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Original Article

Medication adherence in patients with carotid artery stenosis before/after enrollment in CARUSO study

Aderenza alle terapie in pazienti con stenosi carotidea prima/dopo l'arruolamento nello studio CARUSO

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Key words: patients compliance, medical adherence, medication adherence, carotid stenosis, non-adherence.

ABSTRACT

Background: this work analyses the medical therapy adherence of patients enrolled in a clinical study. The primary end-point of this research is to find out if enrolment in a clinical study can improve adherence to antiplatelet and/or lipid-lowering therapy.
Materials and Methods: the first 92 asymptomatic patients with carotid artery stenosis ≥50% enrolled in the CARUSO study were considered. Overall baseline "compliance" to anti-platelet treatment was stratified in patients with good, average, and poor adherence.
Results: overall compliance with anti-platelet therapy was good for 66 patients (95.7%) out of 69 patients already under this treatment. A significant correlation between good adherence to pharmacological therapy and the presence of previous cardiovascular events at the time of enrolment: 92.3% (one event), 84.6% (two events), 50% (three events) *vs* 35.1% of those without events (p<0.001). After 6 months, good adherence was found to extend even to patients with no previous events (p=0.083).
Conclusions: this research showed a positive trend in improving adherence to lipid-lowering therapy (88.3% *vs* 56.7%, p=0.002) and maintenance of a high level (> 95%) of adherence to anti-platelet therapy, after the enrolment in a clinical study.

Background: questo lavoro analizza l'aderenza alla terapia medica dei pazienti arruolati in uno studio clinico. L'end-point primario di questo studio è stato quello di valutare se l'arruolamento in uno studio clinico può migliorare l'aderenza alla terapia antiaggregante piastrinica e/o lipidica.
Materiali e Metodi: sono stati considerati i primi 92 pazienti asintomatici con stenosi carotidea ≥50% arruolati nello studio CARUSO. La compliance complessiva al basale al trattamento antiaggregante è stata stratificata in pazienti con buona, media e scarsa aderenza.
Risultati: la *compliance* complessiva alla terapia antiaggregante è risultata buona per 66 pazienti (95,7%) su 69 già in trattamento. È stata riscontrata una correlazione significativa tra la buona aderenza alla terapia farmacologica e la presenza di precedenti eventi cardiovascolari al momento dell'arruolamento: 92,3% (un evento), 84,6% (due eventi), 50% (tre eventi) *vs* 35,1% di quelli senza eventi (p<0.001). Dopo 6 mesi è stata riscontrata una buona aderenza estesa anche ai pazienti che non avevano avuto eventi precedenti (p=0.083).
Conclusioni: questa ricerca ha evidenziato una tendenza positiva nel miglioramento dell'aderenza alla terapia lipidica (88,3% *vs* 56,7%, p=0.002) e il mantenimento di un livello elevato (>95%) di aderenza alla terapia antiaggregante, dopo l'arruolamento in uno studio clinico.

Introduction

Carotid stenosis is a segmental reduction of the carotid artery's lumen at the bifurcation and, in any case, with involvement of the internal carotid artery in the extracranial tract, generally due to the presence of atheromasia. By degree of stenosis, we mean the degree of reduction of the lumen at the level of the stenosis, which is expressed as a percentage of the diameter of the vessel.[1] By convention, asymptomatic carotid stenosis is defined if no suitable cerebral or retinal ischemic episode has ever occurred in the patient or if the last suitable cerebral or retinal ischemic episode occurred in the patient more than the previous 3 months. This time limit has been redefined based on the latest revisions, since until recently, the limit of 6 months was set to define an asymptomatic stenosis.[1]

Non-adherence to medications is widely recognized as a major public health concern that contributes to patient morbidity, mortality, and healthcare costs.[2,3] The World Health Organization (WHO) defines adherence as the degree to which a person's behavior corresponds with the agreed-upon recommendations from a healthcare provider.

Cardiovascular (CV) benefits shown by statin treatment in Randomized Controlled Trials (RCTs) can only be expected to provide similar clinical benefits in patients who follow the prescribed treatment regimen for a prolonged period, possibly even for a lifetime.

However, 50% or more of patients discontinue statins within 1 year of treatment initiation, and more do so over longer time periods.[4,5] Among adults >65 years, adherence to statins for primary prevention after two years was a dismal 25.4%, while it was only slightly better at 36.1% and 40.1% for patients with chronic Coronary Artery Disease (CAD) and acute coronary syndrome (secondary prevention), respectively. The situation might not be quite as bad as these numbers suggest since some users only temporarily discontinue statin therapy. In one study, 53.8% of new statin users had at least one extended period (at least 90 days) of non-adherence, but about 60% returned to regular statin use within 2 years.[6] A good degree of adherence, with statin therapy in the first 2 years of prescription may reduce hospitalization rates and direct medical costs in the subsequent year.[7]

Shroufi and Powles[8] recently performed a simulation study showing that improving adherence to statins by 50% (from 50% to 75%) would prevent twice as many additional deaths compared to a strategy of lowering the CV threshold (from 20% to 15.5% 10-year risk of Cardiovascular Disease, CVD) for statin therapy. Therefore, improving adherence to statin therapy would be beneficial for patients and other healthcare stakeholders.

Regardless of whether patients with Asymptomatic Carotid Stenosis (ACS) undergo revascularization or not, all patients with ACS should receive intensive medical management to control their risk factors and comorbidities. Such treatment not only reduces the risk of ipsilateral cerebrovascular events, but crucially, it also prevents atherosclerotic events in other vascular beds.[9] There is conflicting opinion regarding antiplatelet therapy in asymptomatic patients because of concerns that inappropriate therapy might increase the risk of major bleeding events without reducing stroke risk. In a systematic review of 17 natural history studies reporting 5-year all-cause mortality in 11.391 patients with >50% asymptomatic A stenosis, 63% of late deaths were cardiac, representing an average cardiac-related mortality of 2.9% per year.[10] Monotherapy with aspirin remains the first-line antiplatelet agent in asymptomatic patients, with clopidogrel reserved for patients who are aspirin intolerant.[11]

The present evaluation has been created in order to analyse the medical therapy adherence for patients enrolled in the CARUSO study (carotid plaque stabilization and regression with evolocumab).[12] The primary end-point of our research is to find out if enrolment in a clinical study can improve adherence to antiplatelet therapy and/or lipid-lowering therapy. Two secondary end-points were also designed: the association between adherence to pharmacological therapy and the presence of previous cardiovascular events at the time of enrolment and after 6 months, and the evaluation of gender-related differences in treatment adherence.

Materials and Methods

All patients were enrolled through a face-to-face interview in which the purpose of the research was explained, and informed consent was obtained. All of them were asked what type of drug therapy they had taken before and with what adherence, and all of them were given antiplatelet therapy and lipid-lowering therapy. A dedicated patient database for the present evaluation was created, including baseline and 6-month follow-up data. Patient demographics, comorbidity, previous antiplatelet therapy and/or lipid-lowering therapy, previous cardiovascular events, and adherence to previous antiplatelet therapy and/or lipid-lowering therapy were collected.

All patients were interviewed by phone call at baseline and 6 months after enrollment. The enrolled patients have been divided between those who, at the time of enrollment, already had ongoing antiplatelet or oral lipid-lowering therapy (statin, fenofibrate) and those who were not taking any type of pharmacological therapy.

This evaluation will be performed in accordance with the ethical principles contained in the 1964 Declaration of Helsinki, and the CARUSO study has been approved by the local ethics committee. Patients enrolled in the CARUSO study had signed an informed consent; screening and evaluation procedures (clinical examination, Doppler Ultrasound, DUS) did not differ from standard medical care. The number of patients screened, randomized, treated, and analyzed had been reported according to Consolidated Standards of Reporting Trials (CONSORT) guidelines.[13]

Statistical analysis

Data was processed in anonymous and aggregate form.

Continuous variables were presented as median and Interquartile Range (IQR) according to their distribution. Categorical variables were represented as frequencies and percentages. For quantitative data, the statistical significance of comparisons between two independent groups was tested with the Mann-Whitney test; the Kruskal-Wallis test was used for comparisons between multiple independent groups. Associations between categorical variables were tested using the Chi-squared test or Fisher's exact test; furthermore, Cramer's V was used where appropriate. A two-sided p-value <0.05 was considered statistically significant.

All analyses were performed with Statistical Package for Social Sciences (SPSS) version 25 (IBM SPSS® for Windows® software; IBM Corp., Armonk, NY, USA).

Results

The first 92 patients enrolled in the CARUSO trial were considered for the present research. Data were available for all those 92 patients at baseline and at 6-month follow-up. There were 58 male (63%) and 34 female (37%) patients. Median age was 73 (IQR: 66-76) years for males and 73 (IQR: 70-77) years for female patients. Thirty-one patients (33.7%) had a type II diabetes. Twenty-three patients out of ninety-two (25%) had a history of previous acute myocardial infarction. Two patients (2.2%) had a history of previous stroke. Considering the overall rate of previous events (Acute Myocardial Infarction, AMI, Previous Coronary Revascularization, CABG, and stroke), 15 patients (16.3%) had one event, 19 patients (20.7%) had two events, and two patients (2.2%) had three events.

At baseline, 87 patients (94.6%) were already under anti-platelet therapy and/or statins.

Seventy-nine (85.9%) out of 92 patients were already under anti-platelet therapy (single or double anti-platelet), seventy-one (77.2%) out of 92 patients were already under statin therapy, and twenty-two (23.9%) were already under ezetimibe.

Concerning treatment compliance, all patients included in the study were evaluated first. Then, separate analyses were made just for patients who completed the whole study without counting drop-off patients. Overall baseline compliance to treatments was stratified into three groups: patients with good adherence (>80% adherence), patients with average adherence (50-80% adherence), and patients with poor adherence (<50%).

Whole compliance to anti-platelet therapy was good (>80%) for 66 patients (95.7%) out of 69 patients already on treatment (data not available n=10). Only an average adherence was recorded for three patients (4.3%); in contrast, no poor adherence was observed.

Overall compliance to lipid-lowering therapy was good (>80%) for 37 patients (56.9%) out of 65 patients (data not available n=6). For twenty-three patients (35.4%), an average adherence was recorded, and for five patients (7.7%), a poor adherence was observed. If we together consider patients with average and poor statin adherence, they represent 43.1% of the whole adherence rate.

No significant gender-related difference in good treatment adherence for anti-platelet drugs was found at the time of enrolment (male 95.5% *vs* female 96.0%, p>0.999) or age-related (≤70 y.o. 100% *vs* >70 y.o. 92.9%, p=0.275). Similarly, for lipid-lowering drugs regarding gender (male 53.8% *vs* female 61.5%, p=0.164) or age (≤70 y.o. 53.8% *vs* >70 y.o. 59%, p=0.160).

Table 1 shows that no statistical significance was found comparing AMI and non-AMI patients, stroke and non-stroke patients, patients who underwent coronary revascularization, and patients who didn't, regarding anti-platelet treatment.

Regarding lipid-lowering treatment, statistical significance was found comparing AMI and non-AMI patients, patients who underwent coronary revascularization, and patients who did not (Table 2).

Table 1. Anti-platelet treatment adherence and previous cardiovascular events.

Anti-platelet adherence	No AMI (N=49)	Previous AMI (N=20)	p-value
Good initial adherence	93.9% (46)	100% (20)	0.551
Average initial adherence	6.1% (3)	0% (0)	
	No stroke (N=68)	**Previous stroke (N=1)**	
Good initial adherence	95.6% (65)	100% (1)	>0.999
Average initial adherence	4.4% (3)	0% (0)	
	No coronary revascularisation (N=38)	**Previous coronary revascularisation (N=30)**	
Good initial adherence	92.1% (35)	100% (30)	0.249
Average initial adherence	7.9% (3)	0% (0)	

Coronary revascularisation: data not registered (n=1). AMI, Acute Myocardial Infarction.

Table 2. Lipid-lowering treatment adherence and previous cardiovascular events.

Lipid-lowering adherence	No AMI (N=48)	Previous AMI (N=17)	p-value
Good initial adherence	47.9% (23)	82.4% (14)	0.042*
Average initial adherence	43.8% (21)	11.8% (2)	
Poor initial adherence	8.3% (4)	5.8% (1)	
	No stroke (N=63)	**Previous stroke (N=2)**	
Good initial adherence	57.1% (36)	50.0% (1)	0.860
Average initial adherence	34.9% (22)	50.0% (1)	
Poor initial adherence	8.0% (5)	0.0% (0)	
	No coronary revascularisation (N=38)	**Previous coronary revascularisation (N=26)**	
Good initial adherence	36.8% (14)	84.6% (22)	0.001*
Average initial adherence	52.6% (20)	11.5% (3)	
Poor initial adherence	10.6% (4)	3.9% (1)	

*statistically significant value, Coronary revascularisation: data not registered (n=1). AMI, Acute Myocardial Infarction.

There was a significant association between good adherence to pharmacological therapy with lipid-lowering comparing patients that had at least one Major Adverse Cardiovascular Event (MACE) patient to other patients at the time of enrolment: 92.3% (one event), 84.6% (two events), 50% (three events) *vs* 35.1% of those without events (p<0.001). After 6 months, good adherence was found to extend even to patients who had no previous events: 80% *vs* 100% (one event), 92.3% (two events), 100% (three events), p=0.083.

Sixty-nine patients (75%) completed the whole 6-month follow-up.

Twenty-three patients dropped off the study: two patients (2.2% out of 92) for adverse events (one for coagulation problems causing spontaneous hematomas; one for onset of secondary neoplastic pathology). Twenty patients (21.7% out of 92) for voluntary unmotivated abandonment, without documented adverse events. One patient experienced a significant increase in the diagnosed carotid artery stenosis that required open surgical intervention.

Nine adverse events were recorded (9.8% among the overall cohort of 92 patients). Details of adverse events are listed in Table 3.

Concerning anti-platelet treatment, among those 69 patients who completed the 6-month follow-up, unclear data were recorded for three patients. Thus, they were not taken into account. Sixty-four (97%) patients out of the remaining 66 had good anti-platelet treatment adherence. Two patients (3%) had an average treatment adherence.

Concerning lipid-lowering therapy treatment, among those 69 patients that completed the 6-month follow-up, for two patients, unclear data were recorded; thus, they were not taken into account. Fifty-eight (86.6%) patients out of the remaining 67 had good lipid-lowering therapy adherence. Nine patients (13.4%) had an average treatment adherence.

Patients evaluated at both baseline and follow-up had a significant increase (31.7%) in adherence to lipid-lowering therapy (88.3% *vs* 56.7%, p=0.002) (Table 4).

The 93.8% of patients that have good adherence to lipid-lowering therapy confirmed a good adherence to anti-platelet treatment, and the 6.2% had average or poor adherence to anti-platelet treatment and improved.

No significant differences in treatment adherence arose according to patients' gender and age class.

Discussion

According to results of our work, enrolment showed a trend in increasing medical treatment adherence. Patients evaluated at both baseline and follow-up had a significant increase (31.7%) in adherence to lipid-lowering therapy (56.7% *vs* 88.3%, p=0.002); baseline anti-platelet therapy adherence was already good out of 69 patients already under this treatment (95.7%).

The 93.8% of patients who had good adherence to lipid-lowering therapy confirmed good adherence to anti-platelet treatment. The 6.2% had average or poor adherence to anti-platelet treatment and improved.

Moreover, patients who experienced at least one or more MACE events are more likely to have a good adherence in lipid-lowering adherence 92.3% (one event), 84.6% (two events), 50% (three events) *vs* 35.1% of those without events (p=0.001). After 6 months, good adherence was found to extend even to patients who had no previous events, 80% *vs* 100% (one event), 92.3% (two events), and 100% (three events), p=0.083.

Causes of non-adherence

Causes of non-adherence are complex and can be broadly classified into three categories.

Patient-related

Low health literacy, lack of understanding of the treated disease, attitudes concerning the effectiveness of the treatment, negative previous experience with pharmacological therapies, presence of psychological problems, and/or cognitive impairment.[14,15]

Table 3. Adverse events at 6-month follow-up.

Adverse events	Total patients (N=92)	Total patients at 6 months follow-up (N=69)
CPK* increase	1.1% (1)	1.4% (1)
Ischemic stroke	1.1% (1)	1.4% (1)
Myalgia	5.4% (5)	4.3% (3)
Myalgia + CPK* increase	1.1% (1)	1.4% (1)
STEMI	1.1% (1)	1.4% (1)
None	75.0% (69)	90.1% (62)
Data not registered (drop out)	15.2% (14)	0.0% (0)

CPK, Creatine Phosphokinase; STEMI, ST Elevation Myocardial Infarction.

Table 4. Adherence to anti-platelet and lipid-lowering therapies over the 6-month follow-up.

6-month treatment adherence	Anti-platelet (N=58)	Lipid-lowering (N=60)
Good initial adherence confirmed	93.2% (54)	57.7% (34)
Increasing in treatment adherence	3.4% (2)	31.7% (19)
No changes in treatment adherence (average or poor)	3.4% (2)	11.6% (7)
Total	100.0%	100.0%

*Patients with data available at both basal and follow-up.

Forgetfulness plays a role, but underlying reasons often contribute to forgetfulness, including lack of prioritization of the importance of medication intake, medication as a reminder of the patient's condition, having to take medications making the patient feel old or bad about themselves, or simply not liking the idea of taking a pill. The shared decision-making between physician and patient that might improve adherence is often compromised by the latter's reluctance to disagree with the authority figure physician.[16]

Physician-related

Complex drug regimens prescribed by physicians and lack of adequate explanation about the disease and the benefits and potential Adverse Events (AEs) of medications all contribute to medication non-adherence, and this is true for statins as well.

Healthcare-related

The economics of the healthcare marketplace severely limits the time a physician can spend with an individual patient. Higher copayments are negatively correlated with adherence,[17] but this may become less of an issue as both simvastatin and atorvastatin have become available as generic drugs.

Interventions to improve adherence

Medication-taking behavior is complex. In general, about 33% will be adherent to therapy just by being given a prescription and asked to take it by their physicians, while about 15-25% will be non-adherent despite any intervention. Thus, interventions to improve adherence are aimed at the middle 50% of individuals who may adhere if given support and encouragement. The interventions to improve adherence are also divided into three groups focused on the patient, health professionals, and the health delivery system. Strategies with some degree of success are multifaceted combinations of patient education, patient-physician communication enhancement, extended care through ancillary health care providers, simplifying drug regimens, and increased patient monitoring and follow-up, but these are labor-intensive and expensive.[18]

In our study, we focused on individually monitoring each patient enrolled, allowing better adherence to treatment. In a recent review on improving adherence to lipid-lowering therapies, Schedlbauer *et al.*[19] found that the most promising interventions involved reinforcement and reminders to patients, which increased adherence by up to 24%. Improving patient information and education increased adherence by 13%.[19]

Other types of interventions include healthcare delivery, where programs have found success in leveraging information technology and patient data and tailoring interventions to patients' attributes. These programs also offer follow-up and patient support by healthcare professionals trained to work closely with patients to improve adherence.[20]

Finally, the physician and patient must be partners in achieving the goals of therapy, and a key strategy is enhancing the dialogue between the physician and patient in order to better educate patients and clear up any misconceptions.[21] There is evidence that providing patients with comprehensive knowledge about statins, even those who have already been on statin therapy, improves adherence and increases the number of people reaching Low-Density Lipoprotein-Cholesterol (LDL-C) lowering goals.[22] However, in spite of statins' widespread use, discontinuation, and nonadherence remain a major gap in both the primary and secondary prevention of atherosclerotic cardiovascular disease. The major reason for statin discontinuation is because of the development of statin-associated muscle symptoms, but a range of other statin-induced side effects also exist. The pain can be a mild discomfort or serious enough to make it hard to do your daily activities.

However, researchers have found a *nocebo* effect when it comes to people thinking they have muscle pain from statins. The real risk of developing muscle pain as a result of taking statins is about 5% or less compared with taking a pill that doesn't contain medicine, called a *placebo*. However, studies have found that nearly 30% of people stopped taking the pills because of muscle aches, even when they were taking a placebo. Therefore, this could be an explanation for why initial adherence to lipid-lowering therapy is lower than that to anti-platelet therapy.

Participants in this research have shown a significant improvement in lipid-lowering drug adherence. The physician-patient relationship is probably one of the reasons for this significant trend. Compared to outsetting, patients are supposed to have more follow-up visits and control. A direct relationship might ameliorate patient comprehension and, therefore, treatment adherence.

There is enormous potential to increase adherence by improving patient-physician communication. O'Malley[23] has criticized the trend towards excessive reliance on technologies at the expense of cultivating communication-based and relationship-based skills, which he argues are likely to be more effective in the psychosocial domains of care, such as enhancing adherence. Practically, the physician should ask questions in a nonjudgmental way to determine if there are problems adhering to the treatment. If a patient admits to non-adherence, he/she is usually telling the truth, but if a patient denies non-adherence, he/she is telling the truth about half the time. During follow-up, the healthcare provider should probe whether patients know why they are taking their medication and the benefits they can expect from adhering to their medications. It is equally important during follow-up for the physician to inquire about the occurrence of AEs and to take such reports seriously. There is evidence that even for well-documented and commonly recognized statin AEs, such as muscular and neurological complaints, physicians often dismiss these as statin-unrelated.[24,25]

Non-communication between physician and patient about statin AEs prevents a risk-benefit profile for statin treatment reassessment. Even in cases where the benefits of statins outweigh the risks, the denial of the patient's symptoms by the physician can lead to a lack of trust and may be a strong contributor to non-adherence.

Compared with men, women are less likely to adhere to statins, according to literature findings. Even if the present study did not reach a significant variation in this trend, our data did not confirm this tendency.[26]

This research has a few limitations in so far as the assessment of therapeutic adherence was carried out on the basis of the answers given by the patient, and not through the use of special assessment instruments based on prescription frequency and dosage.

Conclusions

This study showed a positive trend in improving adherence to antiplatelet therapy and/or lipid-lowering therapy after enrolment in a clinical study. Considering lipid-lowering therapy alone, patients enrolled in the study experienced the most important increase in adherence (31.7%) compared to increasing in anti-platelet therapy (3.4%). It has to be considered that the baseline good lipid-lowering therapy adherence was lower than baseline good anti-platelet therapy adherence (56.9% *vs* 95.7%) within the total cohort of patients.

Those findings are limited by a short-term follow-up (6 months)

and a small sample size. However, the positive trend in treatment adherence for patients enrolled in a clinical study seems to be confirmed by the literature review presented. In our current state of knowledge, the physician and patient must form an alliance to more effectively communicate the importance of statin treatment and establish goals for therapy. A brief discussion, listening to patients' concerns, and discussing potential AEs may make a big difference. Predictors of non-adherence should be used to identify those at statin discontinuation high risk for targeted medical advice. Clinicians should emphasize non-pharmacological approaches in addition to statins for reducing cholesterol levels in all patients, no matter what risk stratification. The most important breakthrough for increasing statin adherence may not be new at all: remembering to involve the patient and making patients an active part of shared decision-making may, in fact, be the best way to achieve statin adherence.

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Authors' contributions: ML, TA, AGa, AGu, substantial contribution to the conception design of the work, acquisition, analysis and interpretation of data for the work, drafting the work and revising it critically for important intellectual content; AC, substantial contribution to analysis and interpretation of data for the work, drafting the work and revising it critically for important intellectual content; GM, drafting the work and revising it critically for important intellectual content; MF, CB, substantial contribution to analysis and interpretation of data for the work, drafting the work and revising it critically for important intellectual content; MB, AM, revising the work critically for important intellectual content. All the authors have read and approved the final version of the manuscript and agreed to be held accountable for all aspects of the work.

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Informed consent: all patients were enrolled through a face-to-face interview in which the purpose of the research was explained, and informed consent was obtained.

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