http://mnj.ub.ac.id/
DOI: 10.21776/ub.mnj.2023.009.01.2
eISSN: 2442-5001 **pISSN:** 2407-6724
Accredited by DIKTI Decree No: 21/E/KPT/2018

MALANG NEUROLOGY JOURNAL MNJ

RESEARCH ARTICLE OPEN ACCESS

THE EFFECTS OF SHORT/LONG-TERM ADMINISTRATION OF DUAL ANTIPLATELET THERAPY ON RESTENOSIS IN PATIENTS WITH CAROTID ARTERY STENTING

İsmail Karluka[1], Hasan Bilen Onan[2], Erol Akgül[3], Erol Hüseyin Aksungur[2]

Correspondence: *drismailkarluka.ik@gmail.com*
[1]*Department of Radiology, Baskent University, Adana Dr. Turgut Noyan Training and Research Center, Adana, Turkey.*
[2]*Department of Radiology, Cukurova University, Balcalı Training and Research Hospital, Adana, Turkey.*
[3]*Department of Radiology, International School of Medicine, İstanbul Medipol University, İstanbul, Turkey.*

Article History:
Received: April 28, 2022
Accepted: November 21, 2022
Published: January 1, 2023

Cite this as:
Karluka İ, Onan BH, Akgül E, Aksungur EH. The effects of short/long-term administration of dual antiplatelet therapy on restenosis in patients with carotid artery stenting. Malang Neurology Journal; 2023.9:6-12. DOI: http://dx.doi.org/10.21776/ub.mnj .2023.009.01.2

ABSTRACT

Background: There is no consensus on the duration of dual antiaggregant therapy after carotid stenting. This study aimed to evaluate the early contribution of dual antiaggregant therapy for three or six months to stent restenosis.

Objective: This study aimed to identify the correlation between stent restenosis and the duration of dual antiplatelet therapy (DAPT) in carotid artery stenting (CAS) subjects by retrospectively scanning a CAS procedure dataset.

Methods: Patients who underwent a CAS procedure received dual DAPT (acetylsalicylic acid (ASA) + clopidogrel) were recruited for this study. The first group was the patients who received dual antiaggregants for three months, and the second group was the patients who received dual antiaggregants for six months. Patients' demographic characteristics, comorbidities, and radiological results were reviewed. Follow-up activities for the following six months were assessed for stent status, complications, and new ischemic lesions.

Results: A total of 65 patients received ASA (acetylsalicylic acid) + clopidogrel for six months, while the remaining 118 patients were treated for three months. The restenosis rates were not significantly different between the two groups. The complication and adverse event frequencies were also similar.

Conclusion: This study revealed that the efficacy of 3-month and 6-month DAPT is similar regarding the restenosis frequency, and there are no significant differences in complication frequency.

Keywords: Carotid stenting, In-stent restenosis, antiplatelet agents

Introduction

Atherosclerotic carotid artery stenosis is a common cause of ischemic strokes. Occlusive events in the carotid bifurcation are responsible for approximately 7%–20% of such strokes. Carotid endarterectomy (CEA) and carotid artery stenting (CAS) are two essential treatment alternatives in carotid artery stenosis.[1] The embolic protection devices used for CAS operations have limited the compound ratio of stroke or death during the procedure performed by experienced persons and in centers with large patient volumes to less than 6%, similar to that of patients undergoing CEA.[1,2]. Before and after CAS procedures, dual antiplatelet therapy (DAPT) is recommended to prevent thromboembolism. Long-term antiplatelet therapy (>1 month) has proven beneficial after coronary artery interventions with bare-metal stents.[3] The American College of Radiology (ACR) and the American Stroke Association (ASA) guidelines recommend DAPT with aspirin (81–325 mg daily) plus clopidogrel (75 mg daily) for a minimum of 30 days before and after a CAS procedure. Ticlopidine (250 mg twice a day) may be used as a substitute for patients with intolerance to clopidogrel.[3,4] The optimal duration of DAPT after stenting does not have a standard, and there is still heterogeneity among neuro-interventionalists regarding the use of DAPTs.[5,6] Furthermore, the antiplatelet resistance tests, which have proven to be important in coronary artery interventions[7], differ by centers in CAS applications and are routinely performed only in a few centers .[5]

There have been two major concerns since the introduction of CAS applications. These doubts revolve around its effectiveness and safety and in-stent restenosis (ISR), which is considered a long-term risk.[1] Post-CAS ISR is a relatively rare complication with an incidence varying between 2-8%.[8] Advanced age, female sex, smoking, diabetes mellitus, dyslipidemia, hypertension, peripheral vascular disease, carotid artery occlusion, and cardiovascular disease on the opposite side were correlated with ISR.[1] The narrowing of the vascular lumen after arterial interventions is intimal hyperplasia and constrictive remodeling.[9] ISR usually occurs

due to neointimal hyperplasia and vascular remodeling in the early postoperative period (e.g., within two years), and implanted foreign material and damage may cause recurrent atherosclerosis in the following periods. The pathogenesis of Early ISR (<6 weeks) and late ISR is different. This is rooted in the stent misplacement or other periprocedural complications.[1] Some authors have suggested that early ISR may be associated with increased platelet aggregation.[1,10]

The CAS procedure has an essential place in the daily practice of our interventional radiology department. Like many centers, DAPT [100–300 mg acetylsalicylic acid (ASA)+75 mg clopidogrel] is initiated before the CAS procedure. Treatment continues for up to 3 and 6 months, depending on bleeding and accompanying comorbid risk factors. This study investigated the relationship between ISR and DAPT duration in the two groups taking DAPT for 3 and 6 months.

Methods

Patient selection

This study was conducted by the Cukurova University Faculty of Medicine Interventional Radiology Department and approved by the local ethics committee. The data belonging to 298 patients with carotid artery stenosis between 2010 and 2016 by color Doppler ultrasonography (CDUS), magnetic resonance angiography (MRA), or digital subtraction angiography (DSA) diagnoses and who underwent CAS after admission to our clinic were analyzed retrospectively. Patient data were obtained from our hospital's automation system and the electronic recording system of the Interventional Radiology Department. A CAS procedure was performed asymptomatic cases with a high degree of carotid stenosis (70%) or symptomatic carotid stenosis (50%). Patients with recent myocardial infarction, severe congestive heart failure, serious pulmonary disease, prior neck radiation, contralateral vocal cord paralysis, tracheostomy, contralateral carotid artery occlusion or severe stenosis, recurrent stenosis after CEA have a high risk of surgical treatment. These patients were considered appropriate indications for CAS. Only patients who started receiving DAPT at least one week before the procedure and continued therapy for six months after the process was recruited for the study.

All individuals who underwent a CAS operation and satisfied the inclusion criteria regardless of the stent type (open-cell stent, close cell stent, double stent) were included in the research population. Each patient was examined for antiplatelet resistance tests before the procedure. The treatment was continued in patients with aspirin resistance by increasing aspirin dose (from 100 mg to 300 mg). The procedure was continued by expanding the aspirin dose up to 500 mg in patients who still exhibited resistance to aspirin despite the second amount (these patients were excluded from the study, considering that they were distorting the data on aspirin's effectiveness). The treatment was also continued in patients with clopidogrel (75 mg) resistance by initiating 2x250 mg ticlopidine. Only the patients using aspirin (100–300 mg) and clopidogrel (75 mg) simultaneously were included in the samples. Ticlopidine (2X250 mg) was not recommended for the long-term treatment (maximum two months) due to its potential side effects (11). Therefore, the patients who continued to use it were excluded from the study. Clinical and radiological characteristics of patients, concomitant diseases, and risk factors for stroke were defined. The patients were clustered into two groups according to their treatment after the procedure. The first group included 100–300-mg aspirin + 75-mg clopidogrel patiens for two months and continued treatment with 100–300-mg aspirin alone. The second group included patients who received 100–300 mg ASA + 75 mg clopidogrel for six months and ongoing treatment with 100–300 mg ASA alone. The stenosis of more than 50% in the stent was defined as ISR, including the in-stent thrombosis.

Patient preparation

Neurological was examined before the procedure for each patient. Coagulation tests (PT/aPTT, bleeding time) and renal function tests were evaluated. N-acetyl cysteine (3x300 mg orally) was prescribed to patients with renal dysfunction before the procedure. Antiplatelet drug resistance was measured using Verify Now (Accumetrics, San Diego, CA, USA), and patients with ASA or clopidogrel resistance were excluded from the research population before the procedure.

Stenting procedure

Sedation and anesthesia were not applied to the patients. Heart rate, arterial blood pressure, and oxygen saturation were monitored. ACT (Activated clotting time) was measured at the beginning. Then, intravenous bolus heparin (5000 IU) was given to the patients, and the maintenance dose was given at 2–3 times the level of basal ACT (1000 IU per hour). The patient was laid on the angiography table in the supine position. According to femoral pulse strength, a local anesthetic was applied to the right or left inguinal region. A Seldinger needle was inserted into the femoral artery, followed by a 5F or 6F introducer.

Diagnostic DSA was performed using 5F vertebral or Simmons II catheters. After assessing stenosis at the workstation, measurements were made with appropriate stents and filters. After diagnostic angiography, the catheter was retracted, and a 6 or 7 F long introducer was inserted. In cases where the filter could not be passed, pre-dilatation (with a balloon 2–3 mm in diameter) was performed before pre-occlusive stenosis. The protection filter was then inserted distally into stenosis. Pre-dilatation with a 2–3 mm balloon was applied to the lesion according to the degree of stenosis. The stents were then adequately implanted. The stent diameters were either equal to or greater than the diameter of the main carotid artery. The balloon dilatation after stenting was performed with 4–7 mm balloons in all lesions according to the stent opening degree. IV Atropine, 0,5 mg, was administered before balloon dilatation or stent deployment as a precaution against bradycardia and hypotension during the procedure. Additional doses of atropine were administered when a more significant amount was necessary. After the first stent deployment, double stents were used in patients with filling defects on DSA.

Follow-up

After the procedure, the patients' femoral access was controlled by angiography and closed by a vascular closure device or direct compression (if there were contraindications such as stenosis or calcified plaque). The patients were kept under observation for 24 h in the clinic and immobilized for 2–6 hours. A low dose of IV heparin, 500–750 IU/h,

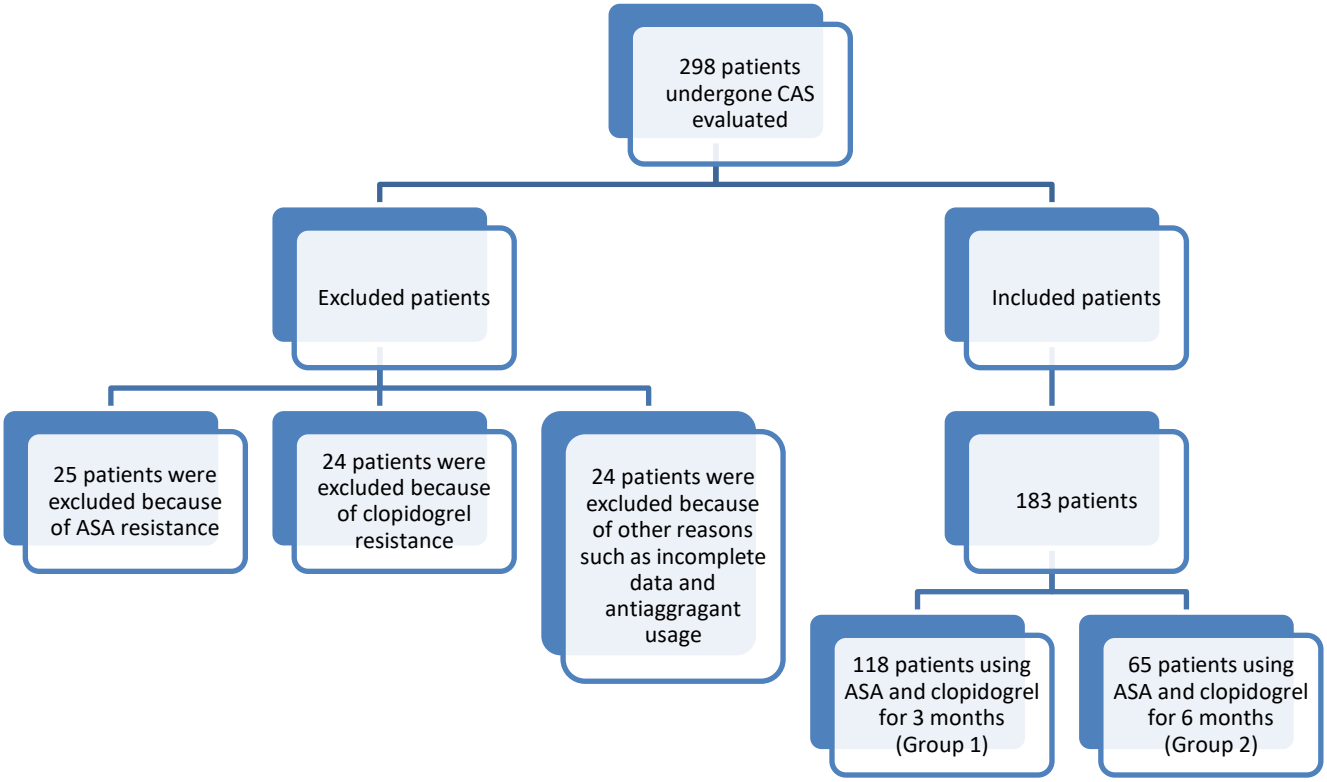

Figure 1. Flow chart of study. CAS: Carotid artery stenting, ASA: Acetyl salicylic acid

was adjusted to be administered 24 h. Neurological were examined immediately after the procedure and 24 h later.

Carotid artery CDUS and cerebral diffusion MRI were performed on the first postoperative day. All patients underwent CDUS at one month and six months after stenting. DSA was performed to confirm the in-stent restenosis in all patients suspected of in-stent restenosis on CDUS 6 months after the CAS procedure. Diffusion MRI was performed on all patients. An increased blood flow rate up to double the average flow or more in the CDUS was a high risk of restenosis. The DSA determined and evaluated restenosis per the NASCET measurement technique.

Statistical analysis

All analyses were performed on SPSS v21. The groups were statistically evaluated for restenosis rates, patient characteristics, morbidity, and mortality rates. The Kolmogorov-Smirnov test was used for the normality tests. Data are given as mean ± standard deviation or median (minimum-maximum) for continuous variables regarding normality and frequency (percentage) for categorical variables. The normally distributed variable (age) was analyzed with a one-way analysis of variance (ANOVA). Non-normally distributed variables were analyzed with the Kruskal–Wallis test. The Bonferroni correction method was used for paired comparisons. Categorical variables were evaluated through the chi-square test. $P<0.05$ values were accepted as statistically significant results.

Results

The content consists of the data and information that have been collected. It should be written using Times New Roman 10 with single space and each new paragraph indents in 3 pt. The finding systematically must be supported by charts, tables, figures or informative illustrations.

The data belonging to the 298 CAS patients were detailed as follows, 25 subjects had aspirin, 24 subjects had clopidogrel resistance, and 42 had used ASA + ticlopidine (2X250 mg) for 1–2 months. These patients were excluded from the research population. Another 24 patients were excluded for various reasons, such as incomplete data and single antiaggregant usage. The remaining patients were categorized into two groups. Group 1 included 118 patients using ASA + clopidogrel for three months, and Group 2 formed 65 patients using ASA + clopidogrel for six months after the CAS procedure. The most pre-procedural neurological symptoms of subjects were found as follows: hemiparesis/hemiplegia (%52), vertigo (%20), and dysphasia (%9), the remaining patients (%19) had different symptoms such as cortical blindness and ataxia. Groups 1 and 2 were similar in age and sex ($p=0.707$ and $p=0.428$, respectively). Diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL), and smoking incidence, which are proven risk factors for carotid stenosis, were also similar in both treatment groups ($p=0.491$, $p=0.878$, $p=0.789$, and $p=0.196$, respectively). There were no significant differences between groups regarding stenosis location (right or left), degree of stenosis, and plaque type ($p=0.622$, $p=0.290$, and $p=0.442$, respectively). The groups' implanted stent types and the pre-operative MRI findings, such as the ischemic lesion side, were similar ($p=0.448$, $p=0.360$, respectively) (Table 1).

Only one patient had a new ischemic focus in Group 1, while two patients in the Group 2 had a new ischemic focus at post-procedural six months ($p=0.207$). However, there were no new ischemic foci on MRI at post-procedural 30 days.

Table 1. Group patients' characteristics and statistical analysis

Variables	Group 1 (n=118)	Group 2 (n=65)	p
Age	67.70 ± 8.34	67.23 ± 7.36	0.707
Gender			
Female	37 (31.36%)	16 (24.62%)	0.428
Male	81 (68.64%)	49 (75.38%)	
Diabetes Mellitus	55 (46.61%)	26 (41.27%)	0.491
Hypertension	100 (85.47%)	56 (87.50%)	0.878
Smokers	36 (48.00%)	33 (61.11%)	0.196
Hyperlipidemia	28 (25.45%)	18 (28.57%)	0.789
Plaque type			
Calcified	21 (17.80%)	17 (26.15%)	0.442
Ulcerated	12 (10.17%)	6 (9.23%)	
Fibroid	9 (7.63%)	7 (10.77%)	
Mixed	76 (64.41%)	35 (53.85%)	
Side of stenosis			
Right ICA	50 (42.37%)	30 (46.15%)	0.622
Left ICA	68 (57.63%)	35 (53.85%)	
Stenosis rates in DSA			
50 - 69%	28 (23.93%)	13 (20.00%)	0.100
70 - 79%	25 (21.37%)	12 (18.46%)	
80 - 89%	24 (20.51%)	6 (9.23%)	
90 - 95%	6 (5.13%)	3 (4.62%)	
Stent Types			
Pre-occlusion	34 (29.06%)	31 (47.69%)	0.448
Open-cell	23 (19.49%)	8 (12.31%)	
Closed-cell	20 (16.95%)	11 (16.92%)	
Double stenting	75 (63.56%)	46 (70.77%)	
Pre-procedural Lesion Side			
Ipsilateral	Ipsilateral	82 (69,49%)	0.360
Contralateral	Contralateral	5 (4,23%)	
Bilateral	Bilateral	31 (26.72%)	
Post-procedural Lesion (new ischemic focus) (MR) (post-procedural six months)	1 (0.84%)	2 (3,07%)	0.207
Procedure-related mortality	0 (0%)	0 (0%)	0.308
Six months after CAS procedure (USG/DSA)			
Patent Stent	66 (57.39%)	38 (62.3%)	0.451
İntimal Hyperplasia	44 (38.26%)	19 (31.15%)	
>50%-70% stenosis	3 (0.00%)	1 (1.64%)	
>70% stenosis	5 (4.35%)	3 (4.92%)	
Occlusion	1 (1.00%)	1 (1.00%)	
Restenosis	9 (7.63%)	5 (7.69%)	1.000

N=number, USG; ultrasonography, MR; magnetic resonance, CAS; carotid artery stenting, DSA; digital subtraction angiography, ICA; internal carotid artery

Only two suffered from major ischemic complications (one from each group, one right MCA and one left MCA infarction). One of these patients had been treated with pharmacological therapy, while the other required mechanical thrombectomy as both experienced regressions of symptoms. None of the patients receiving DAPT had cerebral bleeding during the follow-up period.

One patient from each group suffered from gastrointestinal bleeding that was deemed a complication of antiplatelet treatments. There was no significant difference between the two groups in restenosis (p=1.000) (Table 1). Nine patients (7.63%) in Group 1 and five patients (7.69%) in Group 2 had ISR during six months of follow-up. None of the patients developed stent thrombosis.

Discussion

The absence of a significant difference between the short and long-term DAPT groups in terms of ISR development is the most noteworthy finding of this study.

Furthermore, the frequency of ischemic events and treatment-related complications has been similar in both groups. Considering these findings, short and long-term DAPTs seem to have similar efficacy in preventing restenosis in CAS patients.

The use of aspirin plus clopidogrel has become a mainstay in preventing ISR after CAS. However, the DAPT use is not superior to monotherapy (MAPT) as it is propounded in some studies in the literature. The DAPT and MAPT groups were compared with patients with CAS in a meta-analysis. No significant difference was found between the groups regarding restenosis and bleeding rates. However, the DAPT has been more effective in reducing adverse cerebrovascular outcomes in patients with CAS. This meta-analysis included two studies, and the follow-up period in both studies was 30 days. Thus, only the information about the short-term outcomes was provided.[12,13] Bhatt et al.[14] found that DAPT with aspirin + clopidogrel helped lower the ischemic event rates. This study faced no in-stent thrombosis cases. The risk of bleeding was also not increased. Other studies on the DAPT in patients undergoing CAS support these findings. These studies showed that restenosis rates decreased without

risking patients bleeding.[15] The use of aspirin and clopidogrel combination in CAS has become widespread based on the evidence revealed due to coronary artery interventions. Although the DAPT is recommended after a CAS procedure in many centers worldwide, there is no consensus on treatment duration.[16,17]

There is no consensus on the correlation between stent types and ISR. The most fundamental problem in ISR is intimal hyperplasia.[18] However, moderate to mild restenosis is lower in open-cell stents than in closed-cell stents in previous studies.[19] Nevertheless, there was no difference between the open-cell stent and the closed-cell stent in severe ISR.[19] The timing and etiology of ISR varied. Several scholars stated that residual stenosis was an increased risk factor for early restenosis.[20] Others asserted that the residual stenosis increased the risk during the long period after the CAS procedures.[21] Intimal hyperplasia occurs within 18 months and is usually asymptomatic. The late restenosis (>18 months) often occurs due to atherosclerosis and is more likely to be symptomatic.[20] Many pharmacological agents were tested in experimental studies to prevent neointimal hyperplasia that causes post-CAS ISR. However, no definitive results were reached.[22] Kadoglou et al. [22] showed that the use of ticagrelor and clopidogrel had similar effects on ISR prevention. The effects of these agents on neointimal hyperplasia and ISR in rabbits undergoing CAS procedure could not be demonstrated. However, they discovered that ticagrelor was more effective on intra-stent thrombosis.[22] Another attempt proved no difference in ISR between the cilostazol group after the CAS procedure and the patients who underwent the standard procedure.[23] It was also stated that statins affected the regulation of carotid neointimal hyperplasia.[22,24] Some authors have argued that valsartan can prevent neointimal hyperplasia after a CAS procedure by suppressing endothelial cell damage.[25] Studies on post-CAS restenosis in plaque morphologies have shown that highly calcified carotid plaques are more susceptible to developing ISR.[26] Furthermore, cases of ISRs due to plaque protrusion have been reported.[27] Plaque protrusions can cause rare acute stent thrombosis or subacute ISR.[27,28] The double stent technique or double-layer stents can prevent plaque protrusion.[28,29] The recruits, CAS patients, did not routinely start statins in this study. The use of statin group drugs and valsartan was omitted in this attempt. Moreover, all the stents (open cell, closed cell, double stents) used in the CAS procedures were included. However, there is a similar distribution in both groups using short and long-term antiplatelets, and there is no statistically significant difference regarding the stent type (p=0,448). Besides, there was no difference in plaque morphology (p=0,442). None of the patients had residual stenosis in this study. Moreover, the double stent technique was used in most patients to prevent plaque protrusion in both groups (63.56% vs. 70.77%).

DAPT given to patients is mainly to prevent ISR. However, insufficient evidence comparing periprocedural and postprocedural antiplatelet therapy leads to inconsistent guidelines.[17] ASA recommends using DAPT (clopidogrel/ticlopidine + aspirin) after CAS procedures for at least 30 days after the specialists' positive experiences.[17,30] European Society for Vascular Surgery guideline recommends using aspirin and clopidogrel for at least 30 days unless the treating specialist prefers an alternative long-term treatment regimen.[17,31] Society for Vascular Surgery recommends using aspirin and clopidogrel for precisely 30 days after the procedure and then continued treatment with aspirin alone.[17,32] In a study examining the practices of multiple centers in the USA, aspirin (81 mg/325 mg) and clopidogrel (75 mg) treatment were reported to be applied for three months in 44% of the centers and six months in 26% whereas 30% of the centers use different treatment regimens.[33] Another comprehensive, nationwide study in Taiwan. The groups receiving DAPT for three and six months after CAS procedures were compared. Aspirin and clopidogrel for more than four to 6 weeks did not protect against ischemic stroke and vascular events. No difference was reported in terms of restenosis.[3] The effectiveness and complication rates of short and long-term DAPT use in restenosis prevention were similar in this study. There was no major ischemic stroke or intracerebral hemorrhage, and there was only one patient who developed treatment-related gastrointestinal bleeding in the sample groups.

Contemporary scholars reported various factors associated with restenosis after CAS procedures. It was correlated with advanced age, female sex, smoking, diabetes mellitus, dyslipidemia, hypertension, peripheral vascular disease, carotid artery occlusion, and cardiovascular disease on the opposite side.[1] There was no difference between the groups who received aspirin + clopidogrel treatment for two months and the group who received treatment for six months in terms of hypertension, diabetes mellitus and hyperlipidemia. Therefore, it was determined that similar restenosis rates between groups were not associated with any possible independent factors.

It is also thought that resistance to antiplatelet therapy is a significant problem that may affect the frequency of restenosis and thrombosis. Many case reports present patients with resistance to antiplatelet therapy.[34] Before CAS, regular antiplatelet resistance testing is not regularly recommended in the guidelines.[35] Nevertheless, the antiplatelet resistance is routinely tested before the CAS procedure in the study center. Moreover, this study has excluded the patients with resistance to antiplatelets, and therefore, the results were not distorted by this problem. It is argued that reminding physicians and researchers that antiplatelet resistance contributes to thrombosis and restenosis during and after CAS procedures is essential.

The study's retrospective design, which might cause bias and constraints regarding data evaluation, is a limitation. However, strict inclusion and exclusion criteria exclude antiplatelet-resistant patients, and both groups with similar essential characteristics at the beginning were a considerable advantage. The findings revealed no difference between the groups regarding the restenosis rate. Treatment-related complications of patients were also similar. Despite these findings, there is a need for further prospective studies with strict inclusion/exclusion criteria to determine the DAPT duration.

The efficacy of 3-month and 6-month DAPT in CAS procedures was similar in terms of restenosis frequency, and there was no difference in complications. Further studies with prospective design must confirm these results and determine the necessary length of DAPT in CAS application

Conclusion

This study revealed that the efficacy of 3-month and 6-month DAPT is similar regarding the restenosis frequency, and there are no significant differences in complication frequency.

Acknowledgement

There was no financial and material support for this study.

Conflict of Interest

All authors declare that there is no conflict of interest in this study.

References

1. Dai Z, Xu G. Restenosis after carotid artery stenting. Vascular. 2017. 25(6):576-86. DOI: 10.1177/1708538117706273
2. Gonzales NR, Demaerschalk BM, Voeks JH, et al. Complication rates and center enrollment volume in the carotid revascularization endarterectomy versus stenting trial. Stroke; 2014. 45(11):3320-4. DOI: 10.1161/STROKEAHA.114.006228
3. Jhang K-M, Huang J-Y, Nfor ON, et al. Is Extended Duration of Dual Antiplatelet Therapy After Carotid Stenting Beneficial? Medicine; 2015. 94(40). DOI: 10.1097/MD.0000000000001355
4. Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Neurointerventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery developed in collaboration with the American Academy of Neurology and Society of Cardiovascular Computed Tomography. Journal of the American College of Cardiology; 2011. 57(8):e16-e94. DOI: 10.1161/CIR.0b013e31820d8d78
5. Huibers A, Halliday A, Bulbulia R, Coppi G, De Borst G. Antiplatelet therapy in carotid artery stenting and carotid endarterectomy in the Asymptomatic Carotid Surgery Trial-2. European Journal of Vascular and Endovascular Surgery; 2016. 51(3):336-42. DOI: 10.1016/j.ejvs.2015.11.002
6. Sussman ES, Jin M, Pendharkar AV, et al. Dual antiplatelet therapy after carotid artery stenting: trends and outcomes in a large national database. Journal of neurointerventional surgery; 2021. 13(1):8-13. DOI: 10.1136/neurintsurg-2020-016008
7. Guirgis M, Thompson P, Jansen S. Review of aspirin and clopidogrel resistance in peripheral arterial disease. Journal of vascular surgery; 2017. 66(5):1576-86. DOI: 10.1016/j.jvs.2017.07.065
8. Nishihori M, Ohshima T, Yamamoto T, et al. Overlap stenting for in-stent restenosis after carotid artery stenting. Nagoya journal of medical science; 2016. 78(2):143. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4885814/
9. Goel SA, Guo L-W, Liu B, Kent K. Mechanisms of post-intervention arterial remodelling. Cardiovascular research; 2012. 96(3):363-71. DOI: 10.1093/cvr/cvs276
10. Mazighi M, Saint Maurice J, Bresson D, Szatmary Z, Houdart E. Platelet aggregation in intracranial stents may mimic in-stent restenosis. American journal of neuroradiology; 2010. 31(3):496-7. DOI: 10.3174/ajnr.A1778
11. Love BB, Biller J, Gent M. Adverse haematological effects of ticlopidine. Drug Safety; 1998. 19(2):89-98. DOI: 10.2165/00002018-199819020-00002
12. Barkat M, Hajibandeh S, Torella F, Antoniou G. Systematic review and meta-analysis of dual versus single antiplatelet therapy in carotid interventions. European Journal of Vascular and Endovascular Surgery; 2017. 53(1):53-67. DOI: 10.1016/j.ejvs.2016.10.011
13. Weem SP, van Haelst S, den Ruijter H, Moll F, de Borst G. Lack of evidence for dual antiplatelet therapy after endovascular arterial procedures: a meta-analysis. European Journal of Vascular and Endovascular Surgery; 2016. 52(2):253-62. DOI: 10.1016/j.ejvs.2016.04.023
14. Bhatt DL, Kapadia SR, Bajzer CT, et al. Dual antiplatelet therapy with clopidogrel and aspirin after carotid artery stenting. Journal of Invasive Cardiology; 2001. 13(12):767-71. Available from: https://pubmed.ncbi.nlm.nih.gov/11731685.
15. McKevitt F, Randall M, Cleveland T, Gaines P, Tan K, Venables G. The benefits of combined anti-platelet treatment in carotid artery stenting. European Journal of Vascular and Endovascular Surgery; 2005. 29(5):522-7. DOI: 10.1016/j.ejvs.2005.01.01
16. Enomoto Y, Yoshimura S. Antiplatelet therapy for carotid artery stenting. Interventional Neurology; 2012. 1(3-4):151-63. DOI: 10.1159/000351686
17. Lamanna A, Maingard J, Barras CD, et al. Carotid artery stenting: Current state of evidence and future directions. Acta Neurologica Scandinavica; 2019. 139(4):318-33. DOI: 10.1111/ane.13062
18. Takao N, Hagiwara Y, Shimizu T, et al. Preprocedural Carotid Plaque Echolucency as a Predictor of In-Stent Intimal Restenosis after Carotid Artery Stenting. Journal of Stroke and Cerebrovascular Diseases; 2020. 29(12):105339. DOI: 10.1016/j.jstrokecerebrovasdis.2020.105339
19. Müller MD, Gregson J, McCabe DJ, et al. Stent Design, restenosis and recurrent stroke after carotid artery stenting in the international carotid stenting study. Stroke; 2019. 50(11):3013-20. DOI: 10.1161/STROKEAHA.118.024076

20. Moon K, Albuquerque FC, Levitt MR, Ahmed AS, Kalani MYS, McDougall CG. The myth of restenosis after carotid angioplasty and stenting. Journal of neurointerventional surgery; 2016. 8(10):1006-10. DOI: 10.1136/neurintsurg-2015-011938
21. Kang J, Hong J-H, Kim BJ, et al. Residual stenosis after carotid artery stenting: Effect on periprocedural and long-term outcomes. PloS One; 2019. 14(9):e0216592. DOI: 10.1371/journal.pone.0216592
22. Kadoglou NP, Stasinopoulou M, Giannakopoulos T, et al. Carotid stent restenosis and thrombosis in rabbits: The effect of antiplatelet agents. Journal of Cardiovascular Pharmacology and Therapeutics; 2020. 25(6):570-7. DOI: 10.1177/1074248420931624
23. Takayama K, Taoka T, Nakagawa H, et al. Effect of cilostazol in preventing restenosis after carotid artery stenting using the carotid wallstent: A multicenter retrospective study. American Journal of Neuroradiology; 2012. 33(11):2167-70. DOI: 10.3174/ajnr.A3127
24. Stasinopoulou M, Kadoglou NP, Christodoulou E, et al. Statins' withdrawal induces atherosclerotic plaque destabilization in animal model - A "Rebound" stimulation of inflammation. Journal of Cardiovascular Pharmacology and Therapeutics; 2019. 24(4):377-86. DOI: 10.1177/1074248419838499
25. Suzuki H, Sano T, Umeda Y, et al. Valsartan prevents neointimal hyperplasia after carotid artery stenting by suppressing endothelial cell injuries. Neurological Research; 2015. 37(1):35-42. DOI: 10.1179/1743132814y.0000000408
26. Kim CH, Kang J, Ryu W-S, Sohn C-H, Yoon B-W. Effects of carotid calcification on restenosis after carotid artery stenting: A follow-up study with computed tomography angiography. World Neurosurgery; 2018. 117:e514-e21. DOI: 10.1016/j.wneu.2018.06.068
27. Takigawa T, Matsumaru Y, Kubo T, Fukuhara N, Hayakawa M, Usui M. Recurrent subacute in-stent restenosis after carotid artery stenting due to plaque protrusion: Case report. Neurologia medico-chirurgica; 2009. 49(9):413-7. Available from: https://www.jstage.jst.go.jp/article/nmc/49/9/49_9_413/_pdf
28. Akgul E. A Novel technique for carotid artery stenting: Double stenting with sequential balloon angioplasty: A Case report and technical note. Angiol; 2015. 3(159):2. DOI: 10.4172/2329-9495.1000159
29. Safian RD. Carotid stenting with double layered stents: Double trouble or double benefit? Catheterization and cardiovascular interventions. Official Journal of The Society for Cardiac Angiography & Interventions; 2018. 91(4):758-9. DOI: 10.1002/ccd.27562
30. Akbari SH, Reynolds MR, Kadkhodayan Y, Cross DT, Moran CJ. Hemorrhagic complications after prasugrel (Effient) therapy for vascular neurointerventional procedures. Journal of neurointerventional surgery. 2013; 5(4):337-43. DOI: 10.1136/neurintsurg-2012-010334
31. Olafson EM, DeGrote JR, Drofa A, et al. A case series of 18 patients receiving ticagrelor after carotid stenting. Journal of Pharmacy Practice; 2018. 31(5):519-21. DOI: 10.1177/0897190017729524
32. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke; 2014. 45(7):2160-236. DOI: 10.1161/STR.0000000000000024
33. Faught RW, Satti SR, Hurst RW, Pukenas BA, Smith MJ. Heterogeneous practice patterns regarding antiplatelet medications for neuroendovascular stenting in the USA: A multicenter survey. Journal of Neurointerventional Surgery; 2014. 6(10):774-9. DOI: 10.1136/neurintsurg-2013-010954
34. Köklü E, Arslan Ş, Yüksel İÖ, Bayar N, Koç P. Acute carotid artery stent thrombosis due to dual antiplatelet resistance. Cardiovascular and Interventional Radiology; 2015. 38(4):1011-4. DOI: 10.1007/s00270-014-0959-1
35. Köklü E, Arslan Ş, Gencer ES, Bayar N, Avcı R, Özgünoğlu EC. Six-year outcomes of carotid artery stenting performed with multidisciplinary management in a single center. Anatolian Journal of Cardiology; 2021. 25(6):385. DOI: 10.14744/anatoljcardiol.2020.20420