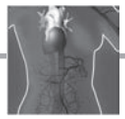
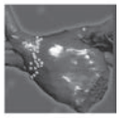


# The protective effect of clopidogrel and atorvastatin in patients undergoing carotid stenting

*"...optimization of periprocedural drug therapy remains an important target to improve the outcome in this population of patients in addition to mechanical cerebral protection."*

**KEYWORDS: atorvastatin reload ■ carotid stenting ■ clopidogrel ■ MRI ■ neuroprotection**

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Over the last few years, the advance in operator's experience, the improvement in technology and the strong demand from patients for a less-invasive alternative to surgery has made carotid artery stenting (CAS) an equally efficient and safe procedure to carotid endarterectomy for the treatment of carotid artery stenosis [1–3]. The introduction of mechanical cerebral protection systems can be considered the cornerstone in the evolution of CAS; these devices aim to prevent emboli from reaching the brain, and their introduction in the majority of procedures is responsible for better outcomes reported in recent clinical trials and registries. Therefore, guidelines strongly recommend the use of embolic protection devices in all procedures [4].

Despite progress in CAS, periprocedural stroke rate remains significant, and has an important physical, mental and social impact on patients' lives. Therefore, indication for treatment of asymptomatic patients is one of the most debatable issues in the literature. In particular, incidence of microembolization, during and after CAS, persists despite the use of cerebral protection devices. Diffusion-weighted MRI (DW-MRI) has been shown to be a sensitive tool in identifying new ischemic cerebral lesions that are caused by emboli during CAS. Cerebral ischemic lesions are observed by DW-MRI in 15–78% of patients after CAS, and most of them are not associated with acute neurological symptoms [5–7].

Clinical implication and impact on prognosis of asymptomatic cerebral microembolism is still debated. Recently, a large study analyzing the role of asymptomatic cerebral ischemic lesions after CAS on prognosis in terms of major adverse cardiac and cerebrovascular event (death, stroke and myocardial infarction) demonstrated that a positive DW-MRI after CAS was not an indicator for an increased risk of major adverse events at a follow-up beyond 30 days [8]. Nevertheless, several studies suggested that silent microembolic cerebral injury could potentially result in focal neurologic signs and cognitive dysfunction, or predispose to cognitive decline and dementia [9].

Thus, optimization of periprocedural drug therapy remains an important target to improve the outcome in this population of patients in addition to mechanical cerebral protection.

Atheromatous plaques and superimposed thrombi are the main sources of microemboli during CAS [10]. Generally, antiplatelet agents are used as premedication to prevent periprocedural complications. In the majority of studies, 75 mg of clopidogrel was administered for at least 5 days before the procedure. However, current guidelines do not specifically indicate a recommended clopidogrel-loading dose in clopidogrel-naive patients undergoing CAS [4]; current practice is to use a 300-mg loading dose, even though there are no clinical trials that support this particular pharmacological strategy. Furthermore, a strategy of more aggressive platelet inhibition may impart protection against thromboembolic procedure-related events and a higher clopidogrel load could be associated with improved prognosis.

In a recent study on patients undergoing CAS, the frequency of clopidogrel low response was significantly higher in DW-MRI-positive patients than in DW-MRI-negative patients (82.2 vs 41.9%; p = 0.001), emphasizing the importance of an optimal antiaggregation in patients during and after CAS [11].

Recently, our group demonstrated, in the ARMYDA-9 CAROTID study, that a pharmacological strategy with a 600-mg clopidogrel load provides neuroprotection in patients undergoing

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CAS [12]. The 30-day cumulative incidence of transient ischemic attack (TIA)/stroke or new ischemic lesions on cerebral DW-MRI occurred in 18% of patients in the 600-mg clopidogrel arm and in 35.9% of those in the 300-mg arm ($p = 0.019$); 1-month incidence of TIA/stroke (pure clinical end point) was also significantly reduced (0 vs 9%; $p = 0.02$).

The more rapid and intense platelet suppression obtained with a higher clopidogrel loading dose at the time of intervention may prevent distal embolization, protect the microvascular bed and counterbalance the postprocedural procoagulant status, thus explaining the results obtained in our study. These clinical and biological effects are similar to those observed in the setting of coronary angioplasty, in which a high clopidogrel load significantly reduced the incidence of periprocedural myocardial infarction compared with the conventional 300-mg dose [13].

> *"...a strategy of more aggressive platelet inhibition may impart protection against thromboembolic procedure-related events and a higher clopidogrel load could be associated with improved prognosis."*

With regards to the contribution of medical therapy to the outcome of CAS, Gröschel *et al.* demonstrated that symptomatic patients with carotid stenosis on statin therapy at the time of procedure have a lower incidence of periprocedural cardiovascular complications compared with statin-naive patients (4 vs 15%; $p < 0.05$), supporting the notion that preprocedural statin treatment may also have a protective effect during carotid interventions [14]. Nevertheless, this study did not explain whether a particular statin, given for a short time pretreatment, with a specific loading before CAS, would be required to produce the observed benefit. In fact, initiation of statin therapy prior to percutaneous carotid intervention is strongly recommended in current guidelines [4].

CAS has been shown to induce platelet activation, thrombosis and inflammation within the vessel wall; these phenomena could theoretically all be reduced by the pleiotropic, LDL-independent effects of statins [15]. Indeed, it has been demonstrated that statins stabilize plaques, improve endothelial function, decrease platelet aggregability and thrombus deposition, and reduce vascular inflammation [16]. In the setting of coronary angioplasty, previous randomized studies have demonstrated that a short-term reload with high-dose atorvastatin prevents periprocedural myocardial infarction in patients undergoing coronary stenting, even in the background of long-term statin therapy [17–18]; rapid restoration of the pleiotropic effects of statins may explain this clinical benefit [19].

The ARMYDA-9 CAROTID study showed that, even in the setting of CAS, a short-term high reload with atorvastatin is associated with clinical benefit. In fact, in addition to the previous described results about aggressive antiaggregation, the study showed that short-term reload with high-dose atorvastatin in statin-treated patients undergoing CAS induces a 16.6% absolute reduction of the cumulative end point, including all ischemic cerebral events, at 1 month (TIA/stroke and new ischemic lesions at DW-MRI) [12]. The LDL-lowering effects of atorvastatin cannot explain this protective effect since the short time of pretreatment (only 12 h) would not be able to produce significant effects on LDL levels. Thus, similar to what was observed in coronary angioplasty, the described benefit may be interpreted as an activation of the pleiotropic effect of statins, limiting periprocedural microembolization and procedural injury, reducing the permeability of the blood–brain barrier, reducing inflammation, and improving vascular endothelial function and cerebral blood flow.

> *"...neuroprotection, in all its modalities, is the most important objective of innovations in the procedure of carotid artery stenting and may be associated with better clinical outcomes."*

In conclusion, indication to endovascular procedure and comparison with carotid endarterectomy is still debated, although published trials have demonstrated a substantial equivalence of endovascular therapy compared with surgery [1,2], and superiority of CAS was demonstrated in high-risk patients [3]. Studies with DW-MRI emphasize a relatively high incidence of microembolization, often asymptomatic, occurring during carotid endovascular procedures. It remains a matter of debate whether cerebral lesions translate into impairment of long-term prognosis and patients' cognitive status; however, these lesions could be considered a sensitive measurable marker of outcome to demonstrate the benefit of new procedural innovations in clinical studies.

Therefore, neuroprotection, in all its modalities, is the most important objective of innovations in the procedure of CAS and may be associated with better clinical outcomes.

The importance of a good periprocedural medical therapy with an optimal procedural

performance is well established in the setting of coronary angioplasty, while it was thus far neglected in the framework of CAS, also owing to the different professional figures that perform this type of procedure.

Currently, we believe that appropriate pharmacological protection would significantly improve the outcome of CAS. In our institution, we recommend a loading dose of 600-mg clopidorel preprocedure and a high-dose atorvastatin reload.

It is not known whether new antiplatelet agents, such as ticagrelor and prasugrel, currently in use for acute coronary syndromes and coronary angioplasty, would be more effective than clopidogrel in carotid stenting; however, to date, clopidogrel is still widely used and is less expensive than ticagrelor and prasugrel in many countries.

Thus, pharmacological neuroprotection should be part of the armamentarium of the operator performing carotid interventions, as well as the mechanical protection devices.

**Financial & competing interests disclosure**

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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