Contemporary medical management of carotid artery disease

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Abstract

Contemporary medical therapy consists of treating all the patient's modifiable vascular risk factors and instituting therapy designed to reduce the risk of thrombosis and the progression of atherosclerosis in order to reduce the risk of future cardiovascular events. Contemporary medical management emphasises the need to support the patient in achieving life-style modifications and to adjust medication to achieve individualised target values for specific quantifiable risk factors. Antiplatelet therapy in the form of aspirin or clopidogrel is routinely used for the prevention of ischaemic stroke in patients who have had a TIA or stroke. There is evidence from a recent trial that the use of combination antiplatelet therapy with aspirin and clopidogrel started within 24 hours of minor stroke or TIA reduces the risk of recurrent stroke compared to the use of aspirin alone and we therefore use aspirin plus clopidogrel in recently symptomatic patients with carotid stenosis pending carotid revascularisation. Anticoagulation with heparins or vitamin K antagonist is not recommended except in patients at risk for cardio-embolic events. Lowering blood pressure to target levels has been shown to slow down the progression of carotid artery stenosis and reduces the intima-media thickness of the carotid plaque, while lowering lipid levels with statins has become an essential element in the medical therapy of carotid artery stenosis. Diabetes management should be optimised. Lifestyle choices including tobacco smoking, physical inactivity, unhealthy diet, obesity, and excessive alcohol intake, are all important modifiable vascular risk factors. The combination of dietary modification, physical exercise, and the use of aspirin, a statin and an antihypertensive agent can be expected to give a cumulative relative stroke risk reduction of

80%. The evidence suggests that intensive medical therapy is so effective that carotid revascularisation may no longer be necessary in many of the patients in whom carotid surgery or stenting is currently performed. Two large on-going trials are therefore comparing the risks and benefits of carotid revascularisation versus intensive medical therapy alone.

Introduction

Medical management plays an important role in the prevention of ischaemic stroke and other cardiovascular diseases in patients with atherosclerotic carotid artery disease. Optimising the management for each individual can be challenging, but small changes in therapy can substantially reduce the risk of recurrent ischaemic stroke. Therefore, it is important that every patient found to have carotid atherosclerosis has an individualised optimum management plan instituted to lower the risk of stroke. This chapter will describe the current concept of modern medical therapy in carotid artery disease in four different sections: the content of medical therapy, the evidence supporting the effect of medication and life style changes, the current recommendations in three different guidelines, and ongoing clinical trials regarding this topic.

Contemporary medical therapy consists of treating all the patient's modifiable vascular risk factors and instituting therapy designed to reduce the risk of thrombosis and the progression of atherosclerosis in order to reduce the risk of future cardiovascular events.[1,2] The main modifiable factors accounting for the development of atherosclerosis in the carotid artery are hypertension, diabetes mellitus, dyslipidaemia, obesity and smoking.[3] Anti-thrombotic therapy reduces the risk of embolization of the carotid plaque and is also considered an important component of medical therapy in carotid stenosis.[4]

In the past, there was a tendency for physicians to recommend life style changes and drug treatment for vascular risk factors without closely monitoring the patient's compliance or response to treatment. However, contemporary medical management emphasises the need to support the patient in achieving life-style modifications and to adjust medication to achieve individualised target values for specific quantifiable risk factors e.g. hypertension. The success of this approach of intensive or so-called 'aggressive' management of vascular risk factors is best exemplified by the results of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial.[5,6] In this trial, patients with recent transient ischaemic attack (TIA) or stroke related to 70–99%

intracranial stenosis secondary to atherosclerosis were randomly allocated to intracranial stenting with intensive medical therapy with versus aggressive medical therapy alone. Aggressive medical therapy included dual antiplatelet therapy with aspirin and clopidogrel for 90 days after randomisation, antihypertensive medication adjusted to achieve a systolic blood pressure lower than 140 mmHg, and statin therapy to achieve a low-density lipoprotein cholesterol target less than 1·81 mmol/L, with repeated advice on smoking, weight control, and exercise. In the group of patients receiving medical therapy alone, a much lower stroke rate occurred compared to a previous study done by the same group of investigators in similar patients. In the earlier trial, the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial,[7] a 30-day rate of stroke or death of 10.7% with a 1-year rate of 25% was recorded with medical therapy alone. In SAMMPRIS, patients randomised to aggressive medical therapy alone had roughly half the rates of events as in the earlier trial with a 30-day rate of stroke or death of 5.8% and a 1-year rate of 12.2%. It is likely that similar benefits could be achieved with intensive treatment regimes in patients with atherosclerosis at other sites, including the carotid artery.

The evidence for the benefits of medical therapy in carotid artery disease

Medical therapy for carotid stenosis has improved over time, with more understanding of the effect of antithrombotic medication on the prevention of cardiovascular diseases, lower targets for blood pressure control and the addition of statins to the medical therapy. The literature has multiple conducted clinical trials in this topic and the evidence is growing progressively.

Antiplatelet therapy in the form of aspirin or clopidogrel is routinely used for the prevention of ischaemic stroke in patients who have had a TIA or stroke. The combination of dipyridamole and aspirin is sometimes used as an alternative. The clinical trial known as PRoFESS conducted by Sacco et al.[8] showed that the effect of clopidogrel alone in on the rates of recurrent stroke is similar to the combination of aspirin with dipyridamole in patients with pervious stroke. Similarly, the MATCH study showed when treatment was started at a mean of 27 days after stroke or TIA, the combination of aspirin and clopidogrel was not superior to clopidogrel alone, and had a higher risk of a major bleeding with the addition of aspirin.[9] In contrast, in the CHANCE study when combination antiplatelet therapy was started within 24 hours of minor stroke or TIA and continued for 21 days, combined aspirin and clopidogrel reduced significantly reduced the risk of recurrent stroke compared to the use

of aspirin alone.[10,11] Dual antiplatelet with low-dose aspirin and clopidogrel has also been shown to be beneficial in coronary heart disease.[12-14] However, current guidelines for the treatment of acute stroke and TIA do not seem to have kept up with this evidence, and most still recommended either aspirin alone, aspirin with dipyridamole, or clopidogrel alone. No large trials have examined the individual benefits of antiplatelet therapy specifically in patients with carotid disease. However, we use the combination of aspirin plus clopidogrel in patients with acute minor stroke and TIA pending carotid revascularisation, as long as the patient does not have an increased risk of bleeding. This combination is then continued for up to 3 months after revascularisation, especially in patients who have had carotid stenting.

Antiplatelet therapy seems not to be effective in preventing cerebral ischaemic events in patients with asymptomatic carotid stenosis, but only one randomised trial has specifically examined this indication.[15] However, antiplatelet therapy is currently recommended in these patients to prevent myocardial infarction.

Unfractioned heparin or low-molecular-weight heparin is not recommended as routine treatment to prevent recurrent stroke because several trials have shown no benefit in the acute situation compared to aspirin therapy. Similarly, oral anticoagulation with vitamin K antagonist is also not recommended in patient with stroke or TIA of non-cardiac origin because trials have shown that anticoagulation is not superior to aspirin in the prevention of long-term stroke recurrence and carries a substantial risk of haemorrhage.[16] Vitamin K antagonists are only recommended in patients at risk for cardio-embolic events e.g. those with atrial fibrillation.[17]

The management of blood pressure has also improved over the last few years due to the availability of different types of anti-hypertensives to achieve lower target blood pressure levels in individuals. Lowering the blood pressure to target levels is shown to slow down the progression of carotid artery stenosis and reduces the intima-media thickness of the carotid plaque.[18,19] However, it is important to manage the blood pressure at a proper range as a too low blood pressure of <110/70 mmHg and a too high blood pressure of >140/90 mmHg are also associated with stroke.[20]

Lowering lipid levels with statins has become an essential element in the medical therapy of carotid artery stenosis. This was evident after the publication of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial[21], which randomly allocated patients with recent stroke or TIA to a high dose of atorvastatin versus placebo. Patients

receiving atorvastatin had a reduction of future stroke risk of 16%.[21] According to a systematic review, this effect is mainly caused by the reduction of LDL-cholesterol.[22] In addition, the use of statins can evidently improve carotid atherosclerosis by inducing a decrease in plaque inflammation and size and slowing down the progression of the atherosclerotic disease.[23,24]

Diabetes is strongly associated with the development of atherosclerosis in the carotid artery,[25] and also increases the risk of stroke.[26,27] A recent cross-sectional study of 1475 persons randomly selected from a normal population, has shown that the glycaemic status is associated with the presence of carotid atherosclerosis.[28] The prevalence of significant carotid stenosis of the persons previously diagnosed with diabetes mellitus was 7.7% in this group, compared to 0.3% in persons with a normal glucose tolerance. Several studies have shown that antidiabetic medication slows the progression and regresses carotid atherosclerosis.[29,30]

Lifestyle choices including tobacco smoking, physical inactivity, unhealthy diet, obesity, and excessive alcohol intake, are all important modifiable vascular risk factors. Tobacco smoking for instance, increases the relative risk of ischaemic stroke by up to 50%.[31] A quantitative modeling study based on a comprehensive review of the meta-analyses of the effect of combined secondary prevention strategies conducted by Hackam and Spence, concluded that the combination of dietary modification, physical exercise, and the use of aspirin, a statin and an antihypertensive agent could give a cumulative relative stroke risk reduction of 80%.[32] The authors reported that the lifestyle risk factor with the largest impact on future stroke is a change in the diet, reducing the risk by 44%, but the review did not take weight loss or the effects of reducing alcohol intake into account. However, it is possible that the benefit of changes in diet was achieved by weight loss rather than the components of a healthy diet. Not many studies have reported the effect of changes in body weight on the risk of cardiovascular events. In practice, it is not only difficult to modify a patient's diet, but it is also relevant that any change in the diet (a reduction of saturated fats or a reduction of total energy consumption) does not result in a large reduction in cholesterol levels compared to statin therapy.

It is well known that obesity is associated with a higher risk of developing diabetes mellitus,[33] but it is also known that obesity can induce hypertension.[34] Both diabetes and hypertension are risk factors for the development of atherosclerosis and therefore maintaining a normal weight should be encouraged in patients with carotid artery stenosis. Heavy alcohol intake of

more than 5 units or more than 60 gram per day is associated with an increased risk of stroke of any type.[35] The same study also showed that light intake of alcohol of 1-2 units or 12-24 gram per day is associated with a lower risk of ischaemic stroke. Changing the five lifestyle choices of smoking cessation, physical exercise, healthy diet, maintaining a healthy weight, and alcohol consumption are clearly just as important as medical treatment to reduce the risk of stroke in patients with carotid artery disease.

Current guidelines for medical therapy of carotid artery disease

There have been several guidelines published in this topic, all of which are described in a recent systematic review.[36] This review included 34 guidelines from 23 different regions or countries and concluded that there are many weaknesses in the guidelines in terms of the accessibility of the guidelines, and the representation of the relevant evidence. This chapter will discuss three currently accepted guidelines, one representing the United States reported by the American Stroke Association (ASA) and American College of Cardiology Foundation (ACCF) and 12 other societies,[37] one representing Europe approved by the European Society for Vascular Surgery (ESVS),[38] and the current National Institute for Health and Care Excellence (NICE) guidelines from the United Kingdom.[48-52] The main difference between the NICE guidelines and the two other guidelines chosen is that the recommendations that we discuss from the NICE guidelines are aimed towards patients with individual vascular risk factors and do not deal specifically with carotid artery stenosis unlike the other two guidelines. Table 1 provides a summary of the main recommendations for medical therapy made in the three chosen guidelines with the level of evidence per recommendation cited in the corresponding publication.

Anti-thrombotic therapy
In the ASA/ACCF guideline, antiplatelet therapy in the form of aspirin alone is recommended in patients with carotid artery stenosis, regardless of whether the patient is symptomatic or asymptomatic. In contrast, the ESVS guideline recommends aspirin with dipyridamole as the first option in patients with symptomatic carotid stenosis, and clopidogrel alone as second option. The NICE guideline indicates that patients with ischaemic stroke should be advised to start clopidogrel. However, the NICE guideline is based on evidence that comes from

randomised controlled trials of patients who experienced ischaemic stroke, and not patients with carotid artery stenosis.

Blood pressure management

It is generally recommended that the target clinic blood pressure value should be maintained to below 140/90 mmHg with antihypertensive medications in patients with asymptomatic carotid artery stenosis and hypertension. In the NICE hypertension guideline, higher target levels of 150/90 are specified for patients aged 80 years or older, while lower target levels of are specified for patients with diabetes and prior stroke or TIA or other risk factors of <130/80. In patients with symptomatic carotid stenosis, the relationship between blood pressure and the risk of further cerebral ischaemia has not been established and there has been concern that the lower targets might risk causing haemodynamic stroke in patients with severe carotid stenosis or occlusion. However, in our experience lowering blood pressure to these target values is safe even in patients with bilateral carotid disease, so long as the blood pressure is lowered slowly and severe hypotension is avoided.

Controlling blood glucose levels in patients with diabetes mellitus

The ASA/ACCF guideline states that there is no evidence that controlling blood glucose levels to achieve a level of glycosylated haemoglobin A1c (HbA1c) at or below 7% has a benefit in the prevention of ischaemic stroke. However, it is recommended that these patients should be prescribed a statin to lower the LDL-cholesterol to a level below 1.8 mmol/l (70 mg/dl). No recommendations are made in the ESVS guideline regarding the control of blood glucose levels. In the NICE guidelines, recommendations are made for patients with DM with a target to lower HbA1c levels to 6.5%.

Lipid lowering therapy

Patients with carotid artery stenosis and hypercholesterolaemia are recommended treatment with statins to achieve a low-density lipoprotein (LDL) value below 2.6 mmol/l (100 mg/dl). In patients with a history of ischaemic stroke or TIA, it is reasonable to reduce the LDL-cholesterol to a level near or below 1.8 mmol/l (70 mg/dl).

Lifestyle changes

In the ASA/ACCF guideline, only the cessation of tobacco smoking is recommended. In the ESVS and NICE guidelines, however, recommendations are also made for the intake of alcohol, weight reduction, and physical activity.

When is medical management alone insufficient in carotid disease?

Patients with symptomatic carotid stenosis have a much higher risk for future recurrent stroke compared to asymptomatic patients. The purpose of the medical therapy for the prevention of cardiovascular events are slightly different in these two groups of patients. In asymptomatic patients, the annual risk of stroke due to the carotid plaque is less than 1% according to a meta-analysis performed in 2009.[39] The annual risk for death due to a non-stroke cause in these patients, are known to be higher than the risk of ipsilateral stroke. It is said that more than 50% of the non-stroke deaths are due to ischaemic heart disease.[40] This suggests that asymptomatic carotid stenosis gives a better indication of atherosclerotic disease elsewhere in the body rather than indicating a particularly high risk of stroke.

The effect of surgical intervention on the risk of stroke in patients with asymptomatic stenosis, was studied in one of the largest randomised controlled trials, the Asymptomatic Carotid Surgery Trial – 1 (ACST-1).[41] In this trial, more than 3000 asymptomatic patients were randomised to immediate carotid endarterectomy (CEA) versus deferral of any carotid surgical intervention. CEA caused some risk of perioperative stroke or death, but immediate CEA almost halved the non-perioperative stroke rate over the next 10 years (10.0% risk of non-perioperative stroke in the immediate CEA group compared to 4.1% in the deferral of CEA group at 5 years, with 16.9% compared to 10.8% at 10 years respectively). Due to this small reduction of the risk in patients who underwent direct surgical intervention, studies are trying to identify the high risk group in the group of patients with asymptomatic carotid stenosis. Current guidelines suggest that surgical intervention is reasonable in patients with high-grade asymptomatic carotid artery stenosis (see table 2), but many experts do not refer asymptomatic stenosis for surgery, preferring intensive medical therapy alone as we have outlined above.

Symptomatic patients have a much higher risk for future recurrent stroke compared to asymptomatic patients. In the Oxford Vascular Study (OXVASC), it was shown that the risk of recurrent ipsilateral stroke is 27% during the first 30 days after a TIA or minor stroke in patients with symptomatic carotid stenosis of more than 50%.[42] This risk is much higher

compared to the 1-year risk of stroke of less than 1% in asymptomatic patients. Therefore it is recommended for patients with high-grade symptomatic stenosis of 70-99% to undergo CEA. CEA was shown to be highly beneficial in reducing this high risk with medical therapy in patients with high-grade symptomatic stenosis of 70-99% in the original CEA trials.[43] The absolute risk reduction of this group was 16.0%. The same review suggest that symptomatic patients with 50-69% stenosis have some benefit of CEA, with an absolute risk reduction of 4.6%. Table 2 provides a summary of the recommendations for surgical intervention according to the ASA/ACCF[37] and ESVS guidelines.[44]

Current ongoing trials in the management of carotid artery disease

The evidence discussed above suggests that intensive medical therapy is so effective that carotid revascularisation may no longer be necessary in many of the patients in whom carotid surgery or stenting is currently performed. The current guidelines are based on trials done more than 20 years ago and thus these trials need to be repeated using current intensive medical therapy regimes at least in patients who are not in the highest risk categories. Two large on-going trials are therefore comparing the risks and benefits of carotid revascularisation versus intensive medical therapy alone. The European Carotid Surgery Trial 2 (ECST-2)[45] and the Carotid Revascularisation and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2)[46] are both investigating the outcome of patients with carotid surgery comparing carotid revascularisation together with current medical therapy versus medical therapy alone in patients with carotid artery stenosis..

ECST-2 is a multicentre, prospective, randomised clinical trial of patients with both symptomatic and asymptomatic carotid artery stenosis, which started recruitment in 2012. The patients in this trial are selected on the basis of the Carotid Artery Risk (CAR) score,[47] which is used to predict the 5-year risk of ipsilateral stroke of patients with carotid artery stenosis. Patients with a 5-year risk of less than 20% are then randomly allocated optimised medical therapy alone or optimised medical therapy with the addition of immediate carotid revascularisation, which is either carotid endarterectomy or carotid stenting according to the preference of the clinicians. Both symptomatic and asymptomatic patients can be enrolled in this trial and the primary outcome is stroke at any time after enrolment and non-stroke death occurring within 30 days of revascularisation. The follow up duration will be a minimum of 5 years up to a maximum of 10 years. This study is unique due to the use of a clinical risk

prediction model to select and exclude patients, dividing patients into a low, intermediate, and high risk score for ipsilateral recurrent stroke, the latter being excluded and recommended for immediate revascularisation.

CREST-2 consists of two randomised controlled trials, and has been randomising patients with asymptomatic high-grade carotid stenosis since 2014. Patients are randomised to carotid revascularisation and intensive medical management or medical management. One of the two trials randomises patients to carotid endarterectomy versus no surgical intervention, the other trial randomly allocates patients to carotid stenting with embolic protection versus no surgical intervention. Patients randomised to this trial have to have asymptomatic carotid stenosis measuring 70% or more in severity. Patients are excluded if they are symptomatic on the ipsilateral side of the carotid stenosis within the last 180 days of randomisation. The primary outcome is ipsilateral stroke, stroke during revascularisation or death at 30 days. The follow up duration is 4 years.

Conclusion

Medical therapy for carotid artery stenosis for the primary and secondary prevention of ischaemic stroke is important and consists of treating several risk factors, including lifestyle modifications. The risk of ipsilateral stroke is different in symptomatic and asymptomatic patients and the purpose of medical treatment is therefore slightly different. Two guidelines from two large groups representing the US and Europe have similar recommendations for patients with carotid artery stenosis. For patients with carotid artery disease with a moderate risk of recurrent stroke, and for asymptomatic high-grade stenosis it is still the question whether surgical intervention with medical therapy or medical therapy alone is superior.

Conflicts of interest

None.

Acknowledgements

proportion of funding from the UK Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme.

References

[1] European Carotid Surgery Trialist's Collaborative Group. MRC European carotid surgery trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. Lancet 1991;337: 1235-43.

[2] North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991;325: 445-53.

[3] Prasad K. Pathophysiology and medical treatment of carotid artery stenosis. Int J Angiol 2005; 24:158-72.

[4] Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of anti-platelet therapy for prevention of death, myocardial infarction and stroke in high risk patients. BMJ 2002;324: 71-86.

[5] Derdeyn CP, Chimowitz MI, Lynn MJ, et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): The final results of a randomised trial. Lancet 2014; 383(9914): 333–341.

[6] Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med 2011; 365: 993–1003

[7] Chimowitz MI, Kokkinos J, Strong J, et al. The warfarin-aspirin symptomatic intracranial disease study. Neurology 1995; 45: 1488–1493

[8] Sacco RL, Diener HC, Yusuf S, et al; PRoFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. N Engl J Med. 2008;359(12):1238-1251.

[9] Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004;364:331–7.

[10] Wang Y, Wang Y, Zhao X, et al; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med. 2013;369(1):11-19.

[11] Wang Y, Pan Y, Zhao X, et al; CHANCE Investigators. Clopidogrel With Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) Trial: One-Year Outcomes. Circulation. 2015;132(1):40-46

[12] Fox KA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial. Circulation 2004;110:1202–8.

[13] Bowry AD, Brookhart MA, Choudhry NK. Meta-analysis of the efficacy and safety of clopidogrel plus aspirin as compared to antiplatelet monotherapy for the prevention of vascular events. Am J Cardiol. 2008;101(7):960-966.

[14] Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005;366(9497): 1607-1621.

[15] Côté R, Battista RN, Abrahamowicz M, Langlois Y, Bourque F, Mackey A. Lack of effect of aspirin in asymptomatic patients with carotid bruits and substantial carotid narrowing. The Asymptomatic Cervical Bruit Study Group. Ann Intern Med. 1995 Nov 1;123(9):649-55.

[16] Halkes PH, van Gijn J, Kappelle LJ, et al. Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. Lancet Neurol 2007;6:115–24.

[17] Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994;154:1449–57.

[18] Cuspidi C, Negri F, Giudici V, Capra A, Sala C. Effects of antihypertensive drugs on carotid intima-media thickness: Focus on angiotensin II receptor blockers. A review of randomized, controlled trials. Integr Blood Press Control 2009;2:1-8.

[19] Wang JG, Staessen JA, Li Y, Van Bortel LM, Nawrot T, Fagard R, Messerli FH, Safar M. Carotid intima-media thickness and antihypertensive treatment: a meta-analysis of randomized controlled trials. Stroke. 2006 Jul;37(7):1933-40.

[20] Bangalore S, Qin J, Sloan S, Murphy SA, Cannon CP; PROVE IT-TIMI 22 Trial Investigators. What is the optimal blood pressure in patients after acute coronary syndromes? Relationship of blood pressure and cardiovascular events in the PRavastatin OR atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT-TIMI) 22 trial. Circulation. 2010;122(21):2142-2151.

[21] Amarenco P, Bogousslavsky JC, Callahan A, Goldstein L, Hennerici M, Sillesen H, et al. A placebo-controlled trial of high-dose atorvastatin in patients with recent stroke or transient ischemic attack. The Stroke Prevention with Aggressive Reduction in Cholesterol Levels (SPARCL) Study. New England Journal of Medicine 2006;355(6):549-59.

[22] Amarenco P, Labreuche J, Lavallee P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. Stroke. 2004;35(12):2902-2909.

[23] Artom N, Montecucco F, Dallegri F, Pende A. Carotid atherosclerotic plaque stenosis: the stabilizing role of statins. Eur J Clin Invest. 2014 Nov;44(11):1122-34.

[24] Herder M, Arntzen KA, Johnsen SH, Eggen AE, Mathiesen EB. Long-term use of lipid-lowering drugs slows progression of carotid atherosclerosis: the Tromso study 1994 to 2008. Arterioscler Thromb Vasc Biol 2013;31(1):12-26.

[25] Pollex RL, Spence JD, House AA, et al. A comparison of ultrasound measurements to assess carotid atherosclerosis development in subjects with and without type 2 diabetes. Cardiovasc Ultrasound. 2005;3():15.

[26] Goldstein LB, Bushnell CD, Adams RJ, et al; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Epidemiology and Prevention; Council for High Blood Pressure Research,; Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011; 42(2):517-584. 96.

[27] Kissela BM, Khoury J, Kleindorfer D, et al. Epidemiology of ischemic stroke in patients with diabetes: the greater Cincinnati/Northern Kentucky Stroke Study. Diabetes Care. 2005;28(2): 355-359.

[28] Mostaza JM, Lahoz C, Salinero-Fort MA, de Burgos-Lunar C, Laguna F, Estirado E, et al. SPREDIA-2 Group. Carotid atherosclerosis severity in relation to glycemic status: a cross-sectional population study. Atherosclerosis. 2015 Oct;242(2): 377-82.

[29] Mazzone T, Meyer PM, Feinstein SB, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. JAMA 2006;296(21): 2572-81.

[30] Esposito K, Giugliano D, Nappo F, Marfella R; Campanian Post-prandial hyperglycemia study group. Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. Circulation 2004;110(2):214-9.

[31] Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. BMJ 1989;298:789–94.

[32] Hackam DG, Spence JD. Combining multiple approaches for the secondary prevention of vascular events after stroke: a quantitative modeling study. Stroke 2007, 38:1881-1885.

[33] Bloomgarden ZT. Obesity and diabetes. Diabetes Care 2000;23(10): 1584-90.

[34] Kotsis V, Stabouli S, Papakatsika S, Rizos Z, Parati G. Mechanisms of obesity-induced hypertension. Hypertens Res 2010;33(5):386-93.

[35] Reynolds K, Lewis B, Nolen JD, Kinney GL, Sathya B, He J. Alcohol consumption and risk of stroke: a meta-analysis. JAMA. 2003 Feb 5;289(5):579-88.

[36] Abbott AL, Paraskevas KI, Kakkos SK, Golledge J, Eckstein HH, Diaz-Sandoval LJ, et al. Systematic review of guidelines for the management of Asymptomatic and Symptomatic Carotid stenosis. Stroke 2015;46: 3288-3301.

[37] Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, 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: executive summary. Catheter Cardiovasc Interv. 2013 Jan 1;81(1):E76-123.

[38] Liapis CD, Bell PF, Mikhailidis DP, Sivenius J, Nicolaides A, Fernandes e Fernandes J, et al. ESVS Guidelines: Section A--prevention in patients with carotid stenosis. Curr Vasc Pharmacol. 2010 Sep;8(5):673-81.

[39] Abbott AL. Medical (non-surgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. Stroke 2009;40: e573-83.

[40] Pickett CA, Jackson JL, Hemann BA, Atwood JE. Carotid bruits as a prognostic indicator of cardiovascular death and myocardial infarction: a meta-analysis. Lancet 2008;371: 1587-94.

[41] Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, et al. Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. Lancet. 2010;376(9746):1074-84.

[42] Fairhead JF, Mehta Z, Rothwell PM. Population-based study of delays in carotid imaging and surgery and the risk of recurrent stroke. Neurology. 2005;65(3):371-5.

[43] Rerkasem K, Rothwell PM. Carotid endarterectomy for symptomatic carotid stenosis. Cochrane Database Syst Rev. 2011;(4):CD001081.

[44] Liapis CD1, Bell PR, Mikhailidis D, Sivenius J, Nicolaides A, Fernandes e Fernandes J,et al; ESVS Guidelines Collaborators. ESVS guidelines. Invasive treatment for carotid stenosis: indications, techniques. Eur J Vasc Endovasc Surg. 2009;37(4 Suppl):1-19.

[45] ISRCTN (Internet), London: Current Controlled Trials, c/o BioMed Central, 2010, Identifier ISRCTN 97744893. European Carotid Surgery Trial 2 (ECST-2) (Internet). 2012 (accessed 11 December 2013). Available at: http://www.controlled-trials.com/ISRCTN97744893.

[46] Lal BK, Meschia JF, Brott TG. CREST-2: Guiding treatments for asymptomatic carotid disease. Endovasc Today 2013; 73–76.

[47] Stroke Prevention Research Unit, Oxford University, UK. Carotid Artery Risk Score (Internet) (accessed 11 December 2013). Available at: http://www.stroke.ox.ac.uk/model/form1.html.

[48] NICE National Institute for Health and Care Excellence. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events. December 2010. Available at: https://www.nice.org.uk/guidance/TA210.

[49] NICE National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management. August 2011. Available at: https://www.nice.org.uk/guidance/CG127.

[50] NICE National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. December 2015. Available at: https://www.nice.org.uk/guidance/NG28.

[51] NICE National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification. July 2014. Available at: https://www.nice.org.uk/guidance/CG181.

[52] NICE National Institute for Health and Care Excellence. Cardiovascular disease prevention overview. February 2016. Available at: http://pathways.nice.org.uk/pathways/cardiovascular-disease-prevention.