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FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2019/2020

Mariana Cintra Jordão Carreira

Tratamento da estenose da artéria carótida em pacientes assintomáticos / Management of the carotid artery stenosis in asymptomatic patients

Março, 2020

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Tratamento da estenose da artéria carótida em pacientes assintomáticos / Management of the carotid artery stenosis in asymptomatic patients

Mestrado Integrado em Medicina

Área: Surgery

Tipologia: Monografia

Trabalho efetuado sob a Orientação de:

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E sob a Coorientação de:

Dr. José Paulo Alves Vieira de Andrade

Trabalho organizado de acordo com as normas da revista:

SPCCTV – Sociedade Portuguesa de Cirurgia Cardiotorácica e Vascular

Março, 2020

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Surgery

TÍTULO ~~DISSERTAÇÃO~~/MONOGRAFIA (riscar o que não interessa)

Management of the carotid artery stenosis in asymptomatic patients

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☒
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Faculdade de Medicina da Universidade do Porto, 23/01/2020

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Dedicatória

Chega ao fim mais uma etapa da minha vida, dando início a outra etapa tão ou mais importante. Tudo isso tem sido possível porque tenho comigo os melhores.

Ao Professor Doutor João Neves, as palavras não chegam para descrever todo o apoio incondicional desde o início da realização deste meu trabalho, até este momento. Agradeço todo o tempo e paciência dispensados para a concretização deste trabalho. Agradeço igualmente toda a sua preocupação e profissionalismo demonstrados ao longo destes meses.

Aos meus pais e irmão, quero agradecer por sempre me terem apoiado incondicionalmente, independentemente do rumo que queria tomar na vida. Obrigado do coração por estarem sempre presentes quando mais precisava. Espero que estejam orgulhosos daquilo que consegui alcançar até agora. Muito mais está para vir.

Ao meu melhor amigo, companheiro, namorado… Artur… só tu sabes o que significas para mim. Sem ti, todo este meu percurso não teria sido possível. Foram 5 anos a contar os dias para voltar para casa, para junto de ti. Tudo isto também é teu. É nosso…

Management of the carotid artery stenosis in asymptomatic patients

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Keywords: Carotid endarterectomy; Carotid stenosis; Best medical therapy.

Word Count: 5574

Abstract

Background: Moderate/severe carotid artery stenosis (CS) has a prevalence of 0.3 to 4.5% in women and 0.5% to 5.7% in men. The bifurcation of the common carotid artery turns this area vulnerable to atherosclerosis due to the features of haemodynamic flow. The exact prevalence of asymptomatic patients with CS remains to be unknown and there is a controversial opinion for the treatment of this patients.

Objective: The authors aimed to review the evidence on the management of the asymptomatic CS and describe its clinical characteristics, diagnosis and treatment management.

Results: The majority of patients with asymptomatic CS should be submitted to conservative management with best medical therapy. However, selective surgical management should be considered if high risk features are present.

Conclusion: Medical intervention has an established role in the current routine management of persons with CS. Only extensive information allows tailored evidence-based decision.

Introduction

The scientific and medical community improved the knowledge of pathogenesis, clinical manifestation, diagnosis and mainly treatment of asymptomatic patients with carotid artery stenosis (CS). In this review, for this patients, a detailed description of the present management is presented.

The aim is to guide physicians regarding the evidence behind and the potential efficacy of commonly prescribed regimens at preventing vascular events and pre-specified composite outcomes in patients with asymptomatic carotid stenosis. A comprehensive review of the literature was carried out to collate data from relevant studies in patients with extracranial moderate to severe asymptomatic stenosis.

Research Strategy

The data used were identified by a search using PubMed and Google Scholar with the keywords / MESH terms "carotid stenosis", in combination with the term "asymptomatic". For this study, the authors focused on publications in the past two decades, using english publications.

Epidemiology of carotid artery stenosis

In Europe, stroke is the second cause of mortality (1.1 million deaths/year) being the most frequent cause of death in Portugal [1,2]. 10 to 15% of strokes are due to thromboembolism from a anteriorly asymptomatic significant/severe carotid artery stenosis[3].

The prevalence of moderate/severe asymptomatic CS (moderate stenosis > 50% to <69% of the lumen is narrowed and severe when ≥ 70%) ranged from 0.2 % for women above 50 years old to 5% for women above 80; and 0.1% to 3.1% in men, correspondingly[4]. The annual risk of stroke for patients with severe asymptomatic carotid stenosis is approximately 2 to 5%[5,6,7,8]. It is also known that CS leads to 10% to 15% of all ischaemic strokes, so it is one of the preventable etiologic factors for stroke[9,10,5].

Pathology and Pathophysiology of Carotid artery stenosis

The presence of the carotid bifurcation turns this area vulnerable to atherosclerosis because of the features of haemodynamic flow (*Figure 1*)[11]. The etiology of carotid artery ischaemic stroke is mainly due to atherosclerotic disease of the extracranial carotid which is consequence of an embolic event with the source on atherosclerotic plaque[12].

Atherosclerotic plaques main structure is formed by a lipid core with infiltration of inflammatory cells, coated with a fibrous capsule[11].

Atherosclerotic plaques are present in intimate layer of the arteries and are the result of a complex atheromatous process:

1. ↑LDL with vessel wall penetration.
2. Phagocytosis in the intima.
3. ↑ vascularization.
4. ↑ deposition of calcium and necrotic cells.
5. Fissures, ruptures and hemorrhages of the plaque.
6. Ulceration and/or release of the plaque.
7. Deposition of platelets, blood coagulation, thrombosis and occlusion of the vessel (*Figure 2*)[13,9].

With the progression of atherosclerosis it is eventual and atherosclerotic plaque rupture and thrombus formation resulting in arterial occlusion or emboly[11]. These thrombotic plaques are more often observed in patients with stroke (66.9%) versus TIA (36.1%) and asymptomatic patients (26.8%)[14]. Initially, this occlusion can be partial resulting on transient ischemic attack (TIA), which has similar symptoms to stroke and frequently last less than 24 hours[11].

Regarding molecular pathways, initiation and progression of atherosclerosis are due to reactive oxygen species (ROS)[15,16,11]. ROS increase the expression of ICAM-1 (intercellular adhesion molecule-1), VCAM-1 (vascular cell adhesion molecule-1) and ELAMs (endothelial leukocyte adhesion molecule) which are cell adhesion molecules[17,18]. These molecules allow the monocyte adhesion to endothelial cells. First, mild oxidation of low-density lipoprotein cholesterol (LDL-C) forms MM-LDL (minimally modified LDL) and then severe oxidation of MM-LDL forms LDL (OX-LDL). This increases Monocyte chemo-attractant protein-1 (MCP-1) due to stimulation of endothelial and smooth muscle cells. OX-LDL allows the differentiation of monocyte to macrophage which is promoted by MCSF (monocyte colony stimulating factor)[19]. The new formed macrophages overexpress receptors for

OX-LDL and produce foam cells which is the early stage of atherosclerosis[20]. Moreover, this mechanism also contributes to the instability of the atherosclerotic plaque which leads to thrombosis (*Figure 3*)[21].

This environment increases the expression of growth-regulating molecules PDGF (platelet-derived growth factor), bFGF (basic fibroblast growth factor), TGF-α and TGF-β and cytokines, such as IL-1 and TNF-α, which stimulates the synthesis of connective tissue and matrix. Progression of atherosclerosis are due to these mechanisms[22].

Clinical presentation: signs and symptoms of Carotid artery stenosis

Unstable/vulnerable atherosclerotic plaques are characterized by extensive inflammation and accumulation of macrophages. Unstable plaques are more prone to rupture, leading to thrombotic and/or embolic events[23]. Unstable plaques are characterized by a thin fibrous capsule, less smooth muscle cells, more inflammatory cells and a vast lipid and necrotic core[24]. Hemodynamic stroke, in which the blood flow to the brain is temporarily suspended and then restored due to hemodynamic fluctuation, is a very rare event.

The majority of atherosclerotic plaques are stable and produce no symptoms, however, when the plaque increases considerably, the carotid artery lumen becomes markedly narrowed. An asymptomatic CS is present when a stable atherosclerotic plaque is detected in patients with no history in the past six months of ipsilateral cerebral or ocular ischemic event[25].

It is known that CS is responsible for approximately 50% of TIAs[26]. The risk of having a stroke in the first month after TIAs is over20%[27].

Risk factors

Risk factors for CS are similar to other cardiovascular diseases: dyslipidemia, hypertension, diabetes, advanced glycation end products (AGEs), obesity, cigarette smoking, lack of exercise, age, and C-reactive protein[28,11].

Studies done by *De Weerd M et al.*, referred that cigarette smoking was the main risk factor for CS and increased the prevalence of CS in more than 50%[29]. Despite these various risk factors, the prevalence of severe CS is higher in patients with diabetes (*Figure 4*)[4].

1. Dyslipidemia

Hypercholesterolemia leads to atherosclerosis due to the generation of ROS [30]. However, LDL-C is the major responsible for the development of atherosclerosis due to the effect of LDL and OX-LDL on endothelial NADPH-oxidase leading to ROS production[31]. A meta-analysis, including 165 792 patients, of randomised trials of statins in association with other preventive measures, demonstrated a 21.1% reduction in relative risk for stroke (95% CI 6.3-33.5, p=0.009). This is possible due to reduction of LDL serum levels and the stabilization of the atherosclerotic plaque[32]. Triglyceride (TG) is also a risk factor for atherosclerosis although contributing less[33]. TG can lead to formation of small dense LDL, can reduce HDL levels and increase inflammatory particles, such as ROS[11].

2. Hypertension

Hypertension also contributes to atherosclerosis by similar mechanisms: unbalance of oxidative stress / anti-oxidants with resulting increase of ROS, increase of proinflammatory cytokines (IL-1β, IL-6, and TNF-α), chemokines and cell adhesion molecules (ICAM-1, sE-selectin, and sP-selectin)[34,35].

It is well known that inflammation leads to atherosclerosis and the best marker of this association is the C Reactive Protein [36]. *Kitiyakara C et al.* refers that increase of ROS precedes the progression of hypertension[37].

3. Cigarette smoking

The prevalence of symptomatic CS is 4.4% in never-smokers versus 7.3% in former smokers versus 9.5% in current smokers. Furthermore, studies refer that smoking 20 pack-years has a significant correlation. Nevertheless with lower amounts of cigarette smoke, no significant association was found[38]. So, similar to other risks factors, cigarette smoking contributes to atherosclerosis by increasing expression of ROS, vascular cell adhesion molecules and proinflammatory cytokines[39]. Serum levels of Advanced Glycation End-products are also increased in cigarette smokers and their interaction with their receptor (RAGE) increases the production of ROS, activates NF-kB and vascular cell adhesion molecules and proinflammatory cytokines[40,41].

4. Diabetes

Hyperglycemia promotes atherosclerosis due to diverse mechanisms such as oxidative stress, AGEs, and protein kinase C. Oxidative stress leads to atherosclerosis mainly due to mitochondrial mechanisms in which hyperglycemia metabolism leads to reduction of NADPH and activation of NADPH-oxidase which contributes to oxidative stress[42,43]. Finally, hyperglycemia leads to activation of DAG (diacylglycerol) which promotes the development of atherosclerosis by activating the pathway of Protein Kinase C [44].

5. Age

The prevalence of CS under 60 years is 0.5% versus <5% above 80 years old. Men under 75 years old have more chance of having CS than women with the same age. Although, after 75 years old, women have more chance of having CS than men[11].The mechanism involved is probably due to increase of inflammatory markers which are naturally increased with aging.

6. Obesity

Obesity is considered an independent risk factor for CS although being also a risk factor for diabetes, hypertension and insulin resistance [45,46].

7. C-Reactive Protein

High sensivity CRP is a proinflamatory protein that increases the production of ROS over activation of neutrophils. So, this marker it is correlated with higher risk of stroke[47]. Other mechanisms includes increased expression of vascular cell adhesion molecules and foam cell formation[48].

Classification and Diagnosis in CS

The majority of plaques responsible for ischemic events are moderate, however there are some high-grade plaques which increase the probability of having a stroke. Thus, the majority of atherosclerotic plaques are stable/asymptomatic[49], however, a study done by Anxin Wang *et al*, concluded that in patients with metabolic syndrome, or its components increased the prevalence of unstable plaque though the more prevalent are the stable plaque[50].

It is of the most relevance in patients with asymptomatic carotid stenosis, to determine the clinical and ultrasonographic plaque predictors of progression or regression of the stenosis. In a study, 1121 patients with asymptomatic carotid stenosis were submitted to several clinical and ecografic assessments during 6 months and 8 years (respectively). Regression was observed in 43 patients (3.8%) and progression in 222 (19.8%). No changes were observed in 856 patients (76.4%). Independent predictors of long term stability were: younger patients, more severe degrees of stenosis, absence of white areas in the atherosclerotic plaque and patients under lipid lowering therapy [51]. Independent predictors of progression were: high

serum levels of creatinine, male gender, patients not under lipid lowering therapy, less severe degrees of stenosis and larger plaque area[51].

However, the clinical value of doing this prediction is limited due to the low frequency of progression (only 19.8% of the patients) and the low associated stroke rate (only 30% of the 30 strokes were in the progression group)[51]. Recent recommendations advocate the increase in the cut-off for surgical intervention (>80%), though the risk increases with degree of stenosis, studies do not support or validate this approach.

The classification of CS can be determined mainly by two methods: NASCET (*North American Symptomatic Carotid Endarterectomy Trial*) and ECST (*European Carotid Surgery Trial*). NASCET is based on distal grade of stenosis while ECST is based on local grade of stenosis[52]. Despite the existence of this two methods, the standard is NASCET method, although ECST can be used moreover[52].

Despite this, *Guidelines 2018 of ESVS* doesn't recommend population screening for asymptomatic patients with CS. Furthermore, *The Society for Vascular Surgery* recommends that this routine screening should only be done in patients with multiple risk factors[53].

Treatment indications for Asymptomatic CSS

Independently of asymptomatic or symptomatic patients with CS, the core treatment is based on controlled of cardiovascular risk factors. However, some of these risk factors are modifiable (CRP, diabetes, obesity, hypertension, smoking, dyslipidemia) but others are not manageable[11].

Lifestyle changes are paramount in the delay of the progression of CS. *Guidelines* recommend: DASH diet (vegetables, fruits, fish) and/or Mediterranean diet (same but with addiction on olive oil), weight reduction (body mass index <25), regular physical exercise (at least 40 min 3/4 times a week), limited consumption of alcohol and sodium (salt restriction to 2–3 g/day of salt), tabagic cessation[54,55,56,57,58].

A study done by *Chiuve SE et al.*, concluded that if all these lifestyle changes were adopted, the risk of stroke could be reduced by approximately 80%, among women[59]. *de Lorgeril M et. al.*, refer that with Mediterranean diet it is possible to reduce the probability of developing a stroke and/or myocardial infarction (about ≥60% chances), if secondary prevention is adopted[60]. However, if primary prevention is adopted, stroke can be reduced by 50%[55].

The management of patients with asymptomatic CS has some debatable aspects due to the annual risk of stroke for patients with severe asymptomatic carotid stenosis is reduced to 2%-5%[5,6,7,8]. Additionally, scientific evidence has proven over the years that medical therapy is decreasing the risk of stroke[61].

For asymptomatic patients with CS < 60%, medical treatment alone is favoured and for asymptomatic patients with CS > 60%, invasive treatment is considered[62,63]. To warrant that the intervention is superior than the isolated best medical treatment, recommendations state that the perioperative risk of stroke in asymptomatic patients with CS should be inferior to 3%[64]. Selected patients on best medical therapy, with clinical and/or imaging features that classify them as having higher probability of suffering a stroke, benefit from surgical procedure. Moreover, the patients that in the present are being treated with best medical therapy and don't benefit from surgical procedure, should be follow with regular carotid ultrasonography[53].

Treatment of Asymptomatic patients with CS

1. Pharmacological agents:

These patients must be treated with intensive medical treatment which is meant to correct the risk factors mentioned previously. If these risk factors can be controlled, the probability of developing a stroke will be lower[65].

1.1. Lipid lowering agents: *Guidelines 2018 of ESVS* recommend high dose statin therapy for primary and secondary prevention. *Asymptomatic Carotid Surgery Trial (ACST-1)* presents results for 10- year risk of stroke/death for asymptomatic patients taking lipid lowering agents (statins) of 13,4% while in patients without taking statins, was 24.1%[66]. Atorvastatin and rosuvastatin are the two pharmacological agents with more support on evidence in reducing LDL to less than 70 mg/dl and also decreasing the levels of CRP to less than 2 mg/l. These results support the use of statins as primary prevention of stroke. The major therapeutic target is to obtain, at least, 50% reduction of the initial value of LDL or reach the value of less than 1.8 mmol L^{-1} (70 mg dL^{-1})[53,67].

1.2. Antihypertensive agents: *Law MR et al.*, refers that a decrease in stroke risk was related to a decrease of systolic blood pressure[68]. *Huo Y et al.*, in 2015, found out that enalapril and folic acid (despite enalapril alone) can reduce the risk of developing a first stroke, so they concluded that enalapril is the pharmacological agent with more evidence on hard outcomes in asymptomatic patients with CS[69]. The major goal in non-diabetic patients is to

reduce arterial blood pressure to 140/90 mm Hg or less while in diabetic patients is 140/80 mm Hg(*Guidelines of hypertension 2018*)[70]. Besides this, if a procedure is to be executed, the perioperative goal is less than 180/90 mm Hg[71].

1.3.<u>Antiplatelet therapy:</u> Inadequate antiplatelet therapy can lead to a greater risk of developing major bleeding events, while not decreasing stroke risk. So, the benefit versus harm has to be carefully measured in every single patient. Thus, the actually scientific evidence recommends that monotherapy with aspirin (instead of dual therapy) is the first option, while clopidogrel is reserved for patients who have contraindications to aspirin. The dose of aspirin should be between 75-325 mg (low-dose aspirin) and 75 mg of clopidogrel (recommendations by *ESVS 2018*)[71].

2. Carotid Endarterectomy (CEA) - surgical procedure

In some patients, it is hard to decide if medical therapy is enough or if a surgical procedure-CEA is necessary. So, a multiple analysis must be developed with the main goal of evaluating the overall risk of that asymptomatic patient posteriorly suffer a stroke. Thus, there are some clinical predictors that may help in the decision such as: age, gender, stenosis severity, progression of stenosis, plaque characteristics, presence of silent emboli and/or microemboli and cerebrovascular reserve.

2.1. <u>Age:</u> Some studies concluded that, despite the age of the patient, it is beneficial to undergo CEA because the risk of suffering a stroke in the next 5

years was lower than with medical therapy. However, further studies refer that half of these patients with more than 75 years old, were dead in the long term follow-up after intervention. Furthermore, after these studies included the perioperative risks, it was concluded that reduced benefit of undergoing CEA in patients older than 75 years[66]. However, in patients with more than 75 years old and with an average life expectancy higher than 5 years old, CEA may be beneficial[71].

2.2.<u>Gender:</u> Multiple studies were performed and concluded that the probability of suffering a stroke within 5 years is decreased by CEA in men but not in women. Women would benefit from CEA only after 10 years of follow-up. This controversial finding is justified by the inherent risk of suffering a stroke without undergoing CEA is lower in women, so it is expected that the benefit need more time to be apparent[72,66].

2.3.<u>Stenosis severity</u>: Despite what happens in symptomatic patients, stenosis severity is not a predictor of future stroke in asymptomatic patients with CS.[63,73]. They also found that patients with 50-69% stenosis has a lower risk of suffering a stroke compared to patients with more than 70% stenosis (0.8% vs. 1.4%)[74]. So, to make the decision of doing CEA, stenosis severity should be conjugated with other clinical features and not considered alone[75]. *Hobson R. W. et al.*, refers that with the presence of low-grade CAS in asymptomatic patients, the best choice of treatment is intensive medical treatment[65].

2.4.Progression of stenosis: *ACST* found out that the patients with stenosis that had developed in two grades, had four times more probability of suffer an ipsilateral neurologic event[76].

2.5.Plaque characteristics: DUS can characterize the atherosclerotic plaques with, for example, the observation of ulceration. That characteristic indicates that the atherosclerotic plaque is unstable, so the probability of developing a thromboembolic event is higher. Furthermore, the risk is also higher if plaque is echolucent and with more lipids than fibrotic components[77,78].

2.6.Presence of silent emboli and/or microemboli: Moreover, the identification of features of the atherosclerotic plaque, CT (computed tomography) or MRI (magnetic resonance imaging) can be performed to identify silent emboli and transcranial doppler (TCD) to identify microemboli. This could be relevant because their presence perhaps can predict the increase of developing a ipsilateral stroke[79,80].

2.7.Cerebrovascular reserve: A reduced cerebrovascular reserve occurs when an incomplete circle of Willis is present or when intracranial or contralateral occlusive disease is present. This situation reduces cerebral perfusion pressure and is defined by transcranial doppler flow on cerebral vessels. According to *Gupta A. et al*., there is a significant association with a reduced cerebrovascular reserve and stroke[81].

So, with the integration of this clinical features it is more possible to select an high risk patient with asymptomatic CS which benefit fromCEA[82,83]. And, as *AHA (American Heart Association)* recommends, only this type of patients should be treated with CEA.

Conclusion

With current best medical therapy, asymptomatic patients with CS have an annual risk of ipsilateral stroke of approximately 0.5%[84]. So, the main goal is to promote the control of risk factors[11].

Due to elevated mortality and morbidity associated with CS, over the years, the identification of high risk asymptomatic patients with CS has become one of the major goals in vascular surgery. The timely identification leads to timely treatment and this will lead to a decrease in morbidity and mortality[12].

Guidelines 2018 of ESVS recommend that multidisciplinary team (MDT) should be present and it should be composed by neurologists and vascular surgeons. This will allow an optimal treatment in patients undergoing CEA[71].

Selim M H et al., referred that medical treatment is more cost-effective than CEA and approximately only 50% of the patients benefit from CEA[85].

The management of asymptomatic patients with CS remains a challenge, but it is already known that medical and surgical treatment are developing faster and in the future stroke risk will continue to decrease[86].

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Anexos

Normas de Publicação de Trabalhos da Revista da *SPCCTV – Sociedade Portuguesa de Cirurgia Cardiotorácica e Vascular*

Consultado e retirado no site do respectivo link https://www.spcctv.pt/revista/normas.html no dia 03/02/2020.

"A Revista da SPCCTV destina-se à publicação de artigos originais nos campos da Cirurgia Cardiotorácica e Vascular. Os manuscritos serão revistos pelos Editores e por revisores externos, e a sua aceitação dependerá do seu interesse, originalidade e validade científicas. A língua oficial da revista 'e o Português, mas a submissão de Artigos Originais, Artigos de Revisão, Casos Clínicos e Imagens em Cirurgia integralmente em língua Inglesa 'e fortemente recomendada. Caso desejem, os autores podem enviar uma versão em Inglês (para indexação) e outra em Português, para a revista impressa. E obrigatória a submissão dos resumos em Inglês.

Artigos

São aceites submissões nas seguintes categorias:

Tipo de Artigo	Limite de palavras	Nº Máximo de Autores	Nº Máximo de referências	Nº Máximo de tabelas e figuras
Artigo Original	5000	8	25	8
Artigo de Revisão	s/limite	8	s/limite	s/limite
Caso Clínico	1000	5	10	4
Imagens em Cirurgia	50	4	0	2
Carta ao Editorial	850	4	8	2
Editorial	1000	2	10	2

A contagem de palavras deve incluir resumo e bibliografia, excluindo legendas e tabelas.
A cada edição, uma imagem seleccionada figura na capa da revista impressa.
Os editoriais apenas podem ser submetidos mediante convite do corpo editorial.
As Cartas ao Editor, Imagens em Cirurgia e Editoriais dispensam o envio de Resumo.

Formatação

A submissão devera ser feita integralmente em formato electrónico. Os ficheiros de texto devem ser submetidos em formato *Word*, com páginas numeradas no canto inferior direito, tipo de letra *Times New Roman*, tamanho 12, duplo espaço e justificados. As imagens devem ser submetidas em ficheiros individuais, em formato .*tiff*, com uma definição mínima de 300dpi.

Elementos Obrigatórios

A. Carta de Submissão

Os manuscritos devem ser acompanhados de uma Carta de Submissão que terá de incluir:

- Declaração de originalidade.
- Concordância de todos os autores com o teor do artigo e aprovação da versão final.
- Transferência da propriedade intelectual para a Revista.
- Declaração da presença ou ausência de conflitos de interesse. Se existentes, os Autores devem revelar as relações comerciais com tecnologias em estudo, as fontes de financiamento, a sua filiação Institucional ou Corporativa, incluindo consultadorias.
  Nota: Os Autores poderão ser responsabilizados por falsas declarações.

B. Página de Título

Esta deve incluir o Título sem abreviações e em Maiúsculas; o nome e apelido dos autores e o(s) nome(s) e local(ais) da Instituição(ões) de afiliação de cada autor. O nome, endereço, telefone e email do autor correspondente, deve ser inscrito no fundo da página de título. No caso do manuscrito ter sido apresentado nalguma Reunião, esta deve ser discriminada juntamente com a data de apresentação. A contagem total de palavras do artigo (incluindo os resumos, mas excluindo tabelas, figures e referências) deve ser referida.

C. Resumo (Abstract)

O Resumo, por ser a secção mais lida de todos os artigos, é fundamental. Deve ser factual, sem abreviações (excepto unidades do SI). Deve incluir o Titulo e Autores, e ser estruturado em Objectivos – problema em estudo ou objectivo do estudo, Métodos, explicando como o estudo foi realizado, Resultados, revelando os dados encontrados e sua importância e Conclusão, revelando a conclusão do estudo. O limite máximo de palavras no resumo é 250.

D. Texto

O texto deve ser organizado nos seguintes elementos:

Introdução: deve revelar o objectivo da investigação e fazer uma revisão bibliográfica curta do estado da arte em relação ao problema em estudo.
Material e Métodos: estes devem ser descritos em detalhe com a informação adequada sobre Estudos Humanos ou Animais como atrás referido. O uso de abreviações deve ser limitado às unidades de medida do SI ou às de uso comum. As tecnologias devem ser nomeadas através do seu nome genérico, com o seu nome comercial, nome e local do fabricante entre parêntesis. As técnicas estatísticas de análise de dados devem ser descritas em detalhe.
Resultados: estes devem ser considerados a parte mais importante do artigo. Por tal, é importante que sejam descritos de forma concisa mas simultaneamente realçando os todos os resultados de forma completa, através de tabelas ou figuras, incluindo os comentários dos autores no texto.
Discussão: a discussão deve ser clara e breve, devendo incluir a interpretação da significância dos resultados e da sua relação com outros trabalhos publicados na mesma área. A importância dos resultados e as limitações metodológicas, se existirem, devem ser enunciadas.
Agradecimentos: a existirem, devem ser referidos no final do texto.
Referências: devem ser apresentadas sequencialmente de acordo com a ordem de uso no texto e apresentadas como números entre parêntesis rectos. Comunicações pessoais e dados não publicados não devem ser incluídos na lista de referências, embora possam ser referidos no texto. Nas referências

todos os autores devem ser referidos e os jornais ou revistas apresentados de acordo com as abreviações usadas no *Index Medicus*. As referências devem ser apresentadas do seguinte modo:
Revistas [1] Dinis da Gama A, Perdigão J, Ministro A, Evangelista A, Damião A, Garcia Alves A. *The utilization of the "simplified technique" in the simultaneous management of independent thoracic and abdominal aortic aneurysms.* A clinical report. RevPort Cir Cardiotorac V 2009;3:149 155.

Livros [2] Antunes M J. A Doença da Saúde. Lisboa: Quetzal 2001:167- 176. Vários Autores [3] Fragata J, Martins L. Como evitar o erro em Medicina. Em: Fragata J, Martins L, autores. O Erro em Medicina. Lisboa:Almedina, 2008:313-348. Publicações Online (O DOI é referência obrigatória e a única necessária para citações de artigos de publicações online)

Publicações Online (O DOI é referência obrigatória e a única necessária para citações de artigos de publicações online) [4] Azevedo O, Almeida J, Nolasco T, Medeiros R, Casanova J, Bartosch C, Almeida J, Pinho P. Massive right atrial myxoma presenting as syncope and exertional dyspnea: case report. Cardiovascular Ultrasound doi:10.1186/1476-7120-8-23.

E. Tabelas

As tabelas devem ser numeradas de acordo com a sequência de aparecimento no texto, e enviadas num ficheiro conjunto a parte do texto, em formato *Word*. Devem incluir numero e cabeçalho, assim como legenda se necessária.

F. Cabeçalho e Legendas de Figuras

O cabeçalho e legendas de figuras devem ser entregues num ficheiro conjunto à parte do texto, em formato Word, mencionando o número correspondente ao ficheiro de imagem enviado.

G. Figuras

As figuras devem ser numeradas de acordo com a sequência de aparecimento no texto, e enviadas em ficheiros individuais, referenciando o

respectivo número. Apenas são aceites ficheiros em formato *.tiff* com um mínimo de 300dpi.

Submissão Eletrónica

A submissão electrónica de manuscritos deve ser realizada para: manuscritos.revista@spcctv.pt.
Apenas são consideradas validas as submissões que cumpram as regras anteriormente descritas. Após a submissão, os Editores confirmarão a boa recepção do manuscrito junto do autor correspondente.

Manuscritos aceites para revisão

Os manuscritos revistos devem ser enviados convenientemente titulados – revisão1, revisão2, etc, incluindo novas figuras e tabelas caso necessário. Os comentários dos editores e/ou revisores devem ser discutidos ponto a ponto numa carta anexa e as alterações propostas discutidas. As alterações devem ser visíveis utilizando a função "*track changes*" do Word."

Figures

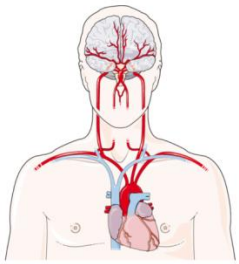

Figure 1. Anatomy of carotid arteries.

https://smart.servier.com/

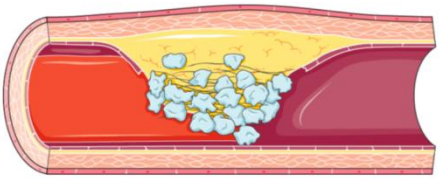

Figure 2. Atherothrombosis.

https://smart.servier.com/

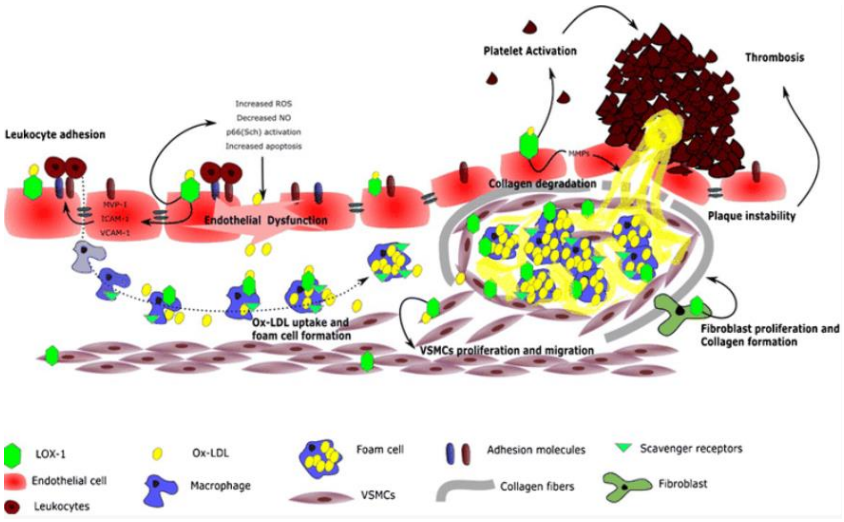

Figure 3. Molecular mechanism of atherosclerosis and posterior thrombosis[21].

Mehta AJKVKPPL. Oxidative Stress in Atherosclerosis. Genet Genomics. 2017.

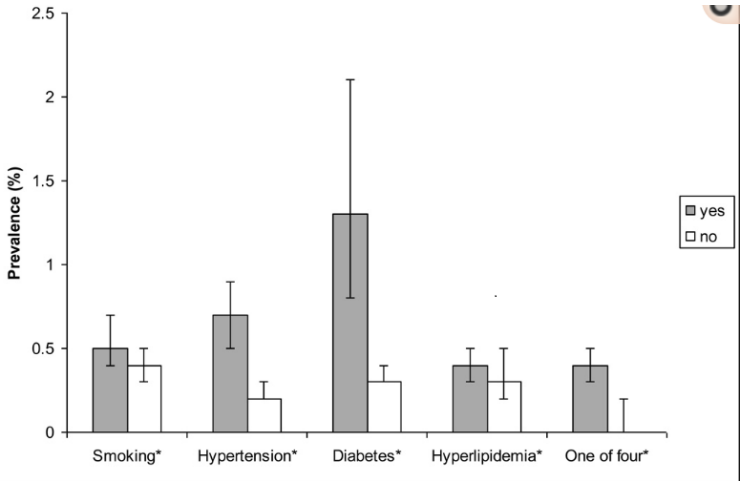

Figure 4. Prevalence of severe CAS risk factors[4].

M. de Weerd, J.P. Greving, B. Hedblad, M.W. Lorenz, E.B. Mathiesen, D.H. O'Leary, , M. Rosvall, M. Sitzer, E. Buskens and MLB. Prevalence of asymptomatic carotid artery stenosis in the general population: an individual participant data meta-analysis. Stroke. 2010;41:1294-1297.