International Journal of Neurosurgery
2022; 6(1): 11-18
http://www.sciencepublishinggroup.com/j/ijn
doi: 10.11648/j.ijn.20220601.13
ISSN: 2640-1940 (Print); ISSN: 2640-1959 (Online)

Carotid Artery Disease: Multivariate Analysis of a Single Center in Mexico City

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To cite this article:

Daniel Alejandro Vega-Moreno, José Ramón Aguilar-Calderón, María Elena Córdoba-Mosqueda, Víctor Andrés Reyes-Rodríguez, Mauricio Daniel Sánchez-Calderón, José Omar Santellán-Hernández, Diego Ochoa-Cacique, Carlos Betancourt-Quiroz, Mario Alberto Dueñas-Espinoza, Andrés Alberto Moral-Naranjo, Martha Elena González-Jiménez, Ulises García-González. Carotid Artery Disease: Multivariate Analysis of a Single Center in Mexico City. *International Journal of Neurosurgery.* Vol. 6, No. 1, 2022, pp. 11-18.
doi: 10.11648/j.ijn.20220601.13

Received: March 2, 2022; **Accepted**: April 14, 2022; **Published**: May 10, 2022

Abstract: Introduction. Stroke is the fourth leading cause of death in the United States and the leading cause of disability. Of these, carotid artery disease is responsible for up to 15% to 30% of strokes. The objetive is knowing the risk factors and their impact on four possible scenarios in the diagnosis and treatment of carotid artery disease. 1: significant stenosis measured by ultrasound Doppler carotid, 2: significant stenosis measured by diagnostic cerebral angiography, 3: plaque ulceration measured by angiography, and 4: carotid stent placement. Material and Methods. A retrospective study was carried out with 29 patients, 12 patients to whom was placed a carotid stent and 17 control patients, Odds ratio was calculated for risk factors: high blood pressure, diabetes, cancer, smoking and dyslipidemia. And then multivariate analysis was performed with the same variables. Results. For the risk factors with statistical significance for carotid ulcer were dyslipidemia and cancer, and for stent placement, smoking, and clinically presented as a transient ischemic attack. For the multivariate analysis, the only factor associated with stent placement was smoking. Conclusions. Of the entire range of risk factors associated with cerebrovascular disease, tobacco use is the factor most strongly associated with a patient with carotid disease ending up in endovascular treatment. So prevention or lifestyle modification is the best tool to avoid these outcomes.

Keywords: Carotid Artery Disease, Ulcerated Carotid Plaque, Carotid Stent, Transient Isquemic Attack, Stroke

1. Introduction

Stroke is the fourth leading cause of death in the United States of America and the main cause of disability [1]. In Mexico, the cumulative incidence of cerebrovascular events is 232.3 per 100,000 people, and an approximate prevalence for probable cerebrovascular events of 7.7 per 1,000 people and 5.1 verified cases per 1,000 people [2]. Furthermore, it is considered the fourth cause of death of Mexican women, representing 6.1% of annual deaths, according to data obtained by the National Institute of Public Health in 2019 [3].

More than 80% of strokes are ischemic [4]. Of wich, carotid artery disease (CAD) is responsible for up to 15% to 30% of strokes [5, 6]. To date, there is not, nor is it recommended any imaging study for the screening of asymptomatic individuals in CAD [7].

The risk factors (RF) for CAD are the same known for cardiovascular diseases [8]. Within the RF studied, a prediction model has been proposed, the "Stenosis Score Chart" that considers cardiovascular RF and correlates them with the risk of suffer significant (>50%) and even severe stenosis (> 70%) in asymptomatic patients. However, the power of the study is limited to the percentage of stenosis, without considering carotid plaque ulceration (PCU), or the risk of ending up in medical or surgical treatment [9].

In our study, we performed a RF analysis for CAD, and we also considered the PCU and the possibility of ending up in treatment with a carotid stent (CS). The importance of recognizing plaque instability is due to the fact that ulceration or instability of the carotid plaque has been correlated with symptoms such as Stroke or transient ischemic attack (TIA), even in plaques that cause low-grade stenosis (≤50%) [10].

The risk of stroke among patients with ecollucent or destabilized plaques, regardless of the degree of stenosis, is up to 13% higher than the risk of stroke among patients with significant stenosis (> 50%) and echogenic or stable plaques [11, 12]. Hence the importance of focusing attention not only on detecting the percentage of stenosis, but also on the factors and mechanisms that generate plaque vulnerability.

We performed a univariate analysis by RF and its relevance for 4 possible scenarios: 1, significant stenosis by carotid Doppler ultrasound (CDU), 2, significant stenosis by diagnostic cerebral angiography (DCA), 3, UCP and 4, treatment by CS. Later, a multivariate analysis was performed for the same scenarios.

2. Material and Methods

A retrospective case-control study was realized. All information was obtained from an internal healthcare system. In a period of two years, from 2016 to 2018 a total of 30 patients with the diagnosis of CAD were analyzed, referred by general medicine or neurology departments, as symptomatic CAD (Stroke or TIA) or asymptomatic (non-specific symptoms), All patients over 40 years and patients who had a CDU and DCA study were considered.

2.1. Population

A statistical analysis with measures of central tendency for the variables age, sex and risk factors; as well as the clinical presentation and its association with RF was performed (Tables 1 and 2, Figure 1).

Table 1. *Demographics aspects.*

Universe	Total = 29 pacients	Median (%)
Men	19	65
Women	10	35
IBM Normal	9	31
IBM Overweight	14	48
IBM Obesity grade I	4	13.7
IBM Obesity grade II	1	3.4
Malnutrition	1	3.4
High blood pressure	24	82
Smoke	16	53.3
Dysilipidemia	10	34.4
Diabetes	12	40
Heart failure	6	20
Cancer	5	17.2
Atrial fibrillation	1	3.4
Hypothyroidism	1	3.4

Table 2. *Clinic presentation and risk factors.*

Independent variable / Clinic presentation.	Stroke (n=5)	AIT (n=14)	Asyptomatic/Screening (n=10)
Men	5 (100%)	9 (64%)	5 (50%)
Women	0	5 (35%)	5 (50%)
High blood pressure	4 (80%)	1 (7%)	9 (90%)
Diabetes	2 (40%)	5 (35%)	5 (50%
Dyislipidemia	1 (20%)	6 (42%)	3 (30%)
Smoke	3 (60%)	8 (57%)	5 (50%)
Heart failure	1 (20%)	3 (21%)	2 (20%)
Cancer	0	5 (35%)	0

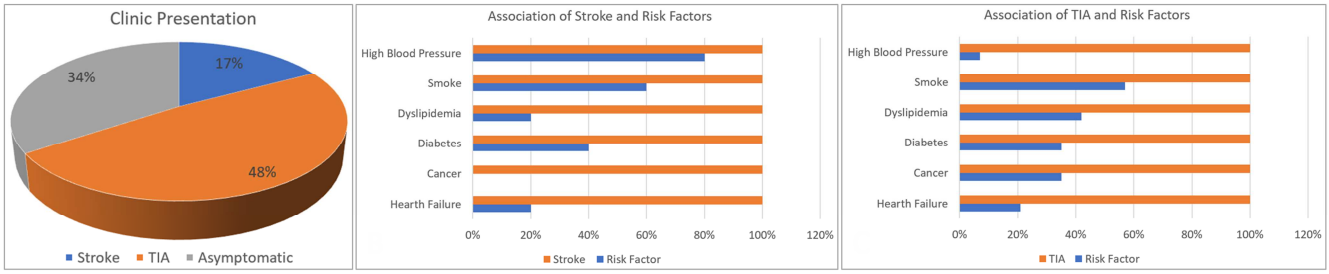

Figure 1. *A. Clinic presentation and referral reason; B. Association of Stroke and RF; C. Association of TIA and RF.*

2.2. Materials

For the RF analysis, a univariate analysis was performed using Cox logistic regression. The factors analyzed individually were:

1. High blood pressure (HBP): defined as a blood pressure greater than 130/80 milimeters of mercury (mmHg) in two different measurements or that were under medical treatment.
2. Diabetes Mellitus (DM): defined as glycated hemoglobin greater than 6.5%, or central glycemia measured twice greater than 125 miligrams/deciliter (mg/dl), or who were under medical treatment.
3. Dyslipidemia: defined as those patients with total cholesterol greater than 200 mg/dl, triglycerides greater than 150 mg/dl, or who were under medical treatment.
4. History of active tobacco use in the last 10 years and at least 5 years.
5. Ischemic heart disease diagnosis and that they were under controlled medical treatment.
6. History in the last 10 years of any kind of cancer.

To obtain the degree of stenosis measured by CDU, it was performed using the Washington method. For the degree of stenosis measured by DCA, it was performed using the NASCET method. The presence of an ulcer due to ACD was defined as: a recess in tangential view or as a double density in frontal projection with the same measurements, 2 millimeters deep and 2 millimeters long.

2.3. Statistic Analysis

The RF were compared for the calculation of Odds Ratio (OR) with four scenarios.

1. the possibility of presenting significant stenosis (> 50%) measured by CDU.
2. the possibility of presenting significant stenosis (> 50%) measured by ACD.
3. the possibility of presenting UCP by DCA.
4. the possibility of have been treated by CS.

Similarly, the clinical presentation (Stroke, TIA or asymptomatic) was evaluated with the same method for the same four outcomes. The results of the univariate analysis are presented in Table 3. For the statistical analysis of Odds Ratio, it was performed using the SPSS IBM version 21 program, with which the confidence intervals (95% CI) were obtained in order to obtain a p <0.05 in all the factors measured.

Subsequently, a multivariate analysis was performed, using a multivariate logistic regression of the same 29 patients for two outcomes: the presence of UCP and placement of SC. For this analysis, were selected those factors that by univariate analysis had yielded a causal relationship.

Therefore, for the multivariate analysis the factors were taken into account:

1. Smoking.
2. Cancer.
3. HBP.
4. Dyslipidemia.
5. DM.

For the UCP scenario, the same five factors were considered. In addition, the Stroke or TIA as a predictor for UCP or for SC placement were jointly analyzed using a bivariate analysis. This analysis was also carried out using the SPSS IBM statistical program, version 21.

3. Results

For the final analysis, one patient was eliminated for not having a CDU, so this analysis was performed with 29 patients. The ages of the patients ranged from 47 to 89 years with a mean age of 71 years. Twelve patients (cases) who were placed SC and 17 patients (controls) who received treatment and medical follow-up due to no indication for endovascular treatment.

Twenty patients with significant stenosis (> 50%) results were obtained by CDU, 12 patients with significant stenosis (> 50%) measured by DCA and 7 patients with PCU, observed by angiography, as well as 12 patients undergoing CS placement. Demographic aspects are presented in tables 1 and 2, and the association of risk factors with the form of clinical presentation. Figure 1.

3.1. Univariate Analysis Results

For the univariate analysis (table 3), the following associations were neatly found for each determined scenario.

1. Scenario 1 (significant stenosis> 50% by CDU): as the only statistically significant factor, DM, with an OR of 12.3 with a CI (95%) of 1.2-118.33, with a p-value <0.5%. Thus, these patients have a 12 times greater risk of presenting significant carotid stenosis measured by CDU if they have the DM factor.
2. Scenario 2 (significant stenosis> 50% by DCA): no statistically significant correlation for this analysis was

obtained.

3. Scenario 3 (UCP demonstrated by DCA): 3 statistically significant factors were obtained: dyslipidemia with an OR of 8.5 (95% CI 1.24 - 57.9) and a p-value <0.05%. History in the last 10 years of cancer with an OR of 28.0, (95% CI of 2.29-128.14) with a p <0.05% and the clinical presentation as TIA, with an OR of 12.87 (95% CI of 1.29-127.14) with a p-value <0.05.
4. Scenario 4 (CS placement). Two statistically significant factors were obtained: smoking, current tobacco consumption, with an OR of 26.4 (95% CI of 2.65-262.69) and a p-value <0.05. And the clinical presentation as TIA, with an OR of 6.75 (95% CI of 1.16-39.19) with a p-value <0.05%.

Table 3. *Univariate analysis. Odds Ratio results.*

Risk factor / OR	Odds Ratio CDU	CI 95%	Odds Ratio ACD	CI 95%
High blood pressure	3.64	0.49-26.7	1.07	0.15-7.64
Smoke	5.05	0.95- 26.6	4.28	0.84-21.76
Dyslipidemia	0.69	0.14-3.4	2.25	0.43-11.52
Diabetes	12.3*	1.2-118.33	1.83	0.40-8.27
Heart Failure	3.21	0.32-32.2	3.75	0.55-25.12
Cancer	0.75	0.10 – 5.43	0.29	0.02-3.04
Stroke	0.75	0.10-5.43	8	0.76-83.87
TIA	2.59	0.51-13.16	1.96	0.38-9.93
Asymptomatic	0.46	0.09-2.22	0.17	0.02-1.06

Table 3. *Continued.*

Risk factor / OR	Odds Ratio UCP	CI 95%	Odds Ratio CS	CI 95%
High blood pressure	1.33	0.12-14.3	0.40	0.05-2.87
Smoke	7.22	0.73-70.2	26.4*	2.65-262.69
Dyslipidemia	8.5*	1.24-57.9	1.71	0.36-8.08
Diabetes	1.08	0.19-6.05	1.83	0.40-8.27
Heart Failure	4.75	0.68-32.71	1.66	0.27-10.09
Cancer	28.0*	2.29-342.15	8	0.76-83.87
Stroke	0.75	0.06-8.08	2.5	0.34-17.94
TIA	12.87*	1.29-128.14	6.75*	1.16-39.19
Asymptomatic	0	0	0.63	0-0.61

* Statistically significant values with a "p" value <0.05.

3.2. Multivariate Analysis Results

For the multivariate analysis (tables 4 and 5) the results were:

Table 4. *Multivariate analysis (MA) for carotid stent.*

Risk Factors / MA	"Beta" value	Standar Error	Significance ("p" value)
Smoke	3.15	1.342	p = 0.009*
Cancer	1.90	1.670	p = 0.245
High blood pressure	-0.695	1.545	p = 0.653
Dyslipidemia	-0.276	1.104	p = 0.802
Diabetes	-0.404	1.130	p = 0.721

*Omnibus tests of model coefficients, chi-square 15.215, with a p-value = 0.009.

Table 5. *Multivariate analysis (MA) for ulcerated carotid plaque.*

Risk Factors / MA	"Beta" value	Standar Error	Significance ("p" value).
Smoke	1.688	1.602	p = 0.292
Cancer	22.224	16360.864	p = 0.999
High blood pressure	20.202	16360.864	p = 0.999
Dyslipidemia	2.112	1.424	p = 0.138
Diabetes	-1.885	1.635	p = 0.249

Omnibus test of coefficients of the chi-square model 17.807 with a p-value = .003.

1. Scenario 1: UCP measured by DCA. All beta-values were obtained above 1, except for the DM (-1.8). However, when demonstrating the veracity of the data, no variable was statistically significant. Therefore, it can be mentioned that in the multivariate adjustment there is no relevant risk factor for the presence of ulcers.
2. Scenario 2: for the CS. The beta-value was obtained again from the 5 RF analyzed, of which smoking obtained a beta-value of 3.5, a standard error of 1.3 and a p <0.009. The rest of the factors yielded statistically non-significant data.
3. Scenarios 3 and 4: the clinical presentation (Stroke and

TIA) and the possibility of presenting PCU or ending in SC were jointly analyzed by means of bivariate analysis, however no relevant or statistically significant data was obtained.

3.3. Result of the Omnibus Test for Model Coefficients

Finally, the omnibus test for model coefficients for the four scenarios in the multivariate analysis, measured by chi-square, were statistically significant ($p < 0.009$ for carotid stent, $p < 0.003$ for UCP, $p < 0.001$ for PCU in association with stroke and TIA and $p < .001$ for CS in association with stroke and TIA) so that all the factors together exert an effect on the dependent variable studied (UCP or CS).

4. Discussion

Pathogenesis underlying the development of plaque is still a matter of study and debate. The predisposition for the formation of atherosclerotic plaque in the carotid artery is attributed to hemodynamic forces. High flow generates a force known as wall shear stress. This force occurs when the normal flow meets a division in its laminar path. What conditions the appearance of secondary flows mainly in the external wall of the vessel [13].

That is, the greatest "stress" or shear force is found on the inner wall, at the division site. However, it causes the tension of the vessel to increase, generating cell alignment and elongation, with subsequent remodeling, the latter appearing on the side walls, conditioning, sometimes, the appearance of stable plaques that generate vessel narrowing [14]. There are multiple associated RF to the formation, remodeling and instability of the carotid plaque, nevertheless, the exact mechanisms of how and how much impact they generate have not been fully explained.

4.1. Smoking

Smoking is a habit prevalent throughout the world, especially among young people and in developing countries [15]. In Mexico, there are 15 million smokers, of which 684 thousand (5%) are adolescents between 12 and 17 years, according to the National Survey of Drug, Alcohol and Tobacco Consumption (ENCODAT) 2016-2017 [16].

It is closely related to inflammatory factors, which play an important role in the pathogenesis of stroke [17, 18]. A linear rise was observed in the incidence of strokes when patients smoke cigarettes, it increases by 12% for an average consumption of 5 cigarettes per day [19].

Furthermore, passive smoking could increase the risk of stroke through multiple mechanisms similar to active smoking; in fact, carotid atherosclerosis has also been associated with passive smoking [20]. As for chronic smoking, it is associated with even endothelial dysfunction, in subjects of a wide age range free of additional cardiovascular risk factors [21]. So far, there are few studies on the relationship between smoking and carotid plaque, as well as its specific mechanisms of involvement [22].

It has been suggested that plaque instability appears to be similar in smokers and non-smokers [23], however something relevant is that the inflammatory response to smoking plays an essential role in the onset and evolution of vulnerable plaque [24]. Some studies found that quitting short-term smoking and the consumption of light cigarettes do not reduce the thickness of the carotid intima-media, and this is related to the vulnerability of the carotid plaque. In a general population, smoking was not associated with an increase in this thickness, although it was independently associated with vulnerability to plaque [22].

4.2. High Blood Pressure

HBP is the most prevalent risk factor for stroke and is therefore considered one of the strongest biomarkers associated with the occurrence of cerebrovascular events [25]. It has been reported in approximately 64% of stroke patients [26]. It is also considered the most important modifiable risk factor for preventing stroke. Controlling BPH has been shown to reduce the incidence of stroke by 30% to 40% [27].

Many studies have said that HBP, DM and others are independent risk factors for carotid stenosis (> 50% stenosis), however these models do not pay much attention to people with a lower level of stenosis (<50%) and with plaque instability [28].

Carotid atherosclerosis was independently associated with variations in blood pressure, especially systolic blood pressure [29]. In particular, BPH has been reported to be an important RF for carotid intimal thickening and plaque development, due to the combined effects of mechanical stress and growth / inflammatory factors on the arterial wall [30].

In hypertension, a statistically significant association has been found between systolic hypertension and the presence of calcifications, macrophages, lipid nuclei > 10% of the plaque area and microvessels, all of which are typical characteristics of vulnerable plaques [31].

Pulse pressure has also been shown to be independently associated with UCP visible on angiography, supporting the hypothesis that cyclical hemodynamic forces are an important determinant of plaque rupture [32].

4.3. Diabetes

DM is an important cause of microvasculopathy and macrovasculopathy, which can lead to inflammation and the formation of atherosclerotic plaques in some organs and systems [33, 34]. The specific effects of DM on carotid remodeling and atherosclerotic plaque composition remain elusive. Although, it is clear that DM is associated with the development of vulnerable plaque regardless of the degree of carotid stenosis [13, 35].

DM was a risk factor for unstable carotid plaque according to univariate analysis [28]. It was found that DM remained significant as a risk factor after adjusting for various cardiovascular RF established in a multivariate regression analysis [36].

Several factors play a role in the formation of vulnerable plaques, including age-associated changes and an increase in the level of glycated hemoglobin [37]. Intraplate neovascularization and UCP have been linked to the progression of atherosclerotic plaque in diabetic patients [38].

In one study (Stijn et al.) was displayed that subclinical carotid atherosclerosis is highly prevalent in patients with DM. In fact, using CDU, subclinical atherosclerosis was demonstrated in 90% of asymptomatic patients but diagnosed with DM, and by carotid ultrasound they revealed that a substantial proportion of the carotid plaques in patients with DM contain intraplate neovascularization and, therefore, vulnerable plaques. Then, the presence of plaque ulceration demonstrated that, in a minority of patients, the plaque surface had ruptured. In the same study, it was demonstrated that UCP, which are markers of the vulnerable plaque type, was detected in 9% of these patients, even in those who were asymptomatic [39].

Patients with DM have different types of carotid plaque compared to individuals without DM. This includes a higher frequency of echogenic and highly calcified plaques. This finding needs to be confirmed but it may well represent a tendency to calcification in these patients [40].

4.4. Dyslipidemia

Hyperlipidemia is a major risk factor for stroke [41]. RF for carotid stenosis are similar to those for other vascular diseases, and the relationship between dyslipidemia and CAD is well known. Elevated levels of serum total cholesterol and low-density lipoprotein cholesterol are established RFs for the genesis and progression of atherosclerotic lesions through various mechanisms [42]. Low-density lipoproteins (LDL) play a central role in this process [13]. Although triglycerides also contribute directly to the development and progression of atherosclerotic plaque, not to its vulnerability [43].

In patients with DM, the progression of carotid stenosis tends to occur more frequently and rapidly when fasting triglyceride levels are higher [44].

In contrast, a study by Mi et al, showed that the control of dyslipidemia in individuals with other RF of stroke may have limited value in the prevention and control of stroke [41]. Therefore, the importance of all the factors and their control is highlighted.

4.5. Cancer

About 15% of cancer patients have concomitant cerebrovascular diseases [45]. Stroke can follow the initial diagnosis of cancer or it can precede the diagnosis of cancerous disease [46, 47]. The most common complication of the central nervous system in cancer patients, after metastasis, are cerebral infarction and hemorrhage [48]. In addition, an increased risk of stroke secondary to CAD has been reported in patients with a history of radiation [49].

The hypercoagulopathy that accompanies cancer and other bleeding disorders are more frequently associated with the development of ischemic stroke [50]. In a cohort study group of 1274 patients admitted with a diagnosis of stroke, 12% had an additional diagnosis of cancer, being urogenital the most common type of cancer [51].

Regarding the pathophysiological mechanisms discussed for the development of cerebrovascular accident in cancer patients, a direct tumor effect, coagulopathy (being one of the main causes) tumor procoagulant activity, as well as adjuvant treatment such as chemotherapy or radiotherapy has been proposed [45].

Radiation therapy and some chemotherapy regimens are known risk factors predisposing to the development of CAD [52]. One study showed increased thickness of the intima-media in most parts of the carotid vessel in adolescents previously treated for cancer and who had survived, even compared to a control group of adults [53].

4.6. Control of Risk Factors

When carotid stenosis is significant (> 50%), the risk of ischemic stroke is doubled, even 3 years after diagnosis. The presence of UCP is associated with an increased risk of stroke, even in patients with stable or non-significant plaques [54]. An up-to-date understanding of the global burden of carotid atherosclerosis is essential to develop effective strategies for prevention and management [55].

5. Conclusions

All the cardiovascular risk factors that have been studied for decades for different heart, cerebrovascular, kidney and even circulatory diseases have significant impacts that annually increase stroke mortality in developed and developing countries. Knowing them is the basis for being able to treat them and anticipate the comprehensive management of these patients.

Tobacco use, as we have seen, is the factor most strongly associated with a patient with carotid disease ending up in endovascular treatment. Therefore, intervening at this point, with changes in lifestyle, as well as timely treatment are the key to the correct management of these patients. It is still unknown how these factors affect the percentage of stenosis and the vulnerability of the plaque, as well as the mechanism by which this happens, however, all of these factors have been shown to infringe the carotid atherosclerotic plaque and them increase the risk of stroke.

Abbreviators

Carotid artery disease (CAD), ulcerated carotid plaque (UCP), carotid stent (CS), transient isquemic attack (TIA), risk factor (RF), carotid Doppler ultrasound (CDU), diagnostic cerebral angiography (DCA).

Acknowledgements

To my family, Leticia, Alejandro and Roberto. Special acknowledgement to Karime Sánchez Gallegos for the final language revision.

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