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# APPROACH TO THE PATIENT WITH DM AND ATHEROMATOUS DISEASE IN OTHER TERRITORIES: CAROTID ARTERIES

## ABORDAGEM DO PACIENTE COM DM E DOENÇA ATEROMATOSA EM OUTROS TERRITÓRIOS: CARÓTIDAS

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## ABSTRACT

Carotid atheromatous disease is responsible for up to 15% of all strokes. Diabetes is one of the most important cardiovascular risk factors for the onset and progression of carotid atherosclerosis. Early control of diabetes and other concomitant cardiovascular risk factors is the most cost-effective intervention to prevent stroke in these cases. Clinical treatment is currently considered the first choice for patients with asymptomatic carotid stenoses. However, in patients with symptomatic stenosis with more than 70% of obstruction, endarterectomy has a high impact on the cardiovascular outcome. The endovascular procedure with stent with filter for neuroprotection is a good option when conventional surgery is not possible.

**Keywords:** Carotid stenosis; Stroke; Diabetes mellitus.

## RESUMO

*A doença ateromatosa carotídea é responsável por até 15% de todos os acidentes vasculares cerebrais (AVC). O diabetes é um dos fatores de risco cardiovasculares mais importantes para o início e progressão da aterosclerose carotídea. O controle precoce do diabetes e dos demais fatores de risco cardiovasculares concomitantes constituem-se na intervenção mais custo-efetiva para prevenir o AVC nesses casos. O tratamento clínico, atualmente, é considerado como primeira escolha para os pacientes com estenoses carotídeas assintomáticas. Entretanto, nos pacientes com estenoses sintomáticas superiores a 70%, a endarterectomia apresenta alto impacto no desfecho cardiovascular. O procedimento endovascular com stent com filtro para neuroproteção é uma opção quando a cirurgia convencional não é possível.*

***Descritores:*** *Estenose carotídea; Acidente vascular cerebral; Diabetes mellitus.*



## CAROTID ATHEROSCLEROTIC DISEASE

Carotid atherosclerotic disease (CAD) is associated with about 15% of all ischemic strokes.[1,2] Diabetes is an independent risk factor for high-grade carotid stenosis.[3]

## PATHOPHYSIOLOGY

Progression of CAD is strongly linked to type 2 diabetes and can be measured by examination of intima-media thickness.[4,5] In a recent study determining the average intima-media thickness, progression of CAD was noted in 87% of patients with type 2 diabetes. This increase in intima-media thickness was most common in patients with low high-density lipoprotein level and associated peripheral arterial disease.[6] Glycemic dyscontrol is an important inducer of atherosclerosis. Overproduction of reactive oxygen species (ROS) induced by hyperglycemia inhibits the action of glyceraldehyde 3 phosphate dehydrogenase (GAPDH), a key enzyme in glycolysis. When free radicals induce DNA breakage, ROS activates the DNA repair enzyme, poly (ADP-ribose) polymerase (PARP). Activated PARP modifies the GAPDH, resulting in endothelial compromise. Endothelial lesion-induced vascular disease related to chronic hyperglycemia results in accelerated atherosclerosis inherent to diabetes.[7,8]

## CLINICAL APPROACH

### Glycemic control

In isolation, an aggressive intervention in blood glucose shows modest effectiveness in reducing major cardiovascular events.[9] A meta-analysis of UKPDS, ACCORD, ADVANCE, and VADT studies with 27,049 participants suggested a small reduction in major cardiovascular events, but no difference in cardiovascular and total mortality.[10] These results lead us to be cautious about the intensification of glycemic control in patients with type 2 diabetes and pre-existing cardiovascular disease. Instead of treating one single factor, intensive intervention should include the management of multiple cardiovascular risk factors. The concept of outcome reduction, through combined actions of cardiovascular prevention, has stood out

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in relation to simple glycemic control. With the emergence of new oral and injectable antidiabetics in the management of type 2 diabetes, the use of older agents when there is a risk of hypoglycemia, such as sulfonylureas and glinides, has fallen out of favor. While metformin and pioglitazone showed cerebrovascular benefits in insulin-resistant patients, SGLT2 inhibitors (empagliflozin and canagliflozin) and GLP1 analogues (liraglutide and semaglutide) have been proven effective in reducing cardiovascular outcomes associated with weight loss and blood pressure level reduction.[11-14] These studies have also shown renal benefits, which can translate into improvement in cardiovascular outcomes in patients with type 2 diabetes and diabetic nephropathy. The LEADER and SUSTAIN-6 studies, with GLP1 analogues, showed reduction in the risk of stroke and cardiovascular events in patients with type 2 diabetes and remarkably high cardiovascular risk. [13,14] The current recommendation is that, in patients with atherosclerotic disease, including carotid stenosis, control of glucose levels should be optimized (Class I, Level C).[15]

### Control of other cardiovascular risk factors

Active and passive smoking are strongly associated with CAD. Current evidence supports the report that smoking cessation is associated with reduced cardiovascular outcomes and especially the prevention of recurrent stroke in patients with carotid stenosis[16,17] (Class I, Level B). In patients with diabetes and CAD, it is recommended to optimize the control of low-density lipoprotein (LDL) cholesterol level (Class I, Level A). In these patients, LDL levels below 70 mg/dL are recommended (Class I, Level C). In patients with diabetes and CAD, it is recommended to maintain the diastolic blood pressure below 85 mmHg. Systolic blood pressure control should be encouraged but with caution in the elderly individuals and in patients with marked carotid stenosis. Systolic blood pressure levels below 110 mmHg were associated with increased cardiovascular outcomes, especially AVCi, in patients with CAD.[18] Studies of the *Heart Outcomes Prevention Trial* (HOPE) and the *Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial* (ONTARGET) showed significant reduction in cardiovascular outcomes in patients with atherosclerosis.[19,20] On the basis of these studies, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers might be considered first-choice options in patients with diabetes and CAD (Class IIa, Level B).[21] The INTERSTROKE study showed that 10 modifiable cardiovascular risk factors relate to 90% of AVCis. In addition to diabetes, the other associated factors were systemic arterial hypertension, dyslipidemia, sedentary lifestyle, smoking, alcohol abuse, diet poor in vegetables and legumes, increased waist and hip circumference, stress/depression, and heart disease.[22] Special attention must be paid to these factors in patients with diabetes and CAD.

## ANTITHROMBOTICS

### Monotherapy

There is no evidence of reduction in cardiovascular outcomes with antithrombotic monotherapy in patients with asymptomatic stenosis greater than 50%.[23] However, patients with CAD have a two-fold risk of acute myocardial infarction.[24] Antithrombotic monotherapy may be performed in patients with asymptomatic stenosis greater than 50% and low risk of bleeding (Class IIa, Level C). In patients with symptomatic CAD, low-dose (100 mg) acetylsalicylic acid is recommended (Class I, Level A). Clopidogrel (75 mg) is an option in cases of intolerance.[25]

### Dual therapy

In the randomized study, *Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance* (CHARISMA), 7% of patients had asymptomatic CAD. In this subgroup, there was no difference in cardiovascular outcomes between monotherapy and dual therapy, even in patients with diabetes.[26] The intervention used in the *Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis* (CARESS) study in patients with symptomatic carotid stenosis showed a 37% reduction in the development of silent microemboli with 7 days of therapy compared to antithrombotic monotherapy.[27] In patients undergoing an endovascular procedure, dual therapy is recommended, with 100 mg acetylsalicylic acid and 75 mg clopidogrel, for at least 30 days after the procedure (Class I, Level B). [28,29]

## SURGICAL AND ENDOVASCULAR TREATMENT

### Asymptomatic CAD

The *Asymptomatic Carotid Atherosclerosis Study* (ACAS) and *Asymptomatic Carotid Surgery Trial* (ACST-1) compared carotid endarterectomy (CE) and clinical treatment in asymptomatic patients with carotid stenosis of 60–99%.[30-32] In the ACAS, the rate of ipsilateral stroke or death in 5 years was 5.1% with CE versus 11.0% with clinical treatment (p=.0001, NNT=18). In 10 years of follow-up, the risk of stroke was 13.4% for CE and 17.9% for clinical treatment (p=.009, NNT=22). ACST-1 reported a 5-year stroke rate of 6.4% for CE and 11.8% for clinical treatment (P=.0001, NNT=19). Fatal/incapacitating stroke developed in 3.5% and 6.1% of patients undergoing CE and clinical treatment, respectively (P=.004, NNT=38). In a combined analysis of these studies, women benefited less from CE.[33] Current data are consistent with a meta-analysis of 41 studies that showed significant reduction in the incidence of stroke in patients undergoing clinical treatment in recent years.[34] In studies completed before the year 2000, the incidence of stroke with clinical treatment was 2.3 per 100 persons per year compared to a rate of 1 per 100 persons per year in studies completed between 2000 and 2010 (p<.001).[35] Despite the significant benefit of CE compared to clinical treatment, the reduction in the risk of stroke was only 4.6% in 10 years.[31,36] Current evidence suggests that the annual incidence of stroke in asymptomatic carotid stenosis is less than 0.5%, which is similar to that observed in patients treated invasively.[34] The presence of contralateral carotid occlusion or more severe stenosis (70–99%) did not increase the benefit of CE when compared to that of clinical treatment.[31, 32, 37] Extremely elderly patients appear to benefit even less from CE, as observed in patients over 75 years of age in the ACST-1 study.[35] For patients with asymptomatic strictures of 60–99%, life expectancy greater than 5 years, risk of complications <3%, and imaging evidence suggesting increased chances

of stroke, CE may be indicated (Class IIa, Level B).[21] The endovascular procedure with *stent* for asymptomatic strictures was compared to CE in five large studies.[38-40] Current data suggest that the endovascular procedure with *stent*, with distal embolization protection, is an alternative to endarterectomy in asymptomatic patients with a periprocedural risk of <3% (Class IIb, Level B).[38-40]

### Symptomatic CAD

Since the publication of the NASCET study, there has been strong evidence to indicate CE in patients with a degree of symptomatic carotid stenosis between 70 and 99% and risk of complications lower than 6% (Class I, Level A, and Class IIa, Level A, for stenoses between 50 and 99%). These recommendations remain despite the fact that clinical treatment has greatly improved over the past 30 years.[41,42] Endovascular treatment with *stent* is an alternative in patients with contraindications to CE. A meta-analysis of symptomatic patients in the CREST, EVA-3S, SPACE, and ICSS studies showed higher stroke rates for up to 30 days with endovascular treatment in patients over 70 years of age. Most strokes were non-disabling. The use of *stent* with embolic protection minimizes that risk.[43-45] For patients with symptomatic carotid stenosis and contraindication to CE, endovascular treatment may be an option (Class IIa, Level B).[44, 46, 47] The precise time to perform CE or endovascular treatment remains controversial, but when they are indicated, they are performed within 14 days after symptom onset (Class I, Level A).[2,48,49] No invasive treatment should be performed in patients with stenoses less than 50% (Class III, Level A).[48]

## IMPACT OF DIABETES ON INVASIVE TREATMENT

Patients with diabetes with symptomatic carotid stenosis greater than 70% have benefited from CE. In patients with diabetes and symptomatic carotid stenosis <70%, the benefit is reduced.[50] A recent study has shown that the presence of diabetes with chronic complications increased the risk of myocardial infarction, stroke, perioperative infection, longer hospitalization, and mortality in patients who underwent CE.[51]

## CONCLUSIONS

Diabetes is associated with atherosclerosis, which is the main cause of CAD. Early diagnosis of CAD in patients with diabetes is of great importance in an aggressive approach to the many modifiable cardiovascular risk factors. In selected patients, an invasive strategy, preferably CE, may prevent recurrent stroke.

## CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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