Depressive symptoms after stroke: risk factors and treatment

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Chapter 1

General introduction and outline
Introduction

Stroke (or cerebrovascular accident) is a leading cause of death and an important cause of persistent disability around the world. In the Netherlands, stroke affects around 46,000 persons each year. Survivors are either diagnosed with ischemic stroke (due to lack of blood flow) or haemorrhagic stroke (due to bleeding). As the global population older than 65 years of age continues to increase by approximately nine million people per year and stroke incidence is associated with ageing, its prevalence is expected to increase significantly around the world. Next to that, the percentage of stroke survivors will most likely increase due to improved healthcare facilities for patients in the acute phase of stroke. Therefore, in the future, stroke survivors may form an increasing demand on rehabilitation services. Generally, stroke puts a high burden on both patients and their caregivers as well as a considerable financial burden on society. Currently, approximately 3–4% of total healthcare expenditures in Western countries are spent on stroke. Even greater healthcare expenditures are likely in the near future with the expected growth of the elderly population and the availability of new and better treatments for stroke patients. As healthcare resources are limited, interest in the economic aspects of stroke and stroke-specific interventions has increased in the past few years.

Functional consequences of stroke

Stroke may be accompanied by functional consequences in many different domains. One year after stroke, 35% of stroke survivors are still functionally dependent and around 70% of them experience considerable long-term sensorimotor, cognitive and/or behavioural impairments and emotional consequences. Sensorimotor impairments entail deficits such as paresis (muscle weakness), spasticity (increased muscle tone), loss of sensibility, pain and visual field deficits. Important cognitive impairments are slow information processing, attention deficits, memory loss, visuospatial deficits, language impairments, and executive problems impairing planning, learning and decision making. Behavioural impairments after stroke can be present, such as, for instance, irritability, lack of impulse control, and apathy. The aforementioned impairments often limit pre-stroke daily routines and activities and may restrict social participation and quality of life. Stroke often causes a high burden of disease not only on patients, but also on partners and family members. Partners of stroke survivors are often forced to adopt a caregiver role, which changes the pre-
stroke relationship dramatically.\textsuperscript{9} Cognitive, behavioral and emotional sequelae of stroke negatively influence caregivers’ well-being.\textsuperscript{10,11} In addition, providing care at home for the stroke patient requires substantial effort,\textsuperscript{12} which brings about considerable change to the caregiver’s life and own health condition.

Emotional problems after stroke
In addition to the sensorimotor, cognitive and behavioural impairments, stroke may lead to significant emotional problems such as depressed mood and anxiety. At least one third of all stroke survivors deal with such emotional complaints during the first year after stroke.\textsuperscript{13} Indeed, in the chronic phase, usually defined as > 6 months, post stroke, the most frequent emotional symptoms are depressive symptoms (23-25\%) and anxiety (19-23\%).\textsuperscript{13–16} Both have a negative influence on quality of life.\textsuperscript{17,18} The definition of ‘post-stroke depression’ has been subject of considerable debate. Also, it seems that there is no consensus in the literature on how to measure ‘depressed mood’, ‘depression’, depressive symptoms’ or ‘emotional complaints’ after stroke. Clinically, post-stroke depression is usually diagnosed by a psychologist or psychiatrist using the DSM-V.\textsuperscript{19} However, in research, post-stroke depression is rarely assessed by a psychologist or psychiatrist based on DSM-V criteria.\textsuperscript{20–22} Instead, in scientific studies, depressive symptoms are customarily assessed by means of questionnaires such as the Beck Depression Inventory (BDI) or Hospital Anxiety and Depression Scale (HADS). These questionnaires offer no strict diagnosis of ‘depression’ post-stroke.\textsuperscript{23} Therefore, some researchers have proposed that ‘post-stroke depression’ assessed with BDI or HADS should be referred to as ‘mood disorder as a specific complication of stroke’,\textsuperscript{24} ‘post-stroke mood disorder’,\textsuperscript{25} or ‘post-stroke depressive complaints’ or ‘depressive symptoms’.\textsuperscript{26} Others have even argued that depressed mood after stroke is mainly a matter of ‘psychological distress’.\textsuperscript{27} The vast amount of research on this topic, however, implies that many stroke patients do experience measureable mood problems that require clinical attention and treatment. In this thesis, we will adopt this latter position and use the term ‘post-stroke depressive symptoms’ for patients with a score of >7 on the HADS-depression subscale. Likewise, ‘post-stroke symptoms of anxiety’ will be used for patients with a score >7 on the HADS-anxiety subscale.
Pathophysiology of post-stroke depressive symptoms

A possible ‘endogenous’ cause of post-stroke depressive symptoms has received much attention in the scientific literature, but so far there is no consensus on what neuroanatomical, neurophysiological or neurochemical brain substrates mood disorders post stroke are attributable to.\textsuperscript{28-30} In contrast, many researchers have argued that the relationship between stroke and post-stroke mood disorders is mediated by the significance that individual patients attribute to the causes and functional consequences of stroke, irrespective of the type, extent, and location of the stroke.\textsuperscript{31-34} From a psychological perspective, it is not surprising that emotional problems such as depressed mood and anxiety are common after stroke. Stroke generally occurs without any warning and patients and their families are unprepared in facing a new situation that drastically changes their independence, life circumstances, hopes, and plans for the future. Nevertheless, in the subacute phase (i.e., the first 6 months post stroke), rehabilitation of sensorimotor and cognitive impairments requires much effort and reactive depressive symptoms or complaints may remain unnoticed. Once this phase is over and patients have returned home, the intensity of rehabilitation decreases and patients and their families need to pick up their lives again. In this phase, social participation may still be severely restricted due to physical and cognitive impairments, chronic fatigue, and other health issues (e.g. pain, disturbed sleep) that are often invisible to and poorly understood by the outside world. As a consequence, patients may become discouraged, which further restricts their participation and initiative\textsuperscript{20} and eventually leads to a vicious circle. Indeed, due to functional limitations, stroke survivors experience reduced independence and are less able to participate in activities that used to be pleasurable or meaningful (e.g., gardening, assisting in preparing a meal; reading; babysitting (grand) children).\textsuperscript{8,35} Particularly in this phase, latent mood problems may be unmasked. Moreover, with increasing age and associated health problems, stroke survivors are more likely to encounter stressful life events such as increased fall risk (due to poor balance, limb paresis, spasticity or visual deficits), bereavement (due to death or disease of close relatives) and social disruption (e.g. change of housing).\textsuperscript{35} Both participation restrictions and stressful life events are risk factors for mood problems after stroke. Inadequate adjustment to these changes may easily lead to depressive symptoms as well as symptoms of anxiety. This notion is in line with behavioural theories that suggest that depressed mood is caused by lack of positive reinforcement when individuals are no longer able to participate in activities that were once meaningful or pleasurable.\textsuperscript{36} From this psychological
perspective, mood problems after stroke are ‘reactive’ in nature, as they result from inadequate adjustment to the (functional) consequences of stroke.

Psychological treatment of post-stroke depressive symptoms

Besides having a major impact on the quality of life, post-stroke depressive symptoms impede functional recovery and rehabilitation due to feelings of hopelessness and apathy, which leads to increased hospitalization and healthcare costs. Therefore, it is important to recognize and treat mood problems as early as possible after stroke. Unfortunately, both during primary rehabilitation and thereafter, symptoms of depression and anxiety are easily missed due to a focus on physical and cognitive impairments. If patients do get treatment for post stroke mood disorders, they are commonly treated with pharmacological agents. However, the benefits of pharmacotherapy are debatable, which is not surprising given the often ‘reactive’ nature of both depressive symptoms and anxiety. Considering that these emotional symptoms (e.g., depressive and anxiety symptoms) are the result of an inadequate adjustment to the (functional) consequences of stroke, one would assume that psychological interventions are a better approach to treatment. Yet, psychological interventions are used less frequently, mainly because their effects remain unclear. Nevertheless, psychological interventions seem promising in terms of (cost-)effectiveness, because they result in fewer side effects than psychotropic medication and have a stronger effect on preventing relapse of symptoms than pharmacotherapy.

Within the broad field of psychotherapy, cognitive behavioural therapy (CBT) seems one of the most promising methods to address symptoms of depression and anxiety post stroke. The core assumption in CBT is that thoughts – rather than external factors such as people, situations, or events – drive feelings and behaviours. If one can change the way one thinks, this can improve one’s feelings and actions, even if the situation itself remains unchanged. An important advantage of CBT over pharmacotherapy is that it is potentially more effective at preventing the relapse of emotional symptoms, as it aims to structurally change irrational cognitions and negative thoughts.

Thus far, only one study investigated the effectiveness of CBT for ‘post-stroke depression’. Lincoln and colleagues applied a treatment protocol in which elements of CBT, such as identifying and challenging negative thoughts as well as planning of joyful activities, were discussed with patients. However, they found inconclusive results with respect to the effectiveness of their intervention. CBT requires effort during treatment sessions and comes with a substantial amount
of homework. Yet, stroke survivors often suffer from impaired cognition, which Lincoln and colleagues (2003) did not take into account in their treatment protocol. In addition, as mentioned earlier, social participation and undertaking meaningful and pleasurable activities play an important role in well-being. However, next to discussing ‘activation’ with their patients, no further steps (such as stimulating an active life style or giving practical suggestions and encouragements directed at joyful activities) were taken by Lincoln and colleagues. In this perspective, the ambiguous results found by Lincoln and colleagues are not surprising.

Augmented cognitive behavioural therapy for depressive symptoms post stroke

The scientific literature shows inconsistent results with regard to the effectiveness of psychological treatment programs for post-stroke depressive symptoms, but there is a strong feeling that implementation of CBT should take into account cognitive impairments (e.g. attention and memory deficits) as well as emotional barriers (e.g. lack of motivation, grief, anxiety) and self-awareness. To stimulate the generalization of treatment results, the use of behavioural exercises that have to be performed in daily life situations is recommended. Despite a lack of evidence, there is sufficient reason to believe that CBT offered by a trained psychologist can be effective when adapted and tailored to the specific needs of stroke survivors, as discussed above. Indeed, in a review by Broomfield, it was suggested that CBT protocols for depressive symptoms in patients post stroke need ‘augmentation’ and an ‘individualized approach’. Moreover treatment protocols should encompass motivational interviewing and grief resolution, be directed at meaningful goals, and integrate executive skills training.

At the start of the present research project a CBT protocol for post-stroke depressive symptoms had been evaluated in a pilot study with promising effects on patients’ mood. This preliminary treatment protocol was evaluated and adjusted where necessary and formed the basis for a new (‘augmented’) CBT protocol. The essence of the applied ‘augmentation’ is that the CBT is built around attainable functional goals, while goal attainment is supported by occupational or movement therapy. Hence, an occupational or movement therapist complements the psychologist and assists the patient in setting and achieving his/her individual goals. In addition, attention is given to concomitant symptoms of anxiety by implementing the training of specific relaxation techniques.
Aim of this thesis

This thesis aims to describe and evaluate a new, augmented CBT protocol for the treatment of post-stroke depressive symptoms, with or without symptoms of anxiety, in comparison to a (presumably ineffective) control treatment (i.e., computerized cognitive training). To determine differences in treatment effect, the effects on both patients and their caregivers will be evaluated. In addition, the effects will be evaluated from an economical perspective. In the present thesis, the following research questions will be addressed:

1. Are psychological determinants important risk factors for post-stroke depressive symptoms?
2. What components should be part of an augmented CBT protocol for depressive symptoms, taking into account the physical, cognitive and emotional sequelae of stroke?
3. Is such an augmented CBT effective in reducing depressive symptoms and improve social participation and quality of life of patients in the chronic phase after stroke?
4. Is such an augmented CBT also beneficial with respect to the perceived burden by caregivers?
5. Is such an augmented CBT for patients with depressive symptoms post stroke effective from an economical perspective?

Thesis outline

In chapter two, the first research question is addressed. A longitudinal cohort study (based on The Restore4Stroke cohort study, see further) provides data to determine the importance of psychological risk factors for developing depressive symptoms and symptoms of anxiety one year after stroke. We hypothesized that psychological factors may be important in addition to previously established socio-demographic, premorbid, and stroke-related risk factors. If an important role for psychological factors can be demonstrated, this would support the role of psychological treatment in preventing and treating post-stroke symptoms of depression and anxiety.

Chapter three addresses the second research question and presents a new, augmented CBT protocol for post-stroke depressive symptoms. In this chapter, we describe the theoretical background of the treatment protocol, followed by the content of the intervention, and a comprehensive discussion.
Chapters four, five, six and seven address the third, fourth and fifth research questions. They present the methods and results of the RCT in which the augmented CBT protocol is compared to computerized cognitive training. Chapter four describes the research protocol in detail. It was hypothesized that patients treated with augmented CBT, tailored to their individual needs, would show a larger decrease in depressive symptoms than those receiving computerized cognitive training. Furthermore, it was hypothesized that the augmented CBT would be more beneficial with respect to alleviating the perceived burden (emotional as well as practical) of caregivers. Subsequently, chapter five presents the results of these interventions on patients and chapter six the possible influence of these results on caregivers. The economic evaluation in chapter seven describes the cost-effectiveness and cost-utility of the RCT from a societal perspective.

Restore4Stroke Research program

The present study is part of a comprehensive rehabilitation research program, Restore4Stroke, in the Netherlands (www.restore4stroke.nl) comprising four interrelated studies. Restore4stroke is funded by the VSBfonds, and coordinated by ZonMw (Dutch Organisation for Health Research and Development). The general aims of Restore4Stroke are to enhance successful social reintegration and to improve quality of life of stroke survivors and their caregivers. Besides the present RCT, three other studies are conducted: a longitudinal cohort study (Restore4Stroke Cohort study), an RCT aimed at evaluating the effects of a self-management group therapy, and an economical evaluation study (€-Restore4Stroke study).
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Chapter 2

Risk factors for symptoms of depression and anxiety one year post stroke: A longitudinal study

Abstract

Objective: To estimate the relative contribution of psychological factors next to socio-demographic and premorbid/stroke-related factors to the risk of developing symptoms of depression and anxiety after stroke.

Design: Multicenter longitudinal cohort study.

Setting: Patients after stroke from 6 general hospitals.

Participants: 331 patients were included at stroke onset and followed-up two and twelve months after stroke.

Main outcome measures: Socio-demographic and premorbid/stroke-related information was recorded during hospital admission, whereas psychological characteristics were determined with postal questionnaires two months post stroke. Symptoms of depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS) two and twelve months post stroke. Multivariable logistic analysis was performed to analyze the influence of socio-demographic, premorbid/stroke-related and psychological characteristics on depressive symptoms (HADS-D > 7) and symptoms of anxiety (HADS-A > 7) one year after stroke.

Results: Early depression, stroke severity, posterior cerebral artery stroke, and neuroticism independently explained the variance of depressive symptoms one year post stroke (discriminative power 83%, adjusted R2-value 36%). Neuroticism and early anxiety independently explained the variance of symptoms of anxiety one year post stroke (discriminative power 88%, adjusted R2-value 44%). Based on these predictive models, nomograms were constructed to visually reflect the individual contribution of each risk factor to the development of long-term mood disorders after stroke.

Conclusion: Psychological characteristics are important risk factors for post-stroke symptoms of depression and anxiety.
Introduction

Mood disorders are very common after stroke with prevalence estimates varying from 31-38% for both depressive symptoms and symptoms of anxiety.\textsuperscript{1,2} Moreover, post-stroke depression and anxiety often co-occur.\textsuperscript{2-6} Recent studies indicate that post-stroke depression is associated with reduced therapy compliance, poorer functional outcome, higher medical costs, reduced social participation, and increased mortality,\textsuperscript{7-10} while post-stroke anxiety and depression have both been associated with lower quality of life.\textsuperscript{2,7} In this perspective, knowledge about risk factors is essential for long-term prevention and treatment of mood disorders post stroke.

The risk factors for mood disorders after stroke that have been reported in the literature are mainly ‘socio-demographic’, ‘premorbid’ and ‘stroke-related.’ The most frequently reported risk factors for depressed mood are female gender, stroke severity (in terms of functional consequences), lack of social support and history of depression.\textsuperscript{11,12} Although less frequently investigated, the reported risk factors for post-stroke anxiety are female gender, age under 65 years, stroke severity, inability to work, pre-stroke treatment for depression, and smoking.\textsuperscript{2} Unfortunately, due to the methodology used in these studies, little is known about the strength of prediction of post-stroke mood disorders based on the above-mentioned socio-demographic, premorbid and stroke-related characteristics.\textsuperscript{2,12} Moreover, the aforementioned risk factors are mostly not amendable.

There are indications that mood disorders after stroke are greatly determined by an individual’s ineffective cognitive and emotional adjustment to the consequences of stroke\textsuperscript{13,14} and, thus, may have an important psychological origin. The Common Sense Model of Levental,\textsuperscript{15} suggests that patients create mental representations of their illness when faced with a chronic disease. The ineffective cognitive and emotional adjustments to the consequences of stroke are expressed in: ‘illness cognitions’, the way patients perceive their illness and its (uncontrollable) consequences; the worries and fears that come along with this adjustment to a new situation; and the concurrent behaviour or coping strategies patients attend to. In addition, a person’s stable characteristics, such as personality traits, are assumed to influence this adjustment process. Previous studies showed that neuroticism was indeed associated with post-stroke depression.\textsuperscript{16-19} In another study avoidance coping was associated with the severity of depressive symptoms after stroke.\textsuperscript{20} Unfortunately, these psychologically oriented studies were either small sized (n ≤ 61),\textsuperscript{16,17,20} used a cross-sectional design,\textsuperscript{16-18,21} or regarded a limited
set of psychological characteristics only.\textsuperscript{16,17,19} Hence, we conducted a longitudinal cohort study to explore possible risk factors for developing depressive symptoms and symptoms of anxiety one year after stroke, as part of the Restore4Stroke cohort study in the Netherlands.\textsuperscript{22} We hypothesized that psychological factors would be important in addition to previously established socio-demographic, premorbid and stroke-related characteristics. Moreover, we aimed to determine the predictive strength of each of these characteristics with regard to symptoms of depression and anxiety one year post stroke. If an important role for psychological factors can be demonstrated, this would support the application of psychological treatment to prevent or treat post-stroke mood disturbances.

**Methods**

**Subjects**

Patients were recruited at stroke units of six participating general hospitals in the Netherlands from March 2011 until March 2013.\textsuperscript{22} Patients were eligible if: (1) they signed informed consent within the first week post stroke; (2) the diagnosis of cerebral stroke (ischemic or haemorrhagic) was clinically confirmed; (3) age was 18 years or older; and (4) they had sufficient knowledge of the Dutch language to complete the planned assessments. Exclusion criteria were: (1) any serious co-morbid condition that might influence study outcomes; (2) pre-stroke dependency in activities of daily living as defined by a Barthel Index of 17 or lower;\textsuperscript{22,23} and (3) pre-stroke cognitive impairments as defined by a score of 1 or higher on the Heteroanamnesis List Cognition.\textsuperscript{24} The study was approved by the medical-ethical committee of the St Antonius Hospital in Nieuwegein as well as by the medical-ethics board of each of the other participating hospitals.

**Design and procedure**

Patients were assessed within one week post stroke (‘stroke onset’) as well as two and twelve months later. Socio-demographic information was provided by patients or patients’ family members at inclusion during the first days of hospital admission. Most premorbid and stroke-related information was obtained from the medical files at inclusion by a specialized stroke nurse. The National Institutes of Health Stroke Scale (NIHSS) and the Barthel Index (BI) were recorded on day 4 after stroke. Collection of information about use of anti-depressants and co-morbidity was performed by a trained research assistant two months post stroke,
as was the assessment of cognitive functioning. All potential psychological risk factors, including symptoms of depression and anxiety, were obtained by means of postal questionnaires two months post stroke. In addition, depressive symptoms and symptoms of anxiety were re-assessed as outcomes one year post stroke by means of postal questionnaires.

Outcomes

Symptoms of depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS). The HADS consists of 14 items and is divided in two subscales directed at either depressive symptoms (HADS-D) or symptoms of anxiety (HADS-A) (7 items per subscale, range 0-21 on each subscale). According to the literature, both depression and anxiety may be defined by a HADS-subscale score >7, yet we will refer to depressive symptoms and symptoms of anxiety throughout this text. The HADS has demonstrated good psychometric properties, including good internal consistency, in patients with stroke.

Potential risk factors

Socio-demographic: Information about sex (male/female), living together (yes/no), age (years), and level of education was obtained. The Dutch classification system of Verhage served as an indicator of the level of education (low range of 1-5, "elementary and secondary school"; high range of 6-7, "higher academic and vocational education").

Premorbid and stroke-related: The following stroke characteristics were recorded: type of stroke (ischemic/haemorrhagic), stroke location (left hemisphere, right hemisphere, brainstem, cerebellum), stroke circulation area (anterior (ACA) / middle (MCA) / posterior (PCA), vertebral – basilar artery (VBA)), and stroke recurrence (yes/no). Stroke severity was assessed with the NIHSS (range 0-42) and level of dependency in activities of daily living (ADL) with the BI (range 0-20; levels: high≤17, low>17). Cognitive functioning was assessed with the Montreal Cognitive Assessment (MoCA) (range 0-30) and co-morbidity with the Cumulative Illness Rating Scale (CIRS) (range 0-52). Furthermore, information about duration of hospital stay (days), location of residence at two months post stroke (home/institution), history of depression (yes/no), and current use of antidepressants (yes/no) was recorded.
**Psychological:** Besides symptoms of depression and anxiety using the HADS, the following personality characteristics were assessed: self-efficacy with the General Self-Efficacy Scale (GSES) (range 10-40);\(^ {34}\) neuroticism and extraversion with the Eysenck Personality Questionnaire – Revised Short Scale (EPQ-RSS-N;EPQ-RSS-E) (range 0-12, both subscales);\(^ {35}\) and pessimism and optimism with the Life Orientation Test-Revised (LOT-R) (range 0-12, both subscales).\(^ {36}\) Furthermore, proactive coping was assessed with the Utrecht Proactive Coping Competence list (UPCC) (range 1-4)\(^ {37}\) and passive coping with the passive coping scale of the Utrecht Coping List (UCL-P) (range 7-28).\(^ {38}\) Both the UPCC and the UCL-P are originally Dutch assessment scales. The UPCC items are scored on a 4 point scale. The UPCC has shown good psychometric properties in stroke patients (e.g., reliability and validity).\(^ {39}\) The UCL-P has shown good internal consistency and high test-retest reliability.\(^ {21,40}\) Finally, illness cognitions were assessed with the Illness Cognition Questionnaire, measuring feelings of helplessness, acceptance and perceived benefits (ICQ) (range 6-24 for each subscale).\(^ {41,42}\) For all psychological factors, higher scores reflect higher levels of the psychological characteristic assessed.

**Statistical analysis**

First, univariable logistic regression was performed to test the associations of each of the socio-demographic, pre-morbid/stroke-related, and psychological factors with ‘depressive symptoms’ (as defined by HADS-D > 7) and ‘symptoms of anxiety’ (as defined by HADS-A > 7) one year post stroke, separately.

Next, multivariable logistic regression with selection procedures was performed to identify those factors that independently contributed to the occurrence of ‘depressive symptoms’ and ‘symptoms of anxiety’ one year post stroke. All factors with \( p < 0.10 \) in the univariable model were valid for selection. The three categories of potential risk factors were introduced in the following order: 1) socio-demographic; 2) premorbid and stroke-related; 3) psychological. With each step a forward selection procedure was used. We also performed a backward selection procedure, which resulted in the same final model. Therefore, only the final model of the forward selection procedure is presented.

Factors selected in previous steps were valid for selection in the following step. The adjusted ORs with 95%CIs of all factors that were maintained in the final model for ‘depressive symptoms’ and for ‘symptoms of anxiety’ separately are presented. Because the final model after the forward selection procedure does not include the variables that are highly correlated to the variables already
selected, the p-values for entry into the model were considered in order to find close alternatives to the final model presented (i.e., the variables selected).\textsuperscript{43} The pseudo-$R^2$ (Nagelkerke) of the final model was calculated to indicate the variance explained. The area under the receiver operating curve (AUC) was used as a measure of predictive discrimination. To evaluate reliability of the created prediction model, an internal validation was performed using 80 bootstrap samples. The cross-validated pseudo-$R^2$ is presented as a measure of calibrated goodness of fit.\textsuperscript{44}

Finally, because the (adjusted) ORs cannot easily be compared between different risk factors, a nomogram was constructed based on the multivariable model to visually reflect the individual contribution of each risk factor to the development of long-term mood disorders after stroke. A nomogram can be used by filling in the scores of an individual on each of the independent risk factors. The total score can be translated into a probability value for developing ‘depressive symptoms’ or ‘symptoms of anxiety’ one year post stroke. Each nomogram is presented with sensitivity, specificity, and positive predictive value at optimal cut-off point under the condition of equal costs of misclassification.

All statistical analyses were performed with SPSS 20 and SAS 9.0 for Windows. The nomogram and the bootstrap analysis were performed using standard procedures in R version 2.6.1.

Results

Patient characteristics and follow-up

A total of 395 patients were enrolled in the Restore4Stroke Cohort study. At one year post stroke, 7 patients (1.7\%) had died, 32 patients (8.1\%) refused to participate and 25 patients (6.3\%) were lost to follow-up. Thus, 331 patients were included in this study. The characteristics of this study sample (socio-demographic, pre-morbid/stroke-related, and psychological) are presented in Table 1. The majority of the patients (92.7\%) had sustained an ischemic stroke in the territory of the Anterior Circulation Area or Middle Circulation Area (71.5\%). Mild stroke (NIHSS median 2.0) was most common, but the range of stroke severity was large (NIHSS range 0-22). Two months after stroke the prevalence of depressive symptoms, and symptoms of anxiety was 22.1\% and 20.1\%, respectively. One year post stroke these percentages were 27.0\% and 21.1\%, respectively. The percentages of patients with both depressive symptoms and symptoms of anxiety were 11.7\% and 13.0\% at two months and one year after stroke, respectively.
### Table 1. Patient characteristics

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**Premorbid and stroke-related**

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<tr>
<td>Stroke location</td>
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<tr>
<td>Left hemisphere</td>
<td>131</td>
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<td>Duration of hospital stay (days)</td>
<td>331</td>
<td>5.7 (1 - 50)</td>
</tr>
<tr>
<td>Location of residence after 2mths (home)</td>
<td>331</td>
<td>207 (83.1)</td>
</tr>
<tr>
<td>Pre-morbid depression</td>
<td>331</td>
<td>17 (5.1)</td>
</tr>
<tr>
<td>Use of antidepressants</td>
<td>300</td>
<td>19 (6.3)</td>
</tr>
</tbody>
</table>
Depressive symptoms

The ORs (with 95%CIs) of the demographic, premorbid/stroke-related, and psychological factors based on univariable logistic regression are presented in tables 2, 3 and 4, respectively. In total, 18 variables were valid for selection. In table 5 the adjusted ORs (with 95%CIs) for the risk factors in the final model are presented. Depressive symptoms at two months post stroke, level of dependency, stroke in the territory of the Posterior Circulation Area, and neuroticism independently contributed to explaining depressive symptoms (HADS-D>7) one year post stroke. The discriminatory power of this model was good (AUC 83% (95%CI:78%-89%)) and the percentage explained variance was acceptable (Nagelkerke R² 38%). After adjustment for internal validation these values were 82% and 36%, respectively. Figure 1 depicts the nomogram for the final model for depressive symptoms (HADS-D>7) at one year post stroke. For
this nomogram, sensitivity was 77%, specificity was 76%, and positive predictive value was 54%.

Table 2. The odds ratios (OR) with 95% confidence intervals (95%CI) for the socio-demographic characteristics with regard to ‘depression’ (HADS-D >7) and ‘anxiety’ (HADS-A >7) using univariable logistic regression analyses.

<table>
<thead>
<tr>
<th></th>
<th>Depression</th>
<th></th>
<th></th>
<th>Anxiety</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>OR</td>
<td>(95%CI)</td>
<td>p</td>
<td>n</td>
<td>OR</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>213</td>
<td>1.10</td>
<td>(0.67 - 1.83)</td>
<td>0.71</td>
<td>214</td>
<td>1.88</td>
</tr>
<tr>
<td>Male</td>
<td>117</td>
<td>1.00</td>
<td>(reference)</td>
<td></td>
<td>117</td>
<td>1.00</td>
</tr>
<tr>
<td>Age (years)</td>
<td>330</td>
<td>1.01</td>
<td>(0.99 - 1.03)</td>
<td>0.30</td>
<td>331</td>
<td>0.98</td>
</tr>
<tr>
<td>Living together</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>233</td>
<td>1.09</td>
<td>(0.64 - 1.87)</td>
<td>0.75</td>
<td>233</td>
<td>1.28</td>
</tr>
<tr>
<td>No</td>
<td>97</td>
<td>1.00</td>
<td>(reference)</td>
<td></td>
<td>98</td>
<td>1.00</td>
</tr>
<tr>
<td>Level of education*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>243</td>
<td>1.31</td>
<td>(0.74 - 2.32)</td>
<td>0.36</td>
<td>244</td>
<td>1.21</td>
</tr>
<tr>
<td>High</td>
<td>86</td>
<td>1.00</td>
<td>(reference)</td>
<td></td>
<td>86</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Living together: married or otherwise.
* Level of education (low:1-5; high:6-7).

Symptoms of anxiety

The ORs (with 95%CIs) from the univariable analyses are presented in tables 2, 3 and 4 for the socio-demographic, premorbid/stroke-related, and psychological patient characteristics, respectively. In total, 16 variables were valid for selection. In Table 5 the adjusted ORs (with 95%CIs) for the risk factors in the final model are presented. Early symptoms of anxiety, assessed at two months post stroke and neuroticism independently contributed to explaining symptoms of anxiety (HADS-A>7) one year post stroke. The predictive discrimination of this model was good (AUC 88% (95%CI: 83% - 92%)) and the percentage explained variance was acceptable (Nagelkerke R² 46%). After adjustment for internal validation these values were 87% and 44%, respectively. Figure 2 depicts the nomogram for the final model for symptoms of anxiety (HADS-A>7) at one year post stroke. For this nomogram, sensitivity was 77%, specificity was 84%, and positive predictive value was 57%.
Table 3. The odds ratios (OR) with 95% confidence intervals (95%CI) for the premorbid and stroke-related characteristics with regard to ‘depression’ (HADS-D >7) and ‘anxiety’ (HADS-A >7) using univariable logistic regression analyses.

<table>
<thead>
<tr>
<th></th>
<th>Depression</th>
<th></th>
<th>p</th>
<th>Anxiety</th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>OR (95%CI)</td>
<td>p</td>
<td>n</td>
<td>OR (95%CI)</td>
<td>p</td>
</tr>
<tr>
<td><strong>Stroke type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>306</td>
<td>1.92 (0.64 - 5.79)</td>
<td>0.25</td>
<td>307</td>
<td>0.79 (0.30 - 2.07)</td>
<td>0.63</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>24</td>
<td>1.00 (reference)</td>
<td></td>
<td>24</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>131</td>
<td>0.68 (0.29 - 1.95)</td>
<td>0.37</td>
<td>131</td>
<td>0.45 (0.19 - 1.08)</td>
<td>0.07</td>
</tr>
<tr>
<td>Right hemisphere</td>
<td>141</td>
<td>0.83 (0.36 - 1.92)</td>
<td>0.67</td>
<td>141</td>
<td>0.54 (0.23 - 1.28)</td>
<td>0.16</td>
</tr>
<tr>
<td>Brainstem</td>
<td>23</td>
<td>0.74 (0.22 - 2.45)</td>
<td>0.62</td>
<td>24</td>
<td>0.87 (0.27 - 2.75)</td>
<td>0.81</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>31</td>
<td>1.00 (reference)</td>
<td></td>
<td>31</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td><strong>Affected circulation area</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA/MCA</td>
<td>211</td>
<td>0.93 (0.47 - 1.85)</td>
<td>0.84</td>
<td>211</td>
<td>0.59 (0.30 - 1.15)</td>
<td>0.12</td>
</tr>
<tr>
<td>PCA</td>
<td>28</td>
<td>2.54 (0.97 - 6.62)</td>
<td>0.06</td>
<td>28</td>
<td>0.54 (0.18 - 1.68)</td>
<td>0.29</td>
</tr>
<tr>
<td>VBA</td>
<td>55</td>
<td>1.00 (reference)</td>
<td></td>
<td>56</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td><strong>Recurrent stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>43</td>
<td>1.54 (0.78 - 3.05)</td>
<td>0.21</td>
<td>43</td>
<td>1.15 (0.54 - 2.47)</td>
<td>0.72</td>
</tr>
<tr>
<td>No</td>
<td>287</td>
<td>1.00 (reference)</td>
<td></td>
<td>288</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>NIHSS</td>
<td>330</td>
<td>1.05 (0.98 - 1.13)</td>
<td>0.14</td>
<td>331</td>
<td>0.98 (0.90 - 1.07)</td>
<td>0.65</td>
</tr>
<tr>
<td>BI</td>
<td>330</td>
<td>0.91 (0.87 - 0.95)</td>
<td>&lt;0.01</td>
<td>331</td>
<td>0.98 (0.93 - 1.03)</td>
<td>0.44</td>
</tr>
<tr>
<td>MoCA</td>
<td>309</td>
<td>0.96 (0.90 - 1.02)</td>
<td>0.20</td>
<td>310</td>
<td>1.01 (0.94 - 1.08)</td>
<td>0.85</td>
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<tr>
<td>CIRS</td>
<td>315</td>
<td>1.12 (1.02 - 1.22)</td>
<td>0.01</td>
<td>316</td>
<td>1.13 (1.03 - 1.25)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Duration of hospital stay (days)</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Institution</td>
<td>330</td>
<td>1.07 (1.03 - 1.12)</td>
<td>&lt;0.01</td>
<td>331</td>
<td>1.03 (0.99 - 1.07)</td>
<td>0.20</td>
</tr>
<tr>
<td>Home</td>
<td>56</td>
<td>2.65 (1.46 - 4.81)</td>
<td>&lt;0.01</td>
<td>56</td>
<td>1.16 (0.58 - 2.30)</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>274</td>
<td>1.00 (reference)</td>
<td></td>
<td>275</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td><strong>Pre-morbid depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17</td>
<td>2.55 (0.96 - 6.82)</td>
<td>0.06</td>
<td>17</td>
<td>3.61 (1.34 - 9.74)</td>
<td>0.01</td>
</tr>
<tr>
<td>No</td>
<td>313</td>
<td>1.00 (reference)</td>
<td></td>
<td>314</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td><strong>Use of antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19</td>
<td>2.10 (0.81 - 5.43)</td>
<td>0.13</td>
<td>19</td>
<td>3.78 (1.47 - 9.77)</td>
<td>0.01</td>
</tr>
<tr>
<td>No</td>
<td>280</td>
<td>1.00 (reference)</td>
<td></td>
<td>281</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACA/MCA, Anterior/Middle Cerebral Artery; PCA, Posterior Cerebral Artery; VBA, Vertebral Basilar Artery; NIHSS, National Institutes of Health Stroke Scale (range 0-42); BI, Barthel Index (range 0-20); MoCA, Montreal Cognitive Assessment (range 0-30); CIRS, Cumulative Illness Rating Scale (range 0-52).
### Table 4. The odds ratios (OR) with 95% confidence intervals (95%CI) for the psychological characteristics with regard to ‘depression’ (HADS-D >7) and ‘anxiety’ (HADS-A >7) using univariable logistic regression analyses.

<table>
<thead>
<tr>
<th></th>
<th>Depression</th>
<th>Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n  OR</td>
<td>(CI 95%)</td>
</tr>
<tr>
<td>HADS-D</td>
<td>307  1.32</td>
<td>(1.22 – 1.42)</td>
</tr>
<tr>
<td>HADS-A</td>
<td>307  1.19</td>
<td>(1.11 – 1.28)</td>
</tr>
<tr>
<td>UPCC</td>
<td>310  0.39</td>
<td>(0.24 - 0.62)</td>
</tr>
<tr>
<td>UCL-P</td>
<td>311  1.29</td>
<td>(1.17 - 1.42)</td>
</tr>
<tr>
<td>GSES</td>
<td>310  0.95</td>
<td>(0.92 - 0.99)</td>
</tr>
<tr>
<td>EPQ-RSS-E</td>
<td>311  0.93</td>
<td>(0.86 - 1.01)</td>
</tr>
<tr>
<td>EPQ-RSS-N</td>
<td>311  1.23</td>
<td>(1.13 - 1.33)</td>
</tr>
<tr>
<td>LOT-R optimism</td>
<td>311  0.80</td>
<td>(0.70 - 0.90)</td>
</tr>
<tr>
<td>LOT-R pessimism</td>
<td>310  1.18</td>
<td>(1.07 - 1.29)</td>
</tr>
<tr>
<td>ICQ helplessness</td>
<td>311  1.20</td>
<td>(1.13 - 1.27)</td>
</tr>
<tr>
<td>ICQ acceptance</td>
<td>315  0.83</td>
<td>(0.80 - 0.89)</td>
</tr>
<tr>
<td>ICQ perceived benefits</td>
<td>311  0.95</td>
<td>(0.90 - 1.00)</td>
</tr>
</tbody>
</table>

Abbreviations: HADS-D, Depression subscale Hospital Anxiety and Depression Scale (range 0-21); HADS-A, Anxiety subscale Hospital Anxiety and Depression Scale (range 0-21); UPCC, Utrecht Proactive Coping Competence list (range 1-4); UCL-P, Passive coping subscale Utrecht Coping List (range 7-28); GSES, General Self-Efficacy Scale (range 10-40); EPQ-RSS-E, Eysenck Personality Scale-Revised Short Scale-Extraversion (range 0-12); EPQ-RSS-N, Eysenck Personality Scale-Revised Short Scale-Neuroticism (range 0-12); LOT-R, Life Orientation Test-Revised (range 0-12); ICQ, Illness Cognition Questionnaire (range 6-24).

### Discussion

The aim of our study was to explore possible risk factors for developing depressive symptoms and symptoms of anxiety one year after stroke. The identified prevalence of 27.0% for depressive symptoms one year post stroke in the present study was in line with the prevalence reported in a recent meta-analysis (33%, 95%CI:23-43),\(^2\) while for symptoms of anxiety one year post stroke the observed prevalence in this study (21.1%) corresponded with the prevalence reported in a recent review (24%, 95%CI:19-29).\(^6\) Our hypothesis that psychological characteristics would be important in addition to the socio-demographic, pre-morbid and stroke-related characteristics previously associated with post-stroke depressive symptoms and symptoms of anxiety was supported by the results from the multivariable logistic regression analyses. For depressive symptoms, early signs of depression, level of dependency, stroke in the territory of the Posterior
Circulation Area and neuroticism were identified as the most important risk factors, whereas for symptoms of anxiety, early signs of anxiety and neuroticism were found to be the most important risk factors. The constructed nomograms based on the final models visually reflect the predictive strength of each of the risk factors. Generally, the overall percentage of explained variance was fair for both the risk factor model for depressive symptoms (36%) and the model for symptoms of anxiety (44%), while the predictive discrimination of both models was good (83-88%).

Table 5. Adjusted odds ratios (OR) with 95% confidence intervals (CI) of the independent risk factors for ‘depression’ (HADS-D >7) and ‘anxiety’ (HADS-A >7), using multivariable logistic regression analyses

<table>
<thead>
<tr>
<th>Depression</th>
<th>Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Premorbid and stroke-related factors</td>
<td></td>
</tr>
<tr>
<td>Affected circulation area</td>
<td></td>
</tr>
<tr>
<td>ACA / MCA</td>
<td>0.72 (0.30 – 1.69)</td>
</tr>
<tr>
<td>PCA</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Psychological factors</td>
<td></td>
</tr>
<tr>
<td>HADS-D</td>
<td>1.15 (1.08 – 1.23)</td>
</tr>
<tr>
<td>HADS-A</td>
<td></td>
</tr>
<tr>
<td>BI</td>
<td>1.92 (1.07 – 1.33)</td>
</tr>
<tr>
<td>EPQ-RSS-N</td>
<td>1.12 (1.01 – 1.26)</td>
</tr>
</tbody>
</table>

Nagelkerke $R^2$ value was 38% for ‘depression’ and 46% for ‘anxiety’, respectively. Abbreviations: ACA/MCA, Anterior/Middle Cerebral Artery; PCA, Posterior Cerebral Artery; VBA, Vertebral Basilar Artery; HADS-A/D, Anxiety subscale Hospital Anxiety and Depression Scale (early signs) (range 0-21); BI, Barthel Index (range 0-20); EPQ-RSS-N, Eysenck Personality Scale- Revised Short Scale-Neuroticism (range 0-12).
From a clinical perspective, our results indicate that the long term risk of symptoms of depression and anxiety post stroke can be estimated based on a relatively compact set of diagnostic information available at two months post stroke. Psychological characteristics, i.e. early mood problems and neuroticism, constitute the core of these diagnostic sets. As can be read from both nomograms (Figures 1 and 2), the early HADS-D and -A scores make the largest contribution to determining the probability of developing depressive symptoms and symptoms of anxiety one year post stroke, respectively. Other identified risk factors for depressive symptoms post stroke support previous studies\textsuperscript{11,12} that found that stroke severity, in terms of functional dependency, makes a unique contribution.
to the risk of developing post-stroke depressive symptoms. Remarkably, stroke circulation area was identified as an independent risk factor for post-stroke depressive symptoms, although its predictive strength was relatively small (see Figure 1). A possible explanation for this finding may be that brain lesions in the Posterior Circulation Area often coincide with visuospatial deficits such as hemianopia that, on the one hand, may have a huge impact on daily functioning but, on the other hand, remain relatively ‘invisible’ for the social environment. This discrepancy may put a disproportionate emotional burden on stroke patients with brain lesions in the Posterior Circulation Area.

Figure 2. The nomogram to calculate the individual probability of HADS-A >7 at one year post stroke based on the identified risk factors. A vertical line can be drawn from the score of each risk factor to the ‘points’ axis on top of the figure. The points for each risk factor can be summed and the sum score can be located on the ‘Total Points’ axis. Then, a vertical line can be drawn from the total points axis point down to the ‘Probability of HADS-A’ axis, which depicts the individual probability of developing anxiety one year post stroke. Abbreviations: HADS-A, Anxiety subscale Hospital Anxiety and Depression Scale – anxiety subscale (early signs); EPQ-RSS-N, Eysenck Personality Scale- Revised Short Scale- Neuroticism.
In this study we aimed to identify the most concise predictive models for symptoms of depression and anxiety one year post stroke. As a consequence, regardless of the many factors that were valid for selection, only a limited set of variables remained in the final models. In both models, of all psychological risk factors, merely neuroticism made a unique contribution in addition to early symptoms of depression and anxiety. This does not imply that other psychological risk factors that were identified in the univariable analyses (Table 4) would not be clinically predictive of depressive symptoms or symptoms of anxiety one year post stroke. Indeed, early signs of anxiety, passive coping and low levels of proactive coping, lack of optimism, and lack of acceptance can still be considered as relevant risk factors for depressive symptoms one year post stroke. Nevertheless, these psychological risk factors no longer showed added predictive value after including ‘early depressive symptoms’ in the multivariable model. This result implies that early signs of depression are highly correlated with these psychological characteristics, which was already found in a cross-sectional analysis of the present cohort two months after stroke. The same line of reasoning applies to the final model for anxiety symptoms, as early signs of depression, passive coping, lack of optimism, pessimism, helplessness and lack of disease acceptance all highly correlated with early signs of anxiety. A high correlation of HADS scores with poor coping and acceptance supports the notion that depressive and anxiety symptoms post stroke often result from ineffective cognitive and emotional adjustment to the consequences of stroke, although a reverse relationship (mood disorders leading to inadequate coping and emotional adjustment) cannot be ruled out. These are important clinical considerations as poor coping and acceptance (as well as psychological strain) may be amendable to psychological intervention early post stroke, for instance by means of cognitive behavior therapy. Indeed, a recent review has demonstrated promising effects of psychological interventions for depression after stroke and opted for finding more evidence for the efficacy of psychological treatment approaches to ameliorate mood problems after stroke.

A major strength of this study is the combination of a large sample size and a longitudinal multi-center study design with hospital-based patient recruitment during the first week post stroke. We also accounted for the hospital effect in our analysis, resulting in hospital-specific risk models. As we found almost identical results (as there are OR, AUC and CI-s), we preferred to present the individually based risk models. In addition, an innovative aspect of our study is that we presented nomograms that visually reflect the individual contribution
of each risk factor. As this study has an exploratory nature, these nomograms merely serve to assist in interpreting the explained variance of the odds ratios. Our results should be further validated in a prospective study, preferably using also other accepted tools to assess symptoms of depression and anxiety, with the ultimate goal to develop nomograms that can be used clinically to individually estimate the probability of developing long term symptoms of depression and anxiety post stroke.

Study Limitations
The present study has several limitations. First, our results cannot be generalized to the entire stroke population. As we included a relatively mildly affected patient sample based on median NIHSS and BI scores, our results may not hold for more severely disabled stroke patients typically admitted to rehabilitation centers or nursing homes. Future studies should, therefore, focus on whether psychological risk factors are dominant for developing mood disorders in more severely disabled stroke survivors as well. Second, although we considered a broad variety of potential socio-demographic, pre-morbid and stroke-related factors, we did not assess the influence of smoking, employment status, social support or ethnicity as was the case in some previous studies. In addition, we did not include certain psychological characteristics that might form an additional risk of developing post-stroke mood disorders, such as lack of openness and self-esteem. Future research should, thus, take these potential risk factors into account. A third limitation may be that we collected the HADS scores by postal mail, which may have influenced the accuracy of the measurements.

Conclusion
Psychological characteristics are important risk factors for developing symptoms of depression and anxiety one year after stroke. As some of these psychological risk factors may be amendable to treatment, early recognition is important to prevent long-term mood disturbances after stroke.
References


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Chapter 3

The effectiveness of an augmented cognitive behavioural intervention for post-stroke depression with or without anxiety: the Restore4Stroke-PSDA trial

Abstract

**Background:** Post-Stroke Depression with or without Anxiety (PSDA) is a common disorder in the chronic phase of stroke. Neuropsychiatric problems, such as PSDA, have a negative impact on social reintegration and quality of life. Currently, there is no evidence-based treatment available for reducing PSDA symptoms. In the recent literature on depression in the general population it has been shown that depression complaints can diminish by cognitive behavioural therapy (CBT). In the current study, the effectiveness of augmented, activation-based and individually tailored CBT on the reduction of depression and anxiety will be investigated in patients with PSDA. Additionally, the effects on various secondary outcome measures, such as quality of life, goal attainment and societal participation will be evaluated. This study is embedded in a consortium of 4 interrelated studies on quality of life after stroke (Restore4Stroke).

**Methods/design:** A multi-centre, assessor-blind, randomized controlled trial is conducted. A sample of 106 PSDA patients, as assessed with the Hospital Anxiety and Depression Scale (HADS depression subscale >7), will be recruited and randomly allocated to either an experimental or a control group. The experimental intervention consists of an augmented CBT intervention. The intervention is based on CBT principles of recognizing, registering, and altering negative thoughts and cognitions so that mood, and emotional symptoms are improved. CBT is augmented with direct in-vivo activation offered by occupational or movement therapists. Patients in the control group will receive a computerized cognitive training intervention. Outcomes will be assessed at baseline, immediately post intervention, and at 6 and 12 months follow up.

**Discussion:** This study is the first randomized clinical trial that evaluates the (maintenance of) effects of augmented CBT on post-stroke depression with or without anxiety symptoms. Together with three other projects, the Restore4Stroke PSDA trial will provide novel information about the (treatment of) emotional problems and quality of life after stroke.

**Trial registration:** Trial registration number: Dutch Trial Register NTR2999
Introduction

Background

Stroke causes a high burden of disease to patients as well as to their caregivers. One year after a stroke, 35% of the patients are functionally dependent, indicating that stroke is a leading cause of disability. Half of all patients have problems in returning to their pre-stroke daily routines. Particularly the ensuing psychosocial problems of stroke survivors have a negative impact on their quality of life. Emotional adjustments are associated with changes in coping strategies which are related to quality of life. Additionally, it has been shown that caregivers experience substantial burden from their partners’ emotional problems as well. Cognitive and emotional complaints are found in many patients in the chronic phase after stroke. Within the first three months, post-stroke depressive symptoms can spontaneously resolve. If this does not occur, these symptoms can take a chronic course. In the chronic phase (usually defined as > 6 months post stroke), the most frequent emotional symptoms are depression (23-25%) and anxiety (19-23%). Post-stroke depression and anxiety often co-occur and interact, but may also be present in isolation. Apparently the post-stroke prevalence of anxiety is almost as high as it is for depression; hence, it is surprising that the literature largely focuses on post-stroke depression (PSD). Stressing the impact and co-occurrence of anxiety on patients with stroke, in the present study, we introduce the new concept of ‘Post-Stroke Depression with or without Anxiety’ (PSDA). Currently, we are not aware of any treatment studies on post stroke anxiety. Studies on the treatment of PSD have generally focused on pharmacological interventions, whereas psychological interventions for PSD have hardly been investigated. Several researchers have investigated the possibility of preventing depression after stroke. Different interventions were evaluated, such as meditation, breathing exercises and visualisation (i.e., encouraging a new way of thinking about disability) and visits by specialist outreach nurses providing information, advice and support. In the intervention studies, a small but statistically significant reduction in psychological distress was reported on a variety of health-related questionnaires. All intervention studies were based on contact with multiple disciplines providing information and support, yet no specific psychological therapies were administered. Nevertheless, there are indications that the treatment of depressive symptoms using cognitive behavioural therapy (CBT) is effective in other chronic illnesses such as cancer and diabetes. Hence, psychological interventions seem
promising in terms of effectiveness, while they have fewer side effects than medication. Moreover, as CBT is aimed at changing irrational cognitions and negative thoughts, it is considered to have a stronger effect on preventing relapse of symptoms than pharmacotherapy.\textsuperscript{5,16,20,22,21} In one of the studies that dealt with treatment of PSD, Lincoln and colleagues, applied a treatment protocol in which identifying and challenging negative thoughts as well as planning of joyful activities was discussed with the patients. The authors found, however, inconclusive results with respect to the effectiveness of such a psychological intervention.\textsuperscript{24,25} CBT requires effort during treatment sessions and often comes with a substantial amount of homework. The inconclusive results could be due to the inclusion criteria that did not take into account cognitive deficits and impaired awareness after stroke. These factors are associated with poorer rehabilitation outcomes\textsuperscript{26} and are, therefore, deemed essential when applying CBT. Next to discussing activation with the patients, no further steps, such as stimulating an active life style or giving practical suggestions and encouragements directed at joyful activities, were taken by Lincoln and colleagues.\textsuperscript{25} Including such an extra step in an intervention could possibly catalyse generalisation of the content of the therapy to daily-life functioning.\textsuperscript{15} Furthermore, in a study with brain-injured patients, a combination of CBT and individual cognitive remediation seemed to diminish psychological distress (e.g., depression, anxiety, coping) and improve attention and cognitive functions. Nevertheless, which of the two therapy ingredients was (most) effective could not be determined.\textsuperscript{27} Implementation of CBT should take into account cognitive impairments as well as emotional barriers and awareness. To stimulate treatment generalisation, the use of behavioural exercises that have to be executed in daily life situations is recommended.\textsuperscript{15} Taken together, the scientific literature shows inconsistent results on the effectiveness of treatment programs for PSD. Despite a lack of clear evidence, there is sufficient reason to believe that CBT offered by a trained psychologist can be effective in PSDA when adapted and tailored to the specific needs of patients with stroke, as discussed above.\textsuperscript{15} Combining the results of earlier research on treatment and prevention of post-stroke depression and according to the recommendations expressed in these studies,\textsuperscript{7} an augmented psychological approach to CBT will be tested in the present study using a Randomised Controlled Trial (RCT) design. An equally intensive control intervention (i.e., computerized cognitive training) was selected with the prospect of improving intervention-related goals (e.g., attention, memory, executive functioning) and attaining previously reported high patient satisfaction.\textsuperscript{28}
The present study is a multi-centre randomized controlled trial (RCT). The primary objective is to evaluate the direct and long-term intervention effects on PSDA symptoms as assessed with the Hospital Anxiety and Depression Scale (HADS). It is hypothesized that patients treated with augmented CBT, tailored to their needs, will show a larger decrease in HADS scores than those receiving computerized cognitive training. The secondary objectives are:

- to evaluate the effects on societal participation, quality of life, goal attainment and coping strategies. It is hypothesized that the augmented CBT will lead to better outcomes in all these domains.
- to assess the level of burden of the patients’ caregivers. It is expected that the augmented CBT will be more beneficial with respect to alleviating the perceived burden (emotional as well as practical) of caregivers.
- to evaluate the relationship between treatment participation of the patients in CBT on the one hand and treatment outcomes on the other hand.

The present study is part of a comprehensive rehabilitation research program, Restore4Stroke, in the Netherlands (www.restore4stroke.nl) comprising four interrelated studies. Restore4stroke aims to monitor, predict and improve the quality of life of patients and their caregivers. Besides the present RCT, three other studies are conducted: a longitudinal cohort study, an RCT aimed at evaluating the effect of a self-management group therapy, and an economical evaluation study. The design of the other studies will be published separately.

**Methods**

**Study population**

We intend to include 106 participants who experience depressed mood with or without symptoms of anxiety after stroke. When physicians, therapists or psychologists in the Netherlands notice such complaints during the rehabilitation process or thereafter, patients can be referred to various rehabilitation centres offering the experimental and control interventions distributed throughout the country. Participants may also be referred by other healthcare professionals or come on their own initiative based on ‘hear say’. They will be eligible if they have sustained any type of stroke in the past, if complaints developed after the stroke and if their depression sub-score on the Hospital Anxiety and Depression Scale (HADS) is above seven. Other inclusion criteria are: (1) being more than three months post stroke; (2) being 18 years or older; (3) having sufficient communication skills (MMSE > 27, communication-related NIHSS items); and (4)
mastering the Dutch language. Exclusion criteria are: (1) pre-morbid disability as assessed with the Barthel Index (score < 19/20); (2) stay in an inpatient setting; (3) co-morbidity that might affect outcome (e.g., cancer or major psychiatric illnesses for which psychological treatment is given at the moment of inclusion); (4) a major depression diagnosis requiring medication; and (5) a pre-morbid major depression diagnosis, or having received psychiatric care for depression.

Procedure
Participants will be screened, enrolled and subsequently treated in several rehabilitation centres or rehabilitation departments of hospitals in the Netherlands. They will be recruited over a period of one year. Each centre is expected to enrol at least 10 patients. The physicians of the affiliated centres are provided with information about the inclusion and exclusion criteria to perform a first test of eligibility (HADS assessment). When individuals are considered to be candidates for the study, they will be informed about the Restore4Stroke PSDA trial by written correspondence and will be asked for permission to be contacted by the primary investigator (JK). In the case of a positive reply, the primary investigator will make an individual appointment to confirm the inclusion and exclusion criteria, to obtain oral and written informed consent, and to perform the baseline assessment (T0).

Participants will be randomly allocated to an experimental group receiving augmented CBT or to a control group receiving computerized cognitive training. All outcome measures will be collected at baseline (T0), after 4 months (post treatment) (T1), and at 6 (T3) and 12 months (T4) follow up (see Figure 1). All assessments will take place in the (patients’ nearest) participating centres. From T1 assessments will be performed by research assistants who are not involved in the delivery of the interventions and who will be blind to the type of intervention in individual participants. Prior to each assessment, the assessor will explicitly ask the participant not to reveal or discuss the content of his/her intervention. Successfulness of assessor blinding will be tested by the primary investigator at the end of each individual intervention period using a short self-constructed questionnaire. During the intervention it is required that any antidepressant medication intake remains stable. Yet, when changes in medication occur these will be registered. This procedure was approved by the Committee on research involving Human Subjects, Nijmegen, The Netherlands, and all local participating centres.
Pre selection of subjects in rehabilitation centres or rehabilitation departments of hospitals

Check for inclusion

Baseline measurement (T0)

Randomisation

Augmented CBT intervention (13-16 sessions, 4 months)

Control intervention (13-16 sessions, 4 months)

Post treatment measurement (T1) (4 months after T0)

Follow up measurement 1 (T2) (10 months after T0)

Follow up measurement 1 (T3) (16 months after T0)

Exclusion of subjects

Figure 1. Flow chart of trial design
Randomization

Stratified block randomization (block size n = 4) will take place by a computer in each participating rehabilitation centre separately. Participants will be stratified according to their anxiety level (cut-off: HADS subscale anxiety score ≤7 vs. > 7). In this way, all blocks will assume a number of participants with and without anxiety complaints and each participating centre will provide both interventions in approximately an equal number of participants.

Interventions

*Augmented cognitive behavioural therapy*

Subjects in the experimental group will be treated with an augmented CBT protocol using ‘CRASS’ communication techniques. The ‘CRASS’ techniques entail Concrete, Repetitive, Accessible, Structured and Specific communicative principles. Therapists will use motivational interviewing and interpersonal therapy techniques. Patients will be taught to recognize, register, and alter negative thoughts, cognitions and concurrent feelings. To encourage daily life integration of the CBT, content sheets will be provided and related homework will be given each session (i.e., one or two assignments per session). The intervention is individually administered and tailored according to specific subjects’ own activity-related goals. The treatment program consists of 10–12 sessions with an experienced health-care psychologist and is augmented with three (or four; depending on HADS anxiety scores) sessions of occupational therapy (OT) or movement therapy (MT). These latter sessions will be provided concurrently with the psychological sessions and serve as a facilitator for reaching the pre-set goals in daily life. Therapy goals will be set in terms of increased participation in meaningful or joyful activities using Activity Card Sorting (ACS). This tool is incorporated to overcome problems with goal-setting because of the passive state PSDA patients can be in. With the ACS, patients can objectify their goals with the help of pictures/photos that represent elderly participating in various activities. In this way, patients are given concrete and accessible incentives to define their own personal goals more easily. The OT/MT will help to initiate and guide patients to execute goal-related activities. If patients’ HADS anxiety sub-score is >7, the protocol will be expanded with an additional (fourth) OT/MT session. Therapists will be informed about the HADS anxiety sub-scores of the patient. The additional session entails relaxation techniques as provided by the Dutch Heart Foundation. The OT/MT can refer to the relaxation techniques
if patients report experienced anxiety during execution of their activities. Next to that, psychologists will address anxiety-related thoughts, cognitions and concurrent feelings when executing CBT.

The protocol framework is set out in five successive phases (see Table 1). The therapist will start with building rapport creating a safe atmosphere. Psycho-education about current mood states will guide and prepare patients for the next phase: Goal setting. Subsequently, CBT will be executed using explanatory schemes about negative and positive cognitions. Themes of the CBT range within patients' own goals and concurrent mood states. From this stage the OT/MT will actively work with patients on their treatment goals as well. CBT succeeds with continuation of learned techniques and concludes with building a relapse plan for future challenging situations.

**Table 1. Content of successive phases of the augmented Cognitive Behavioural Therapy**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Introduction</td>
<td>Building rapport; discussing grief; psycho-education about the relationship between mood and behaviour.</td>
</tr>
<tr>
<td>2. Goal setting</td>
<td>Active goal setting with OT/MT.</td>
</tr>
<tr>
<td>3. CBT principles</td>
<td>Recognising and registration of 'hidden cognitions'.</td>
</tr>
<tr>
<td>4. CBT</td>
<td>Challenging and altering 'negative cognitions'.</td>
</tr>
<tr>
<td>5. Relapse prevention</td>
<td>Building a relapse-prevention plan with taught techniques.</td>
</tr>
</tbody>
</table>

All treatment sessions are supervised by certified health-care psychologists who have sufficient experience with treatment of depression as well as with stroke rehabilitation. The psychologist will supervise the OT/MT and will determine the sequence of the treatment sessions according to the individual needs and capacities of the subjects. The program is executed within a four-month time span, with a minimum of 13 and a maximum of 16 sessions. Each session will take two 20–25 minute-blocks divided by a 10–15 minute break. Treatment will be given at the most nearby participating centre.

**CogniPlus; computerized cognitive training**

Subjects in the control group will be given a computerized cognitive training program (CogniPlus). The amount of training sessions will be equal to that of the experimental group (i.e., 13–16 sessions). The control intervention is individual and patient-tailored as well. Participating centres will be provided with software and a dongle with sufficient training hours. With headphones and coloured patches
attached to two keys on the keyboard, a desktop can be set up for CogniPlus execution. Patients register on the system and for each session, content and results of the training will be saved. The program is an impairment-oriented intervention which suits the stroke population. In specific self-determined cognitive domains (i.e., attention, memory, executive functioning, and visual attention) patients will be executing computer tasks on performance-own related levels. A research or psychological assistant will be present during the training sessions for support or to answer any questions about the intervention. This person will, however, not engage in conversations with the patients about topics other than the cognitive training. To assess deterioration of mood, Visual Analogue Scales (VAS) will be filled out by the participant after each session. The assistant will monitor VAS scores and, when substantial deterioration occurs, will notify the researcher and the psychologist of the department.

Outcome assessment

Patients

Primary and secondary outcome measures are listed in Table 2. The HADS is a depression and anxiety questionnaire developed for use in patients with somatic co-morbidity such as stroke. We will assess domain-specific as well as health-related quality of life. The primary outcome measure is the depression subscale of the HADS. Health-related quality of life will be assessed in general (EQ6D), and stroke specific (SSQoL). Domain-specific quality of life is represented by participation assessment (USER-P), Emotional functioning (HADS), and subjective well-being (life satisfaction questionnaires).

Next to these quality of life related assessments, a semi-structured questionnaire specifically regarding post-stroke depression will be used. The Post Stroke Depression Rating Scale (PSDRS) will accompany HADS results emphasizing the phenomenological aspects of post-stroke depression. This scale comprises a characterization of all depressive post stroke symptoms (e.g., psychological, physical and vegetative aspects). CBT is aimed at different aspects of coping such as regulating emotional reactions and reassuring thoughts (emotion-focused coping), changing stressful situation and learning new skills (problem-focused coping). Consequently, we will assess coping using the Utrecht Proactive Coping Competence scale (UPCC). Goal setting will be performed with the therapist, and Goal Attainment Scaling (GAS) will be carried out by the primary investigator.
Treatment participation will be scored by the therapist per session. The Pittsburgh Rehabilitation Participation Scale (PRPS) is a short quantitative measure that is easy to administer. The PRPS will be completed in each session and can provide: 1) direct feedback on individual treatment participation for the therapist, 2) direct feedback on treatment participation per session in general. If we come across trends in reported participation, the protocol could be adjusted.

**Table 2. Outcome measures**

<table>
<thead>
<tr>
<th>Primary outcome measure</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression and Anxiety</td>
<td>Hospital Anxiety and Depression Scale (HADS)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary outcome measures</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Life</td>
<td>Stroke Specific quality of Life (SSQoL-12)</td>
</tr>
<tr>
<td>General</td>
<td>EuroQuality of Life (EQ6D)</td>
</tr>
<tr>
<td>Domain specific</td>
<td>User-P</td>
</tr>
<tr>
<td>Post-stroke depression</td>
<td>Life Satisfaction questions</td>
</tr>
<tr>
<td>Goal attainment</td>
<td>Goal Attainment Scale (GAS)</td>
</tr>
<tr>
<td>Participation in therapy</td>
<td>Pittsburgh Rehabilitation Participation Scale (PRPS)</td>
</tr>
<tr>
<td>Coping strategy</td>
<td>Utrecht Proactive Coping Competence scale (UPCC)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Caregiver outcome measures</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domain specific quality of life</td>
<td>Hospital Anxiety and Depression Scale (HADS)</td>
</tr>
<tr>
<td>Subjective strain</td>
<td>Caregiver Strain Index (CSI)</td>
</tr>
<tr>
<td>Emotional burden</td>
<td>Involvement Evaluation Questionnaire (IEQ)</td>
</tr>
</tbody>
</table>

**Caregivers**

In addition to patient-related outcomes we will also assess caregivers’ emotional and practical burden with the HADS, the Involvement Evaluation Questionnaire (IEQ) and the Caregiver Strain Index (CSI).

**Statistical analysis**

Statistical analysis will be performed using PASW 18. Baseline characteristics will be presented using descriptive statistics. Differences between groups at baseline will be tested using chi-square and t-tests, depending on the type of variable. General linear model (GLM) analysis will be used to investigate the main effects of Time and Group (experimental vs. control) and the Time x Group interaction. Because it is hypothesized that augmented CBT causes a greater effect on the
HADS than cognitive training and that this effect will last at least 6 months after cessation of the therapy, the primary endpoint will be at 6 months post treatment (T2). Data analysis will be performed by an independent statistician who will be blinded for group intervention. Data will be analysed according the intention-to-treat principle. Alpha will be set at 0.05.

**Power**

With a minimally detectable effect size of 0.6 SD on the HADS, $\alpha = .05$ and $\beta = .80$, minimally 45 participants in each group are required. With an expected drop-out rate of 15%, 106 participants will need to be recruited.

**Discussion**

Currently, no multi-centre RCT has been conducted that has evaluated the effectiveness of an (augmented) CBT intervention on post-stroke depression with or without anxiety. Reduction of PSDA could positively influence psychosocial functioning, rehabilitation outcome and concurrently improve different domains of quality of life. An innovative aspect of the current study is that the CBT intervention takes into account recommendations by Broomfield and colleagues for the design of a post-stroke CBT intervention. Specifically, the proposed CBT is augmented with occupational therapy or movement therapy to facilitate change of behaviour in real life by promoting and encouraging meaningful or pleasurable activities. This augmentation may, however, be a challenging factor in some individuals with lack of initiative. These individuals may find it difficult to cope with the amount of homework. Striving to overcome this problem, only therapists with sufficient experience with the stroke population will deliver the intervention, and treatment participation will be monitored. Next to that, the protocol continually emphasizes CRASS communication principles, and the ACS is offered as a tool to provide input for conversation about joyful activities. Another innovation in the present study is that depressive symptoms are used for inclusion of subjects, but that symptoms of anxiety are not considered a reason for exclusion. In contrast, anxiety complaints will be incorporated as a target for the proposed cognitive behavioural therapy.

An important methodological aspect of the present study is that subjects from different parts of the Netherlands are included, which will enable us to control for possible cultural differences between subgroups. Another methodological strength is that the augmented CBT is compared to an ‘active’ intervention (and
not to ‘usual care’) to control for Hawthorne effects. Lastly, a parallel economic evaluation study within the Restore4Stroke program will shed light on the cost-effectiveness of the proposed intervention.\textsuperscript{30}

Taken together, the Restore4Stroke PSDA trial is an essential part of the Restore4Stroke program that focuses on the effectiveness of an augmented and individually tailored CBT protocol for treating post-stroke depression with or without anxiety. The Restore4Stroke program will: provide longitudinal information about the course of quality of life of patients and caregivers and the influence of personal factors on quality of life, evaluate two interventions designed for stroke patients, and last but not least will evaluate the economical effectiveness of both trials.
References


Chapter 4

An augmented cognitive behavioural therapy for treating post-stroke depression: description of a treatment protocol

Abstract

*Aim:* Currently, no evidence-based treatment is available for mood problems after stroke. We present a new psychological intervention designed to reduce depressive complaints after stroke.

*Method of protocol development:* This intervention was based on cognitive behavioural-therapy principles and was shown feasible in a pilot study. In order to meet the specific needs of stroke patients (concerning both sensori-motor, cognitive and behavioural problems), we incorporated motivational interviewing, grief resolution, and psycho-education. We emphasised for each session to take into account the cognitive deficits of the patients (i.e. be concrete, accessible, structured, specific and repeat information). Moreover, we augmented the psychologist-administered therapy with the contribution of an occupational or movement therapist aimed at facilitating patients’ goal setting and attainment. The intervention consisted of twelve 1-hour sessions with a psychologist and three or four 1-hour sessions with an occupational or movement therapist. Currently, the effectiveness of the intervention is evaluated in a randomised controlled trial.

*Discussion:* The proposed psychological treatment protocol is innovative, as it applies cognitive behavioural therapy in a stroke-specific manner; moreover, it supports goal attainment by incorporating occupational or movement therapy sessions.
Introduction

Following a stroke, approximately 70% of survivors experience considerable long-term sensorimotor, cognitive, and/or behavioural impairments. These impairments often limit normal daily life activities and may restrict social participation, which may lead to feelings of depression. Although the reported prevalence of mood complaints varies, approximately more than 30% of all stroke survivors experience severe emotional complaints that negatively impact their quality of life.

Developing treatment programmes for depressive symptoms in patients after stroke requires a basic understanding of the underlying aetiology. This aetiology has been the subject of considerable debate. Researchers that investigated neuroanatomical and neurochemical substrates of post-stroke depression have not been able to establish that post stroke depression can be attributed to a particular type of stroke or level of stroke severity. Moreover, it has been suggested that the relationship between functional impairments and post-stroke depression is mediated by the significance that the patient attributes to his/her impairments. From this perspective, post-stroke depression may be viewed as the result of an inadequate adjustment to the consequences of stroke. Therefore, it is important to address the reactive aspects of post-stroke depression when developing a psychological intervention for depressive complaints after stroke. Additionally, since post-stroke depression often coincides with increased anxiety, feelings of anxiety should also be taken into account in such an intervention.

Mood disturbances after stroke are commonly treated with pharmacological agents. However, the benefits of pharmacotherapy in the treatment of post-stroke depression are debatable. Psychological interventions are used less frequently, possibly because their effects are also unclear. Yet, such interventions have yielded beneficial effects on mood disturbances in patients with other chronic disorders such as cancer and diabetes. Within the broad field of psychotherapy, cognitive behavioural therapy seems one of the most promising methods to address post-stroke depression. In this respect, it is important to note that cognitive behavioural therapy was recently found to be beneficial for treating post-stroke fatigue. The core assumption in cognitive behavioural therapy is that thoughts - rather than external factors such as people, situations, or events - drive feelings and behaviours. If one can change the way patients think, this can improve their feelings and actions, even if the situation does not change. A key advantage of cognitive behavioural therapy over pharmacotherapy is that it
is more effective at preventing the relapse of emotional symptoms, as it causes structural changes in irrational cognitions and negative thoughts. Another advantage is that cognitive behavioural therapy has a more favourable side-effect profile than pharmacotherapy.16

The goal of the current paper is to present a new psychological treatment protocol for post-stroke depression based on cognitive behavioural therapy, which is currently evaluated in a multicentre randomised controlled trial as part of the Restore4Stroke study in the Netherlands (Dutch Trial Register NTR2999).24 We will first describe the theoretical background of the treatment protocol, followed by the content of the intervention and a comprehensive discussion. Two case descriptions are presented in boxes to illustrate how the protocol can be applied in clinical practice.

Theoretical background

The psychological treatment of post-stroke depression is still in its infancy. The application of conventional cognitive behavioural therapy for post-stroke depression has not yielded unambiguous results yet. To date, only one randomised controlled trial examined the effect of cognitive behavioural therapy on post-stroke depression. In this trial, Lincoln and Flannaghan25 found no group differences of cognitive behaviour therapy versus interviews. The authors acknowledged that their study had several methodological shortcomings, such as early inclusion after stroke (< 1 month), low therapy intensity, and the use of relatively inexperienced therapist who participated in both interventions, thereby running the risk of ‘contamination’. Most importantly, the cognitive behavioural therapy did not take into account individual cognitive and/or sensorimotor deficits, nor were the participants provided with practical advice about how to achieve behavioural change.

Many stroke patients have sensory, motor, and/or cognitive impairments that limit their behavioural potential. Therefore, challenging and modifying irrational and negative thoughts using traditional cognitive behavioural therapy does not necessarily lead to effective behavioural changes. Cognitive impairments may lead to problems with information processing and, for instance, the correct understanding of the content of interventions. Stroke patients also may lack processing speed and can experience memory problems, which complicates the course of therapy. In addition, after having experienced a traumatic event (i.e., stroke), patients regularly misinterpret their bodily sensations, inducing fear
and anxiety, which may hamper the process of behaviour change. Also, grief that accompanies a traumatic event makes the patient less receptive to cognitive behavioural therapy.

In an attempt to take into account these impairments, and to enhance the applicability of cognitive behavioural therapy in the treatment of post-stroke depression, Broomfield et al. (2010) recommended the integration of the following five psychological approaches that will be illustrated in the procedure section:

- Motivational interviewing\(^{26,27}\)
- Grief resolution\(^{28}\)
- Cognitive deficits adaptation\(^{29}\)
- Selective optimisation with compensation\(^{23,30,31}\)
- Executive skills training\(^{23}\)

**Box 1. Motivational interviewing and grief resolution**

Patient MC used to be a consultant in organisation management. After his stroke, he experienced considerable difficulty resuming his professional work, causing loss of self-esteem and sense of identity. When discussing therapy goals, at first, MC aimed to regain his old job. By posing an open-ended question about the way he thought he would attain this goal, MC gradually realised that regaining his former job was out of reach. Moreover, by making a pro-con list, he realised that sticking to the current situation would cost too much energy and lead to many mistakes. Before encouraging him to think about other types of occupation, the psychologist stimulated MC to reflect on and discuss the grief and emotional impact of his vocational loss.

**Method of protocol development**

We previously conducted a pilot study to assess the feasibility of cognitive behavioural therapy in five patients. An existing cognitive behavioural therapy intervention developed for patients with chronic disease\(^{32}\) was modified to fit the cognitive impairments of stroke patients.\(^{33}\) We reduced the amount of information and repeated information several times throughout the intervention. The intervention reduced mood complaints in three out of five patients. Next to that, we showed that the intervention was feasible. After evaluation of this pilot study, we further developed the protocol by incorporating the recent suggestions of Broomfield and colleagues as follows:\(^{23}\)

1. Throughout the treatment, the psychologist used motivational interviewing to enhance the patient’s motivation for behavioural change.\(^{26,27}\) By asking open-ended questions, discussing pros and cons of behaviour change, and
by addressing goal planning to bring about behavioural change, the patient was encouraged to be creative and think autonomously for setting therapy goals and find ways to improve his/her self-efficacy (see box I).

2. Early in the treatment protocol, the psychologist promoted grief resolution by explaining the phases of bereavement and by discussing the effects of reduced physical independence, mobility, cognitive capacity, and emotional control on self-esteem and future perspective (see box 1).

3. Throughout the treatment, cognitive impairments were taken into account when explaining and implementing the principles of cognitive behavioural therapy. In line with “cognitive deficits adaptation”, the psychologist used cognition schemes to explain the relationship between thoughts, feelings, and actions in a step-by-step fashion (see Figure 1). In addition, the intensity of therapy sessions was adjusted to the patient’s cognitive capacities while psychologists were instructed to adjust their communication style to the patient’s functional level through the consistent use concrete, repetitive, accessible, structured, and specific (CRASS) communication principles. For example, therapists communicated the essentials of therapy by talking slowly, illustrating them with tangible examples while avoiding professional jargon. During each session, the psychologist repeatedly mentioned the most important components, thereby ensuring that the patient fully understood all key elements. ‘Take home’ information sheets also described the most important therapy components.

4. The most crucial adjustment of our treatment protocol was based on “selective optimisation with compensation”. Based on this approach, the psychologist-administered cognitive behavioural therapy was augmented with three sessions of occupational or movement therapy to facilitate goal setting and attainment. An occupational or movement therapist supported patients with functional limitations (or doubts about their capacities) by first identifying meaningful personal goals and then helping them to achieve these goals.

5. When a patient reported feelings of anxiety in addition to depressive complaints, cognitive behavioural therapy also addressed anxiety-related thoughts and problems. Moreover, a fourth occupational or movement therapy session was planned to teach the patient relaxation techniques (e.g., breathing exercises), as advised by the Dutch Heart Foundation. The aim of this extra session was to alleviate anxiety-driven bodily tension that might impede the patient’s ability to reach his/her activity-related goals.
An augmented CBT for treating post-stroke depression: Treatment protocol

Event
Other take over
things I used to do

Feeling
Miserable, sad

Behaviour
Lack of initiative, passiveness

Event
Other take over
things I used to do

Thought
They think I am
useless

Feeling
Miserable, sad

Behaviour
Lack of initiative, passiveness

Figure 1. Hidden cognition scheme as it is introduced in the expanded 4-step scheme (bottom row). The top row shows the simplified 3-step scheme.

Procedure
Table 1 gives an overview of the content of the treatment protocol.

Target group
This treatment protocol was designed for the Restore4Stroke randomised controlled trial aimed at patients with chronic mood complaints after stroke; until now, the protocol has been applied in this trial only. Stroke patients with a pre-treatment score of >7 on the depression subscale of the Hospital Anxiety and Depression Scale were eligible for participation (see Table 1). Although the Hospital Anxiety and Depression Scale anxiety sub-score was not regarded for inclusion, it was used to individualise the treatment, for instance to indicate the need of additional relaxation exercises. The following exclusion criteria were applied: insufficient communication skills, a diagnosis of a ‘major depression’ that required pharmacotherapy (based on the medical file), and a history of pre-stroke mood disorder or any co-morbidity that could affect mood.
Table 1. Characteristics of the protocol: Augmented Cognitive Behavioural Therapy

| Inclusion criteria | - Patients with post-stroke depression with or without anxiety as defined by a depression sub-score on the HADS >7.  
|                    | - Any type of stroke in the past.  
|                    | - Depressed mood occurring >6 months post stroke.  
|                    | - Sufficient communication skills.  
| Exclusion criteria | - Patients with pre-stroke physical disability (Barthel Index: <19/20).  
|                    | - Inpatients.  
|                    | - Co-morbidity that could affect mood.  
|                    | - Diagnosis of ‘major depression’ requiring medication.  
|                    | - Diagnosis of pre-stroke depression or previous psychiatric care for depression.  
| Therapists’ competence | Psychologist: healthcare psychologist with CBT experience and familiarity with stroke rehabilitation.  
|                      | Occupational or movement therapist: familiarity with stroke rehabilitation.  
|                      | Both therapists: received training by developer of protocol for correct application.  
| Location | Psychologist sessions: in the psychologist’s office.  
|          | Occupational or movement therapist sessions: in the rehabilitation facility, at various locations within the community, or at the patient’s home.  
| Number of sessions | 15-16 individual sessions over a period of 4 months;  
|                  | 11 sessions with the psychologist and one session with both the psychologist and the occupational or movement therapist;  
|                   | 3-4 additional sessions with the occupational or movement therapist alone.  
| Duration of session | One hour per week, with each session comprised of two blocks of 20-25 minutes separated by a 10-15 minute break.  
| Materials | Protocol booklet for therapist; ACS cards for photo interview; homework assignment booklet for patient.  
| Tailoring | The psychologist has certain degrees of freedom concerning content of the final sessions, either attention to problems with acquired skills or evaluation of the intervention, depending on the patient’s progress.  

Role of therapists

The treatment protocol was administered by a certified, experienced healthcare psychologist who was familiar with treating depression and providing rehabilitation to patients with stroke. Prior to working with the protocol, each psychologist received two hours of training by an expert psychologist with ample experience in cognitive behavioural therapy. If needed, the expert psychologist was available for assistance throughout the intervention. To prepare the goal-setting stage, the psychologist selected either an occupational or movement therapist, depending on the patient’s tentative goals; an occupational therapist was preferred when the goals included optimising activities in the domains of self-care, leisure, household,
and/or work; a movement therapist was chosen when the goals included improving mobility-related activities such as sports and walking. Because of their education and experience, occupational and movement therapists are optimally equipped to assess patients’ individual functional limitations and identify potential compensatory strategies. They worked in parallel with the psychologist to successfully translate the patients’ goals into daily life and help them achieve behavioural change. By maintaining close contact with the individual patient and the treating psychologist, it was ensured that all parties adhered to the same treatment principles, while the psychologist kept the lead in the intervention.

In the case of increased anxiety (i.e., Hospital Anxiety and Depression Scale anxiety sub-score >7), the patient received a fourth session with the therapist that was entirely devoted to teaching relaxation techniques.

Treatment stages

The treatment protocol consisted of 15-16 individual treatment sessions. Twelve sessions were administered by the psychologist, and three (or four) additional sessions by the occupational or movement therapist. The treatment protocol consisted of five successive stages (see Table 2).

1. In stage 1 (three sessions), the psychologist began building rapport with the patient and creating a safe atmosphere by striving to experience the world from the patient’s perspective without judgement or criticism. This was followed by grief resolution, which entailed reassurance of the patient with regard to emotional reactions to the consequences of his/her stroke by explaining that such reactions are normal after a painful and threatening life event (see box I). After that, psycho-education encompassed the provision of information about the consequences of stroke and useful compensatory strategies. In addition, the psychologist emphasised the relationship between becoming more active in daily life and the positive impact on emotions and behaviour.

2. Stage 2 (two sessions) was the goal-setting stage. The first of the two sessions was administered by the psychologist; the second was multidisciplinary and delivered together with the occupational or movement therapist. In line with CRASS principles, the protocol was made ‘accessible’ to the patient using the Activity Card Sorting. This tool facilitated the discussion about the patient’s personal activities and attainable goals. The Activity Card Sorting consists of 78 pictures representing people engaged in a wide array of activities, including leisure, sports, and daily life activities.
<table>
<thead>
<tr>
<th>Topic</th>
<th>Session</th>
<th>Therapeutic content</th>
<th>How: therapeutic techniques</th>
<th>Homework</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 1. Purpose: Helping patients recognise their problems and provide information about post-stroke depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquaintance and psycho-education</td>
<td>1</td>
<td>Building rapport</td>
<td>Introduction, getting to know the patient and creating a safe atmosphere for problem disclosure</td>
<td>Reading (R): information leaflet Assignment (A): problem description</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Recognising bereavement and loss</td>
<td>Grief discussion, checking homework compliance</td>
<td>R &amp; A: see session 1</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Psycho-education</td>
<td>Motivational interviewing techniques to help patients explore what they want to achieve</td>
<td>R: relationship behaviour and mood A: diary of activities and concurrent mood; writing down which ACS pictures are, or have once been relevant.</td>
</tr>
<tr>
<td><strong>Stage 2. Purpose: Goal-setting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goal-setting</td>
<td>4</td>
<td>Goal-setting using Activity Card Sort</td>
<td>Photo-interview, regarding the ‘past, now &amp; future’</td>
<td>R: goal-setting; A: evaluating tentative goals</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Goal selection: Interdisciplinary session with Occupational or movement therapist and psychologist</td>
<td>Working towards 3 attainable goals taking into account individual physical and cognitive capacities</td>
<td>A: evaluating and reading concrete plan for therapy goals</td>
</tr>
<tr>
<td><strong>Stage 3. Purpose: Exploring irrational cognitions and false beliefs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive therapy</td>
<td>6</td>
<td>Introduction CBT: recognising ‘hidden cognition’</td>
<td>Check if patients understand 3-way sequence; fill out one or two schemes with the patient to take home</td>
<td>R: relationship thoughts and mood A: from 3-way to 4-way cognition schemas</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Reflect on ‘hidden cognition’: rational or irrational?</td>
<td>Discuss 3 way sequences from homework assignments and introduce the hidden cognition/thought</td>
<td>R: influence of thought on mood A: 4-way sequences: rational or irrational?</td>
</tr>
</tbody>
</table>
Table 2. Structure of the protocol (psychologists’ sessions) (continued)

### Stage 4. Purpose: Challenging and altering cognitions and false beliefs

<table>
<thead>
<tr>
<th>Stage</th>
<th>Purpose</th>
<th>Session</th>
<th>Description</th>
<th>R:</th>
<th>A:</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Challenging irrational thoughts</td>
<td>Use motivational interviewing to support patients in challenging negative thoughts</td>
<td>reconsidering thought patterns</td>
<td>changing irrational thoughts into helping thoughts</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Changing cognitions</td>
<td>Support patients in replacing negative thoughts</td>
<td>R&amp;A: see session 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Changing cognitions consolidation</td>
<td>Therapists either assist in challenging thoughts or use this session for evaluation</td>
<td>rephrasing irrational beliefs</td>
<td>evaluation of session 8 and 9</td>
<td></td>
</tr>
</tbody>
</table>

### Stage 5. Purpose: Relapse prevention

<table>
<thead>
<tr>
<th>Stage</th>
<th>Purpose</th>
<th>Session</th>
<th>Description</th>
<th>R:</th>
<th>A:</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Signals of relapse and future strategies</td>
<td>Let patients evaluate their attained skills and goals. Support is given on topics patients want to improve</td>
<td>keeping up the good work</td>
<td>signals for negative mood and future goals</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Evaluation and termination</td>
<td>Prepare patients for future situations. Create a take-home relapse plan. Create 4-way sequences for anticipated future situations.</td>
<td>evaluation of goal</td>
<td>set future goals, evaluate own progress</td>
<td></td>
</tr>
</tbody>
</table>
Thus, the stroke patient was given concrete examples to help him/her select personal goals. In preparation for the goal-setting sessions, patients listed the Activity Card Sorting cards most relevant to them as homework assignment to become familiar with the themes of the cards.

- In the first goal-setting session pre-stroke activity levels were discussed, using the Activity Card Sorting cards that the patient had selected. The psychologist and patient then discussed the patient’s current activity levels. Finally, activities that could help achieve the patient’s desired future situation were addressed, resulting in five tentative therapy goals. The content of these goals determined whether the psychologist contacted either the occupational or movement therapist. The psychologist introduced the patient to the therapist and together they prepared the multidisciplinary session.

- During the second session, each goal was discussed with respect to its feasibility. The psychologist and therapist together with the patient designed a concrete and realistic plan. This plan encompassed three specific agreed-upon therapy goals, taking into account the patient’s cognitive and physical limitations. This plan detailed the contents and timing of the three additional sessions in the following two stages with the occupational or movement therapist.

3. In stage 3 (two sessions), the psychologist used cognitive behavioural therapy to help the patient recognise the thoughts that triggered negative mood and behaviour (see box II). In these sessions, the psychologist used schemes to explain negative and positive cognitions and to prepare the homework assignments (see Figure 1):

- First, the psychologist explained a ‘3-step sequence’ of occurrences: events leading to feelings leading to behaviour (event -> feeling -> behaviour). The patient was taught that events engender feelings, which in turn influence behaviour. The patient was then encouraged to think of specific events in his/her daily life that led to negative feelings and subsequent behaviour. When he/she understood this sequence of occurrences, a fourth step (‘hidden cognition’) was added to the explanatory scheme (event -> thought -> feeling -> behaviour).34

- Hidden cognitions are thoughts that are not directly accessible, but can be made explicit by paying specific attention to the sequence of occurrences. During the homework assignments, the patient was advised to to fill in the new ‘4-step sequence’: event -> thought ->
feeling -> behaviour (Figure 1). Once the patient was familiar with this technique, the psychologist explained that hidden cognitions may either have a negative or a positive influence on feelings and behaviour (see box II).34

**Box II. Recognising and adjusting irrational thoughts**

Patient RS suffered from a stroke 1 year earlier. He avoided visiting his football club since he had been involved in an ‘embarrassing situation’ in which he had called a friend by the wrong name. As the psychologist discussed this situation (wrong name for a friend) – his accompanying feelings (shame) – and ensuing behaviour (avoid going to social events), ‘hidden thoughts’ were explored by posing questions such as: ‘what did you think at this particular moment; do people generally get labelled after misnaming a person’. The patient described a hidden thought as ‘off course the other person thinks I am an idiot’. Then, the irrational aspects of this particular thought were further explored by questions such as: ‘Does this thought actually reflect reality; can you imagine a more realistic thought to deal with this situation’. Accordingly, RS asked his friend what he thought of him. These experience made him believe that people did not actually consider him stupid. Moreover, RS now explains people in advance that he sometimes tends to forget names or relevant information. Next to that, he often points out that it would be of help when people would signal his mistakes.

4. In stage 4 (three sessions), the patient was taught to challenge specific irrational, negative thoughts and to change these thoughts into rational ‘helping’ thoughts. The patient and psychologist together analysed concrete examples of 4-step sequences, thereby teaching the patient to use these examples in homework assignments. Primarily, the patient’s three therapy goals were used as a basis to apply the 4-step sequences. During the homework assignments, the patient practised reappraising events based on helping and rational thoughts (see Box II). In this stage, the psychologist repeatedly tested whether the patient fully understood the 4-step sequences and was constantly in close contact with the occupational or movement therapist to follow-up on goal attainment in terms of achieving actual behavioural change.

5. In stage 5 (two sessions), the treatment protocol was devoted to identifying relapse symptoms and evaluation. During the penultimate session, the psychologist discussed a possible future relapse of ‘old’ feelings and behaviours, which entailed listing the feelings that were once problematic. Subsequently, the patient was encouraged to manage recurrences of these feelings by applying the same cognitive behavioural techniques that were
previously taught. Accordingly, he/she prepared a 4-step scheme that could be used in future situations. The patient was stimulated to continue using a homework booklet after the therapy had ended. The last session was used for evaluation by asking the patient’s opinion about the treatment process.

Discussion

Given the urgent need for an effective therapy, we developed an augmented cognitive behavioural therapy protocol for treating depressive symptoms after stroke. Because depression in the chronic post-stroke phase is assumed to be mainly reactive in nature, cognitive behavioural therapy may be the most promising treatment. The augmentation - which was a multidisciplinary approach using co-therapy by both a psychologist and an occupational or movement therapist - was expected to facilitate realistic goal setting and effective goal attainment by taking into account the individual patient’s preferences as well as his/her physical and cognitive capacities. The aim of the intervention was to give patients with depressive symptoms (and possible concurrent feelings of anxiety) the cognitive tools to realise behavioural change, thereby improve their self-efficacy. At the same time, patients were taught to manage the functional consequences of their stroke more effectively. To reach this goal, we incorporated several suggestions from previous studies and we adapted the cognitive behavioural therapy protocol by incorporating motivational interviewing, adding sessions devoted to grief resolution, and addressing cognitive impairments using psycho-education and CRASS communication principles. Wherever possible, the functional consequences of stroke were optimised or compensated. The treatment protocol presented here has several strengths and limitations. The major strength is that the proposed intervention is innovative, as it applies cognitive behavioural therapy in a stroke-adjusted manner, a feature not found in former applications of cognitive behavioural therapy for post-stroke depression. The intervention is also innovative because it supports goal attainment by incorporating occupational or movement therapy sessions. Another strength is that we included the treatment of concurrent anxiety complaints. Anxiety and depressive symptoms often co-occur following stroke. Moreover, feelings of anxiety can hinder the patients’ actual performance of activities. Therefore, we addressed feelings of anxiety in our treatment protocol when applicable. Although we incorporated only a brief intervention for anxiety, we recognise that our treatment protocol may not be suitable for patients with severe anxiety disorders
that require other therapeutic approaches such as systematic desensitisation and graded exposure.34

As for limitations, we acknowledge that a multifaceted treatment protocol is hard to test for its specific efficacy, because the various elements incorporated may differently contribute to mood improvement in different individuals. Indeed, research in the field of psychological interventions for post-stroke depression is in a ‘proof-of-principle’ stage, in which effective treatments or combinations of treatments are still sought-after. More fine-grained analyses of effective or ineffective treatment elements should therefore be subject of future studies.

Although we incorporated nearly all of the suggestions made by Broomfield et al.23 we opted not to include executive skills training in our treatment protocol. Broomfield and colleagues reported that patients with severe executive problems are usually excluded from intervention trials for post-stroke depression, and argued that combining executive skills training with cognitive behavioural therapy may help such patients to better engage in therapy.23 Although we agree that such a combined treatment approach might be of value for some patients, we did not incorporate distinct executive skills training as a standard component because such a treatment is relatively long and complex, which would unduly prolong the treatment in many patients without executive problems.

Clinical message
- Psychological interventions for post-stroke depression should be adjusted to the sensori-motor, cognitive and behavioural impairments observed in many stroke survivors.
- Cognitive behavioural therapy is a promising method for treating post-stroke depressive symptoms and can take into account concurrent feelings of anxiety.
- Cognitive behavioural therapy for post-stroke depression can effectively be augmented with occupational or movement therapy to support individual patients in goal setting and goal attainment, taking into account their physical and cognitive abilities.
References


An augmented CBT for treating post-stroke depression: Treatment protocol


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Chapter 5

Augmented Cognitive Behavioral Therapy for Poststroke Depressive Symptoms: A Randomized Controlled Trial

Abstract

Objective: To evaluate the effectiveness of individually tailored cognitive behavioral therapy (CBT) for reducing depressive symptoms with or without anxiety post stroke.

Design: Multi-center, assessor-blinded, randomized controlled trial.

Setting: Six ambulatory rehabilitation settings in The Netherlands.

Participants: Patients who had a Hospital Anxiety and Depression Scale – subscale Depression (HADS-D) score > 7 at least three months post stroke.

Interventions: Sixty-one participants were randomly allocated to either augmented CBT or computerized cognitive training (CCT). The CBT intervention was based on the principles of recognizing, registering, and altering negative thoughts and cognitions. CBT was augmented with goal-directed real-life activity training given by an occupational or movement therapist.

Main outcome measures: HADS-D was the primary outcome and measures of participation and quality of life were secondary outcomes. Outcome measurements were performed at baseline, directly post treatment, and at four and eight months follow-up. Analysis was performed with linear mixed models using group (CBT vs CCT) as between-subjects factor and time (4 assessments) as within-subjects factor. Results: Mixed model analyses showed a significant and persistent time effect for HADS–D (MD:-4.6, 95%CI=-5.7;-3.75, p<0.00) as well as for participation and quality of life in both groups. There was no significant group x time effect for any of the outcome measures.

Conclusions: Our augmented CBT intervention was not superior to computerized cognitive training for the treatment of mood disorders after stroke. Future studies should determine whether both interventions are better compared to natural history.
Introduction

Approximately one third of all stroke survivors experience depressive symptoms at some point in time,\textsuperscript{1} with a negative impact on the outcome of rehabilitation and quality of life.\textsuperscript{2} Hence, adequate treatment of post stroke depressive symptoms is of utmost importance. Typically, studies on the treatment of depressive symptoms after stroke have focused on pharmacological interventions. However, drug treatment only produces small improvements in mood, while it is associated with a frequent occurrence of side effects,\textsuperscript{3,4} restricting routine prescription. Since post stroke depressive symptoms are strongly associated with individuals’ perception of, and coping with the consequences of stroke,\textsuperscript{5} a psychological treatment approach seems warranted. As CBT is aimed at changing irrational cognitions and negative thoughts, its effects may endure after treatment and chances of relapse of symptoms may be smaller compared to pharmacotherapy.\textsuperscript{6-8} In addition, the side-effect profile of psychological treatment is favorable compared to medication.\textsuperscript{6} However, psychological treatments of post stroke mood disorders have not yet yielded convincing results.\textsuperscript{9,10}

To our knowledge only one randomized controlled trial (RCT) has been reported investigating a psychological treatment of post stroke depressive symptoms.\textsuperscript{10} This study yielded inconclusive results with regard to the effectiveness of CBT. As the authors acknowledged, this work was a pioneering study with several methodological weaknesses that compromised its quality. For instance, cognitive impairments were not considered in the inclusion criteria and therapy content was insufficiently adjusted to the cognitive consequences of stroke. In addition, the training of therapists was limited. Other researchers argued that, in order to optimize the effectiveness of CBT in patients with stroke, cognitive and emotional impairments and limited awareness of deficits should be taken into account.\textsuperscript{8} It was also recommended that CBT should be augmented with real-life activity training to help patients and their caregivers set and attain realistic goals aimed at social participation, taking into account their motor and cognitive impairments.\textsuperscript{8} In addition, anxiety symptoms should be recognized and addressed in the CBT treatment as these are often associated with depressive symptoms after stroke.\textsuperscript{11,12}

In a pilot study, we already assessed the feasibility of a CBT intervention aimed at reducing depressive symptoms in stroke survivors.\textsuperscript{13} Three out of five participants showed positive results on mood and quality of life directly after treatment and these positive results were retained at three months follow-up. These findings justified the conduct of a multi-center RCT as part of the Restore4Stroke study.
in the Netherlands.\textsuperscript{14,15} In the present study we hypothesized that patients treated with individually tailored augmented CBT would show a larger decrease in depressive symptoms and more improvement in social participation and quality of life than those receiving a computerized cognitive training (CCT). CCT was selected as the comparator intervention to control for Hawthorne effects, in the expectation that CCT might improve cognition but not mood.

Methods

Subjects

Participants were recruited over a period of 18 months. They were screened for eligibility by their treating physicians and psychologists during regular outpatient visits in the following six participating rehabilitation centers or hospital rehabilitation departments in the Netherlands: Groot Klimmendaal, Arnhem; St Maartenskliniek, Nijmegen; Adelante, Hoensbroek; Roessingh, Enschede; VieCuri, Venlo; Tolbrug; ’s Hertogenbosch; ViaReva, Apeldoorn. Participants were eligible when they met the following inclusion criteria. They should (1) have sustained any type of clinically confirmed stroke at least three months earlier; (2) score $> 7$ on the Hospital Anxiety and Depression Scale–subscale Depression (HADS-D);\textsuperscript{16,17} (3) be 18 years or older; (4) have only mild cognitive impairments (Mini Mental State Examination score (MMSE)\textsuperscript{18} $> 27/30$ and score positively on the communication-related items of the National Institute of Health Stroke Scale (NIHSS);\textsuperscript{19} and (5) master the Dutch language. Exclusion criteria were (1) pre-stroke major depression requiring psychiatric care; (2) pre-morbid disability as reflected in a Barthel Index score $< 19/20$;\textsuperscript{20} (3) stay in an inpatient setting; (4) severe co-morbidity that might affect mood (e.g., cancer); and (5) post stroke major depression requiring a start with medication.

The study design and methods were previously published\textsuperscript{16} and approved by the medical ethical committee of Nijmegen (The Netherlands) and by the executive boards of all participating rehabilitation institutes. The adjusted time points of assessment were approved post hoc by the same medical ethical committee.

Procedure

After referral to the primary investigator (JK), participants were enrolled based on the inclusion and exclusion criteria. Oral and written informed consent was obtained by JK. Subsequently, patients were randomized to either 4 months of augmented CBT or an equal period of CCT. Interventions were given in the same
Augmented CBT for poststroke depressive symptoms: RCT

Patients assessed for eligibility (n=163)

Patients randomely assigned  (n=61)

Patients not eligable based on HADS depression < 7 (n=83)
- Comorbidity (n=7)
- Not interested (n=5)
- Not specified (n=3)
- Drop-out after baseline measurement (n=4)
  - Started anti-depressants (n=1)
  - Logistic problems (n=1)
  - Not specified (n=2)

Patients assigned to the augmented CBT intervention (n=31)

Patients completed augmented CBT intervention (n=23)

Patients assessed post treatment T1 (n=24)

Did not complete intervention (n=8) due to
- Withdrew from study (n=7)
- Unwillingness (n=1)

Patients assessed at T2 after eight months (n=24)

Did not complete intervention (n=1) due to
- Unwillingness (n=1)

Patients assessed at T3 after twelve months (n=23)

Patients assigned to the augmented CogniPlus intervention (n=30)

Patients completed CogniPlus intervention (n=22)

Patients assessed post treatment T1 (n=28)

Did not complete intervention (n=8) due to
- Unwillingness (n=6)
- Personal reassons (n=2)

Patients assessed at T2 after eight months (n=24)

Did not complete intervention (n=4) due to
- Unwillingness (n=2)
- Personal reassons (n=2)

Patients assessed at T3 after twelve months (n=21)

Figure 1. Flow Chart of the Restore4Stroke Trial for depressive symptoms after stroke (CONSORT Diagram)
six rehabilitation institutions as where patients were treated. All outcome measures were collected at four time points. Initially we intended to measure at baseline, directly post treatment, and 6 and 12 months post treatment.\textsuperscript{15} Due to a lower than expected inclusion rate the timing of the assessments was adjusted to baseline (T0), directly post treatment (T1), and 4 (T2) and 8 months (T3) post treatment (see figure 1). All assessments took place in the rehabilitation institute where the patient was treated. Baseline assessments were performed by JK. From T1, all outcome assessments were performed by research assistants who were not involved in the administration of the interventions and who were blind to treatment allocation of the participants. When patients mentioned the content of their intervention to the assessor, this was reported and the subsequent assessment was performed by a different, still blinded assessor.

Randomization

Stratified block randomization (block size 4) was performed by a randomization program for each participating rehabilitation institution separately. Main factors that were expected to affect outcomes were selected for minimization, i.e. rehabilitation institute and patients’ anxiety level (HADS–subscale Anxiety (HADS-A) ≤7 vs. > 7). As a result, for each participating institute, patients with high anxiety scores and those with low anxiety scores were equally allocated to either the experimental or control group.

Interventions

Both interventions were administered during a 4-month time period, with a minimum of 13 and a maximum of 16 sessions. Each session consisted of two 20- to 25-minute blocks divided by a 10- to 15-minute break. Thus, each session lasted approximately one hour. The CBT intervention was administered by a certified healthcare psychologist (‘therapist’) who had ample experience in treating depression as well as with stroke rehabilitation in general. All therapists were additionally trained by JK to master the specific aspects of the current CBT intervention. Goals for attaining daily life activities were primarily set together by the patient and the therapist using pictures from the Activity Card Sort.\textsuperscript{21} Concurrently with the psychological sessions, the CBT intervention was augmented with three sessions of occupational therapy (OT) or movement therapy (MT). During these sessions, an occupational or movement therapist helped patients with establishing and attaining goals aimed at meaningful
activities and social participation. These goals were attuned to the content of the psychological sessions. In the case of a baseline HADS–A score > 7, the protocol was extended with an additional (fourth) OT/MT session aimed at training relaxation techniques as provided by the Dutch Heart Foundation. To implement the recommendations made by Broomfield, therapists were continuously reminded to use concrete, repetitive, accessible, slow and structured communication strategies as proposed by Judd. A detailed description of the applied CBT intervention has been published elsewhere.

We selected CCT as the comparative intervention to control for nonspecific (e.g. Hawthorne) effects. In a previous study, this type of training yielded high satisfaction scores. In the current study, CCT was largely self-administered, but either cognitive trainers or psychological assistants were present to assist the participants during the training. They were instructed not to engage in any conversation with the patients about topics other than the cognitive training. A desktop was set up with a headphone and a keyboard with colored patches attached to two keys. Patients could select any (or a combination) of four specific cognitive domains for training, i.e. attention, memory, executive functioning, and/or visual attention. As patients improved, the Cogniplus program adjusted the level of difficulty for each training task accordingly. In this way, each patient trained at his/her individual level and pace.

Co-interventions
During the study, patients were requested to minimize co-interventions by other therapists and to refrain from starting new medication. Any existing (psycho) pharmacological treatment was continued. All co-interventions were registered in a booklet at each assessment.

Assessments
Baseline assessments consisted of the following characteristics: age (years), sex (male, female), employment (yes, no), time since stroke (months), stroke type (ischemic, hemorrhagic, other), affected hemisphere (left, right, other), mobility (Stroke Impact Scale-subscale Mobility), co-morbidity (Cumulative Illness Rating Scale), level of independence (Barthel Index), and cognition (MMSE). Except for co-morbidity, higher scores reflect better outcomes on the scales mentioned. The primary outcome was the severity of depressive symptoms as assessed with the HADS-D. The HADS has been specifically validated to assess depressive
symptoms in stroke patients. Secondary outcomes were HADS-A for symptoms of anxiety; the Post Stroke Depression Rating Scale (PSDRS) for assessing the more qualitative aspects of mood; coping assessed with the Utrecht Proactive Coping Competence scale (UPCC); quality of life assessed with the Stroke Specific Quality of Life (SSQoL) scale; social participation assessed with the Utrecht Scale for Evaluation of Rehabilitation - Participation (USERP); and subjective well-being assessed with a life satisfaction questionnaire (LS2). Except for HADS and PSDRS scores, higher scores reflect better outcomes.

Statistical analyses
This study was originally powered on the HADS-D at 4 months post treatment (i.e., T2) without accounting for improved precision due to repeated measures (at T1 and T3). To obtain a power of 80% with an $\alpha$-level of 5%, we originally aimed to include a total of 106 participants. In this calculation, adjustments for baseline values (i.e., T0) and post treatment values (i.e., at T2) and a drop-out rate of 15% were taken into account. Due to the lower than expected inclusion rate, we investigated whether accounting for the additionally repeated measures at T1 and/or T3 could provide sufficient power. Using the method as described by De Hoop, we calculated that including an extra post-treatment value (i.e., T1) would provide sufficient power with half the originally planned subjects. This was discussed with and approved by the medical-ethical committee. As a consequence, a minimal number of 53 participants was needed.

Median and ranges or numbers and percentages were used for descriptive statistics in the case of continuous and categorical variables, respectively. After confirming normal distribution of the dependent continuous variables, we used linear mixed models for repeated measures to study the differences between groups for each outcome (dependent variable). The independent fixed variables were group (CBT vs. CCT), baseline score, time point of measurement (T0-T3), the minimization factor HADS–A $> 7$, and the interaction term between point of measurement and group. The participating institute was treated as a random variable. We present the baseline-adjusted mean differences between groups at each time point with 95% confidence intervals. The effects of the intervention on the primary and secondary outcome measures were analyzed according to the intention-to-treat principle using SAS 9.2 for Windows and IBM SPSS Statistics 20 for Windows. Data analysis was performed by an independent statistician who was blinded for group allocation.
Results

Participants

Figure 1 presents the patient flow throughout the study. Trial inclusion took place from January 2011 until August 2012, and ended according to prior agreements with the medical ethical committee. Out of 163 referred patients, 61 ultimately participated. Of these, 31 patients were assigned to the CBT and 30 patients to the CCT intervention. Incomplete interventions occurred once in the CBT group (change in protocol by psychologist) and four times in the CCT group (related to suicidal thoughts (n=1); dissatisfaction with intervention (n=2); no reason/not specified (n=1). Fifty-two patients completed the post treatment assessment, of whom 44 completed the last follow-up. Patient characteristics are listed in Table 1.

Table 1. Patient characteristics at baseline

<table>
<thead>
<tr>
<th></th>
<th>CBT</th>
<th>CCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31 61 (45;79)</td>
<td>30 61 (25;76)</td>
</tr>
<tr>
<td>TSS (months)</td>
<td>26 (2;243)</td>
<td>21.5 (2;138)</td>
</tr>
<tr>
<td>Men</td>
<td>31 19 (61.3)</td>
<td>30 19 (63.3)</td>
</tr>
<tr>
<td>Employed</td>
<td>31 9 (29)</td>
<td>30 13 (43.3)</td>
</tr>
<tr>
<td>Stroke type</td>
<td>28 Infarct 21 (75)</td>
<td>28 Hemorrhage/ other 24 (85.7)</td>
</tr>
<tr>
<td></td>
<td>7 (25)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td></td>
<td>0 Unknown</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Stroke hemisphere</td>
<td>26 Left 15 (57.7)</td>
<td>28 Right 8 (30.8)</td>
</tr>
<tr>
<td></td>
<td>3 (11.5)</td>
<td>11 (39.3)</td>
</tr>
<tr>
<td>SIS mobility</td>
<td>31 65 (13;98)</td>
<td>30 65 (25;100)</td>
</tr>
<tr>
<td>CIRS</td>
<td>31 3 (0;18)</td>
<td>30 5 (0;13)</td>
</tr>
<tr>
<td>Barthel Index</td>
<td>31 20 (17;20)</td>
<td>30 20 (12;20)</td>
</tr>
<tr>
<td>MMSE</td>
<td>31 30 (27;30)</td>
<td>30 30 (24;30)</td>
</tr>
<tr>
<td>HADS</td>
<td>31 Depression 12 (8;20)</td>
<td>30 Anxiety 9 (4;17)</td>
</tr>
<tr>
<td></td>
<td>12 (8;20)</td>
<td>10 (1;18)</td>
</tr>
</tbody>
</table>
Control of bias

More than 95% of all assessments were performed according to the protocol. Some exceptions were: extra pauses (T0, n=1); missing page in assessment booklet (T1, n=1); UPCC questionnaire too difficult to understand (T1, n=1); and UPCC and LS2 questionnaires filled in at home due to time constraints (T1, n=1). Assessor unblinding by the patient occurred in 13% of the T1 assessments, 10% of the T2 assessments, and 9% of the T3 assessments. In the CBT group, one patient had sought contact with a psychologist outside the trial for additional anxiety therapy (T1), and one patient had started antidepressants (T2). In the CCT group one patient commenced with antidepressants at T1.

Interaction effects and group differences

Table 2 presents the primary and secondary outcomes by point of measurement for each group. Changes in HADS-D were never significant between groups (See also, Figure 2). No group differences after treatment were found for any of the primary or secondary outcomes. Therefore, a parallel line model is presented for all variables in Table 3.

![Figure 2](image)

Figure 2. Mean scores for CCT and CBT at all assessment time points
Table 2. Observed median (range) of the primary and secondary outcomes by point of measurement by group

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post treatment</th>
<th>4-month follow up</th>
<th>8-month follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Median (range)</td>
<td>N</td>
<td>Median (range)</td>
</tr>
<tr>
<td>HADS-D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>31</td>
<td>12.0 (8.0;20.0)</td>
<td>24</td>
<td>8.00 (0.0;15.0)</td>
</tr>
<tr>
<td>CCT</td>
<td>30</td>
<td>12.0 (8.0;20.0)</td>
<td>28</td>
<td>9.00 (1.0;14.0)</td>
</tr>
<tr>
<td>HADS-A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>31</td>
<td>9.0 (4.0;17.0)</td>
<td>24</td>
<td>6.5 (2.0;18.0)</td>
</tr>
<tr>
<td>CCT</td>
<td>30</td>
<td>10.0 (1.0;18.0)</td>
<td>28</td>
<td>7.5 (0.0;16.0)</td>
</tr>
<tr>
<td>PSDRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>30</td>
<td>14.0 (3.0;24.0)</td>
<td>23</td>
<td>10.3 (2.0;21.0)</td>
</tr>
<tr>
<td>CCT</td>
<td>30</td>
<td>12.0 (4.0;25.3)</td>
<td>28</td>
<td>9.0 (1.0;21.0)</td>
</tr>
<tr>
<td>UPCC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>31</td>
<td>2.5 (1.5;3.2)</td>
<td>24</td>
<td>2.5 (1.4;3.8)</td>
</tr>
<tr>
<td>CCT</td>
<td>30</td>
<td>2.5 (1.5;3.8)</td>
<td>27</td>
<td>2.4 (1.7;4.0)</td>
</tr>
<tr>
<td>SSQoL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>31</td>
<td>3.2 (2.1;4.7)</td>
<td>24</td>
<td>3.8 (2.2;5.0)</td>
</tr>
<tr>
<td>CCT</td>
<td>30</td>
<td>3.1 (2.0;4.7)</td>
<td>28</td>
<td>3.5 (1.9;4.8)</td>
</tr>
<tr>
<td>USERP freq part A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>31</td>
<td>12.6 (5.0;30.0)</td>
<td>24</td>
<td>14.0 (5.0;35.0)</td>
</tr>
<tr>
<td>CCT</td>
<td>30</td>
<td>14.5 (5.0;50.0)</td>
<td>28</td>
<td>13.4 (5.0;45.0)</td>
</tr>
<tr>
<td>USERP freq part B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>31</td>
<td>45.0 (7.5;82.5)</td>
<td>24</td>
<td>43.8 (20.0;77.5)</td>
</tr>
<tr>
<td>CCT</td>
<td>30</td>
<td>42.5 (15.0;80.0)</td>
<td>28</td>
<td>45.0 (5.0;70.0)</td>
</tr>
<tr>
<td>USERP satisfaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>31</td>
<td>56.3 (19.4;88.9)</td>
<td>24</td>
<td>66.3 (27.8;94.4)</td>
</tr>
<tr>
<td>CCT</td>
<td>31</td>
<td>51.4 (11.1;78.1)</td>
<td>28</td>
<td>62.5 (30.6;88.9)</td>
</tr>
<tr>
<td>USERP restriction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>31</td>
<td>72.5 (50.0;94.4)</td>
<td>24</td>
<td>75.0 (43.6;100.0)</td>
</tr>
<tr>
<td>CCT</td>
<td>30</td>
<td>71.4 (46.9;100.0)</td>
<td>28</td>
<td>75.0 (50.0;94.4)</td>
</tr>
<tr>
<td>LS2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>31</td>
<td>4.0 (2.0;11.0)</td>
<td>24</td>
<td>6.0 (3.0;13.0)</td>
</tr>
<tr>
<td>CCT</td>
<td>30</td>
<td>4.0 (2.0;12.0)</td>
<td>28</td>
<td>5.0 (3.0;11.0)</td>
</tr>
</tbody>
</table>

Abbreviations: HADS-D, Depression subscale Hospital Anxiety and Depression Scale (range 0-21); HADS-A, Anxiety subscale Hospital Anxiety and Depression Scale (range 0-21); PSDRS, Post Stroke Depression Rating Scale (range 0-45); UPCC, Utrecht Proactive Coping Competence list (range 1-4); SSQoL, short Stroke Specific Quality of Life Scale (range 1-5); USERP, Utrecht Scale of Rehabilitation – Participation, (USERP Frequency part A: Vocational activities, USERP Frequency part B: Leisure activities) (range 0-100, each subscale); LS2, two Life Satisfaction questions (range 2-13).
Table 3. Estimated mean differences (95% CIs) between points of measurement for both groups together, using linear mixed model for repeated measurements while adjusting for baseline values.

<table>
<thead>
<tr>
<th></th>
<th>Post treatment - Baseline</th>
<th>Follow up 4 months - Post treatment</th>
<th>Time differences</th>
<th>Follow up 8 months - Post treatment</th>
<th>Follow up 8 months - Post treatment</th>
<th>Overall group difference after treatment period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean(95%CI)</td>
<td>Mean(95%CI)</td>
<td>Mean(95%CI)</td>
<td>Mean(95%CI)</td>
<td>Mean(95%CI)</td>
<td>Mean(95%CI)</td>
</tr>
<tr>
<td>HADS-D</td>
<td>-4.6 (-5.7;-3.6)</td>
<td>1.1 (0.2;1.9)</td>
<td>-1.4 (-2.1;-0.7)</td>
<td>-0.4 (-1.3;0.5)</td>
<td>0.5 (-1.3;2.3)</td>
<td></td>
</tr>
<tr>
<td>HADS-A</td>
<td>-2.6 (-3.6;-1.5)</td>
<td>-0.3 (-1.0;0.4)</td>
<td>-0.4 (-1.3;0.5)</td>
<td>-0.7 (-1.6;0.2)</td>
<td>1.1 (-0.7;2.9)</td>
<td></td>
</tr>
<tr>
<td>PSDRS</td>
<td>-3.4 (-4.9;-2.0)</td>
<td>-0.7 (-1.7;0.4)</td>
<td>-1.2 (-2.5;0.1)</td>
<td>-1.9 (-3.1;-0.7)</td>
<td>0.7 (-1.6;3.0)</td>
<td></td>
</tr>
<tr>
<td>UPCC</td>
<td>0.0 (-0.1;0.1)</td>
<td>0.1 (-0.2;0.1)</td>
<td>0.1 (-0.0;0.2)</td>
<td>0.1 (0.0;0.3)</td>
<td>-0.1 (-0.3;0.1)</td>
<td></td>
</tr>
<tr>
<td>SSQoL</td>
<td>0.3 (0.1;0.5)</td>
<td>-0.1 (-0.2;0.0)</td>
<td>0.2 (0.0;0.4)</td>
<td>0.1 (-0.1;0.3)</td>
<td>-0.2 (-0.6;0.1)</td>
<td></td>
</tr>
<tr>
<td>USERP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency A</td>
<td>0.3 (-1.8;2.4)</td>
<td>-1.6 (-3.7;0.5)</td>
<td>1.2 (-0.7;3.1)</td>
<td>-0.4 (-2.1;1.4)</td>
<td>0.5 (-2.5;3.6)</td>
<td></td>
</tr>
<tr>
<td>Frequency B</td>
<td>0.0 (-4.0;4.0)</td>
<td>3.1 (-0.7;6.9)</td>
<td>-0.1 (-4.0;3.8)</td>
<td>3.0 (-1.4;7.5)</td>
<td>0.3 (-5.1;5.6)</td>
<td></td>
</tr>
<tr>
<td>satisfaction</td>
<td>9.7 (5.4;14.1)</td>
<td>1.6 (-1.1;4.2)</td>
<td>0.4 (-2.8;3.5)</td>
<td>1.9 (-1.5;5.4)</td>
<td>-1.1 (-7.8;5.5)</td>
<td></td>
</tr>
<tr>
<td>restriction</td>
<td>2.9 (-0.4;6.2)</td>
<td>-0.2 (-3.0;2.5)</td>
<td>3.0 (-0.4;6.4)</td>
<td>2.8 (-1.0;6.7)</td>
<td>0.4 (-4.4;5.3)</td>
<td></td>
</tr>
<tr>
<td>LS2</td>
<td>1.3 (0.7;2.0)</td>
<td>0.4 (-0.1;0.9)</td>
<td>0.2 (-0.3;0.8)</td>
<td>0.6 (0.0;1.3)</td>
<td>-0.5 (-1.6;0.5)</td>
<td></td>
</tr>
</tbody>
</table>

Note: The interaction between time and group never reached the level of statistical significance. Therefore, a parallel line model is presented for all variables.

Abbreviations: HADS-D, Depression subscale Hospital Anxiety and Depression Scale (range 0-21); HADS-A, Anxiety subscale Hospital Anxiety and Depression Scale (range 0-21); PSDRS, Post Stroke Depression Rating Scale (range 0-45); UPCC, Utrecht Proactive Coping Competence list (range 1-4); SSQoL, short Stroke Specific Quality of Life Scale (range 1-5); USERP, Utrecht Scale of Rehabilitation – Participation (range 0-100, each subscale); LS2, two Life Satisfaction questions (range 2-13).
Time effects

Table 3 depicts the estimated mean differences (MD) between points of measurement, adjusted for baseline values, for all outcomes and for both groups together. A post treatment effect was found for the primary outcome HADS-D (MD=-4.6, 95%CI=-5.7;-3.6). The overall time effect of HADS-D from post treatment to 8-months follow-up was not significant. Yet, HADS-D showed a significant increase from post treatment to 4-months follow-up (MD=1.1, 95%CI=0.2;1.9), followed by a significant decline from 4-months to 8-months follow-up (MD=-1.4, 95%CI=-2.1;-0.7) for both groups.

A post treatment effect was also observed for HADS-A (MD=-2.6, 95%CI=-3.6;-1.5), PSDRS (MD=-3.4, 95%CI=-4.9;-2.0), USERP–subscale Satisfaction(MD=9.7, 95%CI=5.4;14.1), SSQOL (MD=0.3; 95%CI=0.1;0.5), and LS2 (MD=1.3, 95%CI=0.7;2.0), but not for UPCC. However, UPCC showed a significant change from post treatment to 8-months follow-up (MD=0.1, 95%CI=0.0;0.3) as did PSDRS (MD=-1.9, 95%CI=-3.1;-0.7) and LS2 (MD=0.6, 95%CI=0.0;1.3).

Discussion

The aim of our study was to evaluate the effectiveness of individually tailored cognitive behavioral therapy for reducing depressive symptoms with or without anxiety after stroke. The results of our multicenter RCT indicate that there was significant and persistent improvement of depressive and anxiety complaints after treatment, although this was independent of the type of intervention. In addition, the subjective ratings of patients’ participation level (USERP-satisfaction) increased after treatment, as did quality of life (SSQol) and life satisfaction (LS2). These results appear to be similar to those of Lincoln and Flannaghan10 even though our CBT was of longer duration and higher intensity, was augmented with occupational or movement therapy, was provided by well-trained psychologists, and took cognitive impairments and anxiety complaints into account. Like our study, Lincoln and Flannaghan10 found no differences between intervention groups (i.e., no intervention, attention placebo, CBT),33 although they did find a small decline (3-4 points) in median score on the Beck Depression Inventory (BDI; range 0-63) for each group directly after the intervention period. Notably, the relative improvements that were observed in the present study were larger (i.e., 3-4 points on HADS-D; range 0-21), which suggests that both treatments may have caused a beneficial effect. As our study lacked a ‘no intervention’ control group, it cannot be ruled out that any beneficial effect of either CBT
or CCT was non-specific or that HADS-D scores simply improved due to ‘regression to the mean’. However, the observed improvements were relatively large, whereas recent literature shows that depressive symptoms post stroke (measured with the BDI) remain stable over the first two years. In addition, our Restore4Stroke consortium recently reported non-significant fluctuations in post stroke depressive symptoms (maximally 2 points change in HADS-D) over the first two years. These findings point toward the possibility that the observed decline in depressive symptoms after treatment in the present study may actually represent a beneficial effect of both CBT and CCT. This notion raises the question what the effective component of CCT might have been, as we took care that cognitive trainers and psychological assistants were instructed not to address issues other than the cognitive training. Interestingly, in a recent evaluation of CCT, Åkerlund and colleagues showed that patients with acquired brain injury who suffered from depressive complaints demonstrated mood improvements after CCT which suggests that cognitive training may improve mood through motivational mechanisms or perhaps through cognitive improvement. Irrespective of the underlying mechanism, it may be that such effects occurred in our study. Unfortunately, at the initiation of our study, beneficial effects results of CCT on mood problems were not yet known.

Quality of life scores as well as satisfaction with life and with participation equally and persistently improved in both groups after treatment as did anxiety level. Pro-active coping did not immediately respond after the intervention, but it improved during follow-up, together with life satisfaction and qualitative aspects of mood. In a recent study from our Restore4Stroke consortium, change in depression scores was associated with subjective experience of participation, emphasizing that rehabilitation should focus on resuming occupational activities when treating depressive complaints after stroke. Although in the present study this approach was applied in the CBT intervention, it remains to be explained why we found no group differences for any of the secondary outcomes, and why CBT and CCT had similar effects.

Limitations

Apart from the absence of a ‘no intervention’ control group, the main limitation of the present study is the relatively small patient sample and the recruitment through rehabilitation institutes, which limits the generalizability of our results. It is well known that recruiting patients with depressive symptoms for participation in research is notoriously difficult. Patients who did participate may have been
more motivated than those who did not, which may have led to selection bias. This too would limit the generalizability of our results. Although we did not reach the inclusion as originally planned, the risk of false negative outcomes for group by time interactions seems to be small because no trends were observed towards significant interactions. We were not able to directly compare our results to those of Lincoln and Flannaghan,\textsuperscript{10} as we used HADS-D instead of BDI as a primary outcome. This choice was determined by the intention to prevent overestimation of depressive symptoms due to general symptoms (e.g. fatigue) of stroke. Unlike the BDI, the HADS does not include fatigue as a symptom of depressed mood.

Conclusion
This RCT showed persistent improvement of depressive symptoms, anxiety symptoms, quality of life, satisfaction with life and participation after both cognitive behavioral therapy and computerized cognitive training in patients with depressive complaints minimally three months after stroke. This finding implies that, for now, both types of interventions may be considered to improve depressive symptoms after stroke. Future research should determine whether both interventions are better compared to natural history and what underlying mechanisms are responsible for such effects.
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Chapter 6

Treating patients with post-stroke depressive symptoms: What happens to caregivers well-being?

Submitted: Kootker JA; Van Heugten CM; Kral B; Rasquin, SMC; Geurts ACH; Fasotti F. Treating patients with post-stroke depressive symptoms: What happens to caregivers' well-being?
Abstract

Depressive and anxiety symptoms after stroke have a high impact on patients’ daily life functioning and their rehabilitation. These emotional consequences of stroke also have negative effects on caregivers’ well-being.

Objective: We investigated the concomitant effects of two patient-directed interventions on caregivers’ well-being. The treatments that stroke patients received consisted of an augmented cognitive behavioural therapy (CBT) or a computerised cognitive training (CCT) to alleviate depressive symptoms post stroke.

Design: Randomised controlled trial. Caregivers were assessed at baseline, post treatment, and 4 and 8 months post treatment. Linear mixed models for repeated measures were used for statistical analysis.

Subjects: Fifty caregivers of stroke patients that received either CBT (n=23) or CCT (n=27).

Outcome measures: Emotional burden (IEQ-BI), practical burden (CSI), mental health (GHQ), and emotional complaints (HADS).

Results: Caregivers of patients who received CBT reported significantly higher GHQ levels and less worrying about patients’ well-being. In addition, there were positive time effects on IEQ-BI, particularly the subscales Worrying, Supervision and Tension.

Conclusion: The results suggest that augmented CBT aimed at improving patients’ emotional, behavioural and social functioning positively affects some aspects of caregivers’ well-being. Future studies should take into account the concomitant effects of patient-directed interventions on caregivers well-being as well as on their possible role in the implementation and effect of these interventions.
Introduction

Stroke survivors are frequently left with physical, cognitive and emotional problems in the chronic phase of their illness.\textsuperscript{1,2} The majority of these patients are discharged home after a hospital stay, although they may still need practical support as they face limitations in daily routines. Their spouses are often obliged to adopt a caregiver-role. This may change the independent, pre-stroke relationship dramatically.\textsuperscript{3} Providing care at home for a patient after stroke requires considerable effort.\textsuperscript{4} According to Cameron and colleagues (2011), it is not so much the physical, but rather the psychological sequelae of stroke that influence caregivers’ well-being. Furthermore, stroke survivors’ depressive symptoms were found to be a ‘significant challenge’ for caregivers.\textsuperscript{2} Caregivers often experience negative effects on their own emotional stability. This is expressed by high prevalence rates of depression, anxiety and lower life satisfaction in caregivers.\textsuperscript{5-7} In patients with acquired brain injury, Geurtsen et al. showed that caregivers experience a high level of emotional burden, indicated by concern, worries and feelings of responsibility for the patients’ well-being.\textsuperscript{2,3,8-11} Geurtsen et al. proposed that caregivers’ emotional burden may be an ‘anticipatory construct’ that depends on expectations of patients’ emotions and functioning,\textsuperscript{12} since they found that emotional burden was not associated with a more stable construct, mental health. Moreover, caregivers experience restrictions in their societal participation, for instance with regard to employment and recreational activities\textsuperscript{13,14} which may lead to social isolation and limited support from family and friends.\textsuperscript{15} Conversely, the well-being of caregivers may also influence the well-being of patients. Indeed, depressive symptoms in caregivers may worsen the post-stroke depressive symptoms in patients and negatively affect patients’ rehabilitation and well-being.\textsuperscript{16,17}

A small number of studies have investigated the effect of interventions specifically aimed at the caregivers of patients with stroke,\textsuperscript{18} but there are no clinical practice guidelines yet\textsuperscript{19,20} In their Brain Integration Program study, Geurtsen and colleagues showed that interventions for patients with acquired brain injury can have a concomitant positive effect on caregivers’ emotional burden and mental health.\textsuperscript{21} Their intervention was activity-focused and directed at balancing daily life activities with the practical and physical consequences of an acquired brain injury.\textsuperscript{21} Their study showed that a positive effect on caregivers’ worrying and mental health was already apparent during the waiting list phase, indicating that at least some changes in emotional burden were anticipatory and caused by
hopes and expectations of caregivers rather than by actual patient improvement.\(^9\) We recently studied the effects of an augmented cognitive behavioural therapy compared to computerised cognitive training for post-stroke depressive symptoms in a randomised controlled trial.\(^22\) The cognitive behavioural therapy was aimed at ameliorating patients’ emotional, behavioural and social functioning, which was complemented (‘augmented’) with activity oriented goal attainment supported by a movement of occupational therapist.\(^23\) Interestingly, we found that both interventions were equally effective for reducing post-stroke depressive symptoms. Caregivers’ practical and emotional burden, mental health and emotional complaints were also assessed in this study. The results of these assessments are reported in the present paper. As opposed to cognitive training, cognitive behavioural therapy is directed at cognitive and behavioural change, which has a possible influence on caregivers’ well-being.\(^2\) Therefore, we will compare both caregiver groups in the current study.

**Methods**

**Participants and design**

All patients participated in a randomised controlled trial, as part of the Restore4Stroke study in the Netherlands. For methodological details of the study design we refer to a previous publication.\(^24\) Sixty-one patients with stroke and with a baseline score >7 on the depression subscale of the Hospital Anxiety and Depression Scale (HADS)\(^25\) were included in the main trial.\(^22\) Patients were randomly assigned to either the experimental cognitive behavioural therapy (CBT) or to computerised cognitive training (CCT; Cogniplus) as a control intervention. For details of the CBT treatment protocol, we refer to another publication.\(^23\) Both interventions lasted 4 months.

All caregivers were invited to participate as well. At inclusion of the patients, all caregivers were informed by the primary researcher about the purpose of the study by means of a letter. They were considered eligible if they had a relationship with the patient at the moment of inclusion, were at least 18 years old, and had adequate knowledge of the Dutch language. After every patient assessment session, caregivers received questionnaires in hardcopy booklets which they returned by post. If necessary, they were reminded by phone in case the booklets were not returned within 2 weeks. Socio-demographic data were collected at inclusion: caregivers’ age, gender, education level, marital status, and financial situation. In addition, caregivers answered questions about the
type of relationship and frequency of contact with the patient, and about the presence of children in their household. Caregiver outcome data were collected at the same time points as patient outcome data were obtained at enrolment (before randomisation), directly after the intervention (after 4 months), and at 4 and 8 months follow-up. The study was approved by the Committee on research involving Human Subjects, Nijmegen, The Netherlands and by all participating institutes. Written informed consent was collected from all caregivers at enrollment.

Outcome measures

General Mental Health

The General Health Questionnaire (GHQ) is a 12-item self-report instrument and was used for the measurement of mental health with a Likert-scoring method. Lower scores indicate that caregivers experience lower mental health. This scale has shown good internal consistency and test-retest reliability.

Emotional Burden

Emotional burden was measured with the Involvement Evaluation Questionnaire for Brain Injury (IEQ-BI). This scale is a 31 item self-report questionnaire in Dutch, covering four subscales: tension, supervision, worrying, and urging. The subscale “tension” refers to a strained interpersonal atmosphere; “supervision” refers to control on a patient’s behaviour; “worrying” addresses painful interpersonal cognitions; and “urging” refers to any kind of action to stimulate the patient to undertake activities. All subscales were scored on a 5-point Likert scale. Lower scores indicate lower levels of caregiver burden. The IEQ-BI has shown good internal consistency, discriminant validity and responsiveness.

Practical Burden

The Caregiver Strain Index (CSI) was used as a brief instrument to identify strain on caregivers. The CSI contains 13 items measuring the levels of stress experienced by caregivers. Questions can be answered with yes (1) or no (0). A score ≥ 7 indicates the existence of caregiver strain. The CSI has shown good internal consistency and test-retest reliability.

Symptoms of Depression and Anxiety

Depressive and anxiety symptoms in caregivers were measured with the HADS.
The HADS consists of 14 items. Seven items constitute the subscale depression (HADS-D), while the other seven items form the subscale anxiety (HADS-A). All items were rated on a four-point scale ranging from 0 to 3. A score 3 indicates the highest experienced level of emotional distress. The HADS has shown good internal consistency and good test-retest reliability.

Statistical Analysis

To analyse group differences for each of the outcome measures, we used linear mixed models for repeated measures with adjustment for baseline values. Analyses were performed using the intention-to-treat principle. The dependent variables were the outcome measures (i.e., IEQ-BI total; IEQ-BI supervision; IEQ-BI tension; IEQ-BI worrying; IEQ-BI urging; CSI; GHQ; HADS-D; HADS-A). The independent variables were Treatment (CBT vs. CCT) and Time (4 time points, T0-T3). Treatment and Time effects are presented as mean differences (MD) with 95% confidence intervals (CIs). The level of significance was set at 0.05. Analyses were performed with SAS 9.2 for Windows and IBM SPSS Statistics 20 for Windows. Data analysis was performed by an independent statistician who was blinded for group allocation.

Results

The 61 patients enrolled in the Restore4Stroke study had a median age of 61.5 years, 62.9% were men, and 72.9% had suffered an ischemic stroke. Caregivers of 50 patients were included in the present study, of whom 23 were related to a patient who received CBT. The socio-demographic and psychological characteristics at baseline are displayed for each group in Table 1. Sixty-four percent of the total group were women and the median age of both sexes was 58 years (range: 30-82). Due to patient drop-out, the data of 4 caregivers at 4-month follow-up and of 7 caregivers at 8-month follow-up were lost. The post-treatment data of 6 other caregivers were lost, either because their partners did not complete the treatment or because they were unwilling to continue. Table 2 shows the median values and ranges for each of the outcome measures for both treatment groups at four time points.

Table 3 shows the overall treatment effects on all outcome measures as well as the post-hoc analyses per point of measurement corrected for baseline values. The GHQ showed a significant overall treatment effect in favour of the CBT.
group (MD=1.78; 95%CI=0.43 - 3.13, p=0.01; see Figure 1 for observed means). Post-hoc analyses showed significant group differences directly post treatment (MD=1.82; 95%CI=0.20 - 3.44, p=0.03) and at 4 months post treatment (MD=2.60; 95%CI=0.34 - 4.87, p=0.02), but no longer at 8-months follow-up (MD=1.59; 95%CI=0.25 - 3.43, p=0.09). As for the IEQ-BI, a significant overall treatment effect in favour of the CBT group was found only for the subscale worrying (MD=1.9; 95%CI=0.56 - 3.24, p< 0.01; see Figure 2 for observed means). Post-hoc analyses showed significant group differences only at 8 months post treatment (MD=2.64; 95%CI=0.83 - 4.45, p< 0.01). No significant treatment effects were found for any of the other outcomes.

Table 1. Caregivers’ demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CBT</th>
<th></th>
<th>CCT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>median (min-max)/n (%)</td>
<td></td>
<td>median (min-max)/n (%)</td>
</tr>
<tr>
<td>Sex</td>
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<td>10 (37)</td>
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<td>Men</td>
<td>8</td>
<td>15 (65.2)</td>
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<td>Women</td>
<td>15</td>
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<td>23</td>
<td>58 (36-82)</td>
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<tr>
<td>Age (yrs)</td>
<td>27</td>
<td>19 (30-78)</td>
<td>23</td>
<td>19 (30-78)</td>
</tr>
<tr>
<td>Educational level*</td>
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<td>27</td>
<td>2 (7.4)</td>
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<td>High</td>
<td>9</td>
<td>14 (60.9)</td>
<td>25 (92.6)</td>
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</tr>
<tr>
<td>Low</td>
<td>14</td>
<td>15 (60.9)</td>
<td>12 (46.3)</td>
<td></td>
</tr>
<tr>
<td>IEQ-BI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (0-108)</td>
<td>22</td>
<td>18.5 (3-45)</td>
<td>24</td>
<td>18.5 (4-54)</td>
</tr>
<tr>
<td>Tension (0-36)</td>
<td>24</td>
<td>7 (0-16)</td>
<td>23</td>
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<td>23</td>
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<td>Worrying (0-24)</td>
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<td>22</td>
<td>6 (1-14)</td>
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<td>Urging (0-32)</td>
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<td>6 (0-21)</td>
<td>23</td>
<td>7.5 (0-20)</td>
</tr>
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<td>GHQ (0-12)</td>
<td>26</td>
<td>3 (0-10)</td>
<td>23</td>
<td>1 (0-11)</td>
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<td>6 (0-12)</td>
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<tr>
<td>HADS</td>
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<td></td>
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</tr>
<tr>
<td>Depression (0-21)</td>
<td>27</td>
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<td>23</td>
<td>4 (0-11)</td>
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<td>Anxiety (0-21)</td>
<td>27</td>
<td>7 (0-13)</td>
<td>23</td>
<td>6 (1-15)</td>
</tr>
</tbody>
</table>

*based on education system of Verhage. CBT: Cognitive Behavioural Therapy, CCT: Computerised Cognitive Training, IEQ-BI Total: Involvement and Evaluation Questionnaire - Brain Injury Total (0-108), IEQ-BI Tension: Involvement and Evaluation Questionnaire - Brain Injury tension subscale (0-36), IEQ-BI Supervision: Involvement and Evaluation Questionnaire - Brain Injury supervision subscale (0-24), IEQ-BI Worrying: Involvement and Evaluation Questionnaire - Brain Injury worrying subscale (0-24), IEQ-BI Urging: Involvement and Evaluation Questionnaire - Brain Injury urging subscale (0-32), CSI: Caregiver strain index (0-13), GHQ: General Health Questionnaire (0-12), HADS-D: Hospital anxiety and depression scale depression subscale (0-21), HADS-A: Hospital anxiety and depression scale anxiety subscale (0-21).
Table 2. Observed median (range) of the caregiver outcomes by point of measurement by group

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Baseline</th>
<th>Post treatment</th>
<th>4 month follow-up</th>
<th>8 month follow-up</th>
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<td>N</td>
<td>median (min;max)</td>
<td>N</td>
<td>median (min;max)</td>
</tr>
<tr>
<td>IEQ-BI Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBTI</td>
<td>23</td>
<td>17 (3;45)</td>
<td>18</td>
<td>14 (2;65)</td>
</tr>
<tr>
<td>CCT</td>
<td>24</td>
<td>18.5 (4;54)</td>
<td>24</td>
<td>17.5 (1;51)</td>
</tr>
<tr>
<td>IEQ-BI Tension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>23</td>
<td>7 (0;16)</td>
<td>18</td>
<td>4 (0;27)</td>
</tr>
<tr>
<td>CCT</td>
<td>24</td>
<td>6.5 (1;19)</td>
<td>24</td>
<td>6 (0;20)</td>
</tr>
<tr>
<td>IEQ-BI Supervision</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>23</td>
<td>1 (0;7)</td>
<td>18</td>
<td>0.5 (0;7)</td>
</tr>
<tr>
<td>CCT</td>
<td>24</td>
<td>1 (0;8)</td>
<td>24</td>
<td>1 (0;5)</td>
</tr>
<tr>
<td>IEQ-BI Worrying</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CBT</td>
<td>23</td>
<td>5 (0;17)</td>
<td>18</td>
<td>3.5 (0;21)</td>
</tr>
<tr>
<td>CCT</td>
<td>27</td>
<td>6 (1;14)</td>
<td>24</td>
<td>5.5 (0;16)</td>
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<tr>
<td>IEQ-BI Urging</td>
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<td>23</td>
<td>6 (0;21)</td>
<td>18</td>
<td>5.5 (0;19)</td>
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<tr>
<td>CCT</td>
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</tr>
<tr>
<td>GHQ</td>
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<td></td>
</tr>
<tr>
<td>CBT</td>
<td>23</td>
<td>3 (0;10)</td>
<td>17</td>
<td>1 (0;9)</td>
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<tr>
<td>CCT</td>
<td>26</td>
<td>1 (0;11)</td>
<td>23</td>
<td>3 (0;12)</td>
</tr>
<tr>
<td>CSI</td>
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<td></td>
</tr>
<tr>
<td>CBT</td>
<td>23</td>
<td>7 (0;13)</td>
<td>20</td>
<td>5.5 (0;13)</td>
</tr>
<tr>
<td>CCT</td>
<td>27</td>
<td>6 (0;12)</td>
<td>24</td>
<td>6 (0;11)</td>
</tr>
<tr>
<td>HADS-D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>23</td>
<td>5 (0;13)</td>
<td>18</td>
<td>5.5 (0;11)</td>
</tr>
<tr>
<td>CCT</td>
<td>27</td>
<td>4 (0;11)</td>
<td>24</td>
<td>6 (0;17)</td>
</tr>
<tr>
<td>HADS-A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>23</td>
<td>7 (0;13)</td>
<td>18</td>
<td>6 (0;13)</td>
</tr>
<tr>
<td>CCT</td>
<td>27</td>
<td>6 (1;15)</td>
<td>24</td>
<td>6 (0;17)</td>
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</tbody>
</table>

CBT: Cognitive Behavioural Therapy, CCT: Computerised Cognitive Training, IEQ-BI - Involvement and Evaluation Questionnaire (0-108), IEQ-BI Tension subscale (0-36), IEQ-BI Supervision subscale (0-24), IEQ-BI Worrying subscale (0-24), IEQ-BI Urging subscale (0-32), CSI: Caregiver strain index (0-13), GHQ: General Health Questionnaire (0-12), HADS: Hospital anxiety and depression scale (HADS) Depression subscale (0-21), HADS Anxiety subscale (0-21)
### Table 3.
Estimated mean differences (95% CIs) between groups at various time points using linear mixed model for repeated measurements while adjusting for baseline values. For each variable CCT was the reference group.

<table>
<thead>
<tr>
<th></th>
<th>Post treatment</th>
<th>4-month follow-up</th>
<th>8-month follow-up</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MD (95% CI)</td>
<td>p</td>
<td>MD (95% CI)</td>
<td>p</td>
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<tr>
<td><strong>IEQ-BI Total</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CBT</td>
<td>2.11 (-3.02-7.23)</td>
<td>0.41</td>
<td>1.40 (-3.92-6.71)</td>
<td>0.60</td>
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<tr>
<td><strong>IEQ-BI Tension</strong></td>
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<td></td>
<td></td>
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<tr>
<td>CBT</td>
<td>0.25 (-2.65-3.14)</td>
<td>0.86</td>
<td>0.46 (-2.46-3.37)</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>IEQ-BI Supervision</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>0.30 (-0.45-1.06)</td>
<td>0.42</td>
<td>-0.07 (-1.03-0.89)</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>IEQ-BI Worrying</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>1.60 (-0.22-3.42)</td>
<td>0.08</td>
<td>1.25 (-0.42-2.93)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>IEQ-BI Urging</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>0.42 (-1.38-2.22)</td>
<td>0.64</td>
<td>-0.30 (-2.51-1.91)</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>GHQ</strong></td>
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<tr>
<td>CBT</td>
<td>1.82 (0.20-3.44)</td>
<td>0.03</td>
<td>2.60 (0.34-4.87)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>CSI</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>1.18 (-0.29-2.66)</td>
<td>0.11</td>
<td>1.04 (0.65-2.72)</td>
<td>0.22</td>
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<tr>
<td><strong>HADS-D</strong></td>
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<td></td>
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<tr>
<td>CBT</td>
<td>0.93 (-0.62-2.48)</td>
<td>0.23</td>
<td>1.27 (-0.28-2.82)</td>
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<tr>
<td><strong>HADS-A</strong></td>
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<td></td>
</tr>
<tr>
<td>CBT</td>
<td>0.10 (-1.72-1.93)</td>
<td>0.91</td>
<td>0.03 (-2.06-2.12)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

CBT: Cognitive Behavioural Therapy, CCT: Computerised Cognitive Training, Involvement and Evaluation Questionnaire (IEQ-BI) - Brain Injury Total (0-108), IEQ-BI Tension subscale (0-36), IEQ-BI Supervision subscale (0-24), IEQ-BI Worrying subscale (0-24), IEQ-BI Urging subscale (0-32), CSI: Caregiver strain index (0-13), GHQ: General Health Questionnaire (0-12), Hospital anxiety and depression scale (HADS) Depression subscale (0-21), HADS Anxiety subscale (0-21).
Figure 1. GHQ Score (0-12). Differences between caregivers in CBT group and CCT group. T0 = at inclusion, T1 = post treatment, T2 = 4 month post treatment, T3 = 8 month post treatment.

Figure 2. IEQ Worrying Score (0-24). Differences between caregivers in CBT group and CCT group. T0 = at inclusion, T1 = post treatment, T2 = 4 month post treatment, T3 = 8 month post treatment.

Time effects
For both groups, a significant overall time effect was found on the IEQ-BI total score (MD=3.55; 95%CI=0.38 - 6.72, p=0.03), IEQ-BI supervision (MD=0.54; 95%CI=0.01 - 1.08, p=0.05) and IEQ-BI worrying (MD=1.18; 95%CI=0.11 - 2.24,
Treating patients with post-stroke depressive symptoms: caregivers well-being?

p=0.03), IEQ-BI Tension (MD=1.71; 95%CI=0.43 - 3.00, p=0.01). The IEQ-BI urging, GHQ, CSI or the HADS did not show any significant time effects.

Discussion

In the present study we evaluated the concomitant effects on caregivers’ well-being when stroke survivors with depressive symptoms received either augmented cognitive behavioural therapy (CBT) or computerised cognitive training (CCT). Caregivers’ well-being was operationalised in terms of mental health, emotional burden, practical burden and depressive and anxiety symptoms. This study showed that caregivers reported better mental health and lower levels of worrying when their spouses received CBT compared to CCT. These findings suggest that an intervention for reducing depressive symptoms post stroke may indeed be able to influence caregivers’ well-being.2,36 Although the effects were small, they are remarkable since the results from this trial did not show differential intervention effects in terms of patient-related outcomes. That is, depressive symptoms of patients decreased over time regardless of the type of intervention they had received.22 This lack of group differences in patient-related outcomes raised the question whether we had found a non-specific (e.g. Hawthorne) effect, although both interventions brought about a similar level of ‘attention’. Indeed, the two interventions were similar in that they were weekly administered to the patient by a therapist or assistant in a rehabilitation centre.22,23 Yet, the interventions differed in their content. Whereas the CBT group received a psychological treatment complemented with activity oriented goal attainment supported by a movement of occupational therapist,23 the CCT group merely received supervised cognitive training modules on a computer. Moreover, the CBT augmented with specific goal attainment led to a vast amount of homework, which was not the case for CCT. Although the caregivers were not directly addressed in either intervention, a potential reason for the differential effects on caregivers in the present study may be related to interaction in the home situation. Having a partner that commits to homework to achieve activity oriented goals may have had concomitant positive effects on the caregiver. As providing such homework can easily be added to any type of psychological intervention, future research should take into account the concomitant effects of patient-directed interventions on caregivers well-being, particularly when such interventions include homework to achieve activity related goals. Caregivers may also play a supportive role in the implementation and effect of home-based interventions.
The chronicity of patients’ impairments following stroke may play a role in the absence of other effects on the caregivers. Although emotional complaints of patients improved after treatment, their physical and cognitive impairments following stroke were still the same. These remaining impairments continued to limit patients in the performance of daily activities and to restrict them in their social participation. Hence, caregivers retained a ‘caregiver-role’ and their practical burden remained unchanged. This is a relevant consideration, as particularly the CSI is sensitive to practical burden which may explain why it did not show any change. Our pattern of results is congruent with the notion of Geurtsen et al.9 and Davis et al.37 that practical burden, mental health and emotional burden are different constructs.9,37 Therefore, future intervention studies directed at the improvement of the emotional consequences of stroke should focus on all those constructs when their impact on caregivers is assessed. Evidence for the effectiveness of specific interventions primarily directed at caregivers of stroke patients is still lacking18,38 but, currently, the effects of a complex intervention program for caregivers of stroke survivors, taking into account both practical burden and mental health, are being investigated.19

This study has several limitations. First, the analyses that were performed were not adjusted for multiple testing, as all caregiver-related measures were meant as secondary outcomes within the trial.22 Therefore, our results should be interpreted with caution and need replication including caregiver well-being as a primary outcome. Second, the absence of any effects on caregivers’ emotional complaints could be a consequence of using the HADS. The HADS was originally developed as a questionnaire for use in patients with somatic co-morbidity. As a consequence, the items of this questionnaire have not been validated to identify and monitor emotional complaints in a ‘healthy’ caregiver group.40

In conclusion, our results suggest that augmented, activity-oriented CBT aimed at improving stroke patients’ emotional, behavioural and social functioning may positively influence relevant aspects of caregivers’ well-being. An alternative, current perspective on alleviating caregiver burden is to focus interventions directly on the problems and needs of the caregiver.41 Therefore, future intervention studies directed at the improvement of the emotional consequences after stroke need to take into account the caregivers as relevant targets for assessment, irrespective of whether the intervention itself is primarily aimed at patients or their caregivers.
References


Chapter 7

An economic evaluation of an augmented cognitive behavioural intervention vs. computerized cognitive training for post-stroke depressive symptoms.

Abstract

Introduction: Stroke survivors encounter emotional problems in the chronic phase after stroke. Post-stroke depressive symptoms have major impact on health-related quality of life (HRQoL) and lead to increased hospitalization and therefore substantial healthcare costs. We present a cost-effectiveness and cost-utility evaluation of a cognitive behavioural therapy augmented with occupational and movement therapy to support patients with a stroke with depressive symptoms in goal-setting and goal attainment (augmented CBT) in comparison with a computerized cognitive training program (CogniPlus) as a control intervention.

Methods: A trial-based economic evaluation was conducted from a societal perspective with a time horizon of 12 months. Stroke patients (aged 18+ years) with signs of depression (Hospital Anxiety and Depression Scale (HADS) – subscale depression > 7) were eligible to participate. Primary outcomes were the HADS and Quality Adjusted Life Years (QALYs) based on the three-level five-dimensional EuroQol (EQ-5D-3L). Missing data were handled through mean imputation (costs) and multiple imputation (HADS and EuroQol), and costs were bootstrapped. Sensitivity analyses were performed to test robustness of baseline assumptions.

Results: Sixty-one patients were included. The average total societal costs were not significantly different between the control group (€9,998.3) and the augmented CBT group (€8,063.7), with a 95% confidence interval (-5,284, 1,796). The augmented CBT intervention was less costly and less effective from a societal perspective on the HADS, and less costly and slightly more effective in QALYs, in comparison with the control treatment. The cost-effectiveness and cost-utility analyses provided greater effects and fewer costs for the augmented CBT group, and fewer effects and costs for the HADS. Based on a willingness to pay (WTP) level of €40,000 per QALY, the augmented CBT intervention had a 76% chance of being cost-effective. Sensitivity analyses showed robustness of results.

Conclusion: The stroke-specific augmented CBT intervention did not show convincing cost-effectiveness results. In addition to other literature, this study provided new insights into the potential cost-effectiveness of an adjusted cognitive behavioural therapy intervention. However, as our study showed a 76% chance of being cost-effective for one outcome measure (QALY) and did not provide convincing cost-effectiveness results on the HADS we recommend further research in a larger population.
Introduction

Stroke is a leading cause of death and a source of persistent disability around the world.\(^1\) Annually, 6.7 million people die from stroke, representing 12% of all global deaths\(^2\) As a disease of aging, the prevalence of stroke is expected to increase significantly around the world in the years ahead as the global population older than 65 years of age continues to increase by approximately nine million people per year.\(^3\) Stroke survivors often encounter severe cognitive and emotional consequences.\(^4\) Post-stroke depressive symptoms occur frequently in the chronic phase after stroke.\(^5\)\(^-\)\(^9\) Recent data from the National Stroke Association (United Kingdom) show that approximately one-third of stroke survivors is affected by varying degrees of post-stroke depression amongst other symptoms.\(^10\) In addition, these symptoms often coincide with increased feelings of anxiety.\(^11\) Besides the major impact on health-related quality of life (HRQol),\(^12\) post-stroke depressive symptoms are associated with increased hospitalization and therefore substantial healthcare costs.\(^13\)

Stroke puts a high burden of disease on patients and their caregivers, as well as a considerable financial burden on society. Currently, approximately 3–4% of total healthcare expenditures in Western countries are spent on stroke.\(^14\) Even greater healthcare expenditures are likely in the near future, with expected increases in the elderly population and the availability of new and better treatments for stroke patients. As healthcare resources are limited and choices have to be made, interest in the economic aspect of stroke and cost-effective stroke-specific interventions has increased in the past few years.\(^15\)

Previous research has been used to evaluate different interventions focusing on the treatment of post-stroke depressive symptoms, such as pharmacological interventions\(^16,17\) yet evidence for the effectiveness of stroke-specific psychological interventions is limited.\(^18\) This is mainly related due to possible lack of efficacy of the interventions under investigation, but also caused by poor study design.\(^19\) There are, however, indications that the use of cognitive behavioural therapy (CBT) might be both effective and cost-effective, based on the treatment of other chronic conditions.\(^20\)\(^-\)\(^25\) Psychological interventions, such as CBT, seem promising in terms of effectiveness because they result in fewer side effects than medication and have a stronger effect on preventing relapse of symptoms than pharmacotherapy.\(^20,26,29\) With respect to psychological interventions, fewer side effects and reduction in relapse are potentially strong indicators for cost-effectiveness. Furthermore, the characteristics of CBT seem to suggest it ought to
be an especially good fit to meet the needs of people who suffer from post-stroke depression.\textsuperscript{17} Depressed stroke survivors endorse significantly more negative conditions than non-depressed stroke survivors.\textsuperscript{30,31} In addition, there is good evidence that remaining active, expressing emotion and finding positive meaning ensures good psychological adjustment in other chronic illnesses.\textsuperscript{32} The current study describes the cost-effectiveness and cost-utility of a cognitive behavioural therapy augmented with occupational and movement therapy to support stroke patients with depressive symptoms in goal setting and goal attainment (augmented CBT) for stroke patients suffering from post-stroke depressive symptoms, in comparison with a computerized cognitive training program (CogniPlus) as a control intervention. Our aim was to determine the cost-effectiveness of both interventions from a societal perspective.

\textbf{Methods}

\textbf{Guidelines}

The current study and economic evaluation were performed according to the Consolidated Health Economic Evaluation Reporting Guidelines (CHEERS).\textsuperscript{33}

\textbf{Design}

The current study describes an economic evaluation which was linked to the Restore4stroke CBT study: a multi-centre randomized controlled trial (RCT) conducted in five rehabilitation centres and in the rehabilitation department of one general hospital in the Netherlands. The Medical Ethics Committee of the Radboud University Medical Centre and the executive boards of the participating institutes approved the study. The inclusion of participants took place between February 2012 and October 2013. All patients provided written informed consent. The RCT was registered in the Dutch Trial Register as NTR2999. Detailed information on the methods of this RCT and the current study can be found elsewhere.\textsuperscript{15,34}

\textbf{Eligibility criteria}

Patients where included if they: (1) suffered any type of stroke in the last three months and complaints in mood (indicating possible symptoms of anxiety or depression) occurred post stroke, (2) were 18 years or older, (3) scored $\geq 7$ on the HADS depression subscale (HADS-D),\textsuperscript{35} (4) mastered the Dutch language, and (5)
had sufficient communication skills based on the Mini-Mental State Examinate\textsuperscript{36} \(> 27\) and had normal score \((> 0)\) on communication items of the National Institutes of Health Stroke Scale items.\textsuperscript{37} Patients were excluded if they: (1) scored \(< 19/20\) on the Barthel Index\textsuperscript{5} indicating premorbid disabilities, (2) were staying in an in-patient setting, (3) suffered from co-morbidity that might affect outcomes (e.g. cancer or major psychiatric illnesses for which psychological treatment was being given at the moment of inclusion), (4) were diagnosed with a major depression requiring medication, or (5) were diagnosed with a pre-morbid depression or had received psychiatric care for depression.

**Interventions**

The augmented CBT intervention was individually administered and tailored according to specific subjects’ own activity-related goals. These goals could capture domains as e.g. self-care, leisure, household, work, and improvement of mobility-related goals such as movement and walking. The CBT treatment program consisted of 10–12 sessions with a certified healthcare psychologist, experienced in the treatment of depression and stroke rehabilitation. The augmentation part of the intervention was specifically aimed at supporting patients in goal setting and goal attainment. This part consisted of three sessions of occupational therapy (OT) or movement therapy (MT) provided by an occupational or movement therapist. Each of these sessions was comprised of 20-25 minutes blocks divided by a 10-15 minute break. If a patient’s score on the HADS subscale anxiety (HADS-A) was \(> 7\), the protocol was expanded with an additional (fourth) OT/MT session.\textsuperscript{38} All treatments were provided at the closest participating centre and the complete program was executed within four months.

The control group was provided with an individual, patient-tailored computerized cognitive training program (CogniPlus).\textsuperscript{39} In specific self-determined cognitive domains (e.g. attention, memory, executive functioning, and visual attention) patients executed computer tasks on their own performance level. This impairment-oriented intervention consisted of 13-16 sessions provided at participating centres under the supervision of a research assistant or psychological assistant, for a period of four months. We chose to compare the augmented CBT intervention to an ‘active’ intervention (and not usual care) to control for Hawthorne effects. Evidence from Spikman et al.\textsuperscript{40} showed that a similar control group did not improve in executive functioning, and that generalisation of what was assessed in the control intervention to daily life did not occur. Further information on the justification of both interventions can be found elsewhere.\textsuperscript{15,34}
Procedure
Treating physicians and healthcare psychologists of the participating institutes were informed about the inclusion and exclusion criteria of the study. Accordingly, they recruited eligible patients at participating centres. Potential participants were contacted by the primary researcher (JK) and informed about the intervention. In case of a positive reply, an individual appointment was made to confirm the inclusion and exclusion criteria, to obtain written consent, and to conduct the baseline assessment. Patients were randomly allocated to either the augmented CBT group or control group. Stratified block randomization (block size four) was conducted, in which level of anxiety was a minimization factor (HADS-A > 7 vs ≤ 7). Follow-up assessments took place at the nearest participating centre for each patient and were conducted by a research assistant who was blinded to the type of intervention provided to the patient. Prior to each assessment, the assessor explicitly asked patients not to talk about the content of their intervention. The success of assessor blinding was ensured with a short self-constructed questionnaire at the end of each assessment.

Time horizon
Patients were randomly allocated to one of the interventions after the baseline assessment (T0). Assessments took place post treatment (T1), at eight months follow-up (T2) and at twelve months follow-up (T3).

Sample size
Based on a minimal detectable effect size of 0.6 the standard deviation (SD) on the HADS (α=0.05; β=0.80), a minimum of 45 participants per group was required. With an expected dropout of 15%, 106 participants needed to be recruited. However, due to recruitment difficulties we were not able to include the minimum amount of participants necessary. Reconsidering the proposed analysis of the Restore4stroke CBT study, it was decided to add the T1 measurement next to T2 to estimate the effect of treatment outcomes. These repeated measures at T1 and T2 would reduce variance, double the power and reduce the required sample size. Therefore, a new power (n=53; α=0.05; β=0.80) allowed us to continue with fewer participants than originally planned. The Medical Ethics Committee approved an amendment containing these changes.
Outcome measures

The main outcome for the cost-effectiveness analysis (CEA) was depression and anxiety, assessed by the HADS (total score). The HADS is a 14-item questionnaire (seven questions concerning ‘depression’ and seven questions concerning ‘anxiety’) on a 4-point scale. Higher scores on the HADS indicate greater levels of depression and/or anxiety. The validity and reliability of the HADS has been determined in previous research.41 The main outcome for the cost-utility analysis (CUA) was health-related quality of life (further referred to as QoL), as measured by the five-dimensional three-level EuroQol (EQ-5D-3L).42 The five EuroQol dimensions are mobility, self-care, usual activities, pain/discomfort and anxiety/depression. To estimate the utility of health states described by patients, we used the Dutch tariff.43 Quality adjusted life years (QALYs) were calculated by means of the area under the curve method. Higher QALYs indicate more improvement in QoL.

Resource use and costs

A 19-item self-report cost-questionnaire was constructed to collect cost data from a societal perspective, based on the steps described by Thorn.44 The validity and feasibility of generic self-report questionnaires has been investigated elsewhere.45 As a societal perspective is a broad perspective in which all relevant costs for the whole population are incorporated,46 we included four main cost categories in this study: intervention, healthcare, patient- and family-related, and productivity costs. A bottom-up approach was used to determine intervention costs (e.g. intervention materials, consultation hours with a psychologist). Healthcare costs covered care provider utilization (e.g. general practitioner and medical specialist consultations), complementary medicine, home care and medication. As a guideline for calculating healthcare costs we used the Dutch Manual for Costing.47 Medical and personal aids were based on costs per user within the aid category provided by the Dutch care institute and the costs of prescription medicines were valued by the price per dosage for drug costs in the Netherlands.49,50 Travel costs and costs of informal care were included as patient- and family costs. Travel costs were calculated by multiplying the average distance with standard price weights provided by The Dutch Manual for Costing,47 corrected for the costs of public transport and parking costs. Shadow prices were used to determine the costs of informal care, which were equal to the hourly wage rates.
of professional caregivers (i.e. housekeepers). Productivity costs were valued according to the human capital approach. This approach states that productivity costs are calculated by multiplying the number of sick days by the costs of labour, corrected for different age categories. The human capital approach is the international standard in calculating productivity costs, whereas its counterpart, the friction cost method, is subject to variability in the national economic cycles. Furthermore, due to changes in Dutch legislations, it is unlikely for employees that they are being replaced, making it imperative to include long-term absenteeism as well.

Currency, price date and conversion
All costs reported in this study were expressed in Euro’s (€). Consumer price indices were used to adjust all costs to the index year 2012. Discounting was not necessary since the follow-up period of the current study did not exceed one year.

Analytic methods
Intention-to-treat was used to analyse data. Missing values for resource use were handled by individual mean imputation, the recommended imputation methods on dealing with intermittent data in economic evaluation studies. Missing data on the main outcomes were handled by multiple imputation (MI). MI is a technique often used to analyse data sets with missing values; it is the process of replacing each missing data point with a set of plausible values to generate complete data sets. Since baseline utility measurements are included when calculating QALYs we consider any baseline difference in utility scores as a potential bias, regardless of whether or not this difference is significant or not. Therefore, we used a regression based correction method to correct for baseline differences in utility scores.

An incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental costs by the incremental effects, and an incremental cost-utility ratio was calculated by dividing the incremental costs by the differences in QALY. We used non-parametric bootstrapping (5000 replications) to estimate the uncertainty surrounding the ICER, due to the highly skewed cost distribution. Bootstrapped cost-effectiveness and cost-utility pairs were presented in cost-effectiveness planes (CE-planes). Statistically significant differences in costs were determined by means of a 95% confidence interval (further referred to as CI). If
the CI entailed a ‘0’ value, no statistical differences in costs were found. Furthermore, a cost-effectiveness acceptability curve (CEAC) was made to express the probability of the augmented CBT intervention being a cost-effective alternative in comparison with the control intervention. A CEAC shows the probability of an intervention to be a cost-effective alternative for a certain threshold; the amount of money society is willing to pay (WTP) to gain one unit of effect (e.g. a one-point improvement on the HADS or one QALY). For the HADS, the WTP threshold is an unknown quantity. A previous study on manual psychological therapy for dementia patients used a WTP level of €500 per one-point improvement on the HADS. The minimal important difference of the HADS has not been established, but in patients with chronic obstructive pulmonary disease (COPD) a minimal important difference of 1.6 was found. The WTP threshold for a QALY differs per country or even within countries. In the Netherlands, the Dutch Council of Public Health and Care published a report in 2006 regarding the burden of disease in the Netherlands, estimating a QALY threshold for stroke at €40,000 Euros. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21 or Microsoft Excel (bootstrapping).

Sensitivity analyses

To test the robustness of assumption made in the base case analyses, we conducted four one-way sensitivity analyses. First, the price for a rehabilitation day treatment was decreased to €117, equal to a regular rehabilitation consultation. Second, the friction cost method was used to calculate productivity costs instead of the human capital approach. Third, we compared our base case societal perspective for calculating costs with a healthcare perspective. Finally, as different sets of tariffs exist to calculate utilities, we analysed the impact of the use of Dutch tariffs versus United Kingdom (UK) tariffs.

Results

Sample

One hundred sixty-three patients were assessed regarding their eligibility for participation in this study (Figure 1). Eighty-three patients were found ineligible based on their HADS-D score (≤7) and 15 patients did not meet other inclusion criteria. After baseline measurement, four patients dropped out due to various reasons. Thus, a total of 61 patients were included in this study (Table 1). Thirty-
Patients assessed for eligibility (n=163)

Patients not eligible based on HADS depression < 7 (n=83)
Patients did not consent to inclusion (n=15) due to
- Comorbidity (n=7)
- Not interested (n=5)
- Not specified (n=3)
Drop-out after baseline measurement (n=4)
- Started anti-depressants (n=1)
- Logistic problems (n=1)
- Not specified (n=2)

Patients randomly assigned (n=61)

Patients assigned to the augmented CBT intervention (n=31)

Patients assigned to the augmented CogniPlus intervention (n=30)

Patients completed augmented CBT intervention (n=23)
Patients assessed post treatment T1 (n=24)

Patients completed CogniPlus intervention (n=22)
Patients assessed post treatment T1 (n=28)

Patients assessed at T2 after eight months (n=24)

Patients assessed at T2 after eight months (n=24)

Patients assessed at T3 after twelve months (n=23)

Patients assessed at T3 after twelve months (n=21)

Figure 1. Flow Chart trial (CONSORT Diagram)
one patients (52%) were allocated to the augmented CBT group and 30 patients (48%) to the control group. As presented in figure 1, the percentage of missing data at T1 was 15% (n=9), at T2 was 21% (n=13) and at T3 was 28% (n=17).

Table 1. Baseline patients’ characteristics (n=61)

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Augmented CBT (n=31)</th>
<th>CogniPlus (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n M(SD) / %</td>
<td>n M(SD) / %</td>
<td></td>
</tr>
<tr>
<td>Mean age in years</td>
<td>31 62.2 (8.3)</td>
<td>30 60.0 (10.5)</td>
</tr>
<tr>
<td>Gender (men)</td>
<td>31 61.3</td>
<td>30 63.3</td>
</tr>
<tr>
<td>Paid work</td>
<td>31 29</td>
<td>30 43.3</td>
</tr>
<tr>
<td>Hours worked/week</td>
<td>31 2.3 (5.6)</td>
<td>30 5.5 (12.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stroke characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since stroke in months</td>
</tr>
<tr>
<td>Type of stroke (infarction)</td>
</tr>
<tr>
<td>Affected hemisphere (right)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects</td>
</tr>
<tr>
<td>HADS Total</td>
</tr>
<tr>
<td>HADS Anxiety</td>
</tr>
<tr>
<td>HADS Depression</td>
</tr>
<tr>
<td>Utility</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare costs (€)</td>
</tr>
<tr>
<td>Non-healthcare costs (€)</td>
</tr>
<tr>
<td>Total societal costs (€)</td>
</tr>
</tbody>
</table>

Cost analysis
The average total societal costs were greater for the control group (€9,998) in comparison with the augmented CBT group (€8,064), but this difference between the two groups was not significant (CI: -5284, 1,796). Healthcare costs were also greater for the control group (€5,055 compared to €3,771), but this difference was not significant either (CI: -3,039, 465). Specialist visits was the only cost category within healthcare costs that showed significantly greater costs for the control group (€993) in comparison with the augmented CBT group (€539) (CI: -868, -38). The non-healthcare costs were also in favour of the intervention group (€4,926 in comparison with €4,333 in the control group), however, no significant
Table 2. Average resource use and costs per category over 12 months (bootstrapped)

<table>
<thead>
<tr>
<th>Category</th>
<th>Augmented CBT intervention (n=31)</th>
<th>CogniPlus intervention (n=30)</th>
<th>95%CI1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unit price</td>
<td>Average use (SD)</td>
<td>Average costs Euros (SD)</td>
</tr>
<tr>
<td>Healthcare</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>Night</td>
<td>0.5 (2.3)</td>
<td>255.9 (187.7)</td>
</tr>
<tr>
<td>Rehabilitation centre</td>
<td>Night</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>Nursing home</td>
<td>Night</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>General practitioner</td>
<td>Consultation</td>
<td>9.6 (9.2)</td>
<td>285.8 (48.2)</td>
</tr>
<tr>
<td>Specialist</td>
<td>Consultation</td>
<td>4.2 (5.1)</td>
<td>538.8 (113.1)</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>Consultation</td>
<td>23.5 (34.0)</td>
<td>893.2 (233.3)</td>
</tr>
<tr>
<td>Remedial therapy</td>
<td>Consultation</td>
<td>5.5 (11.6)</td>
<td>207.0 (79.8)</td>
</tr>
<tr>
<td>Mensendieck</td>
<td>Consultation</td>
<td>0.5 (2.9)</td>
<td>20.4 (19.1)</td>
</tr>
<tr>
<td>Occupational therapy</td>
<td>Consultation</td>
<td>2.8 (5.4)</td>
<td>64.1 (22.1)</td>
</tr>
<tr>
<td>Activity therapy</td>
<td>Consultation</td>
<td>1.3 (5.4)</td>
<td>46.1 (35.2)</td>
</tr>
<tr>
<td>Speech therapy</td>
<td>Consultation</td>
<td>2.6 (10.9)</td>
<td>88.5 (65.7)</td>
</tr>
<tr>
<td>Social work</td>
<td>Consultation</td>
<td>0.2 (0.8)</td>
<td>12.9 (9.7)</td>
</tr>
<tr>
<td>Psychologist</td>
<td>Consultation</td>
<td>7.0 (8.6)</td>
<td>581.6 (126.4)</td>
</tr>
<tr>
<td>Psychiatric nurse</td>
<td>Consultation</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>Psychiatrist</td>
<td>Consultation</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>Rehabilitation day treatment</td>
<td>Day</td>
<td>1.4 (5.5)</td>
<td>375.9 (264.2)</td>
</tr>
<tr>
<td>Medication</td>
<td>Other</td>
<td>410.0 (114.2)</td>
<td>374.3 (108.5)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td>3,771.3 (551.5)</td>
<td>5,055.3 (713.0)</td>
</tr>
</tbody>
</table>
Table 2. Average resource use and costs per category over 12 months (bootstrapped) (continued)

<table>
<thead>
<tr>
<th>Category</th>
<th>Unit price</th>
<th>Augmented CBT intervention (n=31)</th>
<th>CogniPlus intervention (n=30)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Average use (SD)</td>
<td>Average costs Euros (SD)</td>
<td></td>
</tr>
<tr>
<td>Non-healthcare</td>
<td></td>
<td>Average use (SD)</td>
<td>Average costs Euros (SD)</td>
<td></td>
</tr>
<tr>
<td>Travel costs</td>
<td>Other</td>
<td>289.4 (48.9)</td>
<td>301.3 (41.2)</td>
<td>(-137, 119)</td>
</tr>
<tr>
<td>Productivity costs</td>
<td>Hours/week</td>
<td>0.3 (1.2)</td>
<td>243.5 (206.4)</td>
<td>1.7 (4.3) 1,648.8 (728.5)</td>
</tr>
<tr>
<td>Productivity costs caregiver</td>
<td>Hours/week</td>
<td>0.0 (0.1)</td>
<td>12.9 (12.4)</td>
<td>0.6 (2.1) 615.2 (347.8)</td>
</tr>
<tr>
<td>Paid help</td>
<td>Hours</td>
<td>45.9 (71.2)</td>
<td>1,728.8 (477.2)</td>
<td>28.2 (53.3) 1,061.2 (368.9)</td>
</tr>
<tr>
<td>Unpaid help</td>
<td>Hours</td>
<td>60.4 (141.9)</td>
<td>813.7 (315.7)</td>
<td>40.3 (86.7) 539.9 (204.7)</td>
</tr>
<tr>
<td>Tools(^{3})</td>
<td>Item</td>
<td>157.0 (54.0)</td>
<td>78.6 (33.5)</td>
<td>(-46, 209)</td>
</tr>
<tr>
<td>Home adjustments(^{3})</td>
<td>Item</td>
<td>0.0 (0.0)</td>
<td>134.5 (120.2)</td>
<td>(-400, 0)</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>4,333.6 (745.7)</td>
<td>4,926.0 (835.3)</td>
<td>(-2,778, 1,551)</td>
</tr>
<tr>
<td>Intervention costs</td>
<td>Other</td>
<td>1,129.8</td>
<td>592.1</td>
<td></td>
</tr>
<tr>
<td>Total societal costs</td>
<td></td>
<td>8,063.7 (1,126.1)</td>
<td>9,998.3 (1,370.1)</td>
<td>(-5,284, 1,796)</td>
</tr>
</tbody>
</table>

\(^{1}\)significant difference
\(^{2}\)95% Confidence Interval level
\(^{3}\)Tools: e.g. brace, special glasses; Home adjustments: e.g. toilet or shower adjustment
difference was found (CI: -2,778, 1,551). Both the productivity costs (CI: -3,065, -93) and the productivity costs of the caregiver (CI: -1,354, -27) were significantly greater for the control group. As expected, intervention costs were greater for the augmented CBT group (€1,130 in comparison with €592). Further details are presented in Table 2.

Cost-effectiveness and cost-utility

The CEA for the HADS showed that the augmented CBT group induced fewer costs (€1,913) but also fewer effects (-0.8), resulting in an ICER of €2,395 (Table 3). The majority of bootstrapped ICERs (58%) were located in the southwest (SW) quadrant of the CE-plane (Figure 2) indicating fewer costs and fewer effects for the augmented CBT intervention, and 29% of the bootstrapped ICERs were located in the dominant southeast (SE) quadrant indicating greater effects and fewer costs for the augmented CBT intervention.

Patients in the augmented CBT group gained slightly more QALYs (mean: 0.01) compared to control group patients. More QALYs gained combined with fewer societal costs (€1,913) induced by the augmented CBT group resulted in a dominant ICER. As presented in Figure 3, 31% of the bootstrapped ICERs were located in the SW quadrant (fewer costs and effects) of the CE-plane and 55% of the bootstrapped ICERs were located in the dominant SE quadrant (fewer costs and greater effects).

The cost-effectiveness acceptability curves (CEACs) of the HADS and QALY are also presented in Figures 2 and 3. The slope of the HADS CEAC indicates that with a WTP threshold of €2,500, the probability of the augmented CBT intervention being cost-effective was 49%. Furthermore, greater WTP levels showed an increasing decline in the probability of the augmented CBT intervention being cost-effective. In the Netherlands, there is no fixed WTP threshold for a QALY, but the threshold is dependent on the burden of disease. Based on the burden of stroke, a WTP level of €40,000 was considered acceptable. Using this threshold, the QALY CEAC indicates that there is a 76% chance that the augmented CBT intervention will be cost-effective.

Sensitivity analysis

A sensitivity analysis was performed to estimate the impact of reducing the price of a rehabilitation treatment day, on the cost-effectiveness results. The analysis proved robustness of the base case assumption for this parameter for both the
### Table 3. Mean cost and effect differences between the Augmented CBT group and CogniPlus group, incremental cost-effectiveness ratios and cost-effectiveness plane distributions

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Effect measure</th>
<th>Augmented CBT</th>
<th>CogniPlus</th>
<th>ΔCosts</th>
<th>ΔEffects</th>
<th>ICER¹</th>
<th>Distribution cost-effectiveness plane (quadrant,%)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost-effectiveness</td>
<td>HADS</td>
<td>31</td>
<td>30</td>
<td>-1,912.6</td>
<td>-0.8</td>
<td>2,395.3</td>
<td>NE 29 58 SW 8</td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td>QALY</td>
<td>31</td>
<td>30</td>
<td>-1,912.6</td>
<td>0.01</td>
<td>-160,389.9</td>
<td>NE 55 31 SW 9</td>
</tr>
</tbody>
</table>

¹ICER: incremental cost-effectiveness ratio
²NE (northeast quadrant): SM more effective and more costly compared to EDU; SE (southeast quadrant): SM more effective and less costly compared to EDU; SW (southwest quadrant): SM less effective and less costly compared to EDU; NW (northwest quadrant): SM less effective and more costly compared to EDU

### Table 4. Sensitivity analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>ΔCosts (€)</th>
<th>ΔEffects</th>
<th>ICER²</th>
<th>Distribution cost-effectiveness plane (quadrant,%)³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case HADS</td>
<td>-1,912.6</td>
<td>-0.8</td>
<td>2,395.3</td>
<td>NE 29 58 SW 8</td>
</tr>
<tr>
<td>Unit price day of rehabilitation</td>
<td>-1,787.0</td>
<td>-0.8</td>
<td>2,238.0</td>
<td>NE 29 57 SW 9</td>
</tr>
<tr>
<td>Friction costs</td>
<td>-796.4</td>
<td>-0.8</td>
<td>997.4</td>
<td>NE 23 46 SW 19</td>
</tr>
<tr>
<td>Healthcare perspective</td>
<td>-1,281.4</td>
<td>-0.8</td>
<td>1,604.7</td>
<td>NE 31 61 SW 5</td>
</tr>
<tr>
<td>Base case QALY</td>
<td>-1,912.6</td>
<td>0.01</td>
<td>-160,389.9</td>
<td>NE 55 31 SW 9</td>
</tr>
<tr>
<td>Unit price day of rehabilitation</td>
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<td>0.01</td>
<td>-149,859.6</td>
<td>NE 54 33 SW 9</td>
</tr>
<tr>
<td>Friction costs</td>
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<td>0.01</td>
<td>-66,784.4</td>
<td>NE 46 24 SW 18</td>
</tr>
<tr>
<td>Healthcare perspective</td>
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<td>0.01</td>
<td>107,454.7</td>
<td>NE 6 6 36</td>
</tr>
<tr>
<td>QALY UK tariff</td>
<td>-1,912.6</td>
<td>0.04</td>
<td>-51,797.4</td>
<td>NE 65 22 SW 6</td>
</tr>
</tbody>
</table>

¹Base case analysis values a day of rehabilitation day as a hospital treatment day (€266.53), calculates production costs by means of human capital method, uses the societal perspective to calculate total costs, corrects for baseline differences with regression analysis and calculates utilities with a Dutch tariff. Sensitivity analyses values a rehabilitation treatment day as a rehabilitation contact (€116.81), calculates production costs with the friction cost method, estimates total cost from a healthcare perspective calculates utilities with a UK tariff.

²ICER: incremental cost-effectiveness ratio
³NE (northeast quadrant): SM more effective and more costly compared to Edu; SE (southeast quadrant): SM more effective and less costly compared to Edu; SW (southwest quadrant): SM less effective and less costly compared to Edu; NW (northwest quadrant): SM less effective and more costly compared to Edu
Figure 2. Cost-effectiveness plane HADS and cost-effectiveness acceptability curve HADS.

Figure 3. Cost-effectiveness plane QALY and cost-effectiveness acceptability curve QALY.
HADS and QALY, as it resulted in a slightly lower ICER and no major changes in distributions on the CE-plane (Table 4). Calculating productivity costs by means of the friction cost method resulted in a much lower ICER for both the HADS and QALY and major shifts in distributions on the CE-plane to both ‘west’ quadrants (indicating fewer costs for the augmented CBT group). Estimating total costs from a healthcare perspective resulted in lower ICERs for both outcome measures; this was due to fewer cost categories being included. A major shift on the CE-plane of the QALY is noticeable towards the northeast (NE) quadrant (greater costs and greater effects). Finally, UK tariffs were used to calculate QALYs resulting in a decrease in ICER, and again, a shift on the CE-plane towards the SE quadrant.

Discussion

To our knowledge, this is the first cost-effectiveness analysis performed on a prospective randomized comparison of an augmented CBT intervention versus computerized cognitive training (CogniPlus) for post-stroke depressive symptoms. The results of this study provide evidence that, using the HADS as an outcome, the augmented CBT intervention for stroke patients was less costly and less effective from a societal perspective and less costly and slightly more effective in terms of QALYs, compared to the control treatment. Cost differences between the two groups could be explained by costs of admission to a hospital, specialist consultations and home adjustments, but the larger part of the difference in total costs was due to productivity costs of both the patient and the caregiver which were both significantly less in the augmented CBT group. The fact that, at baseline, 43.3% of the control group had paid work, in comparison with only 29% of the augmented CBT group, and that patients in the control group worked more than twice the number of hours per week might explain this difference. The results of the cost-effectiveness analysis showed that the probability of the augmented CBT intervention being cost effective was 49% for a WTP of €2,500. No fixed WTP threshold for the HADS exists, but previous research used a WTP of €500 per point improvement on the HADS based on expert opinion. A dominant ICER for the QALY was found, indicating greater effects and fewer costs for the augmented CBT group. Combined with a high probability of the augmented CBT intervention being cost-effective, the results from the cost-utility analysis were in favour of the augmented CBT intervention. However, due to the minimal difference in effects (mean: 0.1), these results should be interpreted with caution.
In general, the sensitivity analyses showed robustness of results. For the HADS, a distinct shift in the distribution of bootstrapped ICERs was noticeable when calculating productivity costs with the friction method. This might be expected, since the friction cost method accounts for a shorter period of productivity losses resulting in fewer costs, and a lower ICER with the same difference in HADS score and a slightly greater probability of the augmented CBT intervention being cost-effective. This was also observed for the friction method, employed as a sensitivity analysis with regard to QALYs. A major shift was noticeable when conducting the cost-utility analysis from a healthcare perspective instead of the societal perspective. It appeared that the augmented CBT group induced both greater costs and greater effects leading to a shift on the CE plane towards the NE quadrant. This, and the fact that the difference in effect was minimal, indicated that the majority of total costs for the control group were accounted for by non-healthcare costs.

To our knowledge, this current study provides new but preliminary evidence on the cost-effectiveness of a stroke-specific augmented cognitive behavioural therapy. Four previous studies investigating a comparable intervention in different populations showed similar results. More precisely, recent research on the effectiveness of an online CBT intervention for depressive patients found greater costs for CBT group and a cost per QALY gained of €23.857, which is below the acceptable UK threshold of €27.784 per QALY. Although this study was conducted from a National Health Services (NHS) perspective and the CBT intervention was compared with care as usual, the conclusions drawn from this study where in line with the current study results, indicating the potential cost-effectiveness of CBT. Another study evaluating the effectiveness of CBT for depressive patients in a non-stroke population reported greater costs and greater effects in terms of QALYs, resulting in a base case ICER of €20.714. Two other studies on the cost-effectiveness of CBT for patients with low-back pain and for people with schizophrenia-spectrum disorder also showed the possible cost-effectiveness of cognitive behavioural therapy. It is important to note that these previous studies chose ‘care as usual’ as comparator, whereas the current study chose a computerized training (CogniPlus). The choice of comparator is a critical design parameter in economic evaluation research and may influence study results.

Strengths and limitations

To our knowledge, there has been no previous economic evaluation research on a
stroke-specific cognitive behavioural therapy. Furthermore, the cost-effectiveness and cost-utility analyses in this study were conducted from a societal perspective, which is also considered to be a strength because it provides extensive evidence on a broad range of costs. Finally, both the outcome assessors and research assistants were blinded for the randomised treatment.

The current study was also subject to several limitations. First, due to recruitment difficulties we were not able to include the desired amount of participants, which was the reason for performing a new power calculation. Still, the current study results must be interpreted with caution due to the small sample size. Next, we had to deal with a considerable number (n=17; 28%) of missing values on T3 measurement concerning the HADS and EQ-5D-3L. A multiple imputation (MI) method was used to handle these missing values. There are alternative methods for imputation, such as linear mixed models, but since cost-effectiveness analysis requires individual patient data we believe that MI was the best method for the analyses performed in the current study. Also, productivity costs of the caregivers were estimated with a mean hourly wage and a mean age, since information with respect to the employment of caregivers was limited. Finally, we found and measured differences between interventions within the time horizon chosen for this study. However, with progressing insight, we would argue that it would be interesting to expand the time horizon, by adding extra follow-up measurement moments or using modelling techniques in further research in order to identify the long-term effects of both interventions in comparison to each other.

Concluding remarks

Taking into account the limitations of the current study, we conclude that the preliminary results of the cost-effectiveness of the stroke-specific augmented CBT intervention under investigation were not convincing. As our study showed a 76% chance of being cost-effective for one outcome measure (QALY) and did not provide convincing cost-effectiveness results on the HADS. However, other studies showed the potential for the augmented CBT intervention to be cost-effective in treating depression. Although we have argued why we have chosen an ‘active’ control intervention, it would be very interesting to investigate the effect of including a care as usual group as third study arm in future research. Also, in addition to other literature, this study provided new insights into the potential cost-effectiveness of an adjusted cognitive behavioural therapy intervention. Therefore, for further research we would recommend recruitment of a larger stroke population, i.e. in multiple sites.
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Summary

Post-stroke depressive symptoms with or without anxiety are common in the chronic phase of stroke and have a negative impact on rehabilitation, social reintegration, and quality of life. Currently, there is no evidence-based treatment available for reducing these emotional problems post stroke. The main aim of this thesis was to develop and evaluate a new, augmented cognitive behavioural therapy (CBT) protocol for the treatment of post-stroke depressive symptoms, with or without symptoms of anxiety, in comparison to a (presumably ineffective) control treatment (i.e., computerized cognitive training, CogniPlus). The individual CBT was augmented with individual sessions of occupational or movement therapy to attain specific, practical goals in daily life. In chapter one, the physical and psychological consequences of stroke were introduced, together with current treatment options for post-stroke depressive symptoms and the underpinnings for choosing a psychological treatment approach in this thesis. Thereafter, the outline of this thesis was presented based on the following research questions:

1. Are psychological determinants important risk factors for depressive symptoms post stroke?
2. What components should be part of an augmented CBT protocol for depressive symptoms, taking into account the physical, cognitive and emotional sequelae of stroke?
3. Is such an augmented CBT effective to reduce depressive symptoms and improve social participation and quality of life of patients in the chronic phase after stroke?
4. Is such an augmented CBT also beneficial with respect to the perceived burden by caregivers?
5. Is such an augmented CBT for patients with depressive symptoms post stroke effective from an economical perspective?

In chapter two, the first research question was addressed. A longitudinal cohort study (based on the Restore4Stroke cohort study) provided data to determine the importance of psychological risk factors for developing depressive symptoms and symptoms of anxiety one year after stroke. Depressed mood and anxiety are the most commonly reported emotional disorders after stroke. Better knowledge of their risk factors will aid in developing adequate prevention and treatment strategies. Previous studies on risk factors for post-stroke depressive symptoms
and anxiety have generally focused on socio-demographic, premorbid and stroke-related patient characteristics. Some studies took into account psychological patient characteristics as potential risk factors as well, but these studies were either small sized, used a cross-sectional design, or regarded a limited set of psychological characteristics. Moreover, none of these studies provided quantitative values for the predictive strength of the identified risk factors, limiting the clinical application of their findings. In chapter two, we investigated the relative importance of socio-demographic, premorbid, stroke-related, and psychological patient characteristics for developing depressive symptoms and anxiety at one year post stroke in a large cohort of Dutch subacute patients (N=331) recruited in six general hospitals with a stroke unit. We conducted a longitudinal study to calculate predictive models for both depressive symptoms and anxiety one year after stroke, providing nomograms that can be used to estimate the predictive strength of each identified risk factor. Patients were included at stroke onset and followed up 2 and 12 months after stroke. Socio-demographic and premorbid/stroke-related information was recorded during hospital admission, whereas psychological characteristics were determined with postal questionnaires 2 months post stroke. Symptoms of depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS) 2 and 12 months post stroke. Multivariable logistic analysis was performed to analyze the influence of socio-demographic, premorbid/stroke-related, and psychological characteristics on depressive symptoms (depression subscale of HADS >7) and symptoms of anxiety (anxiety subscale of HADS >7) one year after stroke. The results showed that early depression, stroke severity, posterior cerebral artery stroke, and neuroticism independently explained the variance of depressive symptoms one year post stroke. Neuroticism and early anxiety independently explained the variance of symptoms of anxiety one year post stroke. We concluded that psychological characteristics appear to be stronger risk factors for post-stroke depressive symptoms and anxiety than previously determined socio-demographic and pre-morbid or stroke-related factors, which has clear clinical implications for the prevention and treatment of post-stroke mood disorders. The results from chapter two support a psychological approach to the prevention and treatment of post-stroke depressive symptoms. Currently, no evidence-based treatment is available for mood problems after stroke. Chapter three addressed the second research question and presented a new, psychological intervention for post-stroke depressive symptoms. In earlier research on depression in the general population it has been shown that depressive symptoms can be ameliorated by
CBT. The intervention we developed was based on CBT principles and was shown feasible in a pilot study. In order to meet the specific needs of stroke patients (considering sensorimotor, cognitive, as well as behavioral problems), we incorporated motivational interviewing, grief resolution, and psycho-education in the treatment. In addition, we emphasized for each session to take into account the cognitive deficits of the patients (i.e. to be concrete, accessible, structured, specific, and to repeat information). Moreover, we augmented the psychologist-administered therapy with the contribution of an occupational or movement therapist aimed at facilitating patients’ goal setting and attainment in daily life. The intervention consisted of 12 one-hour sessions with a psychologist and three to four one-hour sessions with an occupational or movement therapist. This psychological treatment protocol is innovative, as it applies CBT in a stroke-specific manner and supports goal attainment by incorporating occupational or movement therapy sessions.

The effectiveness of the CBT intervention was evaluated in a randomized controlled trial (RCT). In chapter four, the research protocol of this part of the Restore4Stroke study was described in detail. It was hypothesized that patients treated with augmented CBT, tailored to their individual needs, would show a larger decrease in depressive symptoms as assessed with the HADS (depression subscale) than those receiving computerized cognitive training (CCT). Additionally, the effects on various secondary outcome measures, among which quality of life (Stroke Specific Quality of Life scale), social participation (Utrecht Scale for Evaluation of Rehabilitation – Participation), and anxiety (HADS – anxiety subscale) were evaluated. Furthermore, it was hypothesized that the augmented CBT would be more beneficial with respect to alleviating the perceived burden (emotional as well as practical) of caregivers. To this aim, a multi-center, assessor-blinded, RCT was conducted. A sample of patients with depressive symptoms (HADS depression subscale >7) in the chronic phase of stroke was recruited and randomly allocated to either an experimental (augmented CBT) or a control (CCT) group. Outcomes were assessed at baseline, immediately post intervention, and at 4 and 8 months follow-up. This study is the first RCT that evaluates the (maintenance of) effects of augmented CBT on post-stroke depressive symptoms with or without symptoms of anxiety.

Chapter five reported the results of the study as outlined in chapter four. Sixty-one patients were randomized to either the CBT (n=31) or CCT (n=30) group. The analysis was performed with linear mixed models for repeated measures and showed a significant and persistent time effect on the subscale depression of
the HADS as well as on anxiety, social participation, and quality of life in both groups. However, there was no significant group x time effect for any of the outcome measures. These result imply that the augmented CBT intervention was not superior to CCT for the treatment of mood disorders after stroke based on patient-related outcomes.

The fourth research question was addressed in chapter six. As emotional symptoms of stroke survivors may also have negative effects on caregivers’ well-being, we invited patients’ caregivers to participate in the Restore4Stroke study as well. We investigated whether the applied interventions (CBT or CCT) influenced caregivers’ emotional burden (Involvement Evaluation Questionnaire for Brain Injury / IEQ-BI), practical burden (Caregiver Strain Index), mental health (General Health Questionnaire), and emotional symptoms (HADS). In total, 50 caregivers were assessed at baseline, immediately post treatment, and at 4 and 8 months follow-up. As in the patient trial, linear mixed models for repeated measures were used for statistical analysis. In contrast to the patients, caregivers of patients who received CBT reported significantly higher levels of mental health and less worrying about patients’ well-being after the intervention, corrected for baseline values. In addition, there were positive time effects on IEQ-BI, particularly on its subscales Worrying, Supervision and Tension. These results are remarkable as the patient trial did not show specific groups effects and suggest that augmented CBT aimed at improving patients’ emotional, behavioral and social functioning may positively affect some aspects of caregivers’ well-being.

The final research question was addressed in chapter seven, in which the cost-effectiveness and cost-utility of the RCT (chapter six) were presented from a societal perspective. As post-stroke depressive symptoms may have major impact on health-related quality of life (HRQol) and may lead to increased hospitalization and, therefore, substantial healthcare costs, a trial-based economic evaluation was conducted from a societal perspective with a time horizon of 12 months. In this study the primary outcomes were the HADS and Quality Adjusted Life Years (QALYs) based on the three-level five-dimensional EuroQol (EQ-5D-3L). Missing data were handled through mean imputation (costs) and multiple imputation (HADS and EuroQol), and costs were bootstrapped. Sensitivity analyses were performed to test robustness of baseline assumptions. The average total societal costs were not significantly different between the CCT group (€9,998.3) and the augmented CBT group (€8,063.7). The augmented CBT intervention was, however, less costly and less effective from a societal perspective based on the HADS, and less costly and slightly more effective in
terms of QALYs, in comparison with CCT. The cost-effectiveness and cost-utility analyses provided greater effects and fewer costs for the augmented CBT group, and fewer effects and costs on the HADS. Based on a willingness to pay (WTP) level of €40,000 per QALY, the augmented CBT intervention had a 76% chance of being cost-effective. Sensitivity analyses showed robustness of results. Overall, we concluded that our stroke-specific augmented CBT intervention did not show convincing cost-effectiveness.
General Discussion

This thesis describes the results of a study on augmented cognitive behavioral therapy for depressive symptoms after stroke. The study was embedded in a larger, more comprehensive research program entitled Restore4Stroke, that was focused on social reintegration and quality of life after stroke. This chapter discusses the present manuscript in the light of its field of research and clinical practice from three different perspectives. First, the profile of the patient with depressive symptoms after stroke is discussed. Second, I elaborate on how to treat patients with depressive symptoms after stroke. Third, this chapter focuses on how to assess and evaluate treatment results. Lastly, some methodological considerations are discussed, followed by future perspectives in the field of depressive symptoms after stroke.

Is there a profile of patients with depressive symptoms after stroke?

As stroke occurs without warning, there is little time to adjust to its consequences in daily life. Both stroke survivors and caregivers suddenly experience the effects that physical and cognitive impairments may have on daily life. These impairments limit their daily routines and hamper their ability to engage in meaningful or pleasurable activities, which has consequences for mood. Behavioral theories of depression suggest that engaging in pleasurable activities that bring a sense of mastery or pleasure influences mood positively.\(^1\) To help patients engage in meaningful activities requires creativity and flexibility of therapists. Goal attainment data of patients in the experimental (cognitive behavioral therapy; CBT) condition of our trial showed that meaningful or pleasurable activities of patients after stroke may vary greatly. For instance, patients reported activities such as baking cookies with grandchildren, playing petanque, attending a football match, or babysitting grandchildren (Figure 1). In a qualitative study of Ekstam, Uppgard, Von Koch and Tham (2007), stroke survivors reported loss of a variety of pleasurable activities that they were used to undertake in their pre-stroke life, such as traveling, car driving, gardening, and reading. Not participating in these daily life activities had negative effects on mood.\(^2\) Of the 27 people Ekstam and colleagues interviewed, the majority reported dissatisfaction even with life as a whole.
In addition to participation restrictions, cognitive impairments may influence mood as they impact on the way people think. Stroke survivors are often less flexible, less accurate, and struggle with problem solving. As a consequence, they are prone to interpret events and circumstances negatively, which makes it difficult to revalue tasks at hand, find other meaningful activities, or change the way they are used to undertake activities. Since cognitive processes are often compromised following stroke, patients may linger on and focus on negative information and thoughts, which is a risk for developing depressive symptoms. In addition, patients after stroke regularly misinterpret their bodily sensations, which induces fear and anxiety. For instance, during normal cycling they may interpret an increased heart rate as a sign of an upcoming recurrent stroke. Moreover, stroke survivors are often elderly adults, in which non stroke-related comorbidities are common. In summary, stroke survivors are less likely to participate in daily life activities than they did during their pre-stroke life and often suffer from negative thoughts, which has detrimental consequences for their activity level and mood.

How to diagnose or define ‘depressive symptoms post stroke’ appears to be intricate. According to the criteria of the Diagnostic and Statistical Manual of mental disorders (DSM-V), post-stroke mood disorders may be (i) a ‘mood disorder due to stroke with depressive features’, (ii) a ‘major depression-like episode’, or (iii) ‘mixed mood features’. For a ‘major depression-like episode’, a depressed mood or a loss of interest or pleasure must be present for at least two weeks, along with at least four other symptoms of depression (e.g., daily insomnia or hyper insomnia; weight loss without dieting, weight gains, or loss of appetite; loss
of energy or fatigue). A ‘mood disorder due to stroke with depressive features’ must entail depressed mood or loss of interest or pleasure along with less than five other symptoms of depression. Based on the earlier DSM version (DSM-IV), depression could only be assessed in patients without an acute brain condition. Thus, the adjusted criteria in the more recent version (DSM-V) indicate that the professional opinion on the presence and the definition of depressive symptoms post stroke has changed.

In the scientific literature there is also a debate about how to distinguish ‘(major) depression’ from ‘post-stroke depressive symptoms’ or from ‘post-stroke depression’. Evident commonalities between these diagnoses are feelings of sadness and behavioral-depressive changes. A critical difference from a major (endogenous) depression is that patients with post-stroke depressive symptoms show more reactive diurnal mood variations and emotionalism, absence of guilt, and rarely present with suicidal thoughts. There is a chance of overestimating mood problems after stroke if somatic symptoms, such as fatigue, are regarded as depressive symptoms. According to the DSM-V, chronic fatigue is a symptom of depression, but in the stroke population chronic fatigue may be a direct result of the brain damage. As the majority of stroke survivors experience chronic fatigue, the severity of depressive symptoms may be overestimated. Yet, recent research claims that somatic complaints do fit in a post-stroke screening for depression, because fatigue severity may be aggravated by depressed mood. Some researchers even mention ‘distress’ post stroke as a relevant mood disorder which indicates that, although the severity of depressive symptoms after stroke may vary greatly, many patients suffer from some form of mood or emotional disorder that may require clinical attention or treatment. In this thesis, we purposely and consistently used the wording ‘depressive symptoms’ to refer to post-stroke mood disorders, acknowledging the distinction with major depression.

How depressive post-stroke symptoms develop over time is not clear as increasing, decreasing, and dynamic incidence rates have been reported in the literature. Up till now, two studies aimed at identifying different post-stroke depression profiles describing the course of the symptoms over time. White and colleagues identified four trajectories based on a longitudinal qualitative analysis: (i) ‘resilience’, a group of patients that appear to be able to adjust to major changes in life; (ii) ‘ongoing crisis’, a group that experiences stroke as an additional burden to already existing life stress; (iii) ‘emergent mood disturbance’, a small group with depressive symptoms in the long term after stroke, occurring
after comorbidities or social issues independent of stroke; and (iv) ‘recovery from mood disturbance’, a group that reports initial fear of stroke recurrence but gradually regains a feeling of control over their life. In the latter group (‘recovery’ profile), independence, participation and self-efficacy was associated with the outcome of rehabilitation. Ayerbe and colleagues described four different trajectories based on a quantitative study of patients’ Hospital Anxiety and Depression Scale (HADS) scores: (i) ‘no depression’, in which depression never develops, (ii) ‘mild depression’, and (iii) ‘moderate depression’, both with increasing depressive symptoms over time, and (iv) ‘severe depression’, in which initially symptoms may decline but then increase in the long term. The ‘ongoing crisis’ profile from the qualitative study on the one hand, and the third and fourth categories of Ayerbe et al. on the other hand seem to reflect the patient group included in the present thesis. Although both studies describe profiles from a different perspective, they provide important information about the stroke population covering multiple time points, indicating that we should attend to the mood problems of patients with a long-term perspective.

Taken together, there is an ongoing debate on what ‘post-stroke depression’ entails and on what point in time after stroke depressive symptoms occur, change, persist, or should be treated. Comparing our patient group with the profiles presented above, there are similarities with the ‘ongoing crisis’ and ‘emergent mood disturbance’ profiles from the qualitative study, and with the ‘moderate’ and ‘severe depression’ group of Ayerbe and colleagues. More knowledge on how post-stroke depression profiles vary and how they should be identified is of great importance. For instance, as the profiles show fluctuations in symptom severity over time, regular assessments are necessary in the chronic phase to prevent overlooking depressive symptoms that appear later after stroke. It is also necessary to reduce the heterogeneity of clinical mood assessments post stroke and to obtain more knowledge of causative and other risk factors for effective prevention and targeted treatment.

There is quite some controversy concerning the risk factors for ‘post-stroke depression’, mainly because there is huge heterogeneity in the study methodology and the populations included. A recent meta-analysis of Shi and colleagues (2017) that analyzed 36 risk factor studies (including the study of chapter 2 of this thesis) showed that a history of mental illness was the most critical risk factor for ‘post-stroke depression’. Other risk factors were sex (female), higher age, neuroticism, family history of depression, severity of stroke, and severity of participation restrictions. In chapter 2, we already showed the importance
of early signs of depression, neuroticism, and stroke severity. From a behavioral perspective, it is not surprising that severity of stroke plays an important role in the occurrence of ‘post-stroke depression’, as higher levels of impairment have a greater impact on daily life activities and on role fulfillment. Next to that, the way patients cope with physical and cognitive changes appears to play a mediating role in experienced mood. In chapter 2, we emphasized that few studies have included psychological factors in their risk analysis. The Restore4Stroke Cohort study by Van Mierlo et al. has shown that early depressive symptoms, one of the risk factors for long-term depressive symptoms post stroke, were highly associated with other psychological factors such as passive coping, lack of optimism, and lack of acceptance.19 In the aforementioned qualitative study of trajectories of depressive symptoms post stroke, White and colleagues also emphasized that an external locus of control was apparent in the trajectories that most fitted our patient group.13 This implies that the way patients adjust to sudden physical and cognitive impairments after stroke has influence on the development of mood disorders. This is an important clinical finding, as coping and acceptance may be amenable to psychological interventions.

Depressive symptoms after stroke, what to do?

Depressive symptoms post stroke are associated with increased mortality, greater disability, and poorer quality of life. They also hamper rehabilitation, prolong hospitalization and, with that, enhance healthcare costs.20-23 Even when depressive symptoms diminish over time, the associated risks seem to remain. Although there is a lack of consensus on how to describe and identify the patients with depressive symptoms post stroke, the majority of studies highlights that most patients experience enhanced emotional strain, stressing the need for an appropriate treatment that remains helpful in the long term. Since the aforementioned risk analysis studies indicate that psychological factors play an important role, a psychological treatment approach seems warranted. The effects of CBT in related and other patient groups showed reduction of complaints, a lower relapse rate, and fewer side effects than pharmacotherapy which implies that, from a societal perspective, CBT is a potentially cost-effective intervention.3,24-28 Because stroke patients’ cognitive functions (e.g., attention, memory, executive functioning, flexibility) may be impaired, a psychological intervention should take into account these impairments and not be too strenuous.3 CBT focuses on changing both behavior and (negative) cognitions, however, CBT as applied in the healthy population may be too demanding for
patients after stroke, as it does not take into account the grief element after stroke, or concomitant physical or psychological consequences.\textsuperscript{29} We, therefore, designed an adjusted psychological intervention, taking into account individual cognitive impairments and grief, so that each patient could comprehend all of its content. The treatment focus was on achieving goals related to meaningful or pleasurable activities, an objective supported (‘augmented’) by individual sessions of occupational or movement therapy. Unfortunately, our trial (chapter 5) yielded no differences in improvement of HADS scores between the experimental group receiving CBT interventions and the control group receiving an equal amount of computerized cognitive training (CCT). We did, however, observe a significant improvement across time for both groups. Both interventions were administered during a similar time period and had a comparable intensity in terms of the duration of sessions. The CBT intervention was administered by a certified healthcare psychologist, who had ample experience with treating depressive and anxiety symptoms as well as with stroke rehabilitation in general. Although CCT was largely self-administered, either cognitive trainers or psychological assistants were continuously present to assist the participants during the training. In chapter 5, we already discussed whether the improvements in both groups could have been due to a nonspecific influence of time or attention, for instance a ‘Hawthorne effect’. At that point in our research, we had not yet analyzed the caregiver data nor evaluated the trial from an economical perspective. Remarkably, chapter 6 showed higher levels of mental health and less worrying about patients’ wellbeing for the caregivers of the CBT group. Moreover, results from the economic evaluation (chapter 7) showed that, in comparison to CCT, the CBT intervention was favorable based on the HADS total score and the QALY analysis.\textsuperscript{30} Although the effect sizes of these results were relatively small, it is important to interpret all patient, caregiver, and economic data to provide directions for more effective treatments from a holistic and societal perspective. A potential reason for the differential effects of the applied treatments on the caregivers may be related to the interaction in the home situation, as caregivers did not attend the therapy sessions. The two interventions were different in that the CBT included (activity-related) individual goal setting (see figure 1). These goals provided guidance to the content of the psychological sessions, while an occupational or movement therapist helped patients with attaining their goals. The CBT intervention coincided with a substantial amount of homework directed at either goal attainment or working with cognition schemes to investigate the relationships between thoughts, feelings and actions (chapter 4). Possibly one of
these components may have had a positive influence on the caregivers as well. For instance, having a partner that either commits to homework to achieve an activity related goal or, as a caregiver, being included in the goal itself (figure 1) may have had concomitant positive effects on the caregiver (chapter 5). As providing homework is often part of a psychological intervention, future research should take into account the concomitant effects of patient-directed interventions on caregivers’ well-being, particularly when such interventions include home assignments to achieve activity related goals. Moreover, caregivers may also play a supportive role in the implementation and the effects of home-based interventions.31

From the Restore4Stroke cohort study by Van Mierlo et al. we were able to infer that post-stroke depressive symptoms may fluctuate approximately 2 points on the HADS-D over a two-year course.12 As the reduction (improvement) in depressive symptoms observed in both patient groups of our trial was much larger (i.e., >4 points on HADS-D), we concluded that both CBT and CCT had beneficial effects on mood. The CBT protocol (chapter 4) was ‘augmented’ with several non-CBT components, making it difficult to indicate the exact components that may have had a beneficial effect or not.33 It may even be that tentative positive effects of, for example, goal attainment were neutralized by too strenuous thought-mediating psychological treatment. Therefore, in order to provide directions for future treatment, it is important to understand what may have caused the positive effects of CCT on mood. During the trial, some patients reported that they hoped to participate in the ‘new computerized treatment’, reflecting favorable expectations that may have positively affected their mood.34 Interestingly, in a study on the improvement of executive functioning in patients with acquired brain injury,35 a similar computerized cognitive training was reported to be ineffective, but with trainees showing a high satisfaction rate. Indeed, CCT provides immediate (positive) feedback on performance. Attaining high levels of (improved) performance may have led to personal satisfaction and improved self-efficacy with concomitant, positive effects on mood.36

Summarizing, our investigation shows that the results of the patient trial do not indicate that CBT is more effective than CCT to improve depressive symptoms after stroke.33 Yet, based on the caregiver data (chapter 6) and from a societal perspective, it appears that CBT has some advantage over CCT.30

As mentioned above, challenging negative or irrational thoughts may be hard for patients with cognitive impairments due to stroke. Limited cognitive flexibility and impaired attention and memory may make it hard to learn alternative ways
Chapter 8

of thinking and behavior. Acceptance and commitment therapy (ACT) (e.g., third wave of behavioral therapy) may, therefore, be an interesting alternative approach to treat post-stroke depressive and anxiety symptoms. ACT does not focus on changing cognitions regarding individual experiences, but rather concentrates on the affective ‘relationship’ one has with one’s experiences. ACT teaches patients to remain active whilst accepting their limitations in a ‘mindful’ way. In ACT six interlinked components are reflected in a hexaflex: (i) cognitive defusion, (ii) acceptance, (iii) contact with the present moment, (iv) self as context, (v) values, and (vi) committed action. This approach seems promising for patients with brain injury. Trials investigating ACT as a means of psychological adjustment after traumatic brain injury have recently commenced. As this psychotherapeutic approach does not entail changing the way stroke patients think and feel, it may be easier to apply with possibly beneficial effects on mood.

Although ACT may be promising for patients that are capable to talk about their problems, the application of any form of psychotherapy is problematic in severely impaired stroke patients, such as those with severe aphasia or apathy. Currently, the BEADS study investigates whether simple ‘behavioral activation’ can treat depressive symptoms post stroke. In the augmented CBT protocol as presented in chapter 4, behavioral activation was instigated by use of the Activity Card Sorting task (ACS) for goal setting. ACS was aimed at facilitating the conversation about goal setting and overcome communicative problems due to the passive state patients with (severe) depressive symptoms might be in. Yet, the use of the ACS may serve as an aid in the activation of aphasic stroke patients as well, and is useful for behavioral treatment such as the BEADS intervention. Severely impaired stroke patients may also benefit from other treatment approaches, such as ‘non-invasive brain stimulation’ (NIBS). Indeed, recent NIBS studies have shown promising effects in reducing depressive symptoms in healthy subjects. For instance, transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique that applies a relatively weak current through the skull, is able to induce cortical plasticity. It is assumed to have the potential to modulate (pathological) plasticity and improve cognition in mood disorders. The first-ever randomized controlled trial of tDSC in ‘post-stroke depression’ has revealed promising results. In addition, clinicaltrials.gov shows that it is currently investigated in a large RCT whether repetitive transcranial magnetic stimulation (rTMS) and/or aerobic exercise training (AET) may be beneficial for ‘post-stroke depression’. Since AET and rTMS are both stand-alone treatments applied to non-stroke related depression, it is important to also investigate their effects in
the stroke population. Both interventions can be applied to many types of stroke patients with depressive symptoms, independent of their cognitive impairments. Taken together, there are several studies investigating which treatment options are effective in improving depressive symptoms after stroke. These studies describe either a behavioral-psychological, physiological, or combined approach to search for a safe and effective treatment. Also, a first step towards the identification of different ‘post-stroke depression profiles’ has been taken.14 Hopefully more knowledge about such profiles will lead to more effective and better individualized treatments for mood disorders after stroke. Regarding the many studies investigating what intervention to provide for whom, we may in the future be able to select a behavioral (only) intervention for cognitively impaired patients or consider NIBS, whereas we may choose ACT for patients with mild cognitive impairments or with low flexibility.

Treatment for post-stroke depressive symptoms: how to assess and evaluate?
In the present thesis we assessed depressive symptoms and symptoms of anxiety with the Hospital Anxiety and Depression Scale. The cut-off score that we used for depressive symptoms as an inclusion criterion (HADS-Depression subscale >7 at one point in time) did not correspond to the DSM definition of major depression.45 We purposively excluded patients with a major depression requiring medication, as well as patients with major depression in their pre-stroke history, as both groups were expected to be less receptive to a psychological intervention. We started the Restore4Stroke trial in the year 2010, assuming that the assessment of chronic fatigue would lead to an overestimation of mood problems. Therefore, we used the HADS as an assessment tool both for inclusion purposes and for evaluating the primary outcome of our trial, as it is not sensitive to chronic fatigue.46 De Man-Ginkel and colleagues7 used the Patient Health Questionnaire-9 as an assessment tool, with fatigue represented in an ‘energy’ subscale.47 The large cohort study of De Man-Ginkel and colleagues provided not only clinical profiles of patients based on different cut-off scores on the PHQ-9, but also produced psychosocial profiles of non-depressed stroke patients, of depressed patients with symptomatic atherosclerotic diseases other than stroke, and of depressed patients in general practice. This makes the PHQ-9 more appropriate as a diagnostic screening tool for research and practice than the HADS, as it even includes more somatic symptoms such as loss of appetite and sleep.7,48 In addition to the HADS, we used the Post Stroke Depression Rating Scale (PSDRS) as one of the secondary outcomes.49 The PSDRS is a scale that
assesses psychological, physical, and vegetative aspects of depressive symptoms after stroke. It provides important phenomenological information on how a patient experiences mood after stroke, based on questions about how he/she would react to specific situations, for example ‘when your team wins’, ‘when you watch an intimate scene on television’, or ‘when a little child walks in’. During the assessments, many of our patients recognized such situations and indicated that how they felt in these situations had changed, but that they hardly ever talked about it. The PSDRS seemed a valid addition to the HADS, but it had not yet been applied to the assessment of depressed mood in a research setting. If, in future research, we are able to stratify patients based on different psychosocial profiles and their expected response to different treatment options, it may be useful to add assessment tools that provide more qualitative information on how patients perceive and manage specific situations, and to improve the diagnostic accuracy of these ‘future’ profiles. The PSDRS may be useful in this respect. The HADS appeared to be a useful screening tool to distinguish between profiles in the study of White and colleagues.\textsuperscript{14} Yet, the qualitative study of White and colleagues\textsuperscript{13} showed that the locus of control (internal or external), coping and self-efficacy seemed important indicators to establish profiles. The illness cognition questionnaire (ICQ, used in chapter 2) may also be of relevance, as it assesses feelings of helplessness, acceptance, and perceived benefits around illness.\textsuperscript{50} Future research may use these assessment tools when validating psychosocial profiles of post-stroke depressive symptoms.

In chapter 2 we investigated the factors that contribute to depressive symptoms one year after stroke. The results showed that psychological factors such as neuroticism and coping were important contributors. Yet, we did not include caregiver characteristics that may have played a role in the development of depressed mood in stroke patients. Kruithof and colleagues\textsuperscript{51} showed that both caregiver and patient characteristics in the sub-acute post stroke phase predicted caregiver outcomes one year later. Caregivers’ burden, anxiety and depressive symptoms, together with patients’ anxiety symptoms, were predictors of caregivers’ burden and anxiety symptoms one year after stroke. The authors stressed that professionals should pay attention to whether and how caregiver and patient influence each other and that they should be regarded from a dyadic perspective. Should assessment of depressive and anxiety symptoms after stroke therefore include caregivers as well? It would indeed be interesting to investigate the role of caregiver characteristics in the development of depressive symptoms and symptoms of anxiety in patients after stroke. This would have clear
implications for the role of caregivers in the treatment of emotional problems in these patients. Involvement in treatment or treatment for caregivers’ mood problems may have a positive influence on patients’ rehabilitation.

Methodological considerations
We investigated patients with depressive post-stroke symptoms that were willing to participate in a trial. The original inclusion phase of one year was extended with another six months, because the inclusion rate was lower than we had expected. Therefore we cannot exclude that some eligible patients with depressive symptoms might have been too passive in terms of their behavior to be willing to participate in a trial, which would imply selection bias and limit the generalizability of our results. This general drawback of RCTs may have been relatively strong in our study, as we specifically aimed at patients with depressed mood. Regarding the design our trial, it would have been preferable to also include a no-treatment condition. Now, we had to descriptively compare both intervention groups to the results of the Restore4Stroke cohort study data from van Mierlo et al. to estimate ‘spontaneous’ mood changes, but a valid comparison within our trial was not possible. However, enrolling patients in a no-intervention condition was problematic for ethical reasons, as eligible patients experienced severe distress and many of them were in need of some form of treatment. Inclusion of a no-treatment arm might also have further slowed down the inclusion rate, as patients might not have accepted the possibility to be randomized to a no-intervention group and, thus, might have refused participation. We also might have included a waiting list control group who would have been randomized to either CBT or CCT after a no-intervention period. However, the duration of the current trial was already long for several reasons. Adding a waiting list period might, thus, have jeopardized the overall feasibility of the trial.

Apart from the absence of a no-intervention control group, the main limitations of the present trial are the relatively small sample size and the recruitment through rehabilitation institutes, which may further limit the generalizability of our results. Next to that, because we expected that CBT would be favorable over CCT, the analyses in chapter 7 were aimed at the effects of the CBT intervention. Therefore, we provide only a societal perspective on the effects of CBT, not of CCT. Moreover, therapists from six different rehabilitation centers carried out our treatments, making monitoring of individual therapy sessions hard to accomplish. We provided training to all therapists and only experienced professionals were allowed to participate, but the CBT intervention was given with certain degrees
of freedom (e.g., building rapport, therapist characteristics). We do not know to what extent within-session factors, such as the role of the therapist, the ‘therapy alliance’, or patient compliance may have influenced the individual effects of the intervention. Indeed, therapy alliance seems to be an important factor for the outcome of psychological treatment.\textsuperscript{52} Therapy alliance is not just the ‘therapeutic relationship’, but reflects an emergent partnership and mutual collaboration between therapist and patient. In hindsight, we should have assessed therapy alliance, as it is a vital component of any therapy where the working relationship is important, such as in cognitive behavioral therapy. Therapy alliance can be easily measured after each session with the ‘Session Rating Scale’,\textsuperscript{53} ‘Outcome Rating Scale’,\textsuperscript{54} or ‘the Working Alliance Inventory’.\textsuperscript{55,56} Furthermore, it was our intention to assess patients’ participation in the therapy sessions, which could have provided indications about the client-therapist relationship. In chapter 3, we mentioned that the Pittsburgh Rehabilitation Participation Scale\textsuperscript{57} (PRPS) would be completed by the therapists after each therapy session. Unfortunately, there were too much missing data on the PRPS, possibly because it was the only assessment we asked of the therapists, while their focus was more on correctly following the treatment protocol.

We already discussed that the patient and caregiver should be regarded from a dyadic perspective. In the risk factor study (chapter 2) we did not take into account the influence of the caregiver, although the role of social support is important. Social support from caregivers and others was not assessed throughout this thesis, but has an important ‘protective role’ against the development of post-stroke depressive symptoms.\textsuperscript{58,59} It would have been interesting to see whether social support would have influenced goal attainment and therapy response in our trial. To this end, we could have included a social support questionnaire and have analyzed how social support might have mediated treatment response.

\textit{Future perspectives}

Although there are several study limitations to acknowledge, we conducted one of the first trials investigating the effect of CBT for post-stroke depressive symptoms. Moreover, we were the first to include caregiver data and to consider the cost-effectiveness and cost-utility of CBT compared to CCT. Apparently, well controlled (cost-)effectiveness studies of psychological treatment for post-stroke depressive symptoms are complex and hard to perform. Many more studies on this topic are needed to develop cost-effective interventions. However, this study is the first to provide an overview of the societal costs in this patient
population. Therefore, this study may serve as a benchmark for future cost-effectiveness studies that investigate other psychological interventions within this patient population (e.g., acceptance and commitment therapy). Moreover, it may be important to stratify patients and their caregivers based on specific psychosocial profiles in order to individually target specific interventions to obtain the best long-term results. Future intervention studies would benefit from consensus on the terminology regarding depressive symptoms after stroke as well as from consensus on the standardized use of assessment tools for including and evaluating patients and caregivers. In addition, to investigate or monitor the impact of different intervention program elements (e.g., therapy alliance) on the analysis of effectiveness a process evaluation is recommended.\textsuperscript{60,61}

Risk analysis studies should further focus on psychosocial factors, including caregiver characteristics and social support, with the aim to determine psychosocial profiles that can be related to the risk of developing depressive or anxiety symptoms and to the response to psychological treatment. Timing is a critical factor in this respect, which may imply the need for specific interventions adjusted to the different phases post stroke. Future cost-effectiveness studies should take into account not only healthcare costs related to the patients with stroke, but integrate healthcare and societal costs related to both the patients and their caregivers.
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Samenvatting
Samenvatting

Depressie- en angstklaichten komen veel voor in de chronische fase na het CVA (cardiovasculair accident), ofwel beroerte. Deze klachten hebben een negatieve invloed op revalidatie, sociale re-integratie en kwaliteit van leven. Momenteel is er geen zogenaamde evidencebased behandeling voor de klachten van deze groep patiënten bekend. Het doel van dit manuscript was daarom om een nieuwe behandeling, gebaseerd op cognitieve gedragstherapie (CGT) voor ‘reguliere’ depressie en aangepast op de doelgroep (patiënten na CVA), te ontwikkelen en evalueren. Om ondersteuning te bieden bij de praktische, activiteitsgerelateerde behandeldoelen van de patiënt werd de ‘aangepaste CGT’ aangevuld met een aantal individuele sessies met ergotherapie of bewegingsagogie. De nieuwe, aangepaste CGT-behandeling werd in een trial vergeleken met een controlegroep, waarbij de deelnemers een cognitieve training op de computer (CCT) kregen.

In hoofdstuk 1 worden de fysieke en psychische consequenties van het CVA geïntroduceerd. In dit hoofdstuk beschrijven we verschillende behandelopties voor de psychische consequenties zoals depressieve klachten. Daarnaast wordt onderbouwd waarom we een psychologische benadering gekozen hebben voor deze klachten in dit manuscript. Vervolgens presenteren we de onderstaande centrale onderzoeksvragen van het manuscript:

1. Zijn psychische factoren belangrijke risicofactoren voor depressieve klachten na een beroerte?
2. Uit welke onderdelen zou een aangepaste CGT-behandeling moeten bestaan wanneer we kijken naar de fysieke, cognitieve en emotionele gevolgen van een beroerte?
3. Is een dergelijke aangepaste CGT-behandeling effectief om depressieklachten te reduceren, om sociale re-integratie te stimuleren en om kwaliteit van leven te verbeteren?
4. Heeft deze aangepaste CGT-behandeling ook een positief effect op de ervaren last van partners van patiënten?
5. Is de aangepaste CGT-behandeling vanuit een economisch perspectief effectief?
In hoofdstuk twee behandelen we de eerste onderzoeksvraag. De Restore4Stroke Cohort-studie (met een longitudinaal design) leverde data waarmee we berekenden of psychische factoren van invloed zijn bij het krijgen van depressie- en angstklachten één jaar na het CVA. Deze klachten zijn de meest voorkomende emotionele klachten na een beroerte. Wanneer we meer te weten komen over de factoren die van invloed zijn bij het ontstaan van deze klachten, zijn we beter in staat om passende preventieve en behandelstrategieën toe te passen op deze beelden. De risicofactoren die in eerdere studies werden onderzocht zijn voornamelijk sociaal-demografisch, premorbide of CVA-gerelateerd, maar de psychische factoren werden veelal buiten beschouwing gelaten. De studies die de psychische factoren wel onderzochten, hadden ofwel lage respondententaantallen, of gebruikten een cross-sectioneel onderzoeksdesign, of bekeken slechts een select aantal psychische factoren. Kortom, geen van deze studies laat enige voorspellende waarden zien van dit soort risicofactoren, waardoor de klinische toepassing van de resultaten beperkt blijft. Dit hoofdstuk (2) laat zien wat de relatieve bijdrage was van sociaal-demografische, premorbide en psychische factoren bij het ontwikkelen van depressie- en angstklachten één jaar na beroerte. Het onderzoek werd gedaan met data afkomstig van een groot cohort van subacute CVA-patiënten (n=331), die werden gerekurt in zes perifere ziekenhuizen met CVA-afdelingen in Nederland. We hebben de longitudinale data gebruikt om modellen te berekenen die de voorspellende waarde van mogelijke risicofactoren voor depressie- en angstklachten na CVA weergeven. Aanvullend op deze calculaties hebben we middels zogenaamde ‘nomogrammen’ visueel weergegeven wat de predictieve bijdrage is van elke individuele risicofactor uit beide modellen (d.w.z. voor angst en depressie). Alle deelnemers werden in het ziekenhuis, enkele dagen na het CVA, in de studie geïncludeerd. Daarna werden ze op twee en twaalf maanden na het CVA gemeten met verschillende vragenlijsten. Rond de opname van de deelnemers in het ziekenhuis werden hun sociaal-demografische, premorbide en CVA-gerelateerde gegevens verzameld. Informatie over de psychische factoren werd verzameld door middel van de metingen die plaatsvonden twee en twaalf maanden na opname. Tevens werden de depressie- en angstklachten op deze beide momenten gemeten. Hiervoor gebruikten we de twee schalen van de Hospital Anxiety and Depression Scale (subschalen Angst en Depressie van de HADS). Er werd een multivariate logistische analyse uitgevoerd om de modellen te berekenen die de belangrijkste risicofactoren voor het ontwikkelen van deze klachten lieten zien (we spreken over depressie- en angstklachten als de scores
op bijbehorende subschalen op de HADS boven de 7 zijn). Uit deze analyses bleken de belangrijkste risicofactoren voor het ontwikkelen van depressieve klachten één jaar na het CVA: vroege depressieklachten, ernst van het CVA, locatie van het CVA (achterste hersenslagader) en neuroticisme. Deze factoren verklaarden onafhankelijk van elkaar de variantie van de depressieve klachten één jaar na CVA. Voor het ontwikkelen van de angstklachten liet het model zien dat de belangrijkste risicofactoren ‘neuroticisme’ en ‘vroege angstklachten’ waren. Deze twee factoren verklaarden onafhankelijk van elkaar de variantie voor angstklachten één jaar na CVA. Uit deze resultaten concludeerden we dat psychische factoren sterkere risicofactoren zijn voor depressie- en angstklachten een jaar na CVA dan eerder werd gedacht. Op psychische factoren kunnen we, in tegenstelling tot de meeste sociaal-demografische, premorbide of CVA-gerelateerde factoren, preventief of curatief inspelen. Hiermee leveren deze resultaten een significante klinische bijdrage aan de preventie en behandeling van emotionele klachten na CVA.

De resultaten uit hoofdstuk twee geven aanleiding om een psychologische benadering te hanteren bij behandeling van depressieve klachten na beroerte. Omdat er nog geen evidencebased behandeling voor dergelijke klachten bestaat, hebben we een nieuwe psychologische behandeling, gebaseerd op CGT, ontwikkeld. Deze presenteren we in hoofdstuk drie. In dit hoofdstuk beantwoordden we daarmee de tweede onderzoeksvraag. Eerder onderzoek naar depressie in de algemene populatie liet zien dat CGT een waardevolle behandelmethode kan zijn. Onze interventie is gebaseerd op CGT-principes. In de eerder uitgevoerde pilotstudie liet dit behandelprotocol positieve resultaten zien. De behandeling die wij ontwikkelden is gericht op de behoefte van de CVA-patiënt. Dit betekent dat we gelet hebben op de sensorimotorische, cognitieve én gedragsproblemen die gepaard kunnen gaan met depressieve klachten na CVA. We hebben daarom in het behandelprotocol elementen ingevoegd als motiverende gespreksvoering, rouwverwerking en psycho-educatie. Daarnaast benadrukten we dat de behandelaar in elke bijeenkomst rekening houdt met mogelijke cognitieve beperkingen van de patiënt en communiceert middels de CRASS-principes (d.w.z.: bieden van duidelijkheid en helderheid, toegankelijkheid, structuur, herhaling en tempoaanpassingen). De patiënt werd tijdens de behandeling gestimuleerd om behandeldoelen te stellen die activiteits- of sociaal gerelateerd waren. Om deze doelen te behalen vulden we het deel van de behandeling dat door de psycholoog wordt verzorgd aan met een optie voor ergotherapie of bewegingsagogie, afhankelijk van wat de specifieke doelen
van de patiënt waren. De hele behandeling bestond uit twaalf bijeenkomsten van één uur met een psycholoog, en daarnaast drie of vier sessies van één uur met de ergotherapeut of bewegingsagoog. Dit protocol is innovatief, omdat het traditionele CGT benadert vanuit het perspectief van de CVA-patiënt en omdat het aanzet tot halen van doelen door o.a. de anvulling vanuit de andere disciplines.

**Hoofdstuk vier** beschrijft het protocol van het onderzoek, ofwel de methode van de Restore4Stroke-studie. Onze verwachting was dat patiënten die behandeld werden met de, op hun individuele behoeften aangepaste, CGT, een verbetering in depressieklachten lieten zien op de HADS ten opzichte van de patiënten die de cognitieve training (CCT) ontvingen. Naast de resultaten van de HADS bekeken we ook enkele secundaire uitkomstmaten, zoals kwaliteit van leven (Stroke Specific Quality of Life scale), sociale participatie (Utrechtse Schaal voor Evaluatie van Revalidatie – Participatie) en angstklachten (HADS-subscala Angst). Ook hebben we naar data gekeken van de partners van de CVA-patiënten tijdens de trial. We verwachtten voor de partners dat zij een verbetering op ervaren last (vanuit emotioneel en praktisch perspectief) zouden laten zien wanneer hun ‘patiëntpartner’ in de CGT-groep zou deelnemen. De effectmeting van de CGT-behandeling werd met een ‘multicenter gerandomiseerde gecontroleerde triaal’ (RCT) uitgevoerd, waarbij de assessor geblinddeerd was. Een steekproef uit de patiëntpopulatie met depressieve klachten na het CVA werd gerandomiseerd ingedeeld in ofwel de experimentele groep (CGT), ofwel de controlegroep (CCT). Op vier tijdsmomenten per deelnemer vonden metingen plaats: voorafgaand aan de randomisatie, direct na de behandeling, en vier en acht maanden na afloop van de behandeling. Deze studie is de eerste RCT die de (langetermijn)effecten van een CGT-behandeling voor depressieve klachten na CVA heeft onderzocht.

**Hoofdstuk vijf** beschrijft de resultaten van de studie vanuit patiëntperspectief. 61 patiënten namen deel aan de studie. De CGT-groep bestond uit 31 patiënten en de CCT-groep telde 30 patiënten. De analyse die we gebruikten voor de effectmeting was ‘lineair mixed models’ voor herhaalde metingen. De resultaten lieten zien dat er voor beide groepen een significante vermindering van depressieklachten in tijd bestond. Daarnaast werden positieve resultaten gevonden voor beide groepen voor angstklachten, sociale participatie en kwaliteit van leven. Let wel, er werd geen significante interactie (groep x tijd) gevonden op alle gebruikte uitkomstmaten. Deze resultaten impliceren dat de CGT-interventie niet beter werkte op depressieklachten dan dat de CCT deed wanneer de patiëntgerelateerde uitkomstmaten werden bekeken.
De vierde onderzoeksvraag wordt in hoofdstuk zes behandeld. Omdat depressie- en angstklachten van patiënten na de beroerte een negatief effect kunnen hebben op het welbevinden van hun partners, werden partners van de deelnemers ook uitgenodigd om mee te doen aan de Restore4Stroke-studie. We onderzochten de emotionele last (Involvement Evaluation Questionnaire for Brain Injury / IEQ-BI), praktische last (Caregiver Strain Index), mentale gezondheid (General Health Questionnaire) en emotionele klachten (HADS). In totaal namen 50 partners deel aan de studie. Zij werden gelijk met hun ‘patiëntpartner’ uitgenodigd om vragenlijsten in te vullen voorafgaand, direct na, en vier en acht maanden na het einde van de behandeling. We gebruikten, net als bij de patiënttrial, ‘linear mixed models’ voor herhaalde metingen in de statistische analyse. In tegenstelling tot de resultaten van de patiëntdata, lieten de resultaten van de partners wel verschillen zien tussen de behandelcondities. Partners in de CGT-groep lieten betere scores zien voor mentale gezondheid en ze maakten zich minder zorgen over het welbevinden van hun patiëntpartner na de interventie. Daarnaast werden positieve effecten voor ‘tijd’ gevonden op de schalen ‘worrying’ (zorgen maken), ‘supervision’ (toezicht houden), en ‘tension’ (ervaren spanning). Deze resultaten zijn opmerkelijk, gezien het gebrek aan verschillen tussen de behandelcondities bij de patiëntdata. In tegenstelling tot de resultaten van de patiënttrial, lijkt de CGT-behandeling een positief effect te hebben op het welbevinden van de patiëntpartners.

De laatste onderzoeksvraag wordt in hoofdstuk zeven behandeld. Hier beschrijven we de resultaten van van de trial vanuit een maatschappelijk-economisch perspectief. Depressieve klachten na een beroerte zijn gerelateerd aan verhoogd gebruik van zorgfaciliteiten waardoor substantiële zorgkosten worden veroorzaakt. Deze studie beschrijft de kosteneffectiviteit en kostenutiliteit van de CGT groep in vergelijking met CogniPlus (CCT) als controle interventie. Primaire uitkomsten van deze studie waren de HADS en Quality Adjusted Life Years (QALYs) gebaseerd op de five-dimensional EuroQol (EQ-5D-3L). De 61 patiënten uit de trial hebben ook deze vragenlijsten afgenomen op alle tijdstippen genoemd in de patiënt trial. De gemiddelde totale maatschappelijke kosten verschillen niet significant tussen de AGT interventiegroep (€8,063.7) en de CogniPlus controlegroep (€9,998.3), met een 95% betrouwbaarheidsinterval van -5,284, 1,796. De resultaten van deze studie laten zien dat de groep patiënten lagere kosten en lagere effecten laten zien op de HADS, en lagere kosten en hogere effecten voor de QALY wat duidt op een dominante incrementele kosteneffectiviteitsratio. Met een aangenomen te betalen prijs van €40,000
per QALY, heeft de CGT interventie 76% kans om kosteneffectief te zijn. Alle sensitiviteitsanalyses gaven aan dat keuzes gemaakt in de oorspronkelijke analyse robuust waren. Concluderend moet gesteld worden dat de resultaten van deze studie met betrekking tot de kosteneffectiviteit van de AGT interventie niet overtuigend genoeg zijn.
Dankwoord
Dankwoord

Het manuscript is klaar, de voorbereidingen zijn klaar. Wie dit leest heeft het gedrukte proefschrift vast en doorgebladerd tot de laatste pagina’s. Ik ben een grote hap volwassenheid verder waarin ik veel waardevols heb geleerd. Zo’n lange periode doe je niet alleen. Daarom is een woord van dank op zijn plaats.

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9 tot 5 met ons hoofd in de data, maar daarbuiten hebben we heel hard kunnen
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Curriculum vitae
About the author
List of publications


Kootker JA; Van Heugten CM; Kral B; Rasquin, SMC; Geurts ACH; Fasotti F. Treating patients with post-stroke depressive symptoms: What happens to caregivers’ well-being? (submitted)
Conferences and presentations:


Improving Quality of Life after stroke; Kootker JA, Fasotti L, Rasquin SMC, Van Heugten CM & Geurts ACH. Oral presentation. Congress on NeuroRehabilitation and Neural Repair. Maastricht, the Netherlands, 2015.
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