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The COMPlaints After Stroke (COMPAS) study: protocol for a Dutch cohort study on post-stroke subjective cognitive complaints

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ABSTRACT

Background: Whereas many studies have assessed post-stroke objective cognitive impairment, only a few have evaluated patients' Subjective Cognitive Complaints (SCC). Although these SCC are found to be common in both the early and chronic phase after stroke, knowledge about their risk factors, course over time, differences with healthy controls, and their diagnostic relevance is limited. The aim of the COMPlaints After Stroke (COMPAS) study is therefore to determine the possible risk factors, prognosis, time course, and predictive value of SCC in the first two years after stroke.

Methods and design: A prospective cohort study is conducted in which patients are compared to non-stroke controls at 3, 6, 12, and 24 months after stroke. Approximately 300 patients are recruited from the stroke units of 3 hospitals in The Netherlands, while 300 controls are sought among the relatives and social networks of participants. A wide range of subjective and objective variables is assessed in both groups using interviews, questionnaires, and neuropsychological assessment. The primary outcomes include SCC and objective cognitive impairment, whereas secondary outcome are quality of life, subjective recovery, and daily life functioning.

Ethics and dissemination: The study is being carried out in agreement with the Declaration of Helsinki and the medical Research Involving Human Subjects Act. The protocol has been approved by the medical ethics committees of the participating centres and all participants give written informed consent. The results will be published in peer-reviewed journals and disseminated to both the medical society and general public.

Discussion: The COMPAS study is the first to systematically evaluate post-stroke SCC in a prospective longitudinal design, taking a wide range of subjective and objective variables into

account. The results obtained can be used to accurately inform patients and their families, and to develop patient tailored intervention programmes to ultimately improve stroke patient care.

ARTICLE SUMMARY

Article focus:

- The aim of the COMPlaints After Stroke (COMPAS) study is to determine the possible risk factors, prognosis, time course, and predictive value of SCC on future cognitive functioning and quality of life within the first 2 years after stroke.
- It will also evaluate whether and how these aspects differ between stroke patients and non-stroke controls.

Key messages:

- This study will determine how post-stroke SCC are related to demographic and clinical characteristics, objective cognitive functioning, subjective stroke recovery, fatigue, mood, stress, personality, quality of life, and daily life functioning.
- This knowledge and insight into post-stroke SCC allows clinicians to more accurately inform patients and their proxies, to choose the most appropriate treatment, and to develop patient tailored intervention programmes, thereby improving stroke patient-centred care**.**

Strengths and limitations:

- The strength of this study is that it is the first prospective cohort study on SCC in stroke patients, systematically evaluating both patients and controls at multiple assessments, while at the same time a wide range of subjectively and objectively measured variables are taken into account.
- A limitation is that the most serious affected patients are unable to participate in the study. This may reduce the generalizability of the results to the stroke population as a whole.

BACKGROUND

Post-stroke cognitive impairment is common after stroke and can be evaluated either objectively, using neuropsychological tests (i.e. Objective Cognitive Performances; OCP), or subjectively, using interviews, or self-report questionnaires (i.e. Subjective Cognitive Complaints; SCC). To date, the majority of the studies on post-stroke cognitive sequelae have focused on OCP without also evaluating patients' SCC. However, individuals' performances in test situations do not always correspond to those in daily life and vice versa.[1 2] Evaluating one can therefore not be used to draw conclusions about the other.

In a recent systematic review, we found that SCC are common in both the early and the chronic phase after stroke, with prevalence rates varying between 28.6% and 92.0%.[3] Complaints about memory, mental speed, and concentration are found to be the most commonly reported. One of the main problems among these studies is however that there is no 'gold standard' to define and measure SCC, resulting in heterogenic findings. In our review we suggested that it is important to differentiate between *content* of SCC (SCCc) and *worrying* about SCC (SCCw), as these are two different concepts.[3] The first focuses on the specific cognitive difficulties respondents say they experience, while the second indicates whether participants find them worrisome, irritating, and whether they say they hinder daily life. A few studies have made this distinction so far. [2 4 5] However, the majority of research on post-stroke SCC has evaluated SSCc and not SSCw, probably without being aware of the difference between these aspects of SCC.[3]

Furthermore, we found that post-stroke SCC tend to increase over time, and that there is moderate agreement between patients and their proxies on prevalence and severity of patients` SCC. [3] SCC were also found to be inconsistently associated with demographic and clinical characteristics, current depressive symptoms and OCP,[3] but 2 studies showed that post-stroke

SCC may predict future emotional and cognitive decline.[5 6] However, most of the research on SCC after stroke carried out so far is limited in that: unvalidated methods for assessing SCC have been used, there was no non-stroke control group, and the focus was on a specific subsample of stroke patients (e.g. home-living patients only), thereby impairing generalizability of the results. While SCC are common among stroke patients, knowledge about the following aspects is only limited or practically non-existent: the risk profile for developing SCC; their course over time; their impact on Quality of Life (QOL), subjective recovery, and Activities in Daily Life (ADL) functioning; and their prognostic implications.

In the general non-stroke population however, SCC have been more frequently evaluated, in particular memory related SCC reported by the elderly. [7 8] Factors found to be associated with these complaints include: demographic characteristics (higher age, women, lower education), psychological distress, somatic complaints, personality traits (neuroticism in particular), and vascular risk factors.[7-11] They are furthermore thought to be clinically relevant in this group because of their association with an increased health care consumption, a reduced QoL, current OCP (this link is not always found), and their predictive value for future cognitive decline.[7 8 12] Whether this also applies to post-stroke SCC is unknown. More systematic research is therefore needed to gain further knowledge about SCC among stroke survivors, to be able to accurately inform patients and their relatives, to develop adequate treatment programmes, and ultimately improve post-stroke care.

We therefore designed the **COMP**laints **A**fter **S**troke (**COMPAS**) study in which we have 4 main aims, including:

- Determine the prevalence, profile and course over time of SCCc and SCCw.
- Identify the risk profile for developing SCC.
- Evaluate their predictive value for future cognitive functioning.

- Determine the effect of SCC on QoL, subjective recovery, and ADL functioning.

Here we describe the design and protocol of the COMPAS study, which is the first prospective cohort study of SCC in stroke patients, evaluating both patients and controls, while at the same time a wide range of variables is taken into account.

METHODS AND ANALYSIS

Design

A multicentre, prospective cohort study of stroke patients and controls is performed. We started in 2009 and the final measurements will be made in 2014. Patients are evaluated 5 times, starting at the clinical phase (T0), followed by an assessment at 3 months (T1), 6 months (T2), 1 year (T3), and 2 years (T4) after stroke. Controls are seen at the same time intervals, starting at T1.

Study population

Stroke patients are recruited consecutively from the stroke units of 3 hospitals in The Netherlands, including the St.Elisabeth and TweeSteden Hospitals in Tilburg, and the Maxima Medical Centre in Veldhoven. The control group consists of a sample from the non-stroke general population and is recruited among the relatives and the social networks of participants in the COMPAS study. Spouses of stroke patients are excluded from the control group since these people are at a higher risk of having physical, cognitive and psychosocial problems themselves due to the fact that their partner has suffered a stroke.[13 14]

Inclusion criteria:

- Clinical diagnosis of a first or recurrent ischemic or hemorrhagic stroke (for patients only).
- At least 18 years old (no upper age limit).

Exclusion criteria:

- Pre-existent health problems interfering with cognitive functioning, including:

- Cognitive decline (as defined by a score > 3.6 on the short version of the Informant Questionnaire on Cognitive Decline in the Elderly; IQCODE).[15]
- A recent history of severe psychopathology (e.g. suicide attempts, alcohol- or drug abuse, diagnosed personality or mood disorders).
- Severe physical co-morbidity (e.g. malignant diseases, progressive neurological conditions).

- Severe communication difficulties (e.g. insufficient understanding of the Dutch language, severe aphasia, blindness, or deafness).

Procedure

Eligible patients receive oral and written information about the study from their treating physician during the clinical phase (T0). Demographic and clinical characteristics are documented and patients are scheduled for the first assessment 3 months after stroke (T1), during which written informed consent is obtained for inclusion to be definite. Subjects acknowledge that they have the intention to complete all 4 assessments, and that they are allowed to end their participation at any time. For the follow-up assessments (T2 – T4), patients are informed by letter and telephone and invited to participate after which an appointment is scheduled.

Potential controls receive oral and written information about the study from the researcher after which they are asked to participate in the study. The rest of the procedure is the same as that for the patient group.

The assessments are administered in a standardized way by trained neuropsychologists and take place at the participating hospitals, or when this is not possible, at the participants' home or residence (e.g. rehabilitation centre).

Measures

Tables 1 and 2 give an overview of the variables assessed and instruments used at each time point.

Outcomes

Primary outcomes of the COMPAS study are SCC and OCP. To measure SCC, 2 instruments are used, namely: the Dutch version of the Cognitive Failures Questionnaire (CFQ)[16 17] and the Checklist for Cognitive and Emotional consequences following stroke (CLCE-24).[5] The CFQ focuses on SCCc and asks subjects to rate 25 items on the frequency of cognitive slips and errors in daily life on a five-point Likert scale ranging from 0 (never) to 4 (very often). SCCw is evaluated by four additional general questions regarding the subjective increase of complaints over time, the degree to which these hinder daily life, are annoying, and are a source of concern. Each of these extra items is rated on a scale ranging from 1 (not at all) to 5 (extremely).

The CLCE-24 is a structured clinical interview developed more recently to evaluate both SCCc and SCCw among stroke survivors.[5] It consists of 13 items concerning cognitive complaints and 9 items addressing emotional and behavioural complaints. Each item is rated on presence and severity, and scored as 0 (no complaint), 1 (doubtful), 2 (complaint present, but not disturbing or annoying), or 3 (complaint present and disturbing daily functioning).

OCP are evaluated using an extensive neuropsychological assessment covering multiple cognitive domains and containing both traditional (e.g. Rey Complex Figure Test[18]) and more ecologically valid tests (e.g. Rivermead Behavioural Memory Test[19]). See Table 1 for an overview of all OCP tests used. In Spreen and Straus [20] and Lezak et al.[21] a detailed description of each of the instrument we use is given.

Secondary outcomes include QoL, ADL functioning, and subjective stroke recovery. Generic QoL is evaluated using the short version of the self-report World Health Organization Quality of Life Questionnaire (WHOQOL-Bref)[22] (26 items) and, because we expect the majority of our population to be elderly (> 60 years), the additional OLD module (WHOQOL-OLD)[23] comprising 24 items. Whereas the first covers overall well-being on the domains 'physical', 'psychological', social relationships' and 'environment', the OLD module evaluates aspects of life which are specific for the elderly, including: 'intimacy', 'sensory abilities', 'autonomy', 'activities in the past, present and future', 'social participation', and 'dying'.

Subjective recovery after stroke is determined by a single item from the Stroke Impact Scale,[24] in which patients are asked to indicate on a scale ranging from 0 ('no recovery') to 100 ('full recovery') how much they feel they have recovered from their stroke.

ADL functioning is assessed in basic activities, including self-care and mobility, using the Barthel Index [25] (10 items), and more complex activities like housekeeping, hobbies, and employment, using the Frenchay Activities Index [26] (15 items).

All of the chosen instruments are (inter-)nationally frequently used in both research and daily clinical practice dealing with stroke patients.

Determinants

Depending on the specific outcome considered, SCC, OCP, QoL, subjective recovery, and ADL functioning are either dependent or independent variables. A wide range of possible determinants are additionally taken into account, based on what is currently known from the literature on SCC in the general and the stroke population. These include: demographic variables, clinical characteristics (those related to stroke included), and health status; premorbid status (i.e. cognitive decline, IQ, cognitive and emotional complaints); comorbid complaints

about mood (i.e. anxiety and depression), fatigue, and stress; personal factors (i.e. coping style, personality traits, and SCC awareness), and the occurrence and impact of positive and/or negative live events. See Table 2 for the specific variables assessed and instruments used.

Table 1 Primary and secondary outcomes in the COMPAS study

	Instrument	T0	T1	T2	T3	T4
Primary outcomes						
SCC	Cognitive Failures Questionnaire [16 17]		X	X	X	X
	Checklist for Cognitive and Emotional Consequences [5]		X	X	X	X
OCP [20 21]						
Global cognitive functioning	Mini-Mental State Examination		X		X	X
Visual perception and construction	Rey Complex Figure Test – copy trial		X		X	X
Mental speed / attention	Stroop Colour word test - card 1 and 2		X		X	X
	Digit Symbol-Coding		X		X	X
Episodic memory	Rivermead Behavioural Memory Test		X		X	X
	Rey Complex Figure Test - immediate and delayed recall trials		X		X	X
	Verbal Paired Associates		X		X	X
Working memory	Digit span Forward and Backward condition		X		X	X
Language	Boston Naming Test - short version		X		X	X
Executive functioning	Controlled Oral Word Association Test – FAS		X		X	X
	Category Fluency Test: animals and occupations		X		X	X
	Stroop Colour Word Test - card 3		X		X	X
	Rule Shift Cards		X		X	X
	Zoo Map		X		X	X

Fine motor dexterity	Purdue Pegboard		X		X	X
Secondary outcomes						
Quality of Life	World health Organization Quality of Life Questionnaire – short form [22]		X		X	X
	World health Organization Quality of Life Questionnaire – Old module [23]		X		X	X
ADL functioning						
Basic ADL	Barthel index [25]	P	X	X	X	X
Instrumental ADL	Frenchay Activities Index [26]		X	X	X	X
Subjective stroke recovery	Item 9 of Stroke Impact Scale [24]		P		P	P

ADL: Activities in Daily Life; C: control group only; OCP: objective cognitive performance; P: patient group only; SCC: subjective cognitive complaints; X: instrument used in both patients and controls.

Table 2. Determinants in the COMPAS-study

	Variable / instrument	T0	T1	T2	T3	T4
Demographic variables	Age, gender, education, marital status, living situation, residence, employment status, hand preference	P	X	X	X	X
Clinical characteristics						
Stroke specific	Life-time history of stroke, type, side, classification according to the Oxford Community Stroke Project [27], severity within 24 hours after admission using the National Institutes of Health Stroke Scale [28], treatment, post-stroke complications, length of hospital stay, discharge destination	P				
General	Vascular risk factors, comorbidity (Cumulative Illness Rating Scale [29]), (re-) admissions to hospital, medication use, current participation in rehabilitation therapy		X	X	X	X
Health status	12-Item Short Form Health Survey [30]		X		X	X
Premorbid status						
Cognitive decline	Informant Questionnaire on Cognitive Decline in the Elderly – short form [15]	P	C			
IQ estimation	Dutch version National Adult Reading Test [31]		X			
Cognitive complaints	Self-made item: "in the previous months (before your stroke), have you experienced cognitive complaints?"	P	C			
Depressive complaints	Self-made item: in the previous months (before your stroke), have you experienced depressive complaints?"	P	C			

Anxiety complaints	Self-made item: in the previous months (before your stroke), have you experienced anxiety complaints?"	P	C			
Current comorbid complaints						
Depressive complaints	Hospital Anxiety and Depression Scale – subscale Depression [32]		X	X	X	X
Anxiety complaints	Hospital Anxiety and Depression Scale – subscale Anxiety [32]		X	X	X	X
Fatigue	Fatigue Assessment Scale [33]		X	X	X	X
Stress	Perceived Stress Scale, 4-item version [34]		X		X	X
Personal factors			X		X	X
Coping style	Utrecht Coping List – 15-item version [35]		X			
Personality trait - neuroticism	Eysenck Personality Questionnaire Revised Short Scale – subscale Neuroticism [36]		X			
Personality trait - extraversion	Eysenck Personality Questionnaire Revised Short Scale - Extraversion subscale [36]		X			
Type D	Type D scale-14 [37]		X			
Participants' awareness of SCC	Cognitive Failures Questionnaire completed by proxy		X	X	X	X
	Checklist for Cognitive and Emotional Consequences completed by proxy		X	X	X	X
Life events	Self-made item concerning the presence and impact of a positive or negative life event: "Last year, did something happen in your life which had a major impact on you? This may be something either pleasant or sad."		X		X	X

P: patient group only; SCC: subjective cognitive complaints; X: instrument used in both patients and controls.

Planned statistical analyses

Cross-sectional analyses will be used to evaluate group differences on each of the individual time points (T1 to T4) and include: Chi-square test for categorical variables, the Mann-Whitney *U* test for ordinal data, and the Student *t*-test or (multivariate) analysis of variances ((M)ANOVA) for continuous dependent variables. Differences across the different time points will furthermore be an analyzed using multilevel analysis, which allows including all available data (i.e. also those from participants with partly missing values).

The course of SCC over time (T1 to T4) will subsequently be evaluated using latent class growth analysis. We will explore whether groups with different trajectories of SCC over time can be distinguished and if so, what their characteristics are.

The predictive value of the determinants for the primary and secondary outcome measures (i.e. SCC, OCP, QoL, subjective recovery, and ADL functioning) at T3 and T4 will be determined using multivariate regression analysis. Potential predictors are defined as variables with at least a marginally significant association ($p < 0.10$) with the outcome. Only these variables will be included in the subsequent regression analyses to determine the most important predictors. In general, effects with a two-tailed $p < 0.05$ are considered statistically significant.

Sample size and power calculation

The sample size needed in the COMPAS study is calculated using the method for multilevel analysis according to Twisk.[38] Based on a high intra-individual correlation across the different time points (rho = 0.70), an alpha level of 0.05, and power of 0.80, there are 180 participants per group needed to be able to detect a small difference (at least 0.2 standard deviation) between the groups. We expect about 40% drop-outs during the two-year follow-

up period due to mortality, comorbidity or refusal to continue participation. Therefore, we aim to include 300 participants at baseline in each group in order to end up with the 180 per group needed.

ETHICS AND DISSEMINATION

Ethical considerations

The COMPAS study is conducted in accordance with the "Helsinki Declaration"(Seoul revision, 2008) and the "medical Research Involving Human Subjects Act"(WMO). The study is non-invasive, imposes no risk on participants, and the protocol has been approved by the medical ethical committees of all participating hospitals (i.e. St. Elisabeth and TweeSteden Hospitals in Tilburg, and the Maxima Medical Centre in Veldhoven) and is registered by the Central committee on Research Involving Human Subjects (number NL31208.008.10). Written informed consent is furthermore obtained from all participants.

Dissemination

The results obtained will be disseminated to the scientific, medical and general public by publication in national and international peer-reviewed journals, by presentation on conferences, and meetings with clinicians dealing with stroke patients.

DISCUSSION

The COMPAS study is the first in which post-stroke SCC are systematically evaluated over time, while a wide range of subjective and objective variables in patients and controls is taken into account. Whereas numerous studies have measured post-stroke OCP, only a few have also evaluated the patients' SCC. Whereas these complaints are found to be common among stroke patients, knowledge about their risk factors, their course over time, differences with the non-stroke population, and their predictive value for future functioning is practically non-existent.

Strong elements of the COMPAS study are its prospective design with multiple assessments during the first two years after stroke, and the extensive evaluations of both subjective and objective variables which, based on the current literature, are potentially relevant to SCC after stroke. This gives us the opportunity to determine a detailed risk profile for experiencing post-stroke SCC. The instruments chosen are furthermore widely accepted and frequently used in daily clinical practice dealing with stroke patients. Both traditional neuropsychological and more ecologically valid tests (e.g. the Rivermead Behavioural Memory Test) are used to evaluate OCP, making it possible to determine whether the ecological validity of tests affects the association between SCC and OCP. Also, a healthy control group is assessed at the same time points as the patients and will be used as a reference group. This enables us to distinguish post-stroke SCC in their prevalence, profile and time course from for example factors which are associated with ageing. A potential limitation of the study is that the most serious affected stroke patients are unable to participate, thereby reducing the possibility to generalize the results to the stroke population as a whole. However, our study differs from those carried out to date in this field in that we

include a broad selection of stroke patients, not only first-ever strokes or patients discharged home.

In conclusion, we feel that the COMPAS study has the potential to contribute to the knowledge on post-stroke SCC. Due to ageing of the population and health care improvements, the number of stroke survivors who will have to deal with post-stroke impairment will increase in the future, and the social and economic burden will rise accordingly.[39 40] Clinicians are frequently confronted with patients having SCC after their stroke, but the meaning and relevance of these SCC has yet to be determined. We aim to elucidate the possible risk factors, prognosis, and the predictive value of post-stroke SCC. This information can subsequently be applied by clinicians in daily practice in order to more accurately inform patients and their proxies and to treat SCC. Our data may also prove useful in the future development of patient tailored intervention programmes to ultimately improve individual stroke patient-centred care, which is the ultimate aim of the COMPAS study.

Authors' contributions

R.M., P.K, and M.R. conceptualized the study. M.S. and R.M. contributed to the procurement of funding. M.R., R.M., and P.K. developed procedures for implementing the protocol. All authors contributed to and have checked the final manuscript.

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Competing interests

None declared.

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