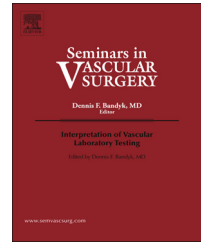


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# Contemporary medical therapies of atherosclerotic carotid artery disease



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## ARTICLE INFO

## ABSTRACT

Contemporary medical therapy consists of identification and treatment of all patient-modifiable vascular risk factors. Specific atherosclerotic disease therapies are designed to reduce the risk of thrombosis, and the disease progression in order to reduce the risk of future cardiovascular events. Contemporary medical management emphasizes the need to support the patient in achieving lifestyle modifications and to adjust medication to achieve individualized target values for specific quantifiable risk factors. Antiplatelet therapy in the form of aspirin or clopidogrel is routinely used for the prevention of ischemic stroke in patients who have had a transient ischemic attack 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 transient ischemic attack reduces the risk of recurrent stroke compared to the use of aspirin alone, and therefore we use aspirin plus clopidogrel in recently symptomatic patients with carotid stenosis pending carotid revascularization. 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 optimized. 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 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 revascularization may no longer be necessary in many of the patients in whom carotid surgery or stenting is currently performed. Two large ongoing trials are therefore comparing the risks and benefits of carotid revascularization versus intensive medical therapy alone.

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## 1. Introduction

Medical management plays an important role in the prevention of ischemic stroke and other cardiovascular diseases in patients with atherosclerotic carotid artery disease. Optimizing the management for each individual can be challenging, but small changes in therapy can substantially reduce the risk of recurrent ischemic stroke. Therefore, it is important that every patient found to have carotid atherosclerosis has an individualized optimum management plan instituted to lower the risk of stroke. This article 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 lifestyle 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, dyslipidemia, 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 lifestyle changes and drug treatment for vascular risk factors without closely monitoring the patient's compliance or response to treatment. However, contemporary medical management emphasizes the need to support the patient in achieving lifestyle modifications and to adjust medication to achieve individualized target values for specific quantifiable risk factors, for example, 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 ischemic attack (TIA) or stroke related to 70% to 99% intracranial stenosis secondary to atherosclerosis were randomly allocated to intracranial stenting with intensive medical therapy versus aggressive medical therapy alone. Aggressive medical therapy included dual antiplatelet therapy with aspirin and clopidogrel for 90 days after randomization, antihypertensive medication adjusted to achieve a systolic blood pressure <140 mm Hg, and statin therapy to achieve a low-density lipoprotein cholesterol target <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 randomized 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.

## 2. 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 ischemic 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 (Prevention Regimen for Effectively Avoiding Second Strokes) conducted by Sacco et al [8] showed that the effect of clopidogrel alone on the rates of recurrent stroke is similar to the combination of aspirin with dipyridamole in patients with previous stroke. Similarly, the MATCH (Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke) 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 (Clopidogrel in High-Risk Patients with Acute Non-Disabling Cerebrovascular Events) 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 revascularization, as long as the patient does not have an increased risk of bleeding. This combination is then continued for up to 3 months after revascularization, especially in patients who have had carotid stenting.

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

Unfractionated 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

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