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Changes in health-related quality of life after carotid stenosis treatment

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ABBREVIATIONS

ACTRIS	Study Endarterectomy Combined with Optimal Medical Therapy Versus Optimal Medical Therapy Alone in Patients with Asymptomatic Severe Atherosclerotic Carotid Artery Stenosis at High Risk of Ipsilateral **S**troke
AF	Atrial Fibrillation
AH	Arterial Hypertension
ANOVA	Analysis of Variance
BMI	Body Mass Index
BMT	Best Medical Treatment
BP	Bodily Pain
CAD	Coronary Artery Disease
CAS	Carotid Artery Stenting
CBF	Cerebral Blood Flow
CEA	Carotid Artery Endarterectomy
CHF	Chronic Heart Failure
CREST-2	Study Carotid Revascularisation and Medical Management for Asymptomatic Carotid Stenosis-2
DM	Diabetes Mellitus
GH	General Health
HRQoL	Health Related Quality of Life
ICH	Intracerebral Hemorrhage
IQR	Interquartile Range
MCS	Mental Component Summary
MH	Mental Health
MoCA	Montreal Cognitive Assessment Scale
mRS	Modified Rankin Scale

NIHSS	National Institute of Health Stroke Scale
NYHA	New York Heart Association
PAD	Peripheral Artery Disease
PCS	Physical Component Summary
PF	Physical Functioning
PHQ-9	Patient Health Questionnaire-9
PSCUH	Pauls Stradins Clinical University Hospital
RE	Role Limitations Due to Emotional Problems
RP	Role Limitations Due to Physical Problems
SF	Social Functioning
SF-36v2	Medical Outcome Survey Short Form 36 version 2
TIA	Transient Ischaemic Attack
VT	Vitality
VSE	Visuospatial / Executive Functions
V1	Baseline Visit 1
V2	Visit 2 (after 6 months)
V3	Visit 3 (after 12 months)

INTRODUCTION

Carotid artery stenosis is a well-known causal risk factor of ischaemic stroke. Approximately 10–15% of all strokes occur due to thromboembolism from previously asymptomatic > 50% internal carotid artery stenosis (Naylor, 2015). In addition to functional disability, stroke patients frequently go on to develop cognitive impairment and depression. The prevalence of post-stroke cognitive impairment ranges from 20% to 80% (Sun, Tan, & Yu, 2014), whereas the prevalence of post-stroke depression has been reported as 31% at any time point within 5 years following a stroke (Hackett & Pickles, 2014).

However, there is less knowledge and evidence regarding neuropsychological symptoms in patients with severe asymptomatic carotid artery stenosis. Several pathogenetic mechanisms for the development of cognitive impairment such as microembolism, hypoperfusion and reduced cerebrovascular reserve (Wang, Mei, & Zhang, 2016; Lal *et al.*, 2017) have been proposed. However, the definite effect of revascularisation on cognitive function in patients with severe carotid stenosis is still unknown because the results of studies on the topic remain controversial (Paraskevas *et al.*, 2014). Besides, the best medical treatment of atherosclerosis has changed in the last few decades, significantly reducing the annual risk of stroke in patients with asymptomatic carotid stenosis (Selim & Molina, 2011). Also, findings regarding the infuence of medical treatment of severe asymptomatic carotid stenosis on cognitive function have been derived from randomised controlled trials conducted before 2000, when the best medical treatment of atherosclerosis was not the same as today.

The questions of whether carotid stenosis causes cognitive impairment and whether carotid interventions improve cognitive function have been discussed in clinical practice of late. For the first time, this topic has been

mentioned in the guidelines of the European Society for Vascular Surgery (Naylor *et al.*, 2018). However, no clear recommendations on this issue were made. Therefore, the results from 2 randomised controlled CREST-2 and ACTRIS trials are awaited in years to come with anticipation (CREST-2, 2014; ACTRIS, 2018).

There are some reports in literature regarding the association of severe carotid stenosis and depression (Coumans & McGrail, 2000; Gressier *et al.*, 2011; Mlekusch *et al.*, 2006). Given the increasing burden of various chronic diseases worldwide (Iadecola, 2013; Ter Telgte *et al.*, 2018) and the increased incidence of depression in cardiovascular patients (Huffman *et al.*, 2013), there is a crucial need for information regarding the association between severe carotid stenosis and depression.Vascular depression as a subtype of late-life depression is of great interest because of its clinical significance and complex basis, which may affect outcomes in the depressed elderly, increase the risk of cognitive impairment and reduce the quality of life (Aizenstein *et al.*, 2016). Therefore, the goal of contemporary management to reduce stroke risk is not only to extend life expectancy but also to ensure a sufficiently high long-term health-related quality of life (HRQoL) (De Smedt, Clays & De Bacquer, 2016).

Scientific novelty and practical importance

The scientific novelty of this research work is justified by the fact that the first randomised controlled CREST-2 and ACTRIS trials are currently ongoing, in which one of the aims is to assess changes of cognitive function in patients with severe carotid stenosis after revascularisation as well as after the best medical treatment only. However, the results of these trials are not yet known.

Currently, this research is one of the several studies which has revealed long-term changes to cognition in patients with severe carotid stenosis both after revascularisation and after the best medical treatment. This study, to our knowledge, is one of the first which evaluates the long-term changes of depressive symptoms in patients with severe carotid stenosis both after revascularisation and the best medical treatment. This is the first study in Latvia in which the frequency of depressive symptoms was assessed in patients with severe internal carotid artery stenosis. Besides, this is one of the few studies in which the long-term changes of HRQoL were evaluated in patients with severe carotid stenosis after revascularisation as well as after the best medical treatment available. Not least, the results of this study have raised a new hypothesis of depression as a potential clinical marker for irreversible brain damage in patients with severe carotid stenosis. This needs to be evaluated in further clinical studies.

The results of this study confirm the association of severe carotid stenosis and cognitive impairment and its changes after the revascularisation, which is important for professionals working in the field of cerebrovascular diseases. These results may influence treatment decision making in patients with severe carotid stenosis.

Author's Personal Contribution

The author of the Doctoral Thesis has independently created a questionnaire for collection of all necessary data; has obtained premissions for the research from an institution which had developed tests and questionairres; managed thelephone calls for each patient's appointment, patient interviews and performed objective neurological examination. The data from each visit were collected, systematised, calculated and analysed.

Aim of the Study

The aim of this study was to assess long-term changes in cognitive function, depressive symptoms, and HRQoL as well as to estimate the frequency of cerebrovascular events and death rates in patients after severe carotid stenosis revascularisation and the best medical treatment only.

Objectives of the Study

1. Evaluate clinical characteristics of patients with severe carotid stenosis in the carotid endarterectomy, carotid stenting and in the best medical treatment groups.
2. Evaluate primary and secondary outcome measures and the frequency of restenosis at 6 and 12 months after severe carotid stenosis treatment in each study group.
3. Evaluate changes in cognitive function at 6 and 12 months after severe carotid stenosis treatment in each study group.
4. Evaluate changes in the frequency of depressive symptoms at 6 and 12 months after severe carotid stenosis treatment in each study group.
5. Evaluate changes in health-related quality of life at 6 and 12 months after severe carotid stenosis treatment in each study group.
6. Compare changes in cognitive function, frequency of depressive symptoms, cerebrovascular events and restenosis and health-related quality of life between study groups after 6 and 12 months.

Hypotheses

1. Patients with severe carotid artery stenosis would have improved cognitive function, depressive symptoms and HRQoL after revascularisation compared to pre-revascularisation period.
2. Patients after carotid stenosis revascularistaion would have less cognitive impairment, depressive symptoms, and significant changes in quality of life compared to patients who did not receive carotid stenosis revascularisation.

1 MATERIAL AND METHODS

1.1 Study Sample

Between March 2015 and October 2017, patients with severe internal carotid artery stenosis (≥ 70% luminal narrowing) and having fullfilled all inclusion criteria were recruited from the Neurology Department, Vascular Surgery Centre and the Latvian Centre of Cardiology at Pauls Stradins Clinical University Hospital for this prospective observational study.

The **inclusion criteria** for all consenting patients were as follows: aged 18 years or older; severe asymptomatic or symptomatic extracranial internal carotid stenosis ≥ 70%; no significant neurological dysfunction after stroke; an indication for carotid artery endarterectomy (CEA) or stenting (CAS); consent to participate in the study at least for the first year after enrollment.

The **exclusion criteria** were major stroke (NIHSS ≥ 4, mRS 3–5), carotid stenosis < 70%, progressive cerebral pathology (tumour, multiple sclerosis, Alzheimer's disease), patients with depression or had antidepressant therapy for any reasons and refusal to attend long term follow-up due to distance or for other reason.

1.2 Study Design

Two hundred and thirteen patients entered the study. Management of severe carotid stenosis was conducted independently of the study by the treating physician based on patient preference and characteristics. Patients who refused to receive carotid endarterectomy (CEA) and/or planned carotid artery stenting (CAS) but was not performed during the study period for unrelated

reasons, were enrolled in the best medical treatment (BMT) group. Therefore, 3 cohorts were formed from the study sample:

1) patients who underwent CEA (CEA group, n = 159);

2) patients who underwent CAS (CAS group, n = 29);

3) patients who received BMT only (BMT group, n = 25).

All patients in this study received recommendations to use pharmacological treatment after discharge from the hospital, including antiplatelet agents, statins, or other hypolipidaemic medications, antihypertensive treatment, strict control of hyperglycaemia if diabetic, counseling for smoking cessation, weight control, and regular physical exercise.

For each patient, 3 follow-up time-points were planned:

First time-point (V1 – Visit 1) – time before planned revascularisation or the time-point when investigation for carotid arteries was performed. At the baseline visit (V1), basic demographic characteristics, anthropometric and lifestyle characteristics, data on comorbidities, use of medications, and neurological examination results were recorded on a standardised form during an interview. After the examination of neurological status, patients were required to undergo a standardised cognitive assessment and complete questionnaires which assessed depressive symptoms and HRQoL.

The author of the study invited patients to come to the second (V2, after 6 months) and to the third (V3, after 12 months) follow-up visits by phone. In each of the follow-up visits (at the V2 and V3), aside from vascular risk factors, new comorbidities, neurological status and medication compliance, cognitive function, depressive symptoms, and HRQoL were also reassessed. In addition to assessment of clinical, neurological, cognitive, depressive symptoms, and HRQoL, an evaluation of extracranial carotid arteries were also performed using a duplex ultrasound to assess the *intima media* thickness and the rate of

restenosis at 6-months and 1-year follow-up periods by a single experienced neurosonographer who was blinded to the patient data.

As the course of the study was one year, primary and secondary outcome measures were analysed. The primary outcome measure was a stroke within 30 days after revascularisation or enrollment in the study; myocardial infarction (MI), perioperative intracerebral hemorrhage, or death. The secondary outcome measure was defined as a cerebrovascular event, acute coronary syndrome or deathduring the 1-year follow-up period, except for the first 30 days, which was the cause for non-attendance of follow-up visits.

1.3 Characteristics of Tests for Assessment of Cognitive Function, Depression and Quality of Life

1.3.1 Assessment of Cognitive Function

The cognitive assessment was performed using the Montreal Cognitive Assessment Scale (MoCA), which evaluates several aspects of executive function. Therefore, it is recommended as a useful screening tool for vascular cognitive impairment which can be administered in 10 minutes (Nasreddine *et al.*, 2005; Pendlebury *et al.*, 2012; Bocti *et al.*, 2013; Cumming *et al.*, 2013; Koski, 2013). It can also be used among patients over 60 years of age (Ciesielska *et al.*, 2016).

The cognitive assessment was performed using the Latvian or Russian MoCA version, according to the patient's native tongue, and instructions given by the authors (Nasreddine Ziad, 2015). The MoCA test is divided into 7 sub-scores that assess 7 cognitive domains: visuospatial/executive, naming, attention, language, abstraction, memory, and orientation. An additional point is given to each patient who had received education for 12 years or less. The

MoCA scores range from 0–30, and a final total score of 26 and above is considered normal (Nasreddine *et al.*, 2005).

1.3.2 Assessment of Depressive Symptoms

Assessment of depressive symptoms was performed using the Patient Health Questionnaire-9 (PHQ-9), which incorporates the DSM-IV depression diagnostic criteria. The PHQ-9 is a self-reporting 9-item questionnaire about the last 2 weeks, and its scores range from 0 to 27. A PHQ-9 score of 10 or greater is recommended as a screening cut off point because it has a sensitivity for major depression of 88%, a specificity of 88% (Kroenke, Spitzer & Williams, 2001).

The PHQ-9, which has been compared with other questionnaires, is proposed to be an acceptable tool for the screening of depressive symptoms (Kroenke, Spitzer and Williams, 2001; Kung *et al.*, 2013). Still, it takes less time, not losing its sensitivity and specificity (Berwick *et al.*, 1991). In this study, validated Latvian and Russian versions of the PHQ-9 depression scale were used according to the patient's native tongue, and instructions given by the authors (PHQ-9 Instruction Manual, 2015).

1.3.3 Assessment of Health-Related Quality of Life

The systemic literature review and meta-analysis indicated that there is currently insufficient evidence of the superiority of any HRQoL assessment scale over others to be used in patients undergoing carotid revascularisation (Essat *et al.*, 2018). While there is no clear consensus of the most suitable instruments for assessing HRQoL in the literature, SF-36 is a well recognised generic HRQoL instrument in vascular surgery (Shan *et al.*, 2015).

The improved SF-36v2 includes 36 items that are grouped into eight subscales: (Ware *et al.*, 2008):

1) Physical functioning (PF) – reflects the importance of distinct aspects of physical functioning and necessity of sampling a range of severe and minor physical limitations;

2) Role limitations due to physical problems (RP) – covers an array of physical health-related role limitations, including limitations in the kind of work or other usual activities, reductions in the amount of time spent on work or other usual activities, difficulty performing work or other usual activities and accomplishing less;

3) Bodily pain (BP) – reflects intensity of bodily pain and the extent of interference with normal work activities due to pain;

4) General health (GH) – addresses the respondent's view's and expectations of his or her health;

5) Vitality (VT) – captures the difference in subjective well-being;

6) Social functioning (SF) – assesses health-related effects on quantity and quality of social activities, asking specifically about the impact of either physical or emotional problems on social activities;

7) Role limitations due to emotional problems (RE) – assesses mental health-related role limitations in terms of time spent doing work or other usual activities, amount of work or activities accomplished and care with which work or other activities were performed;

8) Mental health (MH) – includes four major mental health dimensions (anxiety, depression, loss of behavioral/emotional control, and psychological well-being.

In addition, the SF-36v2 provides summary scales for overall physical and mental health: physical component summary (PCS) and mental component summary (MCS) scores.

HRQoL was measured using the Medical Outcome Survey Short Form 36 version 2 (SF-36v2) paper format in the Latvian and Russian languages (Optum, 2015) within 10 minutes. The unclear questions were explained if necessary. Afterwards, results were entered in the QualityMetric Health Outcomes™ Scoring Software 4.5. programme, where for each item, scores are coded, summed and transformed into a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state).

1.4 Statistical Analysis

Descriptive statistics were used to analyse the demographic and clinical characteristics of the population. Continuous variables were described as a median and interquartile range (IQR) or as means and standard deviation (SD). As majority of the variables were not normally distributed, and there was an imbalance between groups, non-parametric statistics were mainly used to evaluate variables. We used the Pearson's Chi-squared (χ^2) or Fisher's exact tests to compare baseline categoric variables between the groups. For the detection of differences among three treatment groups (CEA, CAS, BMT), the Kruskal-Wallis test or Analysis of Variance (ANOVA) was applied. Changes in continuous variables at V1, V2, and V3 in each treatment group were calculated using the Friedman's test followed by the least significant difference post hoc test using the Wilcoxon signed-rank test for paired continuous data and the McNemar test for paired categorical data.

For the evaluation of the statistical effect size of the Pearson's Chi-squared or Fisher's exact test, Cramer's V was calculated, in which the following categories for assessing of the statistical effect size were used: 0.1 – 0.3 = small; 0.3 – 0.5 = medium; > 0.5 = large. For the evaluation of the statistical effect size of Kruskal-Wallis and ANOVA tests, partial eta squared

(η^2) ($\leq$ 0.01 = small; 0.06 = medium; $\geq$ 0.14 = large) and *Cohen's d* (0.2 = small; 0.5 = medium; > 0.8 = large) were used. As well as, Kendall's coefficient of concordance (Kendall's W) for Friedman's test (0.1 = small; 0.3 = medium; 0.5 = large), coefficient *r* for Wilcoxon signed rank test and coefficient *g* for McNemar test. The small effect size for coefficient *r* is 0.1, but for coefficient *g* – 0.05; medium effect size for coefficient *r* is 0.3, but for coefficient *g* – 0.15; large effect size for coefficient *r* is 0.5, but for coefficient *g* – 0.25.

For the analysis of the contiguity of two features, the Spearman's correlation analysis (denoted by r_s) was used. The study adopted the following correlation closeness classification depending on the size of the correlation coefficient r_s: correlation is weak, if $r_s \leq 0.3$; correlation is medium if $0.3 < r_s < 0.7$; but a correlation is strong if $r_s \geq 0.7$.

A two-sided *p*-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics (version 23 for Windows, IBM Corp., Somers, NY, USA).

2 RESULTS

2.1 Primary and Secondary Outcome

During the one-year follow-up period, primary and secondary outcome measures were observed in 14 patients. The primary outcome causes in the CEA group were perioperative disabling stroke (n = 2), large perioperative MI (n = 1), and perioperative intracerebral haemorrhage (ICH) (n = 1); in the CAS group, periprocedural infection with sepsis and death (n = 1). In the BMT group, there were no primary outcome events during the first 30 days after the initiation of the study. The secondary outcome causes in the CEA group were death (n = 3) and contralateral disabling stroke (n = 2). In the CAS group, death (n = 2) due to traumatic ICH and acute coronary artery disease (CAD), but in the BMT group, one patient had an ipsilateral disabling stroke, and one patient had acute CAD. The data of all these patients were analysed until the time point when the patient was unable to continue the study. However, some patients did not want to continue to participate in the study during the follow-up period due to their social background. In telephone interviews (at V2 or V3), no vascular event or death was reported for subjects who interrupted the study. Therefore, in the CEA group at the beginning, there were 159 patients, whereas after 6 months, only 132 patients continued to participate in the study, and after 12 months, there were 128 patients. In the CAS group, there were initially 29 patients. After 6 months, there were only 27 patients, and after 12 months, there were 25 patients. In the BMT group, there were initially 25 patients. After 6 months there were 24, but after 12 months, only 22 patients continued the study.

In the analysis of the frequency of restenosis, 2 (1.5%) out of 132 patients in the CEA group had restenosis after 6 and 12 months whereas in

the CAS group 2 (7.4%) out of 27 patients (p = 0.136; Cramer's V = 0.15) did.Furthermore, in the BMT group the progression of severe carotid stenosis to occlusion was not observed in any patients.

2.2 Demographic and Clinical Characteristics of Patients

The median age in all three groups was similar: in the CEA group – 71 (IQR: 63; 75); in the CAS group – 71 (IQR: 63.4; 78) and in the BMT group – 74 (IQR: 67; 78) years (p = 0.171, η^2 = 0.01).

There was no statistically significant difference in terms of gender, in each treatment group, men were more common than women (p = 0.226, Cramer's V = 0.118). Comparing age differences between men and women in each group, we observed a statistically significant difference only in the CEA group where women were older than men (p < 0.001, η^2 = 0.1). There were no statistically significant differences between the age of both genders in the CAS and BMT groups (p > 0.05), (Figure 2.1).

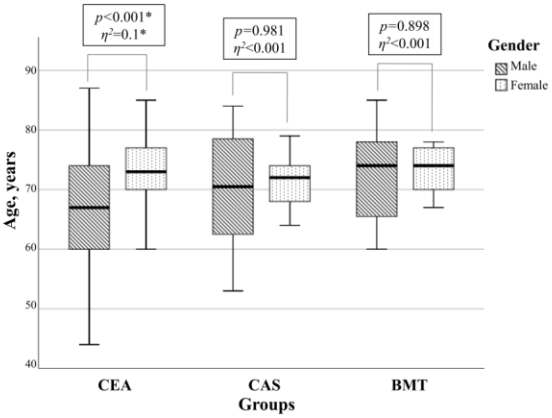


Figure 2.1 **Age differences in the carotid endarterectomy, carotid stenting and best medical treatment groups**

Most patients in the study had asymptomatic carotid artery stenosis. Symptomatic stenosis was more common in the BMT group. However, a statistically significant difference between study groups was not observed (p = 0.072, Cramer's V = 0.165). The neurological characteristics of the patients in each group are presented in Table 2.1.

Table 2.1

Neurological characteristics of patients with severe carotid stenosis

	CEA n = 159	**CAS n = 29**	**BMT n = 25**	***p*-value**	**Effect size**
Cerebrovascular events					
Asymptomatic, n (%)	118 (74.2%)	20 (69%)	13 (52%)	0.072	Cramer's V 0.165
Symptomatic stroke, (NIHSS ≤ 3)	22 (13.8%)	6 (20.7%)	10 (40%)		
TIA	16 (10.1%)	2 (6.9%)	1 (4%)		
amaurosis fugax	3 (1.9%)	1 (3.4%)	1 (4%)		
Stenosis side, n (%)					
right	66 (41.5%)	12 (41.4%)	8 (32.0%)	0.845	Cramer's V 0.057
left	52 (32.7%)	8 (27.6%)	10 (40.0%)		
bilateral	41 (25.8%)	9 (31.0%)	7 (28%)		

CEA – carotid endarterectomy group; CAS – carotid artery stenting group; BMT – best medical treatment group; NIHSS – National Institute of Health Stroke Scale; TIA – transient ischaemic attack

The difference between treatment groups regarding cardiovascular risk factors was not statistically significant, except for CAD and chronic heart failure, atrial fibrillation (AF) and diabetes mellitus (DM). AF was more common in the BMT group (p = 0.001, Cramer's V = 0.255), but DM was in the CAS group (p < 0.001, Cramer's V = 0.281). Although CAD and chronic heart disease (CHD) were more common in the CAS group (p = 0.048 and

p = 0.034), the statistical effect size of the differences was small. The clinical characteristics of the patients in each group are presented in Table 2.2.

Table 2.2

Characteristics of cardiovascular risk factors

	CEA n = 159	**CAS n = 29**	**BMT n = 25**	***p*-value**	**Effect size**
CAD	68 (42.8%)	19 (65.5%)	9 (36.0%)	0.048*	Cramer's V 0.169
CHD					
class II	30 (18.9%)	9 (31%)	10 (40%)	0.034*	Cramer's V 0.197
class III	10 (6.3%)	4 (13.8%)	2 (8%)		
class IV	0	1 (3.4%)	0		
AH					
stage 2	102 (64.2%)	17 (58.6%)	16 (64%)	0.709	Cramer's V 0.094
stage 3	25 (15.7%)	5 (17.2%)	5 (20%)		
AF	15 (9.4%)	6 (20.7%)	9 (36%)	0.001*	Cramer's V 0.255**
PAD	49 (30.8%)	11 (39.3%)	5 (20%)	0.314	Cramer's V 0.105
DM	21 (13.2%)	13 (44.8%)	4 (16%)	<0.001*	Cramer's V 0.281**
Smoking					
non-smoker	54 (34%)	9 (44%)	11 (44%)	0.764	Cramer's V 0.066
current smoker	72 (45.3%)	12 (41.4%)	10 (40%)		
former smoker	33 (20.7%)	8 (27.6%)	4 (16%)		
BMI (mean, SD)	27.12 (4.26)	27.67 (4.27)	27.29 (3.59)	0.805	η^2 = 0.002

CEA – carotid endarterectomy group; CAS – carotid artery stenting group; BMT – best medical treatment group; CAD – coronary artery disease; CHD – chronic heart disease; AH – arterial hypertension; AF – atrial fibrillation; PAD – peripheral artery disease; DM – diabetes mellitus; BMI – body mass index; SD – standard deviation* $p < 0.05$; **effect size Cramer's V = 0.3 (medium)

In the analysis of other comorbidities such as chronic kidney disease, chronic pulmonary diseases, pain, vision impairment, thyroid gland diseases, and previous history of malignancy, there were no statistically significant differences between study groups. Comparing the amount of comorbidities including cardiovascular diseases, the CAS group had more comorbidities (Me = 3 (IQR: 2; 4.75)) than the CEA (Me = 2 (IQR: 1; 3), p = 0.004) and BMT groups (Me = 2 (IQR: 1; 3.5), p = 0.036) although the statistical effect size was small (η^2 = 0.051).

2.3 Characteristics of Cognitive Function

2.3.1 Characteristics of Cognitive Function at Baseline

During cognitive assessment at the beginning of the study, there was no significant difference in the median total MoCA scores between all treatment groups (p = 0.728, η^2 = 0.003). The median total MoCA score in the CEA group was 25 (IQR: 22; 27), in the CAS group – 24 (IQR: 21; 26) and in the BMT group – 25 (IQR: 22; 26). In the analysis of the median MoCA subtest scores, there was no significant difference. Median MoCA subtest scores at baseline in each study group are presented in Table 2.3.

Table 2.3

Median MoCA subtest scores at baseline in each study group

	CEA n = 159	**CAS n = 29**	**BMT n = 25**	***p*-value**	**Effect size η^2**
VSE	4 (3; 5)	4 (2; 5)	4 (2.5; 3.5)	0.183	0.016
Naming	3 (3; 3)	3 (3; 3)	3 (3; 3)	0.344	0.001
Attention	6 (5; 6)	6 (5; 6)	6 (5; 6)	0.592	0.005
Language	2 (1; 2)	2 (1; 2)	2 (1; 2)	0.887	0.001
Abstraction	2 (1; 2)	2 (1; 2)	2 (1; 2)	0.619	0.005
Delayed recall	2 (1; 4)	3 (1; 4)	2 (2; 3.5)	0.943	0.001

Table 2.3 continued

	CEA n = 159	CAS n = 29	BMT n = 25	*p*-value	Effect size η^2
Orientation	6 (6; 6)	6 (6; 6)	6 (6; 6)	0.344	0.001

CEA – carotid endarterectomy group; CAS – carotid artery stenting group; BMT – best medical treatment group; VSE – visuospatial/executive functions; median values (IQR: Q1 – Q3); * $p < 0.05$

For assessment of the interaction between clinical features in patients with severe carotid stenosis and cognitive impairment, the total amount of patients, without dividing in groups, was analysed. There were no statistically significant differences in cognitive function, gender, or those patients with and without depressive symptoms at baseline. Analysing the frequency of cognitive impairment in the presence of comorbidities, cognitive impairment was more common in patients with CAD than in those who did not have CAD ($p = 0.006$, $r = 0.188$). There was no significant difference in the frequency of cognitive impairment between the presence of other comorbidities ($p > 0.05$). Besides, there was no statistically significant difference in cognitive impairment between patients with symptomatic and asymptomatic carotid stenosis ($p > 0.05$). In the analysis of interaction between age and cognitive function, there was a statistically significant but weak negative correlation ($r_s = – 0.267$, $p < 0.001$; 95%CI – 0.137; – 0.388). In a simple linear regression where the dependent variable was the total MoCA score at baseline and the independent variable was age, age as a single feature was seen to affect the total MoCA score in 6% of patients with severe carotid stenosis (constant = 30.6, beta = – 0.94, $p < 0.001$).

2.3.2 Change in Cognitive Function after Endarterectomy

There was a significant increase of the median total MoCA score as a measure of cognitive function at 6 and 12 months after successful CEA in

patients with severe carotid stenosis (p < 0.001, Kendall's W = 0.28). The median total MoCA scores at baseline, 6 and 12 months in the CEA group are presented in Figure 2.2.

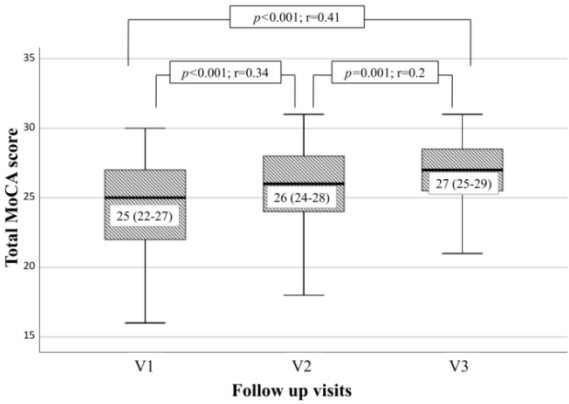


Figure 2.2 **Median total MoCA scores at baseline, 6 and 12 months in the carotid endarterectomy group**

Comparing the median MoCA subtest scores during the follow-up period, there was a statistically significant improvement in attention, language, abstraction, and delayed recall subtest scores. However, the statistical effect size was small. There was no decline in any of the MoCA subtest scores (Table 2.4).

Table 2.4

Median MoCA subtest scores at baseline, after 6 and 12 months in the carotid endarterectomy group

	V1	V2	V3	*p*-value	Effect size
Total MoCA	25 (22; 27)	26 (24; 28)	27 (25; 29)	<0.001*****	0.28******
VSE	4 (3; 5)	4 (3; 5)	4 (4; 5)	0.254	0.013
Naming	3 (3; 3)	3 (3; 3)	3 (3; 3)	0.135	0.019
Attention	5 (6; 6)	5 (6; 6)	5 (6; 6)	0.035*****	0.033

Table 2.4 continued

	V1	V2	V3	*p*-value	Effect size
Language	2 (1; 2)	2 (1; 2)	2 (1; 3)	<0.001*****	0.075
Abstraction	2 (1; 2)	2 (1; 2)	2 (2; 2)	<0.001*****	0.076
Delayed recall	3 (1; 4)	4 (2; 5)	4 (3; 5)	<0.001*****	0.217
Orientation	6 (6; 6)	6 (6; 6)	6 (6; 6)	0.103	0.023

V1 – baseline visit before endarterectomy, V2 – visit 2 (6 months after endarterectomy), V3 – visit 3 (12 months after endarterectomy); VSE – visuospatial/executive functions; Median values (IQR: Q1; Q3); * $p < 0.05$; ****** Kendall's W effect size ≥ 0.3 (medium)

2.3.3 Change in Cognitive Function after Carotid Stenting

Patients in the CAS group also had improved total MoCA scores during the 1-year follow-up ($p = 0.01$, Kendall's W = 0.261). The median total MoCA scores before CAS, 6 and 12 months after CAS are presented in Figure 2.3.

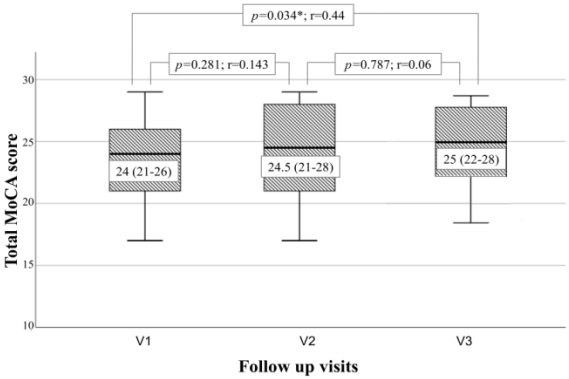


Figure 2.3 **Median total MoCA scores at baseline, 6 and 12 months in the carotid artery stenting group**

Comparing the median MoCA subtest scores during the follow-up period, there was a statistically significant improvement only in the visuospatial/executive subtest scores, but the statistical effect size was small.

The median total MoCA scores at baseline, 6 and 12 months in the CAS group are presented in Table 2.5.

Table 2.5

Median MoCA subtest scores at baseline, after 6 and 12 months in the carotid artery stenting group

	V1	V2	V3	*p*−value	Effect size
Total MoCA	24 (21; 26)	24.5 (21;28)	25 (22;28)	0.01*	0.261**
VSE	3 (2; 5)	4 (3; 5)	4 (3; 5)	0.01*	0.24
Naming	3 (3; 3)	3 (3; 3)	3 (3; 3)	0.368	0.053
Attention	5 (4; 6)	6 (5; 6)	5 (4; 6)	0.572	0.029
Language	2 (1; 2)	1 (1; 2)	1 (1; 2)	0.917	0.005
Abstraction	2 (1; 2)	1 (1; 2)	2 (1; 2)	0.289	0.065
Delayed recall	3 (0.75; 4)	4 (1.75; 4)	3 (1.75; 4)	0.144	0.108
Orientation	6 (6; 6)	6 (6; 6)	6 (6; 6)	0.368	0.053

V1 – baseline visit before carotid stenting, V2 – visit 2 (6 months after carotid stenting), V3 – visit 3 (12 months after carotid stenting); VSE – visuospatial/executive functions; Median values (IQR:Q; Q3); * $p < 0.05$; ****** Kendall's W effect size ≥ 0.3 (medium)

2.3.4 Change in Cognitive Function in the Best Medical Treatment Group

Patients in the BMT group did not show statistically significant changes in the total MoCA scores in 1 year ($p = 0.295$, Kendall's W = 0.081). Comparing the median MoCA subtest scores during the follow-up period, a statistically significant improvement was found specifically in the memory subtest scores. Still, the statistical effect size was small (Kendall's W = 0.242) (Table 2.6).

Table 2.6

Median MoCA subtest scores at baseline, after 6 and 12 months in the best medical treatment group

	V1	V2	V3	*p*-value	Effect size
Total MoCA	25 (22; 26)	26 (23; 27)	26 (23; 28)	0.295	0.081
VSE	4 (3; 4)	4 (3; 5)	4 (2; 5)	0.973	0.002
Naming	3 (3; 3)	3 (3; 3)	3 (3; 3)	1.0	<0.001
Attention	6 (6; 6)	6 (5; 6)	6 (5; 6)	0.507	0.045
Language	2 (1; 2)	1 (1; 2)	2 (1; 3)	0.531	0.042
Abstraction	2 (1; 2)	2 (2; 2)	2 (2; 2)	0.229	0.098
Delayed recall	2 (2; 3)	3 (2; 4)	4 (3; 5)	0.027*	0.242
Orientation	6 (6; 6)	6 (6; 6)	6 (6; 6)	0.999	<0.099

V1 – baseline visit, recruitment in the study, V2 – visit 2 (6 months after recruitment), V3 – visit 3 (12 months after recruitment); VSE – visuospatial/executive functions; Median values (IQR: Q1; Q3); * $p < 0.05$

2.4 Characteristics of Depressive Symptoms

2.4.1 Characteristics of Depressive Symptoms at Baseline

At the beginning of the study, the median PHQ-9 scores were similar in all groups: in the CEA group it was 5 (IQR: 2; 9), in the CAS group it was 6 (IQR: 2; 10) and in the BMT group it was 6 (IQR: 3; 10), ($p = 0.3$, $\eta^2 = 0.014$).

For the assessment of the interaction between clinical features in patients with severe carotid stenosis and depressive symptoms, the total amount of patients, without dividing in groups, was analysed. The median age of patients with depression (Me = 71; IQR 62; 76) was similar with the age of patients without depressive symptoms (Me = 71; IQR: 63.5; 76), ($p = 0.883$, $r = 0.01$). Association between depressive symptoms and symptomatic or asymptomatic carotid stenosis was not observed ($p = 0.134$,

Cramer's V = 0.088). Besides, there was no association with depressive symptoms and the number of days after stroke when the patient was examined (p = 0.133, r = 0.1). However, assessing the interaction between depressive symptoms and gender, women more frequenlty scored ≥ 10 points in the PHQ-9 questionnaire (29.5%, n = 23) than men (17.9%, n = 24) from the total patient amount. However, the difference was not satistically significant (p = 0.06; Cramer's V = 0.134). There was a statistically significant association between depressive symptoms and CAD. Patients with CAD had depressive symptoms more frequently (30.2%, n = 29) than patients without CAD (15.5%, n = 18), p = 0.01, Cramer's V = 0.179. Association between depressive symptoms and CHD, AH, AF, DM and PAD were not observed (p > 0.05). Furthermore, the association between depressive symptoms and education (< 12 school years) was also not observed (p = 0.452, Cramer's V = 0.052).

2.4.2 Change in Depressive Symptoms after Endarterectomy

In the CEA group, there was no statistically significant difference between the frequencies of depressive symptoms (PHQ-9 screening cut-point ≥ 10) before and 6 or 12 months after CEA (p = 0.485, Kendall's W = 0.007).

In the study, from those patients who had depressive symptoms before CEA (n = 31), more than half of them did not feel depressed after 6 months (n = 18; 58.1%), but 41.9% (n = 13) remained depressed. However, the difference between patients who remained depressed, and those whose symptoms improvedat 6 months was not statistically significant (p = 0.17, g = 0.15). The changes in the frequency of depressive symptoms after 6 months in the CEA group are presented in Figure 2.4.

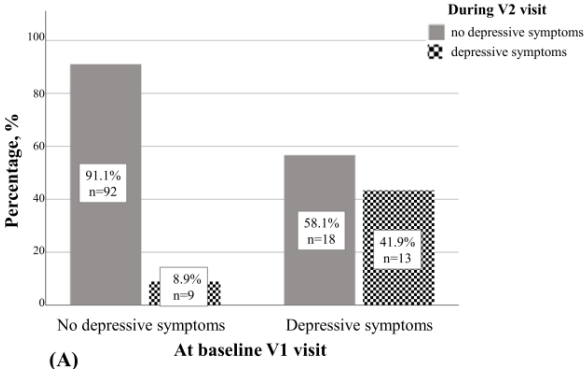


Figure 2.4 **Changes in the frequency of depressive symptoms after 6 months in the carotid endarterectomy group**

Like the V2 visit, after one year of those patients who had depressive symptoms before CEA (n = 27) more than a half did not feel depressed (n = 16; 59.2%) but 40.8% (n = 11) remained depressed. However, the difference was not statistically significant (p = 0.557, g = 0.08). The changes in the frequency of depressive symptoms after 12 months in the CEA group are presented in Figure 2.5.

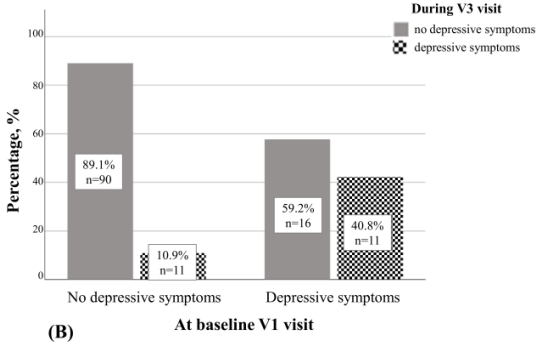


Figure 2.5 **Changes in the frequency of depressive symptoms after 12 months in the carotid endarterectomy group**

2.4.3 Change in Depressive Symptoms after Carotid Stenting

In the CAS group, there was no statistically significant difference between the frequencies of depressive symptoms before and 6 or 12 months after CAS (p = 0.165, Kendall's W = 0.095).

In the analysis of depressive symptoms after 6 months, only one of the 8 patients who had depressive symptoms before CAS got better, while the other 7 patients remained depressed (p = 0.375). The changes in the frequency of depressive symptoms after 6 months in the CAS group are presented in Figure 2.6.

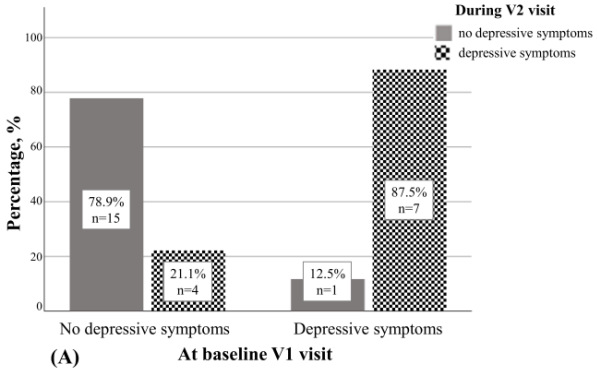


Figure 2.6 **Changes in the frequency of depressive symptoms after 6 months in the carotid artery stenting group**

Likewise, 12 months after CAS, depressive symptoms were not observed in 3 of the 8 patients. The differences between patients who remained depressed, and those whose symptoms improved at 12 months (p = 0.97) was not statistically significant. The changes in the frequency of depressive symptoms after 12 months in the CAS group are presented in Figure 2.7.

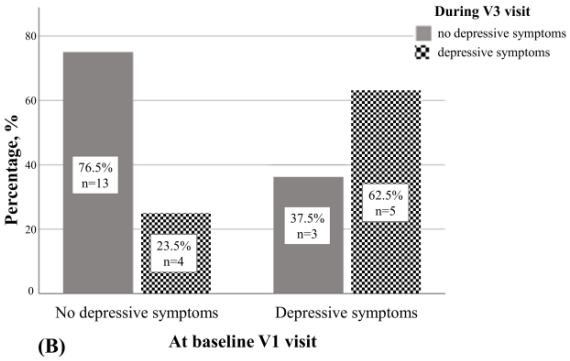


Figure 2.7 **Changes in the frequency of depressive symptoms after 12 months in the carotid artery stenting group**

2.4.4 Change in Depressive Symptoms in the Best Medical Treatment Group

In the BMT group, in the analysis of the frequencies of depressive symptoms, there was no statistically significant difference between the baseline and 6 or 12 months after initiation of BMT (p = 0.819, Kendall's W = 0.013).

The differences between patients who remained depressed and those whose symptoms improved at 6 months was not statistically significant (p = 0.687). In the analysis, from those who had depressive symptoms at baseline, only two (33.3%) out of 6 patients were free from depressive symptoms after 6 months. Likewise, 12 months after BMT, depressive symptoms were not observed in 2 (58.6%) out of 7 patients. The difference between patients who remained depressed and those whose symptoms improved at 12 months was not statistically significant (p = 0.243). The changes in the frequency of depressive symptoms after 6 and 12 months in the BMT group are presented in Figures 2.8 and 2.9.

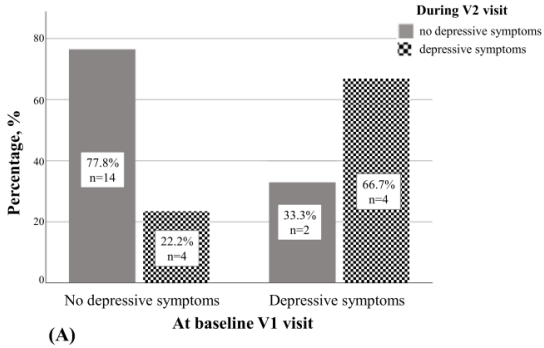


Figure 2.8 **Changes in the frequency of depressive symptoms after 6 months in the best medical treatment group**

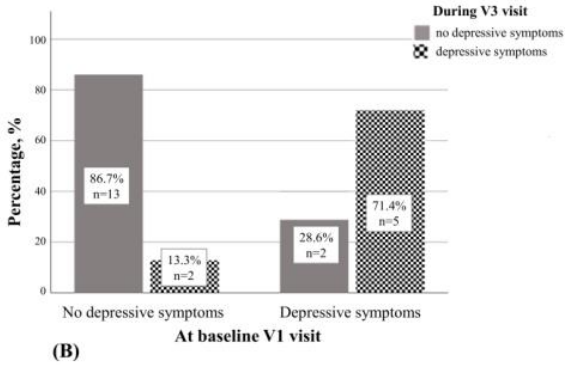


Figure 2.9 **Changes in the frequency of depressive symptoms after 12 months in the best medical treatment group**

2.5 Characteristics of Health-Related Quality of Life

2.5.1 Characteristics of Health-Related Quality of Life at Baseline

At baseline, the SF-36v2 subscale scores were similar in all three study groups. The lowest mean scores (< 50 points) in all groups were for GH, PCS,

and MCS, and the highest (≥ 70 points) were for SF in the CEA and BMT groups. Although the mean SF-36v2 scores for PF and BP were significantly lower in the CAS group than in CEA and BMT groups ($p < 0.05$), the statistical effect size was small (Table 2.7).

Table 2.7

Mean SF-36v2 scores in patients with severe carotid stenosis at baseline

	CEA (n=159)	**CAS (n=29)**	**BMT (n=25)**	***p*-value**	**Effect size η^2**
Physical functioning (PF)	66.6 (22.4)	53.4 (23)	57 (30)	0.036*	0.031
Role-physical (RP)	55.4 (26.7)	47.7 (25.7)	57.1 (27.4)	0.158	0.017
Bodily pain (BP)	60 (27)	48.4 (27.2)	66.7 (26.4)	0.009*	0.044
General health (GH)	47.6 (17)	44.7 (19.5)	47.5 (25.6)	0.297	0.015
Vitality (VT)	56.7 (18.6)	49.7 (20.7)	60.4 (20.1)	0.173	0.017
Social functioning (SF)	71.7 (25.3)	65.1 (27.2)	75.8 (19.2)	0.671	0.004
Role-emotiona (RE)	65 (27.7)	57.9 (27.3)	71.7 (23.1)	0.231	0.014
Mental health (MH)	63.5 (17.5)	62.6 (21.7)	71.3 (15)	0.238	0.014
Physical component summary (PCS)	44 (8.5)	39.7 (8.3)	42.1 (8.9)	0.09	0.023
Mental component summary (MCS)	45.5 (10.1)	44.5 (10.9)	50.1 (7.8)	0.285	0.012

CEA – carotid endarterectomy group; CAS – carotid artery stenting group; BMT – best medical treatment group; SD – standard deviation; *$p < 0.05$

2.5.2 Relationship between Health-Related Quality of Life and Clinical Characteristics

In the analysis of the total amount of patients with severe carotid stenosis at the baseline before treatment, there was a statistically significant but weak negative correlation between age and PCS (r_s = – 0.174, p = 0.011; 95%CI – 0.301; – 0.041). Furthermore, there was significant weak negative correlation between age and MCS (r_s = − 0.168; p = 0.014; 95%CI – 0.295; –0.035). Likewise, there was significant weak negative correlation between age and PF (r_s = – 0.197, p = 0.004; 95%CI – 0.322; – 0.065), RP (r_s = 0.235, p = 0.005; 95%CI – 0.382; – 0.132), SF (r_s = – 0.195, p = 0.004; 95%CI – 0.321; – 0.063) and RE (r_s= – 0.222; p = 0.002; 95%CI – 0.337; – 0.081) domains.

Comparing the mean values of the SF-36v2 domains between gender, women had lower values compared with men in the following domains: PF 57.5 (23.5), RP 46.4 (21.9), BP 53.4 (29.1), GH 43.4 (16), VT 54 (18.5) and PCS 40.6 (7.7). The differences in all previous domains were statistically significant ($p < 0.05$). However, the statistical effect size was small for all p-values (*Cohen's d* < 0.04).

In the assessment of the SF-36v2 domain mean values and the relationship with CAD, the patients with CAD had lower mean values in all domains compared with patients without CAD ($p < 0.02$). However, the statistical effect size was medium or large only for the PF, RF, GH, VT and PCS domains (*Cohen's d* $\geq$ 0.5). Likewise, significantly lower mean values were for the GH, VT, and SF domains in patients with DM. However, the effect size was small in all domains ($p < 0.03$; *Cohen's d* < 0.04). The SF-36v2 mean values were not statistically different regardless whether the patient had or did not have AH, highbody mass index or was a smoker. However, there was a

significant difference of the mean values of PF, RF, PCS for patients with moderate or severe heart failure (≥ III NYHA Class) who had lower PF (50.59 (22.5)), RF (38.6 (23.7)), and PCS (38.16 (8.4)) compared with patients who had CHD Class 0–II ($p < 0.04$, *Cohen's d* > 0.5). Likewise, patients with AF had significantly lower values in PF (52.67 (25.31)), RP (43.96 (25.4)), PCS (39.66 (8.64)) domains to patients without AF ($p < 0.05$) where the effect size was medium in the PF and PCS domains (*Cohen's d* = 0.5), except for RP, for which the effect size was small (*Cohen's d* = 0.4). Significant lower mean BP values were seen in patients with PAD (55.75 (27.15)) compared to patients without PAD (62.07 (28.35)), $p = 0.05$. However, the effect size was small (*Cohen's d* = 0.29). In the analysis of the relationship between the number of comorbidities and mean values of SF-36v2, significantly lower mean values were more common in patients who had more comorbidities in the following domains: PF, RP, BP, GH, VT, SF, and PCS.

In evaluating whether there was a change of the SF-36v2 mean values if patients had symptomatic or asymptomatic carotid stenosis, significantly lower mean values for PF (59.97 (25.09)) and BP (56.35 (28.47)) were observed in patients with symptomatic carotid stenosis. However, the statistical effect size was small (*Cohen's d* = 0.337). There was no significant difference in any of the SF-36v2 domains between patients with unilateral and bilateral carotid stenosis ($p > 0.05$).

Analysing the relationship between HRQoL and cognitive function before revascularisation, a significant difference was not found ($p > 0.05$). However, the mean values of all domains were lower in patients with depressive symptoms as compared with patients who did not have depressive symptoms at baseline ($p < 0.001$; *Cohen's d* ≥ 0,7).

As PCS and MCS aggregate the physical and mental health domain scales, these scales were chosen for the multifactorial regression analysis.

Lower mean values of the physical component summary (PCS ≤ 50 points) were significantly associated with CAD (OR 2.73; 95%CI 1.247; 5.974; p = 0.012) and PAD (OR 4.15; 95%CI 1.597; 10.769; p = 0.003). Contrastingly, lower MCS mean scores were associated with age.

2.5.3 Change of Health-Related Quality of Life after Endarterectomy

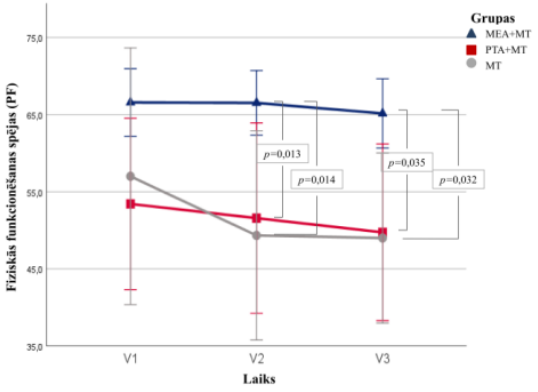
Comparing the mean SF-36v2 scores in the CEA group during the follow-up period, there was no statistically significant difference in any of the 10 subscales. The lowest mean SF-36v2 scores for GH, PCS and MCS and the highest mean SF-36v2 scores for SF remained unchanged after 6 and 12 months. The changes in HRQoL during the follow-up period are presented in Figure 2.10.

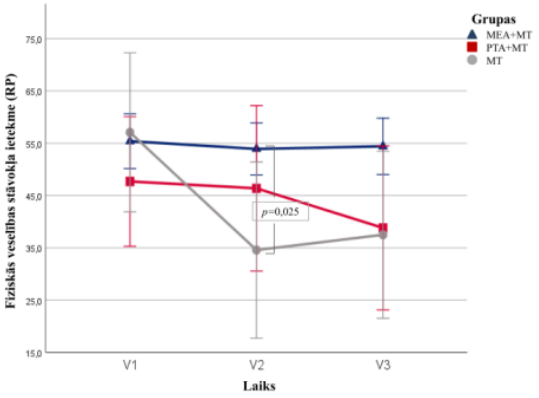
2.5.4 Change of Health-Related Quality of Life after Carotid Stenting

Likewise, comparing mean SF-36v2 scores in the CAS group, there was no statistically significant difference in 9 of the 10 subscales during the follow-up period, except for BP (p = 0.028, η^2 = 0.343). Before revascularisation, the mean BP score was 48.4 (27.2), after 6 months it was 54.3 (30) and after 12 months – 45.2 (17.8). The lowest mean SF-36v2 scores for RP, GH, VT, PCS and MCS remained unchanged after 6 and 12 months. For PF and SF, there were decrements in the mean SF-36v2 scores after 12 months, but the changes were not statistically significant. The highest mean SF-36v2 scores before PTA were in SF which decreased after 6 (70.4 (30.4)) and 12 (57.2 (30.4)) months. The changes in HRQoL during the follow-up period are presented in Figure 2.10.

2.5.5 Change of Health-Related Quality of Life in the Best Medical Treatment Group

Nevertheless, in the BMT group, there were statistically significant differences in the RP mean scores during the follow-up period (p = 0.039, η^2 = 0.392) in which, at the beginning of the study, the mean RP score was 57.1 (27.4), after 6 months it was 34.6 (20.4) and after 12 months – 37.5 (24.4). There were statistically significant changes (p = 0.045, η^2 = 0.38) in the MCS mean scores during the follow-up period as well. At the baseline, the mean MCS score was 50.1 (7.8), after 6 months, it was 47.9 (7.3), and after 12 months it was 44.5 (7.8). The lowest mean scores for GH, PCS, MCS, and the highest scores for SF in the BMT group remained unchanged during the follow-up periods. The results of the mean SF-36v2 scores during the follow-up periods are summarised in Figure 2.10.

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PTA+MT
MT
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15,0
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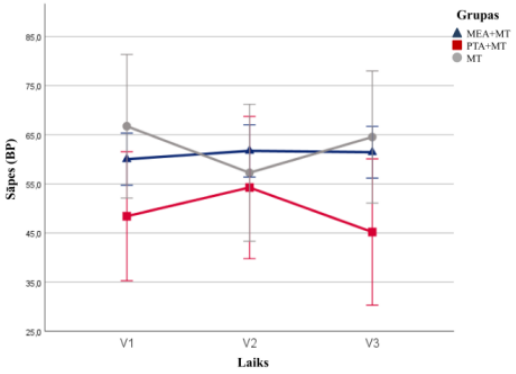
V1
V2
V3
Laiks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PTA+MT
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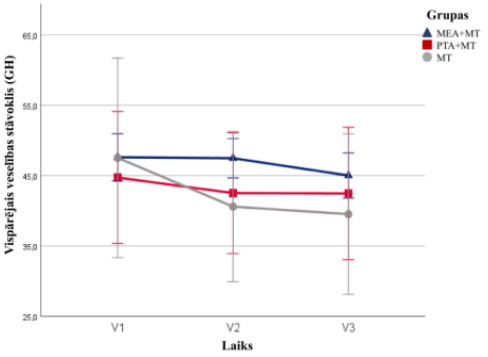
V2
V3
Laiks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MT
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V2
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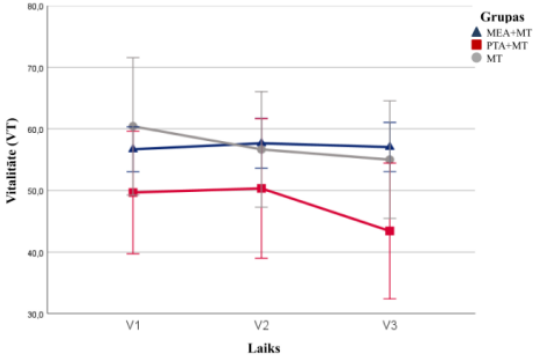
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V2
V3
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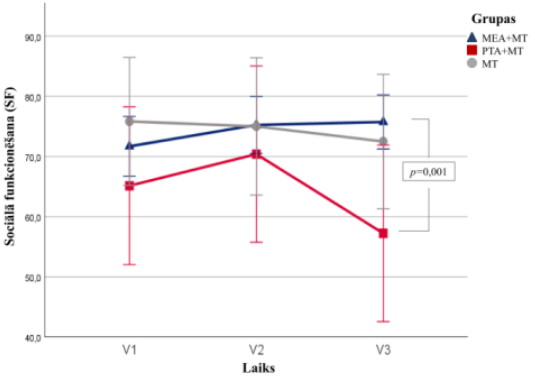
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Sociālā funkcionēšana (SF)
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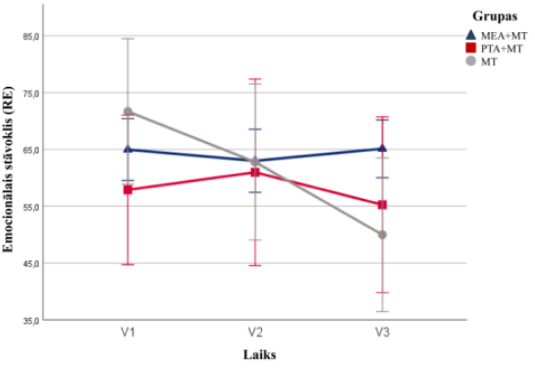
p=0,001
V1
V2
V3
Laiks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PTA+MT
MT
Emocionālais stāvoklis (RE)
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V1
V2
V3
Laiks

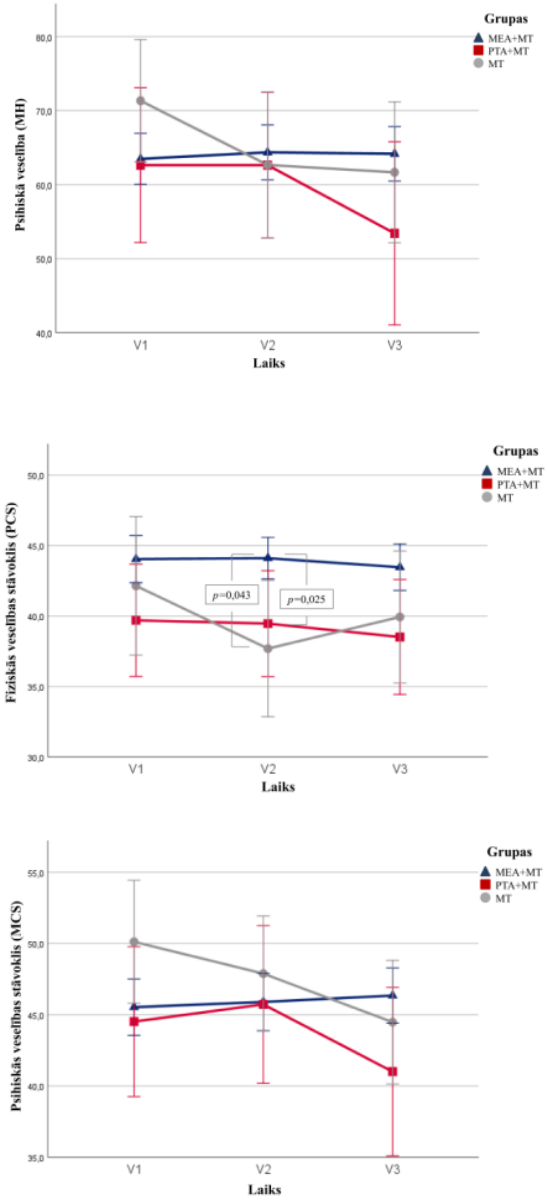

Figure 2.10 **Mean SF-36v2 scoresduring the follow-up period in all study groups**

2.5.6 Comparison of Health-Related Quality of Life between the Study Groups

Compared with the CAS and BMT groups, the patients in the CEA group had better scores at 6 months for 3 of the 10 SF-36v2 subscales. In the CEA group the PF mean value at 66.5 (21.3) was higher than in the CAS group (51.6 (25.6)) and the BMT group (49.3 (24.5)), (p = 0.001, η^2 = 0.076). Role physical had higher values in the CEA group (53.9 (25.2)) than CAS (46.6 (32.8)) and BMT (34.6 (20.4)) groups, (p = 0.012, η^2 = 0.05). Comparing the PCS values in each group, the CEA group (44.1 (7.5)) had statistically significant (p = 0.005, η^2 = 0.061) higher values compared to the CAS (39.5 (7.8)) and the BMT groups (37.7 (8.7)). The difference of the other SF-36v2 domain mean scores at the 6-month follow-up period was not significant (p > 0.05).

By 12 months, although 7 of the 10 subscales (PF, RP, VT, SF, RE, MH, and MCS) had better scores in the CEA group (p < 0.05), the effect size of statistical significance was medium only for the PF and SF domains. The mean values of PF were the highest in the CEA+MT group (65.1 (22.8)), which was significantly different (p = 0.004; η^2 = 0.065) from the CAS (PF mean value was 49 (23.8)) and BMT groups (49 (20)). Likewise, the highest mean SF value was in the CEA group (75.7 (22.9)) compared with the CAS (57.2 (30.4)) and BMT groups (72.5 (20.2), p = 0.002, η^2 = 0.072). Although there was a statistically significant difference in other mean values, the effect size was small. The results of the mean SF-36v2 scores during the follow-up periods are summarised in Figure 2.10.

3 DISCUSSION

Although earlier studies do not show changes in cognitive function after CEA or CAS (De Rango *et al.*, 2008), the current study indicates a significant improvement of cognitive function after revascularisation of severe carotid stenosis, except in the BMT group, in which the observed improvement was not statistically significant.

There are several explanations for the improvement of cognitive function after carotid artery revascularisation. It is known that reduced blood flow in the brain can cause cognitive dysfunction (Marshall *et al.*, 2012;Balucani *et al.*, 2012). Likewise, there are several studies in which severe carotid stenosis showed an association with cognitive impairment (Lal *et al.*, 2017; Popovic *et al.*, 2011; Mathiesen *et al.*, 2004; Jackson *et al.*, 2015; Wang, Mei and Zhang, 2016; Pucite *et al.*, 2017), due to altered cerebral hemodynamics (Silvestrini *et al.*, 2009; Marshall *et al.*, 2012). Significant improvement in the revascularisation group could be explained by the "mechanical" improvement of blood flow and subsequent restoration of cerebral perfusion after CEA and CAS. The increasing blood flow and perfusion after carotid artery revascularisation may improve global cognitive function and several domains such as visuospatial/executive functions, attention and memory (Ghogawala *et al.*, 2013; Fearn *et al.*, 2003; Kishikawa *et al.*, 2003; Wang *et al.*, 2017; Huang *et al.*, 2013).

As cognitive decline was not observed in the BMT group, it may indicate that there could be benefits not only from the "mechanical" revascularisation of carotid stenosis by removing the atherosclerotic plaque, but also from BMT as it alters the pathogenetic mechanisms of cerebral small vessel disease. Reducing the atherosclerotic load in cerebral small vessels, which is a cause for white matter burden (Prins & Scheltens, 2015) and lacunar

strokes due to distal atherosclerosis (Pantoni, 2010), it could positively affect cognitive performance (Shi & Wardlaw, 2016). Therefore, combined medical and surgical or endovascular interventions may halt or reverse cognitive impairment.

On the other hand, the probability of a practice or learning effect of the MoCA test may also be one of the causes or explanations for the improvement in cognitive performance. However, the data of this study show that the improvement of the MoCA test scores could not be a sole result of the learning effect because the improvement of cognitive function was not observed in the BMT group in which the patients did the same tests after 6 and 12 months like the others. There have only been a few studies that evaluate MoCA score changes in healthy, older people, but not in patients with severe carotid stenosis or stroke. The results of these studies indicate that improvement of the MoCA scores may be associated with the learning effect in healthy people if the test is repeated within one year. However, no learning effect was observed if the MoCA test was repeated after over a one-year period (Cooley *et al.*, 2015; Krishnan *et al.*, 2016). Whether this observation could be attributed to patients with significant asymptomatic or symptomatic carotid stenosis is unknown. In the *Cooley et al.* study there was an association between the learning effect and repetition of the MoCA test in a year. However, the learning effect was not observed when neuropsychological tests were used over the same period since besides the MoCA test, all patients also underwent neuropshychological testing (Cooley *et al.*, 2015). The results of this study are in contrast to *Plessers et al.*, in which the learning effect was observed in patients who had neuropsychological tests (Plessers *et al.*, 2015). The results were inconclusive because it is unknown whether improvement of cognitive function in the study and control groups could be explained only by the practice effect or by the

comprehensive management of cardiovascular risk factors in both study groups, which reduces the risk of cognitive decline itself (Baumgart *et al.*, 2015).

In the literature, there are only a few studies that have evaluated and compared the long-term changes in cognitive function after carotid stenosis revascularisation (CEA, CAS) and BMT. Although methodological differences make a meaningful comparison of results across studies challenging, the main conclusions of these findings are similar. In the studies in which cognitive function was assessed, there was an improvement of the total MoCA score in a year after revascularisation (CEA, CAS) observed, except for the BMT group. Furthermore, the CEA group showed improvement in the executive and memory MoCA subtest scores, and the BMT group – in delayed recall subtest scores. In contrast, there was no improvement in some of the MoCA subtest scores in the CAS group. These findings are partially congruent with the current findings (Watanabe *et al.*, 2017). The improvement of these domains is consistent with the results that show association between reduced perfusion of anterior circulation and worse executive and memory function (Alosco *et al.*, 2013). Furthermore, revascularisation and improvement of blood flow in the middle cerebral artery are associated with greater improvement in attention, executive function (Ghogawala *et al.*, 2013) and memory (Wang *et al.*, 2017). In the studies in which changes in cognitive function a year after CEA or CAS versus the control group were assessed with the MoCA test, the results indicated that cognitive function might improve or at least not decline in symptomatic and asymptomatic elderly patients with severe carotid stenosis, who underwent revascularisation (Baracchini *et al.*, 2012; Yan *et al.*, 2014).

Comparing studies in which the long-term effects of different carotid stenosis treatment methods (CEA, CAS or BMT) for cognitive function were assessed, the results also show that revascularisation of carotid stenosis improves long-term cognitive performance, independent of the treatment type

(Wapp *et al.*, 2015; Carta *et al.*, 2015; Dempsey *et al.*, 2017; Kim *et al.*, 2015; Kougias *et al.*, 2015). However, erlier studies have suggested that there is no difference between cognitive function before and after carotid stenosis revascularisation (CEA, CAS) (Aleksic *et al.*, 2006; Altinbas *et al.*, 2011). Comparing the treatment effect of carotid stenosis in older studies, the results of these studies must be interpreted with caution because in recent decades not only pharmacological management of cerebrovascular disease but also the technical equipment and revascularisation skills have improved (Wapp *et al.*, 2015).

In 1997, Alexopoulus *et al.* suggested the "vascular depression" hypothesis, which is supported by the comorbidity of depression, vascular disease and vascular risk factors and by the association of ischaemic lesions to distinctive behavioral symptoms. Disruption of the prefrontal systems or their modulating pathways by single lesions or by an accumulation of lesions exceeding a threshold is hypothesised to be central mechanisms in vascular depression (Alexopoulos *et al.*, 1997). A recent update of the vascular depression hypothesis confirmed that vascular depression could be regarded as a distinct subtype of late-life depression characterised by a specific clinical presentation and associated with vascular risk factors and a variety of cerebrovascular lesions, as shown by structural magnetic resonance imaging (MRI). The mechanisms of how vascular disease may influence the development and course of depression are mechanistic disconnection, inflammation, and hypoperfusion (Aizenstein *et al.*, 2016). Therefore, one of the aims of the current study was to assess the relationship between severe carotid stenosis and depressive symptoms.

Most patients with severe carotid stenosis also have several cardiovascular risk factors that may cause white matter damage. If the small vessels are already impaired, autoregulation of cerebral blood flow is affected

as well (Gupta *et al.*, 2012). Therefore, the presence of severe carotid stenosis and impaired cerebrovascular reserve reduces the cerebral perfusion pressure even more. The development of depression may be decreased by revascularisation of carotid stenosis, which increases cerebral perfusion pressure and may reduce ischaemic lesions due to hypoperfusion.

In contrast to the *Mlekuschet al.* study in which a significant reduction of depressive symptoms was found in patients who underwent CAS (Mlekusch *et al.*, 2006), theresults of the current study did not show statistically significant differences in the frequencies of depressive symptoms at 6 or 12 months not only in the BMT group but also in the CEA and CAS groups. Therefore, it can be argued that there may be a direct causal relationship between severe carotid stenosis and depression and the beneficial effects on the course of depressive symptoms after revascularisation. Nevertheless, other studies have also evaluated changes in depressive symptoms. A comparison of the studies is challenging, as they used different depression assessment scales. However, their conclusions are similar, in that there were no statistically significant differences in mood or depressive symptoms over follow-up periods or between the CEA and CAS groups (Kim *et al.*, 2016; Carta *et al.*, 2015; Aleksic *et al.*, 2006; Feliziani *et al.*, 2010; Wapp *et al.*, 2015). Therefore, supposing that vascular depression may share similar pathogenetic mechanisms with cognitive impairment, lack of reversibility of depressive symptoms could suggest that depression may be a marker for a more severe brain structural damage or dysfunction where these changes are no more reversible. This association may be similar to the hypothesis of cardiovascular disease and depression development. Depression may only be a marker for a more severe cardiovascular disease, which so far cannot be detected using the currently available investigative tools (Hare *et al.*, 2014). These irreversible changes could also explain why patients with vascular depression have a poor response

to depression treatment (Aizenstein *et al.*, 2016). However, this hypothesis is unclear and needs further investigation.

In this study, it was found that patients undergoing CEA had similar mean values of all the SF-36v2 domains at 6 and 12 months compared to the pre-procedure levels. In the CAS group, the mean SF-36v2 scores also did not change during the follow-up period except for BP in which the worst scores were after 12 months. However, in the BMT group, measures of RP, BP, RE and MCS worsened after 6 and 12 months as compared to the SF-36v2 scores at the beginning of the study. Literature review and meta-analysis have shown that CEA and CAS maintain preoperative HRQoL for at least one year, which is partially congruent with the current findings (Shan *et al.*, 2015; Chabowski *et al.*, 2017). In the present study, most of the patients in the CEA and CAS groups were asymptomatic, whereas symptomatic patients had a TIA or minor stroke that was not disabling. Therefore, it is reasonable not to expect superior HRQoL compared to baseline, particularly for previously asymptomatic patients (Shan *et al.*, 2015). However, unlike the CEA and CAS groups, some HRQoL domains, including MCS, worsened in the BMT group. These findings could highlight some anxieties over future ischaemic events or doubts of treatment choice in patients who refused revascularisation of carotid stenosis in the BMT group that could have affected their emotional and mental quality of life. Asmost patients were older and had symptomatic carotid stenosis in the BMT group ($p = 0.072$), a probable reason for the decreased RP values could be a gradual worsening of their neurological deficit due to chronic hypoperfusion of the brain in which brain plasticity is more restricted. The same could also be said about patients with severe asymptomatic carotid stenosis. BMT alone cannot reduce the degree of stenosis and improve the perfusion of the entire hemisphere, build collateral conduits for blood flow or

limit the effects of encephalomalacia and neuronal loss caused by chronic ischaemia (Bauer, Bain and Rasmussen, 2015).

Comparing HRQoL between treatment groups during the follow-up period, it was detected that patients undergoing CEA had better HRQoL at 6 and 12 months after carotid revascularisation relative to patients undergoing CAS or receiving BMT only. Six months after CEA, these benefits were most pronounced for the overall PF, RP and PCS meassures. Whereas at 12 months it was for PF and SF as compared to the CAS and BMT groups. Several studies have compared HRQoL after CEA versus CAS in patients with severe carotid stenosis. Most of these studies report that there are no differences between CEA and CAS at one year with similar HRQoL for CEA and CAS in all domains of the SF-36v2 (CaRESS Steering Committee, 2005; Stolker *et al.*, 2010; Cohen *et al.*, 2011). The reason that these findings contrast with the current could be that in the CAS group, patients with more cardiovascular risk factors were included than in the CEA group. It is known that HRQoL is poorer in patients with cardiovascular risk factors compared to other chronic illnesses, where CAD imposes one of the greatest decrements across a broad range of domains of functioning and perceived HRQoL (J.R. & Swenson, 2004; Martinelli *et al.*, 2008). Also, in the CAS group during the follow-up, BP worsened, which may have affected the overall PCS scores. Although this study is not a randomised controlled trial, to the best knowledge, this study is the first to evaluate HRQoL in long-term patients with severe carotid stenosis following revascularisation and BMT.

Several limitations of this study should be acknowledged. Firstly, the study had non-uniform sample sizes across study groups. It was not completely balanced concerning comorbidities, having a disproportionate percentage of cardiovascular comorbidities in the CAS group and ischaemic events in the BMT group, although there was no statistically significant difference between

groups. The reason for these differences in clinical parameters may be that this was an observational cohort study, not a randomised controlled study. However, to reduce the probability of incorrect results of statistical significance due to different sample sizes, effect sizes were calculated to quantify the magnitude of difference between the study groups. Secondly, lack of brain imaging before and after revascularisation may have resulted in the incorrect classification of symptomatic or asymptomatic carotid stenosis and incorrect classification of the primary outcome measures because mild symptoms may be unnoticed by the patient. However, since most similar clinical studies also did not use brain imaging, the results of this study can be comparable. Finally, not all patients were able to participate in all follow-up visits. Therefore, clinical parameters of these patients were compared with those arriving for all visits. Only patients in the CEA group were analyzed due to the larger number of patients in the group. There was no significant difference in the clinical characteristics, changes in cognitive function, or depressive symptoms between patients who arrived at V2 visit and those who did not. Except for the patients who did not come to V2 visit, the SF-36v2 scores in MH were slightly higher indicating peace and emotional well-being at the beginning of the study. However, of those patients who did not come to the V3 visit, more were women and those with DM. However, the effect size of the significant difference was small. There were no changes in comparing the cognitive function changes and depressive symptoms. Following a comparison of the SF-36v2 scores, those patients who did not come to the V3 visit, had lower PF and PCS values at the beginning. Therefore, those patients who did not come to the V3 visit may have had more physical difficulties, which in turn could theoretically affect the results of the PF and PCS domains. However, it is not possible to pinpoint the reasons for their physical limitations, whether it was due to significant carotid stenosis, cardiovascular disease, or other conditions

such as arthritis. Therefore, further studies are needed where these factors should be taken into account in order to obtain more accurate information on changes in cognitive function, depressive symptoms, and HRQoL following treatment of carotid stenosis.

However, despite the previously mentioned limitations, this study has a larger BMT control group than any previous trials. In addition, not only long-term changes in cognition were evaluated, but also long-term changes in depressive symptoms and HRQoL in patients with severe (≥ 70%) carotid stenosis after revascularisation and in the BMT group. Therefore, this study provides insights into the long-term changes in cognitive function, depressive symptoms and HRQoL until the results of randomised controlled trials are published. The questions and hypothesis which were raised in this study need to be proven and/or taken into account in future studies.

4 CONCLUSIONS

1. The incidence of primary outcome measures in carotid endarterectomy patients was 2.5%. Therefore, this does not exceed the percentage which is recommended in the guidelines. It is difficult to make conclusions regarding the primary outcomes in other study groups due to the small number of patients. The incidence of restenosis was not significantly different between revascularisation groups. A significant progression of carotid stenosis in the medical treatment group was not observed. Secondary outcome measures were more common in the carotid stenting group.
2. Revascularisaton of severe carotid artery stenosis was associated with an improvement of global cognitive function after one year. In the carotid endarterectomy group, this occured sooner and was already observed after 6 months. However, there was no significant improvement or deterioration after a year in patients who received the best medical treatment only.
3. The frequency of depressive symptoms after a year did not decrease significantly following revascularisation or in the best medical treatment group. There was only a tendency for depressive symptoms to decline after carotid endarterectomy.
4. There was no change in health-related quality of life after carotid endarterectomy. However, there was a worsening of domains such as bodily pain, physical functioning, role physical and mental component summary in a year in patients after carotid stenting or the best medical treatment. More likely, it is related to older age, and a higher frequency of comorbidities in these study groups, not to the treatment methods of severe carotid stenosis.

5. Unlike patients who received the best medical treatment, patients after revascularisation showed an improvement in global cognitive function. However, depressive symptoms were less common, and health-related quality of life was better in a year after carotid endarterectomy but not after carotid stenting or best medical treatment only.

5 PRACTICAL RECOMMENDATIONS

1. During the study period, carotid endarterectomy was performed more frequently in low surgical risk asymptomatic carotid stenosis patients which is in contravention with current guidelines. Therefore, the results of this study may highlight the need to perform endarterectomy in symptomatic carotid stenosis patients. Asymptomatic patients should be evaluated in terms of both surgical risk and ischemic stroke risk.
2. Severe carotid stenosis could be one of the modifiable risk factors for cognitive impairment. Therefore, besides assessment of perioperative stroke and death rates, changes in cognitive function in these patients should be evaluated.
3. As it is executed in patients with cardiovascular diseases, an assessment of depressive symptoms should be performed in patients with severe carotid stenosis as a part of everyday practice.
4. Given that health-related quality of life does not worsen after revascularisation of severe carotid stenosis, this should be taken into consideration concerning the choice of carotid stenosis treatment undertaken.

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LIST OF PUBLICATIONS

Publications on the study theme

1. Elīna Pūcīte, Mariuss Šlisers, Evija Miglāne, Dainis Krieviņš, Andrejs Millers, Inese Blimhena, 2015. Health-related Quality of Life among Patients with Severe Carotid Artery Stenosis. *Proceedings of Latvian Academy of Sciences, Section B*. 69(5), 20−30. doi: 10.1515/prolas-2015-0036.
2. Pucite E., Slisers M., Miglane E., Krievins D., Erts R., Jurjans K., Krievina I, 2016. Impact of carotid endarterectomy on cognitive performance and depressive symptoms. *CBU International Conference Proceedings 2016, ISE Research Institute.* 4(0), 608−614. doi: 10.12955/cbup.v4.820.
3. Elina Pucite, Ildze Krievina, Evija Miglane, Renars Erts, Andrejs Millers, Dainis Krievins, 2017. Influence of Severe Carotid Stenosis on Cognition, Depressive Symptoms and Quality of Life. *Clinical Practice & Epidemiology in Mental Health*. 2017. 13, 168−180. doi: 10.2174/1745017901713010168.
4. Elina Pucite, Ildze Krievina, Evija Miglane, Renars Erts, Dainis Krievins, Andrejs Millers, 2019. Changes in Cognition, Depression and Quality of Life after Carotid Stenosis Treatment. *Current Neurovascular Research*. 16(1): 47−62. doi: 10.2174/1567202616666190129153409.

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1. Elīna Pūcīte, Mariuss Šlisers, Evija Miglāne, Dainis Krieviņš, Andrejs Millers, Inese Blimhena. *The frequency of depressive symptoms in*

patients with severe carotid artery disease. Poster presentation Balcone 2015, 8th Baltic Congress of Neurology, Riga, Latvia.

2. Ramona Valante, Evija Miglāne, Elīna Pūcīte, Zanda Priede, Andrejs Millers. *Primary and secondary prevention among patients with initial and recurrent stroke in Latvia*. 24th European Stroke Conference in Vienna, Austria, 2015. Abstract E-book, p. 244.
3. Elīna Pūcīte, Marius Šlisers, Evija Miglāne, Dainis Krieviņš, Andrejs Millers, Jolanta Dadzīte, Ildze Krieviņa. *Health-related quality of life among patients with severe carotid disease*. 25th European Stroke Conference in Venice, Italy, 2016.
4. Elīna Pūcīte, Reinis Ošiņš, Evija Miglāne, Andrejs Millers, Ināra Logina. *Aspirin and clopidogrel resistance in patients with recurrent atherothrombotic stroke*. 25th European Stroke Conference in Venice, Italy, 2016.
5. E. Pucite, E. Miglane, D. Krievins, A. Millers, I. Krievina. *Cognitive performance and depressive symptoms in severe carotid artery patients*. 3rd European Stroke Organisation Conference 2017, Prague, Czech Republic. European Stroke Journal, Volume 2, Issue 1, suppl 2, p. 475.
6. E. Pucite, E. Miglane, A. Millers, I. Logina, A. Novasa, R. Aleksejeva. *Resistence to aspirin and clopidogrel in stroke patients.* 3rd European Stroke Organisation Conference 2017, Prague, Czech Republic. European Stroke Journal, Volume 2, Issue 1, suppl 2, p. 386.
7. Elina Pucite, Ildze Krievina, Tatjana Muravska, Evija Miglane, Dainis Krievins, Andrejs Millers. *Long term health-related quality of life after carotid artery revascularisation or medical therapy*. 9th Baltic Congress of Neurology 2018, Kaunas, Lithuania, page 122.
8. Elina Pucite, Ildze Krievina, Tatjana Muravska, Evija Miglane, Dainis Krievins, Andrejs Millers. *Effect of carotid artery revascularisation on*

the course of cognitive function and depressive symptoms. 9th Baltic Congress of Neurology 2018, Kaunas, Lithuania, page 123.

Reports in national conferences and congresses:

1. Elīna Pūcīte, Evija Miglāne, Andrejs Millers, Zanda Priede. *Cerebrāla infarkta sekundārās profilakses novērtējums* (Eng. Evaluation of secondary prevention of cerebral infarction). RSU Zinātniskā konference 2015.
2. Elīna Pūcīte, Marius Šlisers, Evija Miglāne, Dainis Krieviņš, Andrejs Millers, Jolanta Dadzīte, Ildze Krieviņa. *Simptomātiskas un asimptomātiskas nozīmīgas miega artērijas stenozes salīdzinājums* (Eng. Comparison of symptomatic and asymptomatic significant carotid stenosis). 2016. gada RSU zinātniskā konference 2016.
3. Elīna Pūcīte, Ildze Krieviņa, Evija Miglāne, Dainis Krieviņš, Andrejs Millers. *Kognitīvu traucējumu un depresijas simptomu sastopamība pacientiem ar nozīmīgu aterosklerozi* (Eng. Prevalence of cognitive impairment and depressive symptoms in patients with significant atherosclerosis). RSU Zinātniskā konference 2017.