

# The influence of treatment decision on compliance with medication for patients with asymptomatic carotid artery stenosis – a cross-sectional study.

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## ABSTRACT

**INTRODUCTION:** Treatment decision in patients with asymptomatic carotid artery stenosis (ACS) is a matter of current debate with a recent shift towards isolated best medical treatment (BMT) as treatment of choice in most patients. However, poor medical compliance is one of the main constraints to the success of BMT. We hypothesized that more invasive treatment approaches can influence how patients perceive the severity of their illness and hence, treatment compliance.

**METHODS:** A cross-sectional study was performed including patients with asymptomatic >50% carotid artery stenosis (NASCET method) followed-up as outpatients in a Vascular Surgery department from January 2017 to December 2021.

Optimal BMT was defined according to the European Society of Vascular Surgery Carotid Atherosclerotic Disease 2023 guidelines.

Demographic and risk factor patient data was attained and subsequently a Portuguese translation of the Morisky medication-taking adherence scale (MMAS-4) questionnaire was given to all patients. Several additional questions developed by our group were also applied.

**RESULTS:** A total of 320 patients were identified (186 under BMT alone and 134 submitted to BMT and carotid endarterectomy - CEA). Most patients were male in both groups (75%) and the mean age was similar. Furthermore, patients undergoing CEA presented higher rates of current smoking (51.4% vs 15.9%;  $p<0.001$ ) and lower rates of antiplatelet (80.0% vs. 92.8%;  $p=0.029$ ) and statin (78.6% vs. 94.2%;  $p=0.007$ ) prescription.

Patients in the CEA group also presented with significantly lower medical compliance (40.3% vs. 24.5%,  $p<0.001$ ) despite being more aware of their current medication's name and therapeutic purpose.

**CONCLUSION:** In conclusion, physicians seem to be more aggressive in controlling risk factors in BMT-only patients when compared to CEA-submitted patients. However, patients subjected to CEA may be more aware of ACS, despite having poorer medical adherence.

**Keywords:** Therapeutic Compliance; Best Medical Treatment; Endarterectomy; Asymptomatic; Carotid Artery Stenosis.



## INTRODUCTION

Within the European population, approximately 1.4 million strokes occur annually, making it the second leading cause of mortality and resulting in roughly 1.1 million deaths every year.<sup>[1]</sup> One of the primary causes of ischemic stroke is carotid artery stenosis, and up to 2% of the population may have >50% asymptomatic carotid stenosis (ACS).<sup>[1]</sup>

To prevent cerebrovascular events, management of cardiovascular risk factors such as obesity, arterial hypertension, diabetes mellitus, and smoking is mandatory.<sup>[2]</sup> To receive optimal medical treatment according to the European Society for Vascular Surgery Carotid Atherosclerotic Disease 2023 guidelines, patients with ACS should adhere to a healthy diet, engage in physical activity, quit smoking, and take antiplatelet, anti-hypertensive, statin, and anti-diabetic medication.<sup>[1]</sup>

Nowadays, treatment decision in patients with ACS is a matter of current debate with a recent shift towards isolated best medical treatment (BMT) as treatment of choice in most patients.<sup>[1,3,4]</sup> However, one of the main challenges to the success of BMT is poor adherence to prescribed medication. Individuals with ACS can encounter challenges in complying with medication as a result of diverse elements, including cognitive dysfunction, insufficient knowledge about their ailment, doubtfulness about recommended therapies, psychological health concerns, inadequate monitoring or discharge preparation, unsatisfactory rapport between patients and doctors, obstacles in obtaining medications, skipped appointments, complex treatment regimens and the economic burden of medication.<sup>[1,5,6]</sup>

On the other hand, carotid endarterectomy (CEA), in addition to BMT, is recommended for 60-99% ACS cases with an average surgical risk in the presence of one or more imaging or clinical characteristics associated with an increased risk of late stroke. Also, it should be demonstrated that procedural 30-day stroke/death rate is  $\leq 3\%$  and that patients' life expectancy exceeds five years.<sup>[1]</sup>

A study conducted by Korcarz et al. aimed to determine if an increase in carotid intima-media thickness or carotid atherosclerotic plaque detected during ultrasound screenings could change physicians' treatment plans and patients' motivation regarding health-related behaviours. The study concluded that patients with ultrasound-detected abnormalities were more aware of their cardiovascular risk and had better adherence to lifestyle changes and medication for reducing hypercholesterolemia.<sup>[7]</sup>

We hypothesized that a clinical decision for carotid revascularization (instead of isolated BMT) could impact how patients perceive the severity of their illness and, consequently, their adherence to treatment. Therefore, the objective of our study was to compare therapeutic adherence in asymptomatic patients with >50% carotid artery stenosis who underwent CEA with those who received only BMT.

## METHODS

Ethical approval was obtained prior to the initiation of this study.

### Study design

A cross-sectional study was conducted to compare therapeutic adherence in asymptomatic patients with >50% carotid artery stenosis who underwent CEA or received BMT-only and were followed up as outpatients in our Vascular Surgery department at Centro Hospitalar Vila Nova de Gaia/Espinho in Portugal from January 2017 to December 2021. Two vascular surgeons (FB and PC) administered a survey by telephone from May 1<sup>st</sup> to May 31<sup>st</sup>, 2023. Sociodemographic and risk factor data were obtained from patient clinical records.

### Participants and Recruitment

Asymptomatic was defined as patients without history of neurologic symptoms in the past six months, and >50% carotid artery stenosis was defined by the NASCET method.<sup>[1]</sup>

The CEA group was selected from our surgery records, and the BMT-only group was selected from our duplex ultrasound database. Patients were eligible if they presented with a >50% stenosis.

Duplicated duplex ultrasound records for the same patient were excluded. Patients with previous history of carotid revascularization were deemed ineligible for inclusion in the BMT-only group.

After the initial selection process, patients were contacted by telephone and informed of the study, purposes, and funding. Confidentiality and voluntary participation were assured. Informed and clear verbal consent was obtained from patients who agreed to participate in the study in accordance with the Helsinki Declaration and the Oviedo Convention. Their data was subsequently collected, and questionnaires were administered.

Exclusion criteria were as follows: patients dependent on daily living, who couldn't manage their medication, who did not answer the call after multiple attempts, or uncontactable for other reasons.

### Measures and Instruments

BMT was defined according to the European Society of Vascular Surgery Carotid Atherosclerotic Disease 2023 guidelines: 1 healthy diet (based on grilled and boiled food with restriction of fried food), smoking abstinence, 30 minutes of exercise five times a week, lower-dose aspirin or 75 mg clopidogrel, high-dose statin (with or without ezetimibe), antihypertensive treatment, and optimal glycemic control.

A questionnaire was specifically developed for this study. The questionnaire was based on existing literature on the subject, adapted to the local context. Adherence to medication was the primary outcome. This was defined as those who obtain a score  $\geq 3$  in the adapted MMAS-4 score, consisting of four questions (translated to Portuguese, 1

point per positive answer): Have you ever forgotten to take medication for carotid stenosis? (*Alguma vez esqueceu-se de tomar a medicação para a estenose carotídea?*); Did you ever need help remembering to take the medication for carotid stenosis, or do you always take it around the same time? (*Alguma vez precisou de ajuda para lembrar-se de tomar a medicação para a estenose carotídea, ou toma sempre por volta da mesma hora?*); Have you stopped taking your medication for carotid stenosis when you feel well or healthy? (*Quando se sente bem/saudável, já deixou de tomar a medicação para a estenose carotídea nesse contexto?*); Have you stopped taking your medication for carotid stenosis when you feel it is making you feel ill? (*Quando sente que a medicação para a estenose carotídea está a causar mau estar, já deixou de a tomar nesse contexto?*).

The MMAS-4 (4-items) is a universal assessment tool for self-reported medication adherence that can be tailored to various health conditions such as high blood pressure, diabetes mellitus, elevated cholesterol, human immunodeficiency virus, contraception, and others. The scale comprises four questions that are answered with either "Yes" or "No," and each "Yes" response is scored as 0 while each "No" response is scored as 1. By adding up the individual scores of the four items, a total score ranging from 0 to 4 is obtained, indicating the degree of adherence to medication. The value of Cronbach's  $\alpha$  of our Portuguese MMAS-4 in our study was 0.79, indicating an acceptable value for internal consistency. The MMAS-4 has a Cronbach's alpha of 0.61.<sup>[8-10]</sup>

To use this survey, we have obtained permission for both the utilization and translation of the MMAS-4, along with certification from a specialized company attesting to the accuracy and quality of the translation. MMAS-4 was chosen in detriment of the MMAS-8 because of practically; too many questions over the phone could be inconvenient and limit patient's willingness to participate. We also implemented three additional questions to independently evaluate adherence to healthy diet, physical exercise, and smoking cessation.

Secondary outcomes included comprehension and knowledge of their own medication, which was assessed by eight questions created by our investigation group to inquire if patients knew the name and purpose of the antiplatelet, anti-diabetic, statin, or anti-hypertensive medication. We also assessed the percentage of patients that were prescribed with statin and antiplatelet by the attending physician. The remaining other secondary outcome was the assessment (by phone interview) if patients reported any of the 3-point MACE – excluding death from a cardiovascular cause (nonfatal stroke or nonfatal myocardial infarction) since the procedure for the CEA group or since the doppler exam for the only BMT group.

The questionnaires were conducted by phone because of the target population characteristics (advanced age with multiple comorbidities), and we also believed that it was the most accessible and reliable way to obtain accurate information without misinterpretations from patients; any doubts could be immediately clarified.

A pilot survey was carried out in which the questionnaires were administered to 20 patients (10 from CEA and 10 from BMT-only group) of both sexes to identify and exclude interpretation biases.

### Data Analysis

Data analysis was performed using SPSS Statistics (V.27.0; SPSS). Categorical variables were described using absolute and relative frequencies, n (%), and normally distributed quantitative variables were summarized using means and standard deviation (SD). The normality of the distributions was assessed by resorting to the Kolmogorov-Smirnov and Shapiro-wilk tests. To analyze the association between categorical variables, the  $\chi^2$  test was used. To compare distributions between two independent continuous samples, an independent sample T Test was performed. A level of significance of 0.05 was considered.

## RESULTS

### Sample Characteristics

From 1720 records (1586 Carotid Doppler ultrasound records and 134 surgical records), a total of 1420 was excluded because of duplicates, or due to previous history of carotid revascularization, which was an ineligibility criterion. A pool of 320 (186 BMT-only; 134 CEA) patients qualified for inclusion in the study.

When we started the contact stage, we excluded 44 patients (37 BMT-only; 7 CEA) who were deceased, 11 (2 BMT-only; 9 CEA) who were dependent on daily living, 28 (17 BMT-only; 11 CEA) who did not manage their medication, 86 (51 BMT-only; 35 CEA) who did not answer the call, 10 (9 BMT-only; 1 CEA) for unavailable phone contact, and 2 (1 BMT-only; 1 CEA) refused to participate in the study.

Of the 320 eligible patients, 240 (75%) were male and the mean age was  $70.84 \pm 7.9$ , 264 (82.5%) were hypertensive, 143 (44.7%) were diabetic, 89 (27.8%) were smokers, 221 (69.1%) were dyslipidemic. Furthermore, 278 (86.9%) were prescribed antiplatelets and 287 (89.7%) were prescribed statins.

The characteristics of the sample are summarized in Table 1.

### Outcomes and Comparative Analysis of the Groups (BMT-only VS CEA)

Of all 139 respondents (70 BMT-only; 69 CEA), 64.7% (n=90) patients obtained a score  $\geq 3$  in the MMAS-4 questionnaire (adherence), 14.4% (n=20) were current smokers, 61.2% (n=85) reported have a healthy diet, and 39.6% (n=55) practiced 30 minutes of exercise every day. Moreover, 136 were taking statins, of whom 87.5% (n=119) knew what it was for and 53.7% (n=73) knew the name of the medication. Similarly, 137 were taking antiplatelets, of whom 83.2% (n=114) knew what it was for and 57.7% (n=79) knew the name of the medication. Additionally, 126 were taking antihypertensives, of whom 76.2% (n=96) knew what it was for and 36.5% (n=46) knew the name of the antihypertensive, and 88 were taking antidiabetic medication, of whom 68.2% (n=60) knew what it was for, 38.6% (n=34) knew the name of the antidiabetic. Finally, 5.8% (n=8) reported a 3-point MACE up to the date of contact.

Comparing both groups of patients (CEA vs BMT-only) we found differences respect to smoking (51.4% CEA vs 15.9% BMT-only,  $p<0.001$ ) antiplatelet prescription (80.0% CEA vs. 92.8% BMT-only,  $p=0.029$ ) and statin prescription (78.6% CEA vs. 94.2% BMT-only,  $p=0.007$ ). The remaining data is specified in Table 1.

Significant differences were also found between the BMT-only and CEA groups in terms of BMT compliance (40.3% vs. 24.5%,  $p<0.001$ , respectively).

The complete data of adherence are described in Tables 2 and 3. Furthermore, statin nomination (35.3% CEA vs. 18.4% BMT-only,  $p<0.001$ ), antiplatelet nomination (37.2% CEA vs. 20.4% BMT-only,  $p<0.001$ ), anti-hypertensive nomination (28.6% CEA vs. 7.9% BMT-only,  $p<0.001$ ), and not knowing the purpose of antidiabetic medication (27.3% CEA vs. 4.5% BMT-only,  $p<0.001$ ) were also found to have significant differences. Age difference and the remaining non-significant data are specified in Table 4.

**Table 1.** Demographic and clinic characteristics of patients with asymptomatic carotid stenosis who responded the questionnaire (n=139)

Variables	CEA (n=70)	BMT only (n=69)	p Value
Female - n (%)	14 (20.0)	17 (24.6)	0.511
Age - Mean (SD)	69.1 (7.4)	69.3 (8.1)	0.237
Hypertension - n (%)	61 (87.1)	56 (81.2)	0.334
Diabetes Mellitus - n (%)	28 (40.0)	30 (43.5)	0.678
Smoking - n (%)	36 (51.4)	11 (15.9)	<0.001
Dyslipidemia - n (%)	47 (67.1)	46 (66.7)	0.952
Antiplatelets prescription - n (%)	56 (80.0)	64 (92.8)	0.029
Statins Prescription - n (%)	55 (78.6)	65 (94.2)	0.007

**CEA:** Carotid endarterectomy; **BMT:** best medical treatment; **SD:** standard deviation

**Table 2.** Compliance to best medical treatment (MMAS-4) for patient with asymptomatic carotid stenosis who responded the questionnaire

MMAS – 4 questions (English / Portuguese)	"Yes" n (%)		p value
	BMT-only (n=69)	CEA (n=70)	
1. Have you ever forgotten to take medication for carotid stenosis? / Alguma vez esqueceu-se de tomar a medicação para a estenose carotídea?	6 (8.7)	30 (42.9)	<0.001
2. Did you ever need help remembering to take the medication for carotid stenosis, or do you always take it around the same time? / Alguma vez precisou de ajuda para lembrar-se de tomar a medicação para a estenose carotídea, ou toma sempre por volta da mesma hora?	42 (60.9)	47 (67.1)	0.441
3. Have you stopped taking your medication for carotid stenosis when you feel well/ healthy? / Quando se sente bem/saudável, já deixou de tomar a medicação para a estenose carotídea nesse contexto?	12 (17.4)	33 (47.1)	<0.001
4. Have you stopped taking you medication for carotid stenosis when you think it is making you feel bad? Quando sente que a medicação para a estenose carotídea está a causar mau estar, já deixou de a tomar nesse contexto?	10 (14.5)	35 (50.0)	<0.001

#### Additional questions to evaluate BMT

1. Do you have a healthy diet (based on grilled or boiled food, restricting fried food)? / Tem uma alimentação saudável (à base de grelhados e cozidos, com poucos fritos)?	37 (53.6)	48 (68.6)	0.071
2. Do you execute a walking plan consisting of at least 30 minutes per day? / Executa pelo menos 30 minutos de um plano de marcha todos os dias?	29 (42.0)	26 (37.1)	0.556
3. Are you an active smoker? / Continua a fumar?	12 (17.4)	8 (11.4)	0.317

**BMT:** best medical treatment; **CEA:** Carotid endarterectomy.

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**Table 3.** Distribution of MMAS-4 scores, for patient with asymptomatic carotid stenosis who responded the questionnaire.

Distribution of MMAS-4 scores	BMT-only (n=69)	CEA (n=70)	p Value
Score 0 - n (%)	2 (2.9)	20 (28.6)	
Score 1 - n (%)	5 (7.2)	2 (2.9)	
Score 2 - n (%)	6 (8.7)	14 (20.0)	
Score 3 - n (%)	20 (29.0)	7 (10.0)	
Score 4 - n (%)	36 (52.2)	27 (38.6)	
Score $\geq 3$ - n (%)	56 (81.2)	34 (48.6)	<0.001

**BMT:** best medical treatment; **CEA:** Carotid endarterectomy.

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**Table 4.** Non-significant differences between patients with asymptomatic carotid stenosis who responded the questionnaire, besides adherence information.

Variables	BMT-only (n=69)	CEA (n=70)	p Value
Knowledge of the purpose of statins - n (%)	56 (81.2)	63 (90.0)	0.364
Knowledge of the purpose of antiplatelets - n (%)	55 (79.7)	59 (84.3)	0.731
Knowledge of the purpose of anti-hypertensives - n (%)	46 (66.7)	50 (71.4)	0.448
Anti-diabetic nomination - n (%)	10 (14.5)	24 (34.3)	0.158
3-Point MACE - n (%)	4 (5.8)	4 (5.7)	0.983
Score $\geq 3$ - n (%)	56 (81.2)	34 (48.6)	<0.001

**BMT:** best medical treatment; **CEA:** Carotid endarterectomy; **MACE:** Major adverse cardiac events.

## DISCUSSION

Prior to the initiation of this study, the authors performed a literature search, that revealed a paucity of studies comparing the compliance with BMT among >50% ACS patients who underwent CEA, versus patients who received BMT-only. Most recent studies aim to compare outcomes of patients with or without carotid revascularization and have concluded that compliance to BMT was associated with a lower rate of cerebrovascular events.<sup>[1-4,11]</sup> Since, one of the main challenges for the success of BMT is compliance, our objective was to investigate whether undergoing CEA could influence BMT adherence in ACS patients.

Our study suggests that >50% ACS patients who underwent CEA had lower medical compliance than those who only received BMT. A possible reason for the lack of adherence to prescribed medications could be that patients who underwent CEA felt safer after surgery compared to the BMT-only group. The clinical Trial "Successful implementation of best medical

treatment for patients with asymptomatic carotid artery stenosis within a randomized controlled trial" (SPACE-2)<sup>[2]</sup> also concluded that patients undergoing BMT-only seemed to have higher adherence than those undergoing CEA along with BMT, and they also suggest that this was probably because patients who had not yet undergone surgical intervention felt "afraid" of the progression of stenosis, while those who underwent endarterectomy felt more "secure" after the reduction of stenosis. Additionally, in our study, when patients were asked if they were still smoking, the BMT-only group reported a higher number of current smokers than the group that underwent CEA, although it did not reach statistical significance. However, it's possible that this difference is underestimated due to the small size of the analyzed sample, which was reduced by the loss of a significant number of patients from the initial pool.

Patients who underwent CEA were able to name most of their medications, indicating a significantly better understanding of their treatment compared to the BMT group. Although the literature suggests that understanding one's treatment

is associated with better medication adherence, we did not observe this trend in our study.<sup>6]</sup>

We also observed that physicians were less likely to prescribe BMT (specifically statins and antiplatelets) to patients who underwent CEA compared to those who did not. This finding may suggest that physicians believe patients who underwent CEA have already received adequate care and may not require additional interventions, despite the importance of BMT adherence in preventing future events as well as other cardiovascular events.

No significant differences were observed in the 3-point major adverse cardiovascular events outcomes, which could be attributed to the small sample size.

### Strengths and Limitations of the study

Study limitations include a relatively small sample size, the monocentric nature, the cross-sectional design, and the absence of a formal validation of the questionnaires in Portuguese. Another potential weakness was the social desirability bias. As doctors were calling the patients, they may have given socially acceptable answers, which could overestimate the medical adherence. Additionally, a selection bias may have played a role as patients who did not respond to the surveys may have had lower or higher adherence to BMT with resulting under or overestimation of certain factors.

## CONCLUSION

The results of our study suggest that > 50% ACS patients submitted to CEA have poorer compliance with BMT, despite having a better understanding of their medication regimen. Additionally, physicians may have fewer concerns about their patients adhering to BMT after CEA. So, there is a need to identify what causes loss of compliance and strategies to enhance adherence and awareness to BMT for patients and physicians, as it is critical for preventing cerebrovascular events in this population.

A larger clinical trial that involves a more extensive patient sample undergoing CEA and BMT-only and utilizing the Morisky Medication Adherence Scale-8 (MMAS-8) before surgery and after an adequate follow up period would bolster the external validity of the findings and elucidate whether CEA truly lacks or not medical compliance benefits.

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