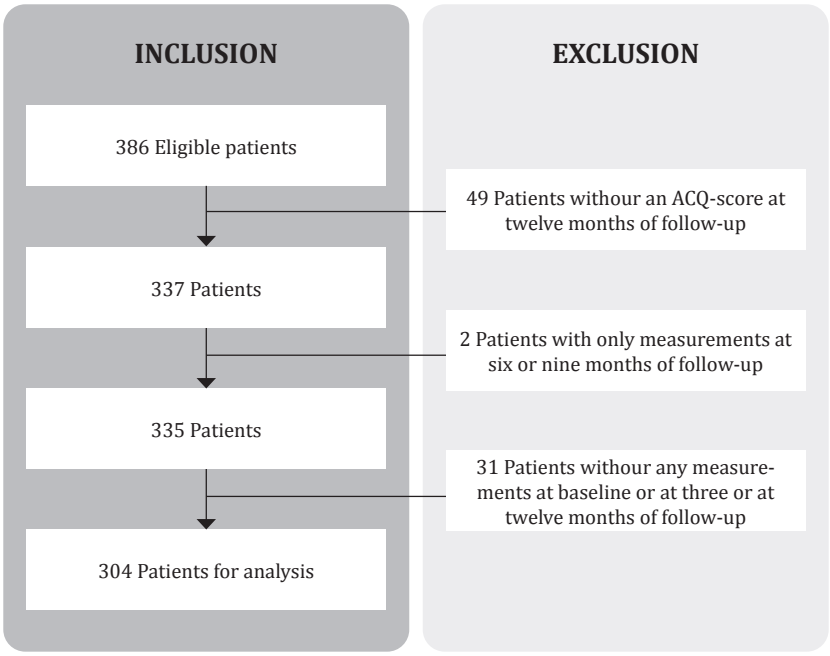

FIGURE 1. *Flowchart of inclusion and exclusion of patients with a diagnosis of asthma in the derivation data set. In the validation cohort, only 5 patients were excluded without any measurement at baseline, or at 3 or 12 months of follow-up. ACQ = Asthma Control Questionnaire.*

TABLE 1. *Baseline characteristics of patients in the derivation dataset (n = 304) and the validation dataset (n = 195). For continuous variables; values are stated as the mean (standard deviation). For categorical variables; values are numbers (percentages).*

	Derivation dataset	**Validation dataset**
Continuous variables		
Age years	40.2 (8.5)	36.3 (8.6)
Age of onset years	21.7 (14.9)	not available**
Body mass index kg/m^2	25.8 (5.0)	not available**
FEV_1	3.25 (0.87)	3.12 (0.76)
Fe_{NO}	24.1 (20.7)	29.5 (29.5)
ACQ score	0.93 (0.74)	1.09 (0.72)
AQLQ	5.87 (0.88)	5.77 (0.81)
Categorical variables		
Female sex	210 (69.1)	136 (69.7)
Current smokers	40 (13.2)	24 (12.3)
Previous smokers	127 (41.8)	62 (31.8)
Severe exacerbation(s) in the previous year	98 (32.2)	24 (12.3)*

* Exacerbation(s) in the previous six months.
** These variables were not assessed in the original trial of the validation data set.
FEV_1 = Forced Expiratory Volume in one second. Fe_{NO} = Fractional exhaled nitric oxide.
ACQ = Asthma Control Questionnaire. AQLQ = Asthma Quality of Life Questionnaire.

Model development

The results of our univariable analyses are presented in Table II. An increase of half a point on the baseline ACQ (defined as the clinically meaningful minimal important difference) resulted in an odds ratio (OR) of 1.87 (95% CI, 1.53-2.28) for guideline-defined future risk to be present. Compared with men, women had an OR of 2.34 (95% CI, 1.27-4.30) and FEV1 an OR of 0.63 (95% CI, 0.45-0.88) per additional liter, and no association was found for Feno concentration. The occurrence of at least 1 severe exacerbation in the previous year showed an OR of 3.17 (95% CI, 1.86-5.39).

TABLE 2. *Univariable odds ratios (95% confidence interval) and corresponding p-values in the derivation dataset.**

Continuous variables	**Odds ratio (CI95%)**	**p-value**
Age years	1.01 (0.98-1.04)	0.41
Age of onset years	1.00 (0.99-1.02)	0.77
Body mass index kg/m^2	1.02 (0.98-1.08)	0.35
FEV_1	0.63 (0.45-0.88)	< 0.01
Fe_{NO}	0.99 (0.97-1.01)	0.19
ACQ-score per 0.5	1.87 (1.53-2.28)	< 0.001
AQLQ per 0.5	0.60 (0.50-0.71)	< 0.001
MARS	0.70 (0.45-1.09)	.12
Categorical variables		
Female sex	2.34 (1.27-4.30)	< 0.01
Current smokers	1.92 (0.96-3.83)	0.06
Previous smokers	1.34 (0.80-2.23)	0.27
Symptoms of allergy	0.99 (0.53-1.84)	0.99
Allergic rhinitis	1.47 (0.74-2.92)	0.26
Having a pet	1.14 (0.68-1.91)	0.62
Severe exacerbation(s) in the previous year	3.17 (1.86-5.39)	< 0.001
Level of education		.47
Low	1.00	
Medium	0.76 (0.38-1.52)	
High	0.64 (0.32-1.29)	
Beclomethasone equivalent dose in ?g		.08
Low (0-400)	1.00	
Medium (400-800)	1.38 (0.66-2.89)	
High (>800)	1.95 (1.07-3.56)	

* Measurements that showed no (significant) univariable association are not presented in this table. These include the MARS questionnaire, allergic symptoms, allergic rhinitis, having a pet, current medication use and level of education. FEV_1 = Forced Expiratory Volume in one second. Fe_{NO} = Fractional exhaled nitric oxide. ACQ = Asthma Control Questionnaire. AQLQ = Asthma Quality of Life Questionnaire.

As shown in Table III, the variables selected in the first multivariable model, with only baseline predictors, were sex, current smoking status, the ACQ score and the

occurrence of an exacerbation in the previous year. The corresponding AUROC was 0.78 (95% CI, 0.72-0.84), and the Hosmer-Lemeshow test yielded no indication of poor fit (P = .45). In the second model, when information on early treatment response was added and current smoking status was updated, the AUROC increased to 0.84 (95% CI, 0.79-0.89), and there was no indication of poor fit (Hosmer-Lemeshow test P = .32); for the calibration plots, see Figure E1 in this article's Online Repository at www.jaci-inpractice.org. Internal validation yielded a correction for optimism of 0.01 decrease in both AUROCs. Final measurements on early treatment response included the first follow-up ACQ assessment with an OR of 1.93 (95% CI, 1.49-2.51) and the occurrence of an exacerbation in the initial 3 months of treatment (OR = 6.40; 95% CI, 1.36-30.06).

TABLE 3. *Multivariable odds ratios (95% confidence interval) and corresponding p-values in the derivation dataset; at baseline (AUROC of 0.78 (CI95% 0.72-0.84)) and after three months of treatment at follow-up (AUROC of 0.84 (CI95% 0.79-0.89).*

	Baseline (last visit)		**Follow-up (current visit)**	
Continuous variables	**Odds ratio (CI95%)**	**p-value**	**Odds ratio (CI95%)**	**p-value**
ACQ score per 0.5, baseline	1.74 (1.41-2.14)	< 0.001	1.27 (0.98-1.63)	0.07
ACQ score per 0.5, after three months as measure of early treatment response	-		1.93 (1.49-2.51)	<0.001
Categorical variables				
Women	2.05 (1.06-3.98)	0.03	2.03 (0.97-4.27)	0.06
Current smokers	1.49 (0.64-3.43)	0.35	1.27 (0.49-3.30)	0.62
Exacerbation(s) in the previous year at baseline	2.45 (1.37-4.38)	< 0.01	2.43 (1.27-4.64)	< 0.01
Exacerbation(s) in the previous three months as measure of early treatment response	-		6.40 (1.36-30.06)	0.02

. ACQ = Asthma Control Questionnaire.

Table IV presents the risk prediction scores corresponding to the second model, with higher scores indicating a higher future risk of uncontrolled asthma and/or exacerbations (see Tables E1 and E2). We established 3 risk categories: low (ranging from 0-4), intermediate (ranging from 5-8), and high (ranging from 9-16). The absolute risk for the low-risk category was 11.7%, for the intermediate-risk category 47.0%, and for the high-risk category 72.7%. In the derivation data set, 64.2% of patients were classified as having a low risk, 23.6% as having an intermediate risk, and 12.2% as having a high risk.

Figure 2a and 2b plot the absolute risk of patients having a guideline-defined future risk per risk prediction score.

TABLE 4. *Construction of the asthma risk prediction score. A total score ranging from 0 to 4 is classified as low level of future risk (11.7%), a total score ranging from 5 to 8 as intermediate level of future risk (47.0%), and a total score ranging from 9 to 16 is classified as high level of future risk (72.7%). The risk prediction score is assessed on the basis of 2 points in time: current visit and visit ~3 months previously.*

Factor	Points
Current visit	
Current smoking	
No	0
Yes	1
Sex	
Men	0
Women	1
ACQ-6 score	
< 0.75	0
0.75-1.50	2
> 1.50	6
Exacerbation(s) since the previous visit (±three months)	
No	0
Yes	4
Previous visit	
ACQ-6 score	
< 0.75	0
0.75-1.50	1
> 1.50	2
Exacerbation(s) in the previous year	
No	0
Yes	2
Total score (range)	**0-16**

ACQ = Asthma Control Questionnaire.

Model external validation

In the validation data set, the risk prediction model, including early treatment response, showed a discriminative AUROC of 0.77 (95% CI, 0.68-0.86), whereas the baseline risk prediction model showed an AUROC of 0.72 (95% CI, 0.64-0.81). The absolute risks per category were, respectively, 14.5%, 33.3%, and 68.0%. Furthermore, 66.7% of patients were classified as having a low risk, 19.4% as having an intermediate risk, and 13.9% as having a high risk.

Sensitivity analysis

First sensitivity analysis, with the use of solely the ACQ as a predictor, resulted in an AUROC of 0.73 (95% CI, 0.66-0.80); see Figure E2 in this article's Online Repository at www.jaci-inpractice.org. Second sensitivity analysis, with solely an ACQ score of greater than or equal to 1.5 as an outcome measure with the developed model, resulted

in an AUROC of 0.87 (95% CI, 0.81-0.90), and with solely the experience of at least 1 severe exacerbation in an AUROC of 0.76 (95% CI, 0.67-0.85). Also, for both outcome measures, we performed the same statistical analysis as for our combined measure; see Table E3 and Table E4, in this article's Online Repository at www.jaci-inpractice.org. Third sensitivity analysis showed no significant difference between included and excluded people: ACQ (0.12; 95% CI, −0.07 to 0.31), AQLQ (−0.13; 95% CI, −0.36 to 0.09), and MARS (−0.03; 95% CI, −0.17 to 0.11).

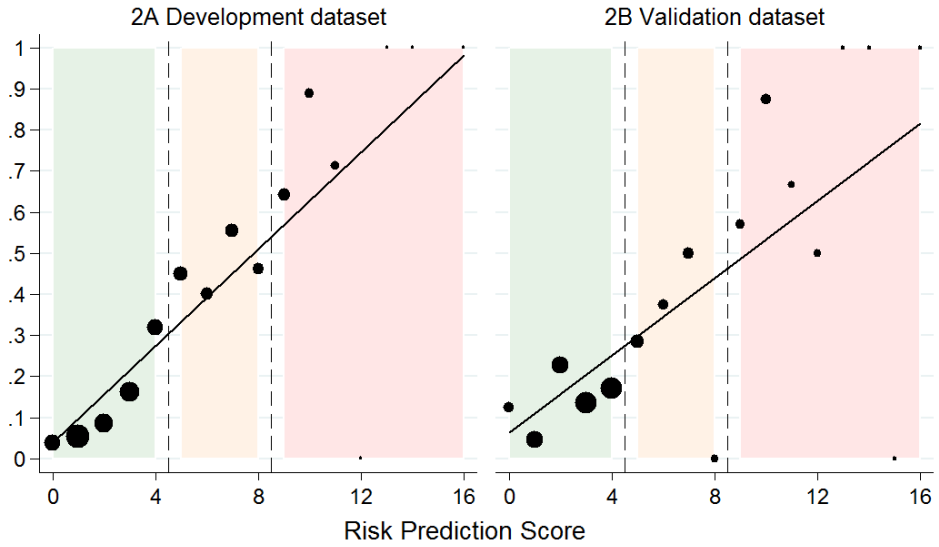

FIGURE 2. *The risk prediction score is on the x-axis, and the absolute risk in the data set is on the y-axis: derivation data set (A) and validation data set (B). Circles represent the number of patients; the larger the circle, the more patients with the same risk prediction score. The green area represents the low-risk category (11.7%), followed by the orange intermediate-risk category (47%) and on the right side the high-risk category (72.7%) as the red area. A regression line was fitted; the absolute risk increases with the increasing risk prediction score (derivation data set, 0.0602x – 0.0259; validation data set 0.047x + 0.017).*

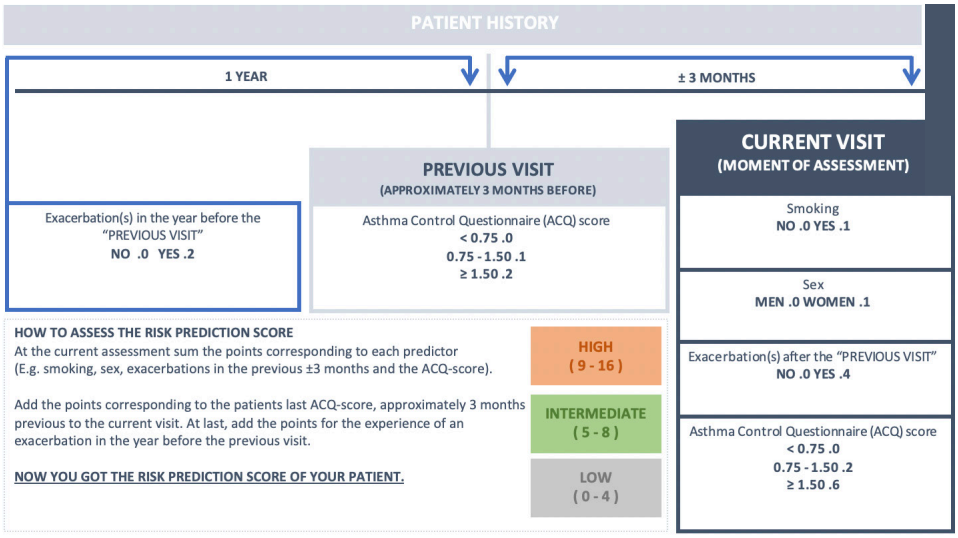

FIGURE 3. *The risk prediction score in clinical practice: simplified users guide. ACQ = Asthma Control Questionnaire.*

DISCUSSION

We developed and externally validated a clinical prediction tool that provides clinicians with an easy-to-use risk prediction score that quantifies both the level of current asthma control and guideline-defined future risk of uncontrolled asthma or exacerbations, by assessing 6 easily accessible variables. Furthermore, including measures of early treatment response improved the predictive properties.

Comparisons with literature

Our study is in line with current asthma management guidelines, focusing on current control and future risk.[1,2,3] In contrast to most studies, our study not only defined future risk by whether or not a severe exacerbation occurs, but we also included the future level of asthma control.[25,26] In clinical practice this is an important addition, because these are patients who should be assessed more regularly. Therefore, a clinical prediction model that combines these outcomes is clinically more relevant than those capturing exacerbations solely.[12] In our study, the derivation data set consisted of 304 patients, of which 83 experienced an event at 12 months; 14% of the patients with an event experienced both a severe asthma exacerbation and scored above 1.5 on the ACQ. Furthermore, 63% solely scored above 1.5 on the ACQ and 23% experienced solely a severe asthma exacerbation; the incidence of events is in line with previous studies (see

Table E3 and Table E4).

In our model we included, at first, the level of asthma control (ACQ score), current smoking status, the occurrence of severe exacerbations in the previous year, and sex, with the ACQ score and the occurrence of severe exacerbations in the previous year as the strongest predictors. This is in line with several other longitudinal studies assessing prediction of future risk.[10,27,28,29,30] Also, an increased future risk for women was found in several other studies; a possible explanation is that women tend to have late onset of asthma, which is a subgroup with more severe asthma.[31,32,33,34]

In our study, we have added predictors representing early treatment response and updated current smoking status; only a few other studies have assessed the change in asthma control over time as a predictor.[35,36] Comparable to our results, those studies showed that this change does indeed predict future risk. An increase of 1 point over 2 weeks on the ACQ increased the risk of an exacerbation by 50% the following 2 weeks.[35] Bateman et al[36] reviewed several studies and showed that the better the level of asthma control, the lower the risk of uncontrolled asthma for the following week; furthermore, the probability of an exacerbation was related to current state of control. Blakey et al[30] found that a combination of 16 predictors gave a similar AUC score as ours (AUROC, 0.87; 95% CI, 0.86-0.87). These included nasal polyps and blood eosinophilia, which are not easily assessed in primary care. Recently, Loymans et al[15] predicted the occurrence of future exacerbations on the basis of patient characteristics in the same data set. Compared with that study we changed the outcome to guideline-defined future risk and added early treatment effect. These changes resulted in an AUROC of 0.84 (95% CI, 0.79-0.89), compared with the AUROC of 0.80 (95% CI, 0.78-0.81) in the study of Loymans et al.

For this study, we assessed early treatment response after approximately 3 months, which is comparable to findings of earlier studies.[10,17,18] Those studies showed that, for the mainstay of patients, analyzing treatment response after the first 3 months will show whether they are on track toward controlled asthma. By using our analysis, we singled out those patients who are not on track. Specifically targeting individuals who appear to be off track greatly improves efficiency of asthma management. We included the occurrence of an exacerbation in the previous 3 months of treatment as an outcome of early treatment response, despite the large upper bound. In our development data set only few patients (n = 15) experienced a severe exacerbation during the specified period; however, because of the clinical importance, we included this predictor in our final risk model.

In sensitivity analysis, we compared our results to solely the use of the ACQ. We are aware that the ACQ does not cover the entire aspect of monitoring a patient in clinical practice. However, it is as close to current practice as possible.

Strengths and weaknesses

The heterogeneous and relatively large study population is a strength of this study, with a variety in baseline characteristics including the degree of asthma control and with limited use of exclusion criteria. Therefore, the study population is representative for the population in general practice. Our study is strengthened by external validation of our developed risk prediction score, which showed an AUROC of 0.77. Furthermore, by adding the ACQ as a predictor in our model, it is possible for the clinician to estimate the current level of control and the level of guideline-defined future risk, all within the same risk model. Eight or less potential predictors were considered at the same time; with 83 patients classified as having an increased future risk, we fulfil the criterion of a minimum of 10 events per variable for prediction research.[37] Although also mentioned as a strength of our study, the ACQ is as yet not routinely used in primary care, because other questionnaires are also available; so it is simultaneously a limitation. However, we assume that the result would not differ greatly from other asthma symptom scores, because outcomes are correlated.[38,39] A second limitation of our study could be the exclusion of patients without an ACQ assessment at 12 months and patients without complete data at either baseline, 3 months, or 12 months of follow-up. Potentially, included patients have a better adherence, because they adhere more to study requirements as well, which would result in selection. However, because of the heterogeneity of the study population, it is not likely to be the case here. In addition, we compared results of a questionnaire on self-reported adherence between participants from this study and people who were excluded and results were similar: mean difference, −0.03 (95% CI, −0.17 to 0.11). However, overall patients willing to participate in a clinical trial may be more compliant. In this study, we added the MARS questionnaire on adherence and this showed no association. Potentially, patients might not have been completely honest about adherence, but asking them is the best we can do in current clinical practice. A third limitation is the choice of cutoff values at approximately 10% and 48% absolute risk of experiencing uncontrolled asthma or exacerbations in the future. Evidence regarding appropriate cutoff values is scarce, and these are the only cutoffs suggested by previous literature.[24] However, because treating physicians might want to apply more or less strict criteria, we have supplied an overview of absolute risks per risk prediction score (see Table E2).

Another limitation is the use of baseline predictors in combination with measurements

of early treatment response after approximately 3 months of treatment, and thereby the delayed risk estimation in clinical practice. However, it is possible to estimate the risk prediction score at one moment in time if there is a known history of ACQ scores and occurrence of exacerbations. To promote, and simplify, the use of the risk prediction score, we developed an online application (see Online Risk Prediction Tool, in this article's Online Repository at www.jaci-inpractice.org).

From previous literature, we know that in general practice up to a third of patients might not be properly diagnosed.[40] The risk prediction score is developed and externally validated in samples representing the population in general practice, so it might have been influenced by wrongly diagnosed patients. However, the problems with physician-diagnosed asthma have not yet been resolved in general practice, so our sample is valid, although of course it would be preferable if diagnosis was more precise. For the application of the risk prediction score in another population, it should be external validated separately.

Clinical interpretation

The developed risk model should be used alongside other important components of a structured asthma review; for example, inhaler technique, adherence, and patient education. The risk prediction score provides the clinician, and patients, with a clear estimate for the guideline-defined future risk; it includes information on the level of asthma control and on treatment response (Figure 3). With the inclusion of early treatment response in the model, a review of effectiveness of treatment is included, thereby minimizing exposure to ineffective treatment. Because a clinician is always short on time, an easy-to-obtain risk prediction score requiring no additional measurements other than questions is quite helpful. Also, especially in general practice, it is useful to know which patients have a high risk; our risk prediction score classifies 57.7% of the patients as having a low risk. These patients could be safely assessed less frequently or, for example, could safely be reviewed by the practice nurse. This allows the clinician more time for an extensive review and medication changes, in the smaller subgroup of patients in the highest risk category.[41,42,43]

Furthermore, we defined the guideline-defined future risk as a combination of exacerbations and uncontrolled asthma, where asthma symptom control is an important outcome for patients themselves. Both outcomes may need different treatment approaches. However, with the risk prediction score we classify patients, and it is up to the clinician to decide on treatment approach, especially in high-risk patients.

CONCLUSION

We developed and externally validated a clinical tool that provides clinicians with 6 easy accessible parameters to quantify guideline-defined future risk, including the assessment of current level of asthma control as a parameter.

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ONLINE SUPPLEMENT APPENDIX 1

SUPPLEMENT TABLE 1. *Based on the regression coefficients of our final model the risk prediction score was developed.*[23]

Variable	Beta	Categories	Reference (W)	Beta * ($W-W_{REF}$)	Points†	Rounded points
Sex	0.719	Male	$\mathbf{0}_{REF}$	0	0	0
		Female	1	0.719	1.455	1
Current smokers	0.247	No	$\mathbf{0}_{REF}$	0	0	0
		Yes	1	0.247	0.5	1
Exacerbation(s) in the previous year at baseline	0.887	No	$\mathbf{0}_{REF}$	0	0	0
		Yes	1	0.886	1.796	2
ACQ score per 0.5, baseline	0.471	< 0.75	$\mathbf{0.37}_{REF}$	0	0	0
		0.75 - 1.50	1.13	0.358	0.725	1
		> 1.50	2.50	1.003	2.031	2
Exacerbation(s) in the previous three months at follow-up	1.878	No	$\mathbf{0}_{REF}$	0	0	0
		Yes	1	1.878	3.802	4
ACQ score per 0.5, follow-up	1.314	< 0.75	$\mathbf{0.37}_{REF}$	0	0	0
		0.75 - 1.50	1.13	0.999	2.022	2
		> 1.50	2.50	2.799	5.666	6
Intercept	-3.714					

† Constant B = 0.494

Variable. The remaining variables of the risk prediction model.

Beta. The regression coefficients corresponding to the variables.

Categories. Variables are categorized into meaningful categories.

Reference (W). The reference value for each category was determined; for the ACQ -score we used the midpoint of each category (range 1st to 90th percentile). Furthermore, we determined the base category for each variable, for the referent ($_{REF}$) profile, with the lowest expected risk.

Beta * ($W-W_{REF}$). We determined how far each category is from the base category in regression units; multiplying the beta by the difference between reference value for the specific category and the reference value for the base category.

Points. In order to compute the risk prediction points, we had to set a constant B for the point system, or the number of regression units that will correspond to one point. We set the constant as the smallest beta (current smokers) and multiplied it by two; we multiplied the constant by two in order to keep the total risk prediction score in a feasible range without loss of accuracy. Points were computed by (*Beta * ($W-W_{REF}$)) * constant B*.

Rounded. Risk prediction points were rounded to the nearest integer.

SUPPLEMENT TABLE 2. *Risk prediction score*

The risk prediction score and the associated guideline-define risk estimate is computed by the following formula:[23]

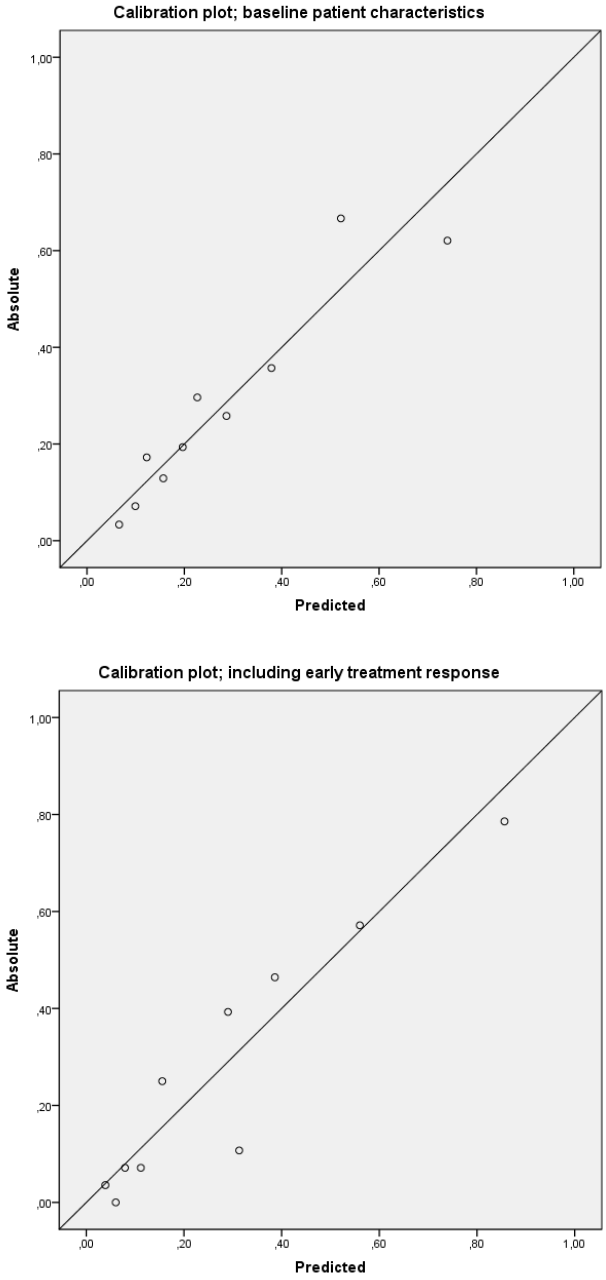
$$\hat{p} = \frac{1}{1 + \exp\left(-\sum_{i=0}^{P} \beta_i X_i\right)}$$

Risk prediction score	Future risk estimate	No future risk in derivation dataset	Future risk in derivation dataset	Absolute risk of future risk based on the derivation dataset
1	0.045	3	0	0
2	0.072	32	1	0.03
3	0.112	51	4	0.073
4	0.172	27	4	0.129
5	0.254	34	5	0.128
6	0.358	14	9	0.391
7	0.478	11	9	0.45
8	0.600	8	6	0.429
9	0.711	6	10	0.625
10	0.801	8	9	0.529
11	0.868	4	9	0.692
12	0.915	2	4	0.667
13	0.947	2	4	0.667
14	0.967	0	1	1
15	0.979	0	1	1
16	0.987	0	1	1

Risk prediction category	Risk prediction score	No future risk in derivation dataset	Future risk in derivation dataset	Absolute risk of future risk based on the derivation dataset
Low	≤ 4	144	14	0.089
Intermediate	5 - 8	39	34	0.466
High	≥ 9	16	29	0.644

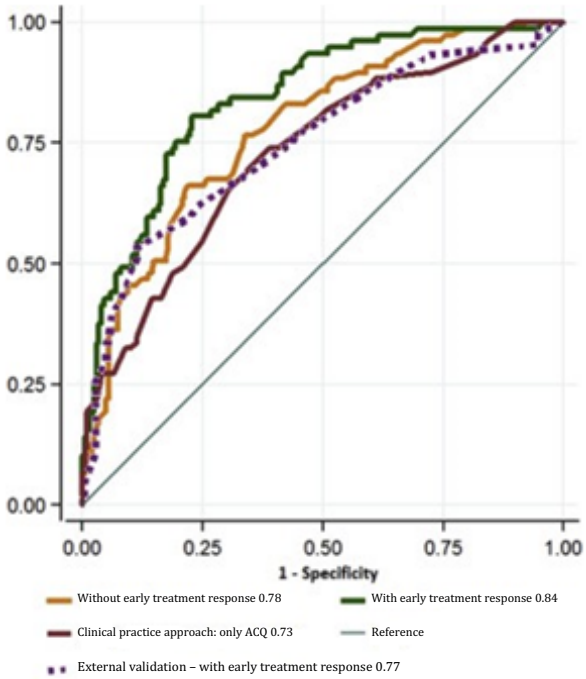
N = 279; complete cases in the derivation dataset.

APPENDIX 2



SUPPLEMENT FIGURE 1. *Calibration plots in the derivation dataset.*

APPENDIX 3



SUPPLEMENT FIGURE 2. *AUROC comparing the models with and without early treatment response to the approach of clinical practice (in the derivation data set). The model with early treatment response differs significantly from the model without early treatment response (P < .01) and from the model representing clinical practice approach (P < .001).*

APPENDIX 4

Sensitivity analysis.

According to asthma management guidelines, clinicians should assess the current level of asthma control alongside the level of guideline-defined future risk of adverse outcomes, while taking into account individual patient characteristics. In practice, it can be difficult to combine all these separate assessments into a single treatment advice, especially if outcomes point to different directions (eg, a patient can have poor asthma control but rarely exacerbate). Therefore, it would be relevant to make a single combined assessment of both current control and risk of future uncontrolled asthma and exacerbations. For this study, we classified patients as having an increased level of future risk if patients experienced uncontrolled asthma at 12 months, defined as an ACQ score of 1.5 or more, or if they experienced at least 1 severe asthma exacerbation during the final 6 months of the trial. A severe asthma exacerbation was defined as a course of oral prednisolone prescribed for worsening asthma for 3 or more days, or an emergency department visit/hospitalization due to asthma.E4

In this Online Repository, we report 2 prediction models for the 2 outcomes, uncontrolled asthma and exacerbations, separately. We performed exactly the same statistical analyses as described in the article, but for solely an ACQ score of 1.5 or more at 12 months as outcome measure, and for solely the experience of at least 1 severe asthma exacerbation during the final 6 months of the trial. The results of all models (models including information on early treatment response) can be found in Table E3 and Table E4.

Furthermore, we assessed model performance (AUROC) of our developed model for the separate outcome measures. For an ACQ score of 1.5 or more at 12 months, the AUROC was 0.87 (95% CI, 0.81-0.90) and for the experience of at least 1 severe asthma exacerbation during the final 6 months of the trial, the AUROC was 0.76 (95% CI, 0.67-0.85).

TABLE 1A. *Multivariable odds ratios (95% confidence interval) and corresponding p-values for different outcome measures, at baseline. Our combined outcome measure with an ACQ score ≥ 1.5 after twelve months, or if they experienced at least one severe asthma exacerbation during the final six months of the trial (AUROC 0.84 (CI95% 0.79 - 0.89). Solely an ACQ score ≥ 1.5 after twelve months as an outcome measure (AUROC 0.84 (CI95% 0.79 - 0.89). Solely the experience of at least one severe asthma exacerbation during the final six months of the trial (AUROC 0.85 (CI95% 0.79 - 0.91).*

	Combined		**Solely ACQ**		**Solely Exacerbations**	
Continuous variables	**Odds ratio (CI95%)**	**p-value**	**Odds ratio (CI95%)**	**p-value**	**Odds ratio (CI95%)**	**p-value**
ACQ score per 0.5, baseline	1.74 (0.41 - 2.14)	< 0.001	1.87 (1.49 - 2.35)	< 0.001	1.35 (0.97 - 1.89)	0.08
ACQ score per 0.5, early treatment response (±3 months)	-		-		-	
Peak flow, early treatment response (±3 months)	-		-		-	
Categorical variables						
Women	2.05 (1.06 - 3.98)	0.03	3.59 (1.54 - 8.33)	0.06	-	
Current smokers	1.49 (0.64 - 3.43)	0.35	2.03 (0.84 - 4.93)	0.12	-	
Rhinitis	-		-		8.23 (1.04 - 65.16)	0.05
Exacerbation(s) in the previous year at baseline	2.45 (1.37 - 4.38)	< 0.01	2.06 (1.07 - 3.96)	0.03	3.05 (1.05 - 8.84)	0.04
Exacerbation(s) in the previous three months as measure of early treatment response	-		-		-	
Beclomethasone equivalent dose in mcg						0.66
Low (0-400)	-		-		1.00	
Medium (400-800)	-		-		4.47 (0.43 - 46.79)	
High (>800)	-		-		11.65 (1.46 - 93.18)	
AUROC	**0.78 (0.72 - 0.84)**		**0.81 (0.76 - 0.87)**		**0.84 (0.74 - 0.94)**	

TABLE 1B. *Multivariable odds ratios (95% confidence interval) and corresponding p-values for different outcome measures, after approximately three months of treatment. Our model with the combined outcome measure, with an ACQ score ≥ 1.5 after twelve months, or if they experienced at least one severe asthma exacerbation during the final six months of the trial, had an AUROC of 0.84 (CI95% 0.79 - 0.89). The model with for solely an ACQ score ≥ 1.5 after twelve months as an outcome measure had an AUROC of 0.84 (CI95% 0.79 - 0.89), and the model with solely the experience of at least one severe asthma exacerbation during the final six months of the trial as an outcome measure had an AUROC of 0.85 (CI95% 0.79 - 0.91).*

	Combined		**Solely ACQ**		**Solely Exacerbations**	
Continuous variables	**Odds ratio (CI95%)**	**p-value**	**Odds ratio (CI95%)**	**p-value**	**Odds ratio (CI95%)**	**p-value**
ACQ score per 0.5, baseline	1.27 (0.98 - 1.63)	0.07	1.27 (0.98 - 4.32)	0.07	1.28 (0.96 - 1.70)	0.09
ACQ score per 0.5, early treatment response (±3 months)	1.93 (1.49 - 2.51)	< 0.001	1.93 (1.49 - 2.51)	< 0.001	1.87 (1.38 - 2.53)	< 0.001
Peak flow, early treatment response (±3 months)	-		-		0.49 (0.29 - 0.81)	< 0.01
Categorical variables						
Women	2.03 (0.97 - 4.27)	0.06	2.05 (0.98 - 4.32)	0.06	-	
Current smokers	1.27 (0.49 - 3.30)	0.62	1.29 (0.48 - 3.42)	0.62	-	
Rhinitis	-		-		2.33 (0.94 - 5.78)	0.07
Exacerbation(s) in the previous year at baseline	2.43 (1.27 - 4.64)	< 0.01	2.43 (1.27 - 4.64)	< 0.01	3.28 (1.47 - 7.30)	< 0.01
Exacerbation(s) in the previous three months as measure of early treatment response	6.40 (1.36 - 30.06)	0.02	6.54 (1.40 - 30.55)	0.02	-	
Beclomethasone equivalent dose in mcg						0.66
Low (0-400)	-		-		1.00	
Medium (400-800)	-		-		1.04 (0.35 - 3.08)	
High (>800)	-		-		1.45 (0.59 - 3.58)	
AUROC	**0.84 (0.79 - 0.89)**		**0.84 (0.79 - 0.89)**		**0.85 (0.79 - 0.91)**	

Chapter 6

Personalized FeNO-driven asthma management in primary care: a FeNO-subgroup analysis of the ACCURATE trial

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ABSTRACT

Background

The aim of this study was to identify patients who benefit most from FeNO-driven asthma management in primary care, based on prespecified subgroups with different levels of FeNO.

Methods

We used data of 179 adult asthmatics from a 12-month primary care RCT with three-monthly assessments of FeNO, asthma control, medication usage, costs of medication, severe asthma exacerbations and quality of life. In the original study patients were randomised to either a symptom driven treatment strategy (Controlled asthma (Ca-strategy)) or FeNO + symptoms driven strategy (FCa). In both groups, patients were categorized by their baseline level of FeNO as low (<25 ppb), intermediate (25-50 ppb) and high (>50 ppb). At twelve months, we compared, for each prespecified FeNO-subgroup, asthma control, asthma-related quality of life, medication usage, and costs of medication between the Ca and FCa-strategy.

Results

We found a difference between the Ca- and FCa-strategy for the mean dosage of beclomethasone strategy of 223 mcg (6;439), p = 0.04) and for the total costs of asthma medication a mean reduction of $159 (33;285), p = 0.03) in patients with a low baseline FeNO level. No differences were found for asthma control, severe asthma exacerbations and asthma-related quality of life in patients with a low baseline FeNO level. Furthermore, in patients with intermediate or high level of FeNO no differences were found.

Conclusions

In primary care, FeNO-driven asthma management is effective in patients with a low FeNO level, for whom it is possible to down-titrate medication, while preserving asthma control and quality of life.

Trial registration

NTR 1756 at www.trialregister.nl

Kewords

Fractional exhaled nitric oxide, feno, asthma management, primary care

BACKGROUND

Asthma is a heterogeneous disease with different underlying components interacting in each individual patient.[1,2] An important component of asthma is eosinophilic airway inflammation, which can even be present in the absence of severe symptoms.[3] Until recently, assessing the severity of eosinophilic airways inflammation proved hard and required more invasive measurements. However, the assessment of airways inflammation became available with the advent of relatively inexpensive equipment for the measurement of the concentration of nitric oxide (NO) in exhaled breath, the so-called fractional exhaled nitric oxide (FeNO).[4] For diagnosing asthma, a FeNO measurement is now recommended as part of the diagnostic algorithm in several guidelines, alongside clinical evaluation, spirometry, and symptom assessments.[5-7]

However, in monitoring asthma after the diagnosis of asthma has been established, whether or not FeNO should be measured is still up for debate.[8] Several studies have shown FeNO could be of use in the monitoring of symptoms, resulting in improved asthma control, reduced exacerbation rate, improvement of quality of life and that it could aid in optimizing titration of inhaled steroid treatment.[9-13] Others have shown opposing results, showing no advantage of FeNO or even that FeNO resulted in worse outcomes.[14-17]

A potential reason for all these different findings might be that FeNO measurements in the management of asthma, only have additional benefit in specific subgroups based on different levels of FeNO at baseline. Several recent landmark papers suggest a shift in the management of asthma towards the treatment of treatable traits, indicating a need for a more precise determination of a person's airways disease.[2,18] It is imaginable that each of these prespecified FeNO-subgroups, have their own set of required measurements as well, and FeNO-driven asthma management might only be of use for a selection of these.

This is also why the Global Initiative of Asthma (GINA) states there is no role for FeNO in asthma management at this point in time and further studies are needed to identify the populations most likely to benefit, and the optimal frequency of monitoring.[8] Additionally, there are also costs to be considered. Although the ACCURATE study showed FeNO-driven asthma management already proved to be cost-effective in primary care, a more targeted deployment could improve upon that.[19]

Ideally, we would like to identify specific subgroup of patients, based on different levels of FeNO at baseline, where FeNO measurement would be of benefit, and simultaneously

subgroups where it does not contribute to improved outcomes. Therefore, the aim of the present study was to identify specific FeNO-subgroups of patients who benefit (most) from FeNO-driven asthma management in primary care, in terms of asthma control, asthma-related quality of life, medication usage and (asthma) medication costs.

METHODS

Study design

This study concerns a subgroup analysis of a dataset from a three-arm pragmatic cluster-randomized trial (RCT) assessing patient preferences and cost-effectiveness of three asthma management strategies in primary care. The first strategy aimed to achieve well-controlled asthma, by making treatment decisions based on conventional control measures of asthma, including the Asthma Control Questionnaire (ACQ) and spirometry (Ca-strategy). The second strategy also aimed for well controlled asthma, but it included an additional FeNO-measurement upon which treatment decisions were based alongside conventional measures (FCa-strategy). In this subgroup analysis we omitted the third strategy, which was aimed to achieve only partly controlled asthma; and therefore treatment plan allowed for more variation in asthma control. During the trial, maintenance asthma medications were adjusted at 3-month intervals, based on 6-item Asthma Control Questionnaire (ACQ) and spirometry with or without FeNO (table 1). A detailed description of study procedures and participants of the Asthma Control Cost-Utility RAndomized Trial Evaluation (ACCURATE) has been published elsewhere (registered at www.trialregister.nl (NL1658 (NTR1756))).[19,20]

TABLE 1. *Treatment strategy algorithms*

	Levels of asthma control		
Strategy	***Controlled***	***Partly controlled***	***Uncontrolled***
Ca-strategy	- 3 mo: no change - > 3 mo: step-down	step-up: treatment choice	step-up: treatment choice
FCa-strategy			
- *Low FeNo level (< 25 ppb)*	step-down	- 3 mo: no change/ change within current step to LABA - > 3 mo: step-down ICS	step-up: LABA
- *Intermediate FeNo level*	no change	step-up: treatment choice	step-up: treatment choice
- *High FeNo level (> 50 ppb)*	step-up/change within current step to ICS	step-up: 1 x ICS	step-up: 2xICS*

Ca = Controlled asthma
FCa = Feno-driven controlled asthma
LABA = Long-Acting Beta-Agonist
ICS = Inhaled Corticosteroids

Study population

Patients were aged 18-50 years, with a doctor's diagnosis of asthma and prescribed inhaled corticosteroids. In primary care the diagnosis of asthma is based on the presence of a characteristic clinical history, which includes recurrent episodes of dyspnoea, wheezing and/or cough.[21] An additional measurement of lung function can enhance diagnostic confidence, if it shows reversibility, which is defined as an increase of ≥12% and 200 ml in FEV1 after bronchodilator therapy.[22,23] Follow-up was 12 months and patients filled out online questionnaires at approximately three-monthly intervals. We included all patients where data of all outcome measurements was available at 12 months as a secondary complete case analysis.

Baseline prespecified FeNO subgroups

We distinguished between three prespecified subgroups, based on different levels of FeNO at baseline, which were classified as low (< 25 ppb), intermediate (25-50 ppb) and high (> 50 ppb). Classification cut-offs were based on the American Thoracic Society.[24,25] At baseline, FeNO level was measured in general practice for all patients in both strategies, according to international guidelines with the NIOX-MINO (Aerocrine, Solna, Sweden).[26,27]

Outcome measurements

The three specific subgroups, based on different baseline levels FeNO, were evaluated on five different outcomes after twelve months of treatment; level of asthma control, asthma-related quality of life, medication usage, total medication costs, asthma specific medication costs and the occurrence of at least one severe exacerbation.

The level of asthma control was measured with the ACQ, which can be subdivided into low (ACQ < 0.75), medium (ACQ 0.75-1.50) and high (ACQ > 1.50) level of asthma contr[ol.28] Asthma-related quality of life was measured by the Dutch version of the Asthma Quality of Life Questionnaire (AQLQ)-Juniper. The Asthma Quality of Life Questionnaire was able to detect changes in patients who responded to treatment or who had natural fluctuations in their asthma ($p < 0.001$) and to differentiate these patients from those who remained stable ($p < 0.001$).[29] The usage of inhaled corticosteroid medication was recalculated into the beclomethasone equivalent based on recommendations by the Dutch pharmaceutical guidelines and a panel of respiratory experts.[19, 30] Medication costs (in dollars) were assessed based on medication prescriptions obtained from electronic patient records, completed with the patient's report on medication purchased elsewhere, separate for total medication usage and asthma medication only.[27] Benefit could for example either be defined as a reduction in medication usage, while asthma

control, quality of life and exacerbation rate remained similar, or as an improvement of asthma control or quality of life. The minimal important difference (MID) is defined as 0.5 points in asthma control (ACQ) and asthma-related quality of life (AQLQ). A severe asthma exacerbation was defined as a course of oral prednisolone prescribed for worsening asthma for three or more days, or an emergency department visit/ hospitalisation due to asthma.[31]

Analysis

First, baseline levels were calculated for asthma control, asthma quality of life and medication usage per FeNO-subgroup and per treatment strategy (Ca and FCa). Second, the mean level of all outcome measurements was assessed at twelve months: asthma control, asthma quality of life, medication usage, total costs of medication, asthma specific medication costs and the occurrence of at least one severe asthma exacerbation. Whether there was a difference in baseline values and/or outcomes at twelve months between the Ca and FCa-strategy was assessed by Mann-Whitney U test (method of choice especially due to the low number of patients) or by Fisher's exact test for occurrence of at least one severe exacerbation (a binary variable) ($p < 0.05$). All analyses were performed separately per FeNO-subgroup. As a post-hoc analysis we pooled the intermediate and high FeNO-subgroups (> 25 ppb) because of the low number of patients in these FeNO-subgroups separately. STATA statistical software version 14 (Statacorp, College Station, Texas, USA) was used for all analyses.

RESULTS

Patient characteristics

We included 179 patients in this study, patients of whom data of all outcome measurements was available at 12 months (so-called complete case analysis), 94 in the Ca-strategy and 85 in the FCa-strategy (table 2). In patients within the Ca-strategy the mean age was 41.6 (SD 6.8) years and 68% was female, and the mean asthma duration was 18.2 (SD 13.3) years. In patients within the FCa-strategy the mean age was 41.2 (SD 8.1) and 74% was female, and the mean asthma duration in years was 19.7 (SD 14.2).

Prespecified FeNO-Subgroups

At baseline, no significant differences were found for asthma control (ACQ-score), quality of life (AQLQ-score) and medication usage (beclomethasone equivalent) for any FeNO-subgroup between the Ca- and FCa-strategy (table 1; *online supplement*).

TABLE 2. *Patient Characteristics*

	Ca-strategy	FCa-strategy
Continuous variables		
Patients (n)	94	85
Mean age (SD)	41.6 (6.8)	41.2 (8.1)
BMI (SD)	25.9 (4.7)	26.3 (5.6)
Asthma duration in years (SD)	18.2 (13.3)	19.7 (14.2)
Baseline FeNO in ppb (SD)	20.5 (21.3)	23.1 (22.9)
Beclomethasone equivalent dose in mcg (SD)	853 (702)	824 (634)
Mean baseline ACQ (SD)	0.91 (0.76)	0.94 (0.68)
Mean baseline AQLQ (SD)	5.87 (0.88)	5.80 (0.93)
Categorical variables		
Sex % F	68	74
Long Acting Beta Antagonist (LABA) use (%yes)	61	51
Current smokers (% yes)	10	11
Previous smokers (% yes of current non-smokers)	33	36
ACQ-subgroup (%)		
Low (< 0.75)	50	39
Medium (0.75-1.50)	34	45
High (> 1.50)	16	17

Ca = Controlled asthma
SD = standard deviation
PPB = parts per billion
ACQ = Asthma Control Questionnaire
AQLQ = Asthma Quality of Life Questionnaire
FCa = Feno-driven controlled asthma
BMI = body mass index
MCG = microgram
%F =percentage female

At twelve months, in the low FeNO-subgroup there were no differences in ACQ-score and AQLQ-score between the Ca- and FCa-strategy. However, the dosage of inhaled corticosteroid medication (converted to beclomethasone equivalent) and total costs of asthma medication were reduced in the FCa- as compared to the Ca-strategy by 223 mcg (6;439), p = 0.04) and $159 (33;285), p = 0.03), respectively (figure 1; table 3a). At twelve months mean dosage of beclomethasone for patients with a low FeNO-level increased with 80 mcg within the Ca-strategy and decreased with more than 150 mcg within the FCa-strategy. Furthermore, no significant differences were found for the experience of at least one severe asthma exacerbations.

At twelve months, in patient with intermediate or high FeNO levels no differences were found between the strategies (table 3b and 3c). For patients with an intermediate and high FeNO level the beclomethasone dosages decreased in the Ca-strategy, where there was an increase for patients within the FCa-strategy. Pooled analysis of the intermediate and high FeNO-subgroups did not result in a significant difference at twelve months between the Ca-strategy and FCa-strategy either (table 3d).

TABLE 3. *12-months outcomes per prespecified subgroup (based on FeNO-level)*

A. Subgroup with low level (< 25 ppb)

	Ca-Strategy (N = 71)	**FCa-Strategy (N = 63)**	**Difference (95% CI)**	**p-value**
ACQ	0.90 (0.75)	1.01 (0.80)	-0.11 (-0.38;0.15)	0.40
AQLQ	5.97 (0.87)	5.85 (0.95)	0.12 (-0.20;0.43)	0.66
Beclomethasone equivalent (mcg)	954 (644)	731 (621)	223 (6;439)	0.04
Cost of all medication ($)	836 (634)	723 (761)	113 (-126;351)	0.17
Cost of asthma medication ($)	568 (406)	409 (322)	159 (33;285)	0.03
≥ 1 severe exacerbation (n) ††	14 (20%)	8 (13%)	-	0.35

B. Subgroup with intermediate level (25-50 ppb)

	Ca-Strategy (N = 14)	**FCa-Strategy (N = 13)**	**Difference (95% CI)**	**p-value**
ACQ	0.73 (0.69)	0.58 (0.47)	0.15 (-0.32;0.62)	0.71
AQLQ	6.28 (0.57)	6.28 (0.64)	0.00 (-0.48;0.48)	1.00
Beclomethasone equivalent (mcg)	621 (591)	754 (533)	-132 (-580;315)	0.38
Cost of all medication	511 (451)	587 (580)	-76 (-486;334)	0.80
Cost of asthma medication	323 (408)	428 (461)	-105 (-449;239)	0.66
≥ 1 severe exacerbation (n) ††	2 (14%)	2 (15%)	-	1.00

C. Subgroup with high level (50 ppb)

	Ca-Strategy (N = 9)	**FCa-Strategy (N = 9)**	**Difference (95% CI)**	**p-value**
ACQ	0.90 (0.65)	0.98 (1.10)	-0.08 (-0.98;0.82)	0.79
AQLQ	6.09 (0.75)	6.32 (0.98)	-0.23 (-1.09;0.65)	0.20
Beclomethasone equivalent (mcg)	556 (662)	756 (613)	-200 (-837;437)	0.42
Cost of all medication	334 (193)	511 (279)	-177 (-416;63)	0.35
Cost of asthma medication	247 (172)	301 (170)	-54 (-225;116)	0.54
≥ 1 severe exacerbation (n) ††	1 (11%)	2 (22%)	-	1.00

D. Combined subgroups with intermediate/high level (>25 ppb)

	Ca-Strategy (N = 23)	**FCa-Strategy (N = 22)**	**Difference (95% CI)**	**p-value**
ACQ	0.80 (0.67)	0.74 (0.79)	0.05 (-0.38;0.49)	0.58
AQLQ	6.21 (0.64)	6.30 (0.77)	-0.09 (-0.52;0.34)	0.39
Beclomethasone equivalent (mcg)	596 (606)	755 (553)	-159 (-508;190)	0.19
Cost of all medication	442 (376)	556 (473)	-114 (-370;142)	0.44
Cost of asthma medication	293 (332)	376 (369)	-83 (-294;128)	0.42
≥ 1 severe exacerbation (n) ††	3 (13%)	4 (18%)	-	1.00

Ca = Controlled asthma FCa = Feno-driven controlled asthma
ACQ = Asthma Control Questionnaire AQLQ = Asthma Quality of Life Questionnaire
† As a post-hoc analysis we pooled the intermediate and high FeNO-subgroups (> 25 ppb) because of the low number of patients in these FeNO-subgroups separately. †† Fisher's exact test

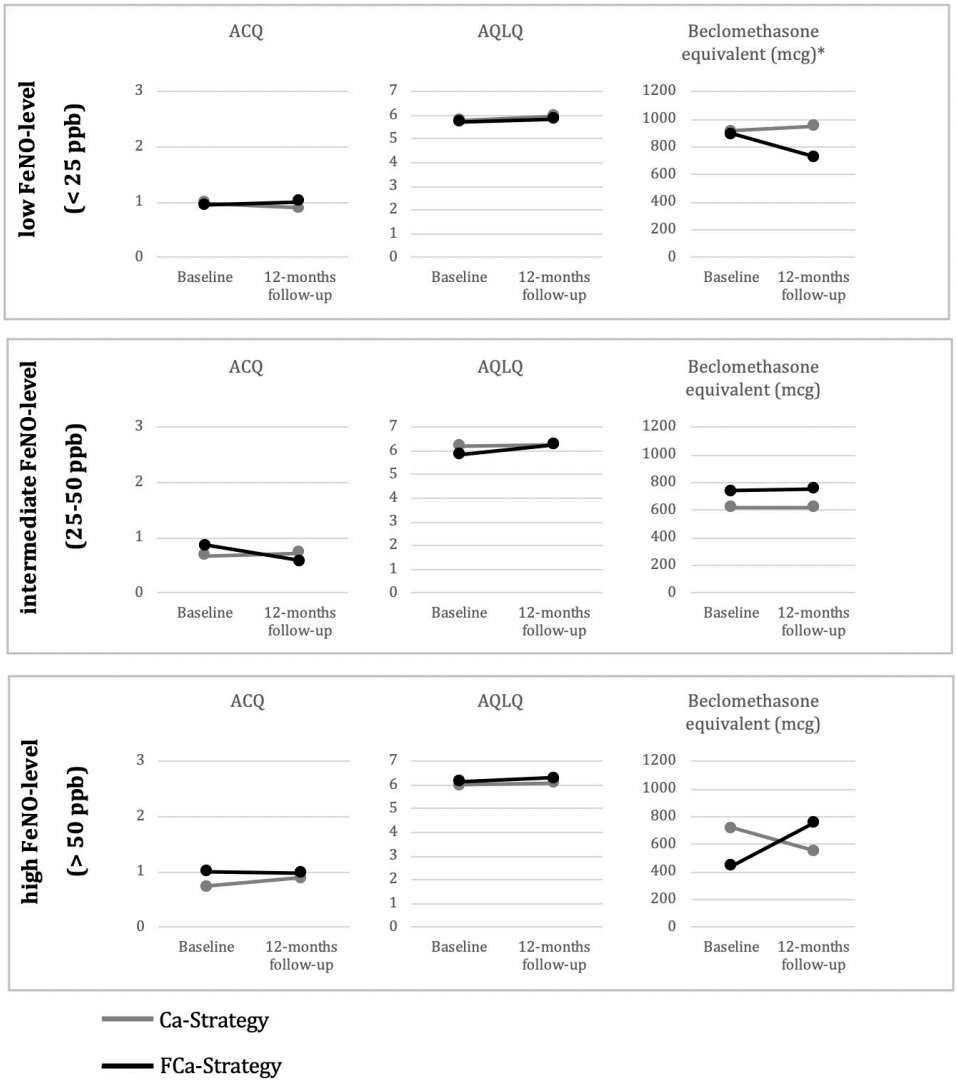

FIGURE 1. *Mean-differences between the Ca-stratefy and the FCa-strategy over a 12-months period for Asthma Control Quistionaire (ACQ), Asthma Quality of Life Questionaire (AQLQ) and Beclomethasone equivalent; per prespecified subgroup (based on FeNO-level)*

** p = 0.04*

DISCUSSION

Our aim was to identify a specific FeNO-subgroup of patients who may benefit (most) from FeNO-driven asthma management in primary care. We found patients presenting with a low FeNO level at baseline, benefit from a FeNO and symptom-based treatment algorithm compared to only symptom based, in terms of a reduction in asthma medication usage and costs, while asthma control and quality of life do not differ between the Ca-strategy and FCa-strategy. Therefore, our data suggest that down-titrating in patients with low FeNO level is possible and safe.

This finding is in line with other studies. First of all, as a deepening study of Honkoop et al. (2015) we showed the FeNO-driven asthma management yields benefits in terms of costs especially in patients with a low FeNO level at baseline.[19] Also, even with less medication use with this strategy compared to conventional asthma management, asthma control and quality of life remain similar. Therefore, our results showed the possibility of safely down-titrating in patients with low FeNO-level with FeNO-driven asthma management.[32] Note that our findings showed no down-titrating in patients with conventional asthma management; although both patient-groups weren't any different at baseline.

We cannot conclude that patients with a low FeNO level benefit from FeNO-driven asthma management in terms of clinical outcomes. However, use of as little medication as possible without the loss of asthma control or quality of life is worsening of as it is an important treatment goal according to international asthma guidelines.[8] Our results show that this can be achieved in patients with low baseline FeNO-level and, furthermore down-titrating medication in patients with FeNO-driven asthma management also results in significant lower asthma medication (costs), compared to patients with the same FeNO levels in conventional asthma management. This adds to the ongoing discussion of appropriate prescribing, for example in the Choosing Wisely campaign: an initiative that seeks to advance a dialogue on avoiding unnecessary medical tests, treatments and procedures.[33]

In the subgroups of patients with intermediate and high FeNO-levels, we found increased medication usage. Study populations with a high(er) representativeness of patients with intermediate to higher FeNO-levels could lead to contradictory findings showing that FeNO-driven asthma management will lead to increased medication usage.[34,35] For example, study populations based on patients treated in secondary care, it was shown that 45% of the patients has intermediate to high FeNO-levels.[35] In that setting FeNO-

driven asthma management is likely to lead to more medication usage due to the higher representativeness of patients with intermediate and high FeNO-levels. Even more so, if one considers that the cut-offs for intermediate and high FeNO, and therefore a decision to increase treatment, has been as low as 10 to 20 ppb before the publication of the current guidelines in 2014.[36] Unfortunately, in the intermediate and high subgroups we did not assess any benefit or harm in the comparison between asthma treatment based on FCa versus Ca-strategy. It could still be questioned if increased medication usage is necessary in patients with high FeNO-level, but the decreased number of exacerbations suggest it does, however, the study sample is small and no significant differences were found.

Strengths and limitations

In this study, the majority of patients in primary care (70%) are classified as having a low FeNO level, with less patients classified as having an intermediate or high level of FeNO. This does not affect our concluding remarks about the possibility of down-titrating medication in patients with low FeNO level in primary care. However, due to lack of power for the intermediate and high FeNO levels we cannot state our concluding remarks about both with confidence. Unfortunately, it was not possible to explore whether specific groups based on the frequency of severe asthma exacerbations benefit most from FeNO-driven, as suggested by Petsky et al. (2016).[13] Our data provided only information about the presence of previous severe exacerbations as a dichotomous variable. A potential limitation of our study is that the GP's diagnosis of asthma was not reassessed. However, Lucas et al.[37] showed that asthma was correctly classified in 73% of primary care patients of all ages in The Netherlands. Furthermore, in real life, these patients are being treated for asthma, and this will affect the clinical usefulness of any treatment strategy.

Clinical implication

Many patients in primary care have low FeNO level. Therefore, using FeNO-driven asthma management for those patients supports a safe reduction of ICS use without loss of asthma control and quality of life. Symptoms of asthma can be caused by a lot of different factors. Sometimes these symptoms will remain even if no inflammation is present (for example in obese asthma patients). In those cases asthma management relying on symptoms tends to maintain or even increase medication usage. FeNO-driven asthma management showing no signs of inflammation allows for down titrating. Additionally physicians and patients are reluctant to decrease medication usage and a measurement showing no inflammation reassures them that decreasing is safe. Consequently, this strategy results in a reduction in medication costs, with a cost-

efficient intervention.[19]

Conclusion

With FeNO-driven asthma management down-titrating medication in primary care patients with low FeNO level is possible and safe, while preserving asthma control and quality of life. FeNO-driven asthma management can be of substantial aid in reducing the use of inhaled corticosteroid.

ABBRIVATIONS

ACQ. Asthma Control Questionnaire

AQLQ. Asthma Quality of Life Questionnaire

BMI. Body mass index

Ca-strategy. Controlled asthma strategy

CI. confidence interval

FCa-strategy. Fractional exhaled nitric oxide-driven controlled asthma strategy

FeNO. Fractional exhaled nitric oxide

ICS. Inhaled Corticosteroids

LABA. Long-Acting Beta-Agonist

MCG. Microgram

NO. Nitric oxide

PPB. Parts per billion

SD. Standard deviation

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ONLINE SUPPLEMENT

TABLE 1. *Baseline characteristics per prespecified subgroup (based on FeNO-level)*

A. Subgroup with low level (< 25 ppb)

	Ca-Strategy (N = 71)	**FCa-Strategy (N = 63)**	**Difference (95% CI)**	**p-value**
ACQ	0.98 (0.80)	0.95 (0.73)	0.04 (-0.23;0.30)	0.93
AQLQ	5.78 (0.92)	5.74 (0.93)	0.04 (-0.28;0.35)	0.80
Beclomethasone equivalent (mcg)	915 (716)	895 (619)	20 (-210;250)	0.72

B. Subgroup with intermediate level (25-50 ppb)

	Ca-Strategy (N = 14)	**FCa-Strategy (N = 13)**	**Difference (95% CI)**	**p-value**
ACQ	0.68 (0.69)	0.87 (0.28)	-0.19 (-0.61;0.24)	0.14
AQLQ	6.26 (0.72)	5.85 (0.98)	0.41 (-0.27;1.08)	0.16
Beclomethasone equivalent (mcg)	621 (683)	738 (762)	-117 (-690;456)	0.56

C. Subgroup with high level (50 ppb)

	Ca-Strategy (N = 9)	**FCa-Strategy (N = 9)**	**Difference (95% CI)**	**p-value**
ACQ	0.74 (0.46)	1.01 (0.83)	-0.27 (-0.94;0.40)	0.48
AQLQ	5.99 (0.71)	6.17 (0.88)	-0.17 (-0.97;0.63)	0.35
Beclomethasone equivalent (mcg)	722 (570)	444 (407)	228 (-217;772)	0.26

D. Combined subgroups with intermediate/high level (>25 ppb)

	Ca-Strategy (N = 23)	**FCa-Strategy (N = 22)**	**Difference (95% CI)**	**p-value**
ACQ	0.70 (0.60)	0.92 (0.56)	-0.22 (-0.57;0.13)	0.16
AQLQ	6.16 (0.71)	5.98 (0.93)	0.18 (-0.32;0.67)	0.68
Beclomethasone equivalent (mcg)	661 (629)	618 (646)	43 (-341;426)	0.87

Ca = Controlled asthma
FCa = Feno-driven controlled asthma
ACQ = Asthma Control Questionnaire
AQLQ = Asthma Quality of Life Questionnaire
CI = confidence interval
† As a post-hoc analysis we pooled the intermediate and high FeNO-subgroups (> 25 ppb) because of the low number of patients in these FeNO-subgroups separately.

Chapter 7

General discussion;
including a summary.

OVERALL THESIS AIM

Most health care costs for chronic conditions are used by a small subgroup of patients with an unfavourable prognosis. The main objective of this thesis was 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. In this final chapter, we first recapture the main findings of the thesis; secondly, we discuss two conceptually distinct constructs of predictors of prognosis that can be applied in different chronic conditions: the level of control of the chronic condition, and information on early treatment response. Thirdly, we discuss the clinical implications and future perspectives. Finally, we present our main conclusions based on this thesis.

SUMMARY OF MAIN FINDINGS

In **chapter 2** we described and quantified the impact of treatment duration on mental healthcare utilization in patients with depressive and anxiety disorders. This study serves to demonstrate the relevance of early identification of patients with an unfavourable prognosis. Patients with a longer treatment course have a high impact on use of mental healthcare resources, with 60% of all contacts dedicated to 25% of patients. Thereby, treatment density is highest for patients with a prolonged treatment course (>2 years) over the entire course of treatment, with no decrease over time.

In **chapter 3** we aimed to improve clinical prediction of a prolonged treatment course based on baseline characteristics, and explored the additional predictive value of early treatment response (after 2-6 months of treatment) in symptoms, in patients with depressive and anxiety disorders. In this setting, we especially aimed to assess the role of a composite symptom severity score as an indicator for a prolonged treatment course. Results showed that number and severity of symptoms (symptom rating) at 2-6 months after treatment initiation is a strong predictor for prolonged treatment course. Other clinical predictors were outperformed by the inclusion of this indicator and therefore not included in the final risk prediction model. This allows for easy clinical risk profiling relatively early in the course of treatment; classifying patients as having a low or a high predicted risk of a prolonged treatment course. For depressive disorders, for patients with the highest scores, the positive predictive value for a prolonged treatment course was 60% (sensitivity 0.38, specificity 0.81). For anxiety disorders, for patients with the highest scores, the positive predictive value for a prolonged treatment course was 52%

(sensitivity 0.55, specificity 0.75). Although the sensitivity of the score is not very high, the positive predictive value is sufficient to consider patients with a high-risk score for evaluation and monitoring of rational medication switches, add-on psychotherapy, application of social activation and early rehabilitation techniques or interventions to reduce adverse life circumstances. No formal external validation study was performed.[1] We consider it likely that the prediction will improve with repeated measurement over time.

In **chapter 4** we explored whether we could identify patients with a high probability of persistent uncontrolled hypertension (systolic blood pressure > 140 mmHg) after approximately two months of (anti-hypertensive) treatment, based on patient characteristics and early treatment responses assessed by self-monitored blood pressure measurements. We showed that higher levels of systolic blood pressure at approximately two months, in addition to baseline systolic blood pressure, predicts persistent uncontrolled hypertension after one year of treatment. Other (patient characteristic) predictors did not contribute to the prediction.

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. Performance of the risk prediction improved when including information on early treatment response in terms of level of asthma control, compared to a model with only baseline characteristics (respectively an Area Under the Receiver Operating Characteristics (AUROC) of 0.84 and 0.79). The risk prediction model includes six easy to obtain predictors; sex, Asthma Control Questionnaire (ACQ)-score and exacerbations in the previous year at baseline and at 1st follow-up ACQ, smoking status and exacerbations in the previous three months (indicating early treatment response). The risk prediction model classifies 57.7% of the patients as having a low risk (absolute risk 11.7%) for future adverse outcomes. These patients could be assessed less frequent or, for example, could safely be reviewed by the practice nurse.[2]

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. FeNO-measurement is a quick and easy way to assess airway inflammation. Our results showed FeNO-driven asthma management is effective in patients with a low FeNO level, where it is possible to down-titrate

medication (such as inhaled corticosteroids) while preserving asthma control and quality of life. In primary care approximately 70% of FeNO measurements is low, and therefore, using FeNO-driven asthma management could be of enormous aid in reducing inhaled corticosteroids use without a reduction in control of asthma symptoms.

PREDICTING AN UNFAVORABLE PROGNOSIS

In this thesis we explored four chronic medical conditions (depressive disorders, anxiety disorder, hypertension and asthma) with the aim to identify patients with an unfavourable prognosis early in their treatment course. We considered variables at initiation of the treatment, as well as variables early in the treatment course. Our approach revealed two conceptually distinct constructs of predictors of an unfavourable prognosis.

The first construct of predictor of an unfavourable prognosis identified, was the **level of control** of the chronic condition; the level of symptoms in depressive and anxiety disorders, systolic blood pressure in individuals with hypertension and the level of asthma control for asthma patients. One might consider the level of control of the chronic condition to be a resultant of a broad range of underlying risk factors, as several studies in depressive and anxiety disorders, hypertension and asthma have shown: for example comorbid conditions, medication adherence and other patient characteristics as coping strategy, body mass index, inactivity or age.[3-11] By using one single variable, the level of control of the chronic condition, as proxy for a broader range of variables, the prediction of an unfavourable prognosis is clearly simplified.

The second construct of predictor of an unfavourable prognosis identified in this thesis, was information on **early treatment response**. This early treatment response, i.e. after 2-6 months, had additional predictive ability for unfavourable prognosis, compared to baseline measurements of condition severity only. In patients with hypertension and asthma the final prediction model included both a measure of baseline condition control, as well as a measure of early treatment response: in patients with depressive and anxiety disorders baseline condition control was not included, however, early treatment response was.

In the following paragraphs we will elaborate in more detail on both constructs of predictors.

Level of control: a possible reflection of a multitude of predictors

We found the level of control of the chronic conditions to be a prominent predictor for an unfavourable prognosis, which we observed for all conditions studied. The level of control of the chronic conditions could be the resultant of commonly known predictors and/or risk factors, which largely lose their predictive ability if the level of control is included in the prediction model. The level of control of a chronic condition captures not only condition specific characteristics as for example the number of symptoms experienced by the patient, but the level of control of a chronic condition is also determined by e.g. comorbid conditions, medication adherence and other patient characteristics as coping strategy, body mass index, inactivity or age.[3-14]

In patients with depressive and anxiety disorders, data were limited to administrative variables that were available for this study and we had no exhaustive set of variables with for example family history and personality traits such as neuroticism. However, with the level of symptom severity in the prediction model, a proxy of a multitude of predictors was included as it for example captures not only disorder specific, but also comorbid symptoms. This finding is in line with many previous studies, where the level of symptom severity also tends to outperform other predictors, also predictors not measured in this thesis.[3-7]

In patients with hypertension, a model containing only systolic blood pressure was capable of predicting persistent uncontrolled hypertension, without contribution of any additional predictors (e.g. age and medication adherence). In other words, systolic blood pressure possibly serves as a proxy of other common risk factors of hypertension.[8] For example, age was not included, but systolic blood pressure rises with age, or another example, the presence of a family history of hypertension increases the risk of an elevated systolic blood pressure. In patients with asthma we included two variables as proxies, with the Asthma Control Questionnaire-score and the occurrence of severe exacerbations.[15,16]

Information on early treatment response

The addition of early treatment response increased the predictive performance of risk prediction for an unfavourable prognosis. For this thesis, we defined early treatment response, measured after 2-6 months of treatment, relative to the same measurement at baseline. Therefore, change over time was included in our risk prediction model, in addition to baseline variables. Note that we do not state that the baseline assessment on itself is without meaning; at baseline the level of control of the chronic condition still predicts an unfavourable prognosis, albeit less discriminating.

Early treatment response is a proxy of different aspects concerning treatment effectiveness, e.g. adequateness of initial treatment and/or drugs, the mutual trust between clinician and patient and behavioral aspects such as treatment adherence.[17-26] Detailed data on the type of treatment and/or drugs could perhaps add to our prediction, but these data were not at our disposal in this thesis.[27,28] Treatment response adds an insight that can be acted upon; guiding decisions in the treatment plan. This will be discussed under the heading *long treatment trajectories: challenges in clinical practice*.

In **chapter 3**, in patients with depressive and anxiety disorders, the observation that addition of the 1st follow-up assessment to the prediction model outperforms the baseline level of symptom severity, and thereby the rate of change deserves some further elaboration. This finding is consistent with the assumption that patients with high symptom severity at 1st follow-up were likely to score high at the baseline level of symptoms, or even higher. These might be the patients with poor initial recovery, which in turn might be predictive of an unfavourable prognosis. Patients with a low(er) level of symptom severity at the 1st follow-up could consist of a mix of patients improving from a higher level of symptom severity at baseline or remaining low which heralds' better outcome overall.[29] Consistent with these assumptions and our findings, the rate of change, and thereby the baseline assessment no longer added information at the moment of first follow-up. It is the level of symptom severity at the moment of assessment, 2-6 months after the initiation of treatment, that determines risk of an unfavourable prognosis in patients with a depressive or an anxiety disorder. Presumably, the prediction will further improve when repeated, for example, after 9-12 months.

In patients with hypertension, and in patients with asthma, both baseline variables and early treatment response were included in our risk prediction model and thereby we included the rate of change. In patients with hypertension treatment response was assessed after approximately two months of treatment, in patients with asthma information on early treatment response was assessed after approximately three months, which is comparable to findings of earlier studies.[24,25,30,31]

PREDICTING UNFAVOURABLE PROGNOSIS: A NOTE OF CAUTION

In this thesis we developed risk prediction models for four medical conditions. Our findings should be interpreted with some considerations.

- The developed risk prediction models in this thesis show that in different chronic conditions the introduction of early treatment response in risk estimation seems a valuable opportunity to improve clinical practice; the use of measurements of early treatment response after approximately three months after initiation of treatment based on assessment at baseline. From patient and regulatory perspective, predicting prognosis at baseline has some advantages, especially for clinical decision making about the nature of the presenting problem and deciding which treatments will be most appropriate.[32,33] However, the initiated treatment does not always improve health outcomes as expected, or could be substantially reduced without adverse effects.[34] The inclusion of early treatment response supports medical decision making *after* the initiation of treatment.[35], thereby taking the effect of this treatment into account.[54]

- Data were limited to what was available and we had no exhaustive set of variables. We cannot exclude the possibility that other factors such as patient and/or family history, childhood trauma, specific co-morbidity, or personality characteristics (e.g. neuroticism) may add to the prediction.[36-41] as Also, detailed information on the type of treatment and/or drugs could perhaps add to our prediction, but these data were not at our disposal in this thesis.[27,28]

- For the four conditions in this thesis, we robustly found that early treatment response predicted an unfavourable prognosis. It should however be kept in mind that we did not study treatment effects; it thus still could be that a marginal early treatment response is a reflection of a somewhat effective treatment. A predicted unfavourable course based on a limited early treatment effect should thus not automatically lead to a termination of that treatment (see further).

- Generally, prediction models are in need of external validation to avoid overfitting, and it is known that many prediction models fail the validation test when applied to an external cohort.[42,43] For asthma, we did apply our risk prediction model to an external validation dataset and calculated the AUROC, which yielded an AUROC of 0.77; compared to an AUROC of 0.84 in the derivation dataset, suggesting reasonable generalizability of our findings. For depressive disorders, anxiety disorders and hypertension we were not able to perform an external validation.

- In this thesis we studied four chronic conditions, and whether the general

conclusions apply to a broader range of chronic conditions needs further research, as for example diabetes or chronic obstructive pulmonary disease (COPD).

LONG TREATMENT TRAJECTORIES: CHALLENGES IN CLINICAL PRACTICE

With the identification of patients at risk of an unfavourable prognosis in an early stage of treatment we offer a momentum to reconsider treatment, contributing to the development of personalized medicine and potentially leading to a more efficient use of healthcare resources by optimizing treatment.[44] This perfectly fits the adoption of value-based healthcare where the aim is to increase the value that is derived from the resources available e.g. the Choosing Wisely campaign: an initiative that seeks to advance a dialogue on avoiding unnecessary medical tests, treatment and procedures.[34,45]

For the developed risk prediction models, we considered it crucial to use data that is readily applicable in a clinical setting. For the models this means the use of variables that are easy to obtain or to measure.[46] In clinical practice risk prediction is most useful when people are stratified into clearly distinct categories of high or low risk; such categories can be used to inform treatment decisions. Thereby, the developed risk prediction models could be integrated in everyday practice, as for example in routine outcome monitoring or as (online) decision support tools. The ultimate goal is of course to influence the disease course in such way that the risk of an unfavourable prognosis is reduced; however, identification of such a patient group does not automatically translate into a better prognosis. That would require a strategy to influence such prognosis, for example by altering or intensifying treatment.[47]

In **Chapter 3, Chapter 4** and **Chapter 5** we provide clinicians with an early and clear estimate of unfavourable prognosis; patients can be easily classified as having a low or a high predicted risk. The inclusion of early treatment response allows for personalized clinical risk profiling relatively early in the course of treatment and identifies patients with high risk score for evaluation and monitoring of rational medication switches, add-on treatment, application of social activation and early rehabilitation techniques or interventions to reduce adverse life circumstances.

For depressive disorders and anxiety disorders, for patients with the highest scores, the positive predictive values for a prolonged treatment course were respectively 60% and

52%, the positive predictive values are sufficient to consider patients with a high-risk score for evaluation.[1]

For patients with hypertension, we derived an easy to calculate score which ranged from -1 to 12. For 57% of patients with a risk score of 5 to 12 points, the positive predictive value of prolonged treatment course was 65%, compared to 5% for patients with a score of -1 to 4 points. At this cut-off level sensitivity was 0.96 and specificity 0.64. For a risk score of 5-12 points either baseline systolic self-monitored blood pressure was ≥ 150 mmHg or after approximately two months of treatment systolic self-monitored blood pressure was ≥ 130 mmHg. Patients without or with minimal decrease of systolic blood pressure (high risk patients) for evaluation should thus be specifically considered.

In patients with asthma, after 3 months of treatment, 16.1% of the asthma patients was classified as having a high risk for an unfavourable prognosis, on the other hand the risk prediction model classifies 57.7% of the patients as having a low risk. For patients with a low risk, and although treatment could be continued, other options might be considered as well, such as a reduction in dose, by also a less frequent treatment control, or a shift in control from general practitioner to practice nurse are options. In **chapter 6** we provided an example of stepped-care asthma management is effective in patients with a low FeNO level, where it is possible to down-titrate medication while preserving asthma control and quality of life. This allows the clinician more time for an extensive review in the smaller subgroup of patients in the highest risk category.

The patient's perspective

One of the most important aspects of having a chronic medical condition regards the chances of getting and maintaining the medical condition controlled, with minimal adverse events and good health related quality of life. With the developed risk predictions, we support medical decision making on continuing, altering or even terminating treatment.[48] Even if the initiated treatment will be continued, it could be a moment to inform about the future course and to guide clinicians and patients in shared decision making on further treatment, if any. Thereby, the communication between clinicians and patients may improve, and patients tend to feel safer when they participate in their own treatment plan; which creates individualisation of treatment.[49] Furthermore, for this thesis we aimed our predictors to be easily accessible, followed by a clear and easy understandable risk prediction score, it is easier for a patient to visualise their own risk and end goal, and possible feel more urge to change some things (*see the supplement for examples, appendix 1*) .

ROUTINE HEALTH CARE DATA

Standard management of chronic medical conditions, depending on the specific condition, generally consists of frequent (routine) patients visits involving the assessment of symptoms, health related quality of life, medication adherence, laboratory measurements and additional clinical parameters.[50,51] Resulting in *routine healthcare data*, and providing a unique opportunity to improve clinical practice in facilitating continuous tailoring of treatment; and data that is increasingly used for research purposes.[46]

The potential of routine healthcare data gains a growing awareness for research purposes as it is perceived as highly representative for daily practice, the sample sizes are large, and routine healthcare data consist of a continuously input of information on the state of condition control of the patient, with a potential linkage to other databases.[52] If gathered validly, routine health care data can support clinicians in personalized medicine, as a continuously input leads to an ongoing way to support medical decision making on continuing, altering or even terminating treatment.[44,48] Thereby, it is likely that large databases will provide the base for studies on predictors of health outcomes with more power for statistical modeling, while minimizing costs and effort.[53] Increasingly, routinely healthcare data are used to study the effectiveness of treatment. Demonstrating the effectiveness of treatment is difficult, as confounding by indication is difficult to disentangle.[54] It should be kept in mind that routine healthcare data are mostly not collected for research purposes, but healthcare driven. This could imply that data is not complete, the level of details is less than desired, or the information is not uniformly coded. Therefore, the researcher always has to ensure the completeness, validity, and applicability of the data for the question of interest.[55-57] Other challenges to be considered are for example standardized collection of data within and across providers and/or institutions, or privacy-issues; who has access to patient data and how this information will be acted upon.

CONCLUSIONS

The fact that most healthcare resources are spend on a small subgroup of patients with an unfavourable prognosis has long been recognized, and is also supported by **chapter 2** of this thesis. Therefore, we emphasize, change is needed in terms of an improved identification of patients with an unfavourable prognosis, early in their treatment course, which may facilitate proactive approaches to improve outcomes. We discussed two conceptually distinct constructs of predictors of prognosis in order to improve

the identification of patients with an unfavourable prognosis. First, the level of control of the chronic condition as a predictor could reflect to some extent the presence of a multitude of other risk factors, which largely lose their significance if the level of control is included in the prediction model. Second, information on early treatment response had better predictive ability for long-term outcomes and so acts as a proxy for treatment effectiveness. Treatment effectiveness depends on different aspects e.g.adequateness of initial treatment and/or drugs, the mutual trust between clinician and patient and behavioral aspects such as treatment adherence. Treatment response adds an insight that can be acted upon; guiding personalized decisions in the treatment plan. Consider patients with high risk scores for evaluation and monitoring of rational medication switches, add-on treatment, application of social activation and early rehabilitation techniques or interventions to reduce adverse life circumstances. For patients with a low risk, treatment could be continued, or treatment could be safely assessed less frequent or, for example, in primary care, could be reviewed by the practice nurse. This allows the clinician more time for an extensive review and medication changes, in the smaller subgroup of patients in the highest risk category. We want to emphasize that with the risk prediction score we classify patients, it is ultimately up to the clinician to decide on treatment approach.

In conclusion, this thesis leads to improvement of personalized medicine and thereby could increase the efficient use of healthcare resources, with the early identification of patients at risk of an unfavourable prognosis.

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Addendum

NEDERLANDSE SAMENVATTING

Introductie

Wereldwijd hebben 3.4 miljard mensen één of meer chronische aandoeningen. Chronische aandoeningen vormen niet alleen een aanzienlijke last voor patiënten en hun families, waarbij de zelfredzaamheid en deelname aan activiteiten in de samenleving in het geding zijn, maar chronische aandoeningen hebben ook een impact op de maatschappij, vooral door de kosten die deze aandoeningen met zich meebrengen, bijvoorbeeld ziektekosten of kosten door productiviteitsverlies. Een chronische aandoening wordt gedefinieerd als een gezondheidstoestand of langdurige ziekte (≥ 3 maanden) met aanhoudende klachten en weinig tot geen progressie. In dit proefschrift wordt gefocust op vier chronische aandoeningen, namelijk: depressieve stoornissen, angststoornissen, hypertensie en astma.

De behandeling van deze chronische aandoeningen is gericht op het verbeteren van het dagelijks functioneren van de patiënt, het minimaliseren van symptomen en behoud van de kwaliteit van leven. Het belangrijkste doel van de behandeling is dan ook om de chronische aandoening onder controle te krijgen, en te houden. De geïnitieerde behandeling leidt echter niet altijd tot de gewenste resultaten. Het uitblijven van de gewenste resultaten leidt tot een groep van patiënten waarbij de behandeling zonder duidelijk effect wordt voorgezet; dit brengt met zich mee een verhoogd risico op symptomen en onnodige kosten voor de maatschappij. Dit zijn patiënten met een ongunstige prognose, in de zin dat de ingezette behandeling geen positief effect op de aandoening heeft.

Het doel van het in dit proefschrift beschreven onderzoek was om patiënten met een verhoogd risico op een ongunstige prognose vroegtijdig in de behandeling te identificeren, en hiermee mogelijk een proactieve benadering te faciliteren en daarmee de prognose te verbeteren. Om dit doel te bereiken, hebben we risicomodellen ontwikkeld waarmee de behandelaar op een gemakkelijke manier patiënten kan identificeren met een verhoogd risico op een ongunstige prognose.

De risicomodellen zijn ontwikkeld op basis van patiëntkenmerken, klinische variabelen en tevens informatie over de vroege behandelings respons van de patient.

Depressieve stoornissen en angststoornissen

Depressieve- en angststoornissen zijn de meest voorkomende psychische stoornissen, met een prevalentie van respectievelijk 298 en 273 miljoen patienten wereldwijd,

en in vergelijking met andere psychische stoornissen worden deze stoornissen geassocieerd met de meeste arbeidsongeschiktheidsdagen per jaar en de hoogste economische lasten. Ongeveer 20% van de patiënten met een depressieve stoornis is niet hersteld na twee jaar behandeling, voor angststoornissen is dit meer dan 50% van de patienten. Een langdurige behandeling wordt vaak geassocieerd met de leeftijd van de patiënt, huisvestingssituatie, familiegeschiedenis, de ernst van de symptomen en co-morbide aandoeningen. Daarnaast hebben verschillende studies over specifieke (medicamenteuze) behandelingen aangetoond dat respons op de behandeling binnen twee tot acht weken een indicatie van verder herstel kan zijn.

Hypertensie

Hypertensie, ofwel verhoogde bloeddruk, is één van de meest prominente risicofactoren van cardiovasculaire morbiditeit en sterfte. Wereldwijd hebben meer dan 1 miljard mensen hypertensie. Voor de meer dan 75% van de patiënten blijft de controle van de bloeddruk suboptimaal, daarmee houden deze patiënten een vehoogd risico op bijvoorbeeld beroertes en coronaire hartziekten. Een langdurige ongecontroleerde bloedruk wordt vaak geassocieerd met roken, therapietrouw, leeftijd, opleidingsniveau, etniciteiten, body mass index (BMI) en de bloeddruk bij aanvang van behandeling. Ondanks de vaak genoemde voordelen van het herhaaldelijk meten van de bloeddruk, wordt slechts beperkt gebruik gemaakt van deze metingen in prognostisch modellen.

Astma

Astma is een veelvoorkomende chronische ademhalingsziekte, en treft ten minste 235 miljoen mensen wereldwijd, waarvan 50-60% de astma niet onder controle heeft. Ongecontroleerde astmapatiënten lopen een verhoogd risico op een bezoek aan de spoedeisende hulp, een ziekenhuisopname, of zelfde de dood, als gevolg van een ernstige exacerbatie (astma-aanval). Ongecontroleerde astma wordt vaak geassocieerd met roken, lagere sociaaleconomische status, lage thereapietrouw, comorbiditeiten en etniciteit. Bovendien suggereren verschillende studies van lange termijn resultaten dat de controle van astma al kan worden beoordeeld op een evaluatie van drie maanden.

De belangrijkste bevindingen van dit proefschrift

In hoofdstuk 2 hebben we de impact van behandelingsduur op het gebruik van de geestelijke gezondheidszorg beschreven en gekwantificeerd voor patiënten met depressieve- en angststoornissen. Deze studie toont de relevantie van de vroegtijdige identificatie van patiënten met een ongunstige prognose; patiënten met een langere behandelingsduur hebben een grote invloed op het gebruik van de middelen in de geestelijke gezondheidszorg. In de geestelijke gezondheidszorg wordt meer dan 60%

van de middelen besteed aan slechts 25% van de patiënten met een behandelingsduur van minimaal twee jaar. Tevens heeft deze studie aangetoond dat de intensiteit van de behandeling bij deze patienten al in de eerste zes maanden hoger ligt ten opzichte van patiënten met een kortere behandelingsduur, en de intensteit van de behandeling neemt niet af na verloop van tijd.

In hoofdstuk 3 hebben we ons gericht op het vroegtijdig identificeren van patiënten met een langere behandelingsduur; te weten patiënten met depressieve- en angststoornissen. De resultaten van deze studie tonen aan dat, na een behandeling van 2-6 maanden, een hoger aantal en/of meer ernstige symptomen (de symptoomscore) een sterke voorspeller zijn voor een langere behandelingsduur. Met deze informatie wordt het gemakkelijker om relatief vroeg in de behandeling patiënten te indentificeren met een verhoogd risico op een ongunstige prognose; een langere behandelingsduur. Ongeacht de symptoomscore bij start van de behandeling.

In hoofdstuk 4 hebben we ons gericht op het vroegtijdig identificeren van patiënten met een verhoogd risico op aanhoudende hypertensie; gedefnieerd als een bovendruk > 140 mmHg. Patiënten hebben voor deze studie zelf thuis de bloeddrukmetingen gedaan. De resultaten van deze studie tonen aan dat een combinatie van een verhoogde bloeddruk bij de start van de behandeling, en een verhoogde bloeddruk na twee maanden behandeling, een sterke voorspeller is voor aanhoudende hypternsie na één jaar behandeling.

In hoofdstuk 5 hebben we ons gericht op het vroegtijdig identificeren van astmapatiënten met een verhoogd risico op een ongunstige prognose, zoals (ernstige) exacerbaties, beperking van de luchtstroom en/of neveneffecten van medicatie. De resultaten van deze studie tonen aan dat de identificatie van patiënten met een verhoogd risico verbetert wanneer we karakteristieken bij de start van de behandeling combineren met informatie na drie maanden behandeling. Het risicomodel wordt opgebouwd met de variabelen geslacht, de mate van astmacontrole (ACQ-score) en de indicatie van exacerbatie in het voorgaande jaar bij start van de behandeling, na drie maanden behandeling worden de variabelen rook-status, de ACQ-score en de indicatie van exacerbaties in de voorgaande drie maanden toegevoegd aan het risicomodel.

In hoofdstuk 6 hebben we bij astmapatiënten onderzocht of zij meer baat hebben bij een FeNO-gedreven behandeling, of een traditionele symptoom-gedreven behandeling. FeNO staat voor de hoeveelheid stikstofmonoxide (NO) in uitgeademde lucht. De hoeveelheid NO is groter als er een ontsteking in de luchtwegen zit. Voor deze studie

hebben we onderscheid gemaakt tussen vooraf gedefineerde subgroepen op basis van FeNO (laag, medium, hoog). De resultaten van deze studie tonen aan dat een FeNO-gedreven behandeling effectief is voor patiënten met een laag FeNO-niveau, waarbij het gebruik van medicatie veilig kan worden afgebouwd met behoud van astmacontrole en kwaliteit van leven. In de huisartpraktijken heeft ongeveer 70% van de astmapatiënten een lage FeNO-meting, een FeNO-gedreven kan behandeling kan hier dan ook erg waardevol zijn.

Het voorspellen van een ongunstige prognose

In dit proefschrift komen vier chronische medische aandoeningen aan bod met als doel patiënten met een ongunstige prognose vroegtijdig in de behandeling te identificeren. Bij de ontwikkeling van risicomoddelen zijn verschillende variabelen getoetst; patientskenmerken, klinische waarden en tevens informatie over de vroegtijdige behandelings respons van de patient. Deze aanpak toonde twee conceptueel verschillende constructen van voorspellers van een ongunstige prognose.

1. Niveau van controle: een weerspiegeling van een veelheid van voorspellers

Het niveau van controle van een chronische aandoening is een sterke voorspeller van een ongunstige prognose; de symptoomscore in depressieve- en angststoornissen, de bovendruk bij patiënten met hypertensie, en het niveau van astmacontrole bij patiënten met astma. Het niveau van controle van de chronische aandoening kan beschouwd worden als een gevolg van een breed scala aan onderliggende factoren, bijvoorbeeld comorbide condities, therapietrouw en patiëntkenmerken als BMI, fysieke inactiviteit en leeftijd. Deze factoren verliezen grotendeels hun voorspellend vermogen als de mate van controle wordt opgenomen in het voorspellingsmodel. Door gebruik te maken van één enkele variabele, het niveau van controle van de chronische aandoening is de voorspelling van een ongunstige prognose duidelijk vereenvoudigd.

2. Informatie over vroegtijdige behandelings respons

De toevoeging van vroegtijdige behandelings respons verhoogde de voorspellende prestaties voor het risico op een ongunstige prognose. In dit proefschrift hebben we de vroegtijdige behandelings respons gedefinieerd als een additionale meting na 2-6 maanden behandeling. Bij patiënten met hypertensie en astma omvatte het uiteindelijke voorspellingsmodel zowel een start-meting van het niveau van controle als een additionele meting van de vroegtijdige behandelings respons. Bij patiënten met depressieve en angststoornissen omvatte het voorspelligsmodel enkel de vroegtijdige behandelings repsons. Vroegtijdige behandelings respons is het resultaat van verschillende aspecten met betrekking tot de effectiviteit van de behandeling zoals het

type behandeling en/of medicatie, het wederzijds vertrouwen tussen behandelaar en patiënt, therapietrouw of andere gedragsaspecten.

Conclusie

Een groot deel van de kosten in de gezondheidszorg wordt besteed aan een relatief kleine groep van patiënten met een ongunstige prognose, reeds erkend, en tevens ondersteund door hoofdstuk 2 van dit proefschrift. Het is dan ook van groot belang om patiënten met een ongunstige prognose vroegtijdig in de behandeling te identificeren, waarmee proactief een momentum wordt gecreerd om de behandeling te heroverwegen.

We bespraken twee conceptueel verschillende concepten met betrekking tot de verbetering van de identificatie van patiënten met een ongunstige prognose. Ten eerste kan het niveau van controle van de chronische aandoening beschouwd worden als een gevolg van een breed scala aan onderliggende factoren, die grotendeels hun voorspellende betekenis verliezen als het controleniveau in het voorspellingsmodel is opgenomen. Ten tweede verhoogt informatie over vroegtijdige behandelings respons de voorspellende prestaties voor het risico op een ongunstige prognose. De vroegtijdige behandelings respons is het resultaat van verschillende aspecten met betrekking tot de effectiviteit van de behandeling zoals het type behandeling en/of medicatie, het wederzijds vertrouwen tussen behandelaar en patiënt, therapietrouw of andere gedragsaspecten. Beide constructen kunnen een belangrijke rol spelen bij de vroegtijdige identificatie van patiënten met een ongunstige prognose in chronische aandoening niet beschreven in dit proefschrift (e.g. COPD, Diabetes).

Voor patiënten met een verhoogd risico op een ongunstige prognose kan bijvoorbeeld worden overwogen om extra evaluatiemomenten aan de behandeling toe te voegen, of het gebruik van andere medicatie kan worden overwogen, evenals sociale activatie of verhoogde focus op de vermindering van ongunstige leefomstandigheden. Voor patiënten met een laag risico kan de geintiteerde behandeling worden voortgezet, het aantal evaluatiemomenten kan worden verminderd, of de evaluatiemomenten kunnen door de praktijkondersteuner worden uitgevoerd (in de eerstelijnszorg). Als gevolg hiervan heeft de behandelaar meer tijd voor een uitgebreide evaluatie, en eventueel medicamenteuze veranderingen, in de kleinere groep van patiënten met een verhoogd risico.

Kortom, dit proefschrift draagt bij aan de ontwikkeling van gepersonaliseerde geneeskunde, mogelijk leidend tot efficiënter gebruik van het zorgaanbod door het optimaliseren van de behandeling. Met de vroegtijdige identificatie van patiënten met

een verhoogd risico op een ongunstige prognose, bieden we een momentum om de behandeling te heroverwegen. Het uiteindelijke doel is natuurlijk om de prognose van de chronische aandoening dusdanig te beïnvloeden dat het risico op een ongunstige prognose wordt verkleind. De identificatie van patiënten met een verhoogd risicio op een ongunstige prognose vertaalt zich echter niet automatisch in een betere prognose; het is uiteindelijk aan de behandelaar om te beslissen over de voorzetting van de behandeling.

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Suzanne

CURRICULUM VITAE

Suzanne Boer werd geboren op 29 november 1989 te Schiedam. In 2008 behaalde zij haar gymnasium diploma aan het Stedelijke Gymnasium te Schiedam, waarna zij begon met de opleiding Psychologie aan de Universiteit Leiden. Na haar academische bachelor is zij in 2012 begonnen aan de masteropleiding Methodologie en Statistiek in de Psychologie, met een onderzoeksstage bij TNO; met twee wetenschappelijke publicaties als resultaat. In 2013 is zij gestart met haar promotieonderzoek op de afdeling Klinische Epidemiologie, de afdeling Psychiatrie, en de afdeling Medische Besliskunde van het Leids Universitair Medisch Centrum onder begeleiding van prof. dr. O.M. Dekkers, prof. dr. A.M. van Hemert en dr. J.K. Sont. Tijdens het promotietraject volgde zij verschillende epidemiologische cursussen. De resultaten van het promotieonderzoek zijn beschreven in dit proefschrift. Tevens heeft zij de resultaten gepresenteerd op verschillende nationale en internationale congressen. Sinds oktober 2017 was zij werkzaam als Data Scientist bij ABN AMRO, te Amsterdam. Per september 2020 heeft zij ABN AMRO ingeruild voor Albert Heijn, te Zaandam.

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