REVIEW

A new approach to statin therapy in carotid atherosclerosis: Targeting indices of plaque vulnerability in addition to lipid-lowering. A narrative review

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ABSTRACT

Novel imaging techniques and biomarkers have emerged as surrogate markers of carotid plaque vulnerability. In parallel, statin administration in patients with established carotid atherosclerosis not requiring revascularization has reduced the number of consequent cerebrovascular events. This reduction is not only attributed to the lipid-lowering properties of statins but also to their pleiotropic actions. The present literature review aimed to summarize the stabilizing effects of statins on carotid plaques based on imaging modalities and biomarkers and propose an alternative approach to their implementation. Moreover, we assessed the perioperative use of statins in patients undergoing carotid revascularization and the impact of aggressive vs. conventional statin therapy. Recent studies using: (1) ultrasound indices of plaque echogenicity; (2) fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) scans for plaque inflammation assessment; or (3) magnetic resonance imaging (MRI) scans quantifying intraplaque hemorrhage, and lipid-rich necrotic core (LRNC) have shown quite promising results in evaluation of carotid plaque vulnerability. Based on those imaging modalities, a growing number of studies have demonstrated a very modest carotid plaque regression due to/induced by statins, while their stabilizing impact is disproportionally higher. Other studies assaying several biomarkers (e.g. inflammation, etc.) have confirmed a statin-induced carotid plaque stabilization. All the aforementioned benefits followed a dose-dependent pattern of statins, on top of the low-density lipoprotein cholesterol (LDL-C) target in current guidelines. In the case of symptomatic patients with carotid atherosclerosis suitable for revascularization, robust evidence implicates a significant statin-related reduction of perioperative cardiovascular risk only in patients undergoing endarterectomy.

Key words: statins, carotid plaque vulnerability, pleiotropic effects, biomarkers

INTRODUCTION

Carotid atherosclerosis has been associated with acute ischemic cerebrovascular events and high morbidity and mortality in western countries [1]. It is undoubtful that symptomatic patients with carotid atherosclerosis should be treated with invasive methods. So far, the risk stratification of asymptomatic patients with established carotid atherosclerosis has been based on the degree of carotid artery lumen encroachment. However, such an approach cannot predict ischemic strokes or transient ischemic attacks (TIAs) that occur frequently in patients with more or less moderate carotid stenosis. The unstable carotid plaque, prone to rupture, is strongly related to cerebrovascular ischemic events and does not parallel the degree of carotid stenosis [2]. Unstable plaques have specific characteristics, like lipid accumulation, inflammatory cell infiltration, less calcification, thin fibrous cap, etc. [3]. The early detection of those plaques before symptoms occurrence remains a great challenge for imaging techniques. In the absence of a "gold standard" imaging modality, several imaging markers have been

proposed, such as low echogenicity on ultrasound, high inflammatory burden on positron emission tomography (PET) scans, and large lipid core or neovascularization on magnetic resonance imaging (MRI) views, monitoring the aforementioned pathophysiologic mechanisms. Despite the growing evidence, their application in current clinical decision-making and risk stratification of patients with carotid atherosclerosis is limited.

Moreover, the presence of vulnerable carotid plaques is associated with a high risk of not only ischemic strokes but also other atherosclerotic cardiovascular events implicating a systematic process in a "vulnerable" patient [4, 5]. As an adjunct to vascular imaging, a long list of circulating molecules, known as biomarkers, has been proposed for the detection of vulnerable plaques and "vulnerable" patients [6–8]. Among biomarkers, those depicting inflammation [9], vascular calcification [10], and neovascularization [11] have been more studied showing a strong relationship with histopathological features of carotid plaque vulnerability and cardiovascular events [12, 13].

The majority of patients with carotid atherosclerosis are asymptomatic, requiring close monitoring and intensive pharmaceutical therapy to prevent the destabilization of initially stable carotid plaques. Statins have long been the mainstay of treatment of patients with asymptomatic significant (>50%) carotid stenosis [14]. The current guidelines recommend a target of serum low-density lipoprotein cholesterol (LDL-C) <70 mg/dl or decreasing by ≥50% if the initial LDL-C level ranges between 70 and 135 mg/dl in patients with peripheral artery disease [15]. Such a pharmaceutical approach is associated with reduced all-cause and cardiovascular mortality and cerebrovascular morbidity [16, 17]. In the case of patients requiring carotid revascularization (symptomatic and asymptomatic), most, but not all, studies have shown favorable outcomes from the perioperative use of statins [18, 19].

In all aforementioned algorithms with statins, their prescription is entirely guided by LDL-C levels. However, their efficacy is dose-dependent, and it is attributed not only to their lipid-lowering effects but additionally to the pleiotropic actions leading to the improvement of carotid plaque texture and the reduction of the overall cardiovascular risk [20]. Therefore, it is wise to modify the therapeutic target of statin therapy to a composite end-point combining LDL-C reduction with favorable changes in plaque stability and the patient's risk profile quantified by imaging techniques and biomarkers. The present literature review summarizes the stabilizing mechanisms of statins using imaging- and biomarkers-based data in either asymptomatic patients with carotid atherosclerosis under pharmaceutical treatment or patients undergoing carotid revascularization, supporting an alternative target of their usage. We also comment on the perioperative manipulation of statins ending up with more aggressive therapy.

SEARCH STRATEGY

This is a traditional literature review with a more critical appraisal of the targets of lipid-lowering therapy in patients with carotid atherosclerosis. A literature search in the English language was conducted for publications in MEDLINE and EMBASE, Web of Science, Cochrane, and Google Scholar databases from 1990 to June 2021. The reference lists of the identified articles were checked for any additional relevant articles. The following search terms, in titles and abstracts, including Medical Subject Headings (MeSH) were used: carotid plaque, carotid artery stenosis, carotid atherosclerosis, carotid artery disease, lipid-rich necrotic core, magnetic resonance imaging, plaque imaging, carotid artery stenting (CAS), carotid endarterectomy (CEA), statins, and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. Two investigators (NV and EK) independently performed the literature search. We further limited our literature search by setting the following inclusion criteria: randomized and non-randomized prospective studies, published only in the English language, enrolling at least 10 patients in each pharmaceutical arm. We excluded studies with retrospective or cross-sectional or review designs and those using animals, children, or adolescents. Applying several terms and inclusion and exclusion criteria, we attempted a more systematic approach to reviewing the existing literature. However, we did not follow the methodology of full systematic review, weakening the power of our review.

Based on abstracts and titles, we initially found 1649 potentially eligible studies. After full-text screening, we excluded another 1584 studies because they did not provide adequate information (conference abstracts, small samples, wrong design, etc.). We ended up with 65 clinical trials including five systematic reviews and meta-analyses for several aspects of our subject (Figure 1).

EFFECTS OF STATINS ON IMAGING-BASED ASSESSMENT OF CAROTID PLAQUE VULNERABILITY

Effects of statins on MRI-based carotid plaque vulnerability

High-resolution MRI has been recently proposed for the evaluation of atherosclerotic plaque vulnerability. MRI can illustrate in detail the components of the atherosclerotic plaque, arterial wall, and surrounding soft tissues [21–24]. Notably, it can adequately quantify the main features of the vulnerable plaque, IPH, ulceration, lipid-rich necrotic core (LRNC), calcification, intraplaque neovascularization (IPN), and inflammation [25–27]. Both intraplaque hemorrhage and LRNC have emerged as predictors of both cardiovascular and cerebrovascular events in patients with carotid atherosclerosis, indicating their clinical significance as indices of systemic, high cardiovascular risk [28, 29].

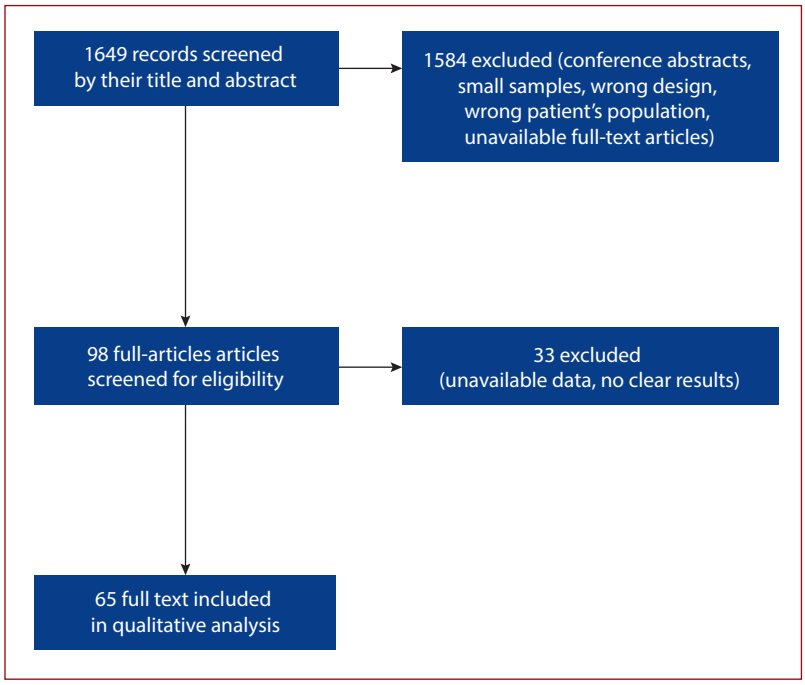

Figure 1. Flow chart showing a selection of studies in the literature review

Despite some integral technical limitations, such as being time-consuming, showing artifacts, and contrast-induced artifacts, MRI can assess non-invasively statin-induced changes in carotid plaque morphology [23, 30]. A recent systematic review [31] included seven prospective studies (a total of 361 patients with carotid atherosclerotic disease) and examined changes in LRNC volumes and lumen volumes after statin therapy for at least one year. The vast majority of prospective studies reported a significant reduction in LRNC volumes, without any significant change in plaque burden. The small sample size of included studies and their large heterogeneity in doses and types of statins were important limitations of that meta-analysis.

Lipid-core regression can be a representative mechanism of statin-induced plaque stabilization [32]. The latest prospective studies [22, 33] using 3T MRI imaging have confirmed the statin-induced reduction in lipid percentage and lipid volume within the carotid plaque after intensive statin therapy. Notably, MRI images showed a dose-dependent counterregulatory effect of pitavastatin (4 mg/d vs. 2 mg/d) on lipid core, plaque thickness, and lumen area [22]. In parallel, MRI can detect IPN, which is associated with a high risk of plaque rupture and consequent events [34–36]. A recent prospective study (Du et al. 2019 [34]) reported a significant reduction in adventitial and IPN over two years with rosuvastatin therapy. Notably, that effect peaked in the first 3 months after rosuvastatin initiation.

Therefore, MRI has the potential to quantify carotid plaque vulnerability and stabilizing effects of statin therapy by assessing the changes in lipid content and neovascularization [33, 34]. Future studies will clarify whether an MRI-based algorithm could tailor the optimal statin therapy in patients with carotid atherosclerosis.

Effects of statins on ultrasound-based carotid plaque vulnerability

Ultrasonography of the carotid arteries is an old, widely used imaging modality for the assessment of carotid plaque morphology. Carotid ultrasound constitutes a cost-effective, easily performed, non-invasive, reproducible technique for the evaluation of the degree of carotid stenosis and the vulnerability of carotid atheromatous plaques. Plaques rich in lipid and hemorrhagic content appear echolucent while those with fibrous or calcific content appear echogenic. Prospective studies have documented the strong association between low echogenicity and carotid plaque vulnerability, the latter clinically manifested with neurological symptoms and/or ipsilateral to plaques ischemic lesions on brain scans [12]. Moreover, plaque echolucency has been also associated with a high occurrence of adverse cardiovascular events, as an expanded measure of "vulnerable" patients [5]. The traditional role of ultrasound in this context is the estimation of the grayscale median (GSM) or the integrated backscatter. Both scales have been applied in carotid atherosclerosis, but their validation as prognostic modalities requires more evidence.

A meta-analysis of nine studies (566 patients) published in 2015, investigated the impact of statins on carotid plaque echogenicity [37]. The important finding of that meta-analysis was the statin-induced amelioration of carotid plaque echogenicity and other features of plaque stability, independently of changes in the plaque size (e.g.

thickness, area, volume). Most importantly, the authors described a dose-dependent pattern of statin-induced plaque echogenicity since it was more profound when higher doses were administered. Probably, the pleiotropic (e.g. anti-inflammatory) rather than lipid-lowering properties of statins, might provide a plausible explanation for this pattern. Since 2015, three more studies [38–40] have been published investigating the effect of statins on carotid plaque echogenicity. Those studies examined different statin class members (atorvastatin 20–80 mg/d, pitavastatin 2 mg/d, pravastatin 10 mg/d) in patients with already existing carotid plaques and stroke or hypercholesterolemia for 6–12 months. All three studies showed an increase in carotid plaque echogenicity. Notably, statin-related reduction in high-sensitivity C-reactive protein (hs-CRP) was inversely correlated with the increase of the GSM [38]. Advances in carotid ultrasound allow for the measurement of carotid total plaque area, which has been associated with a high rate of cardiovascular events (stroke/myocardial infarction/revascularization) [41]. Intensive pharmaceutical interventions, among them statin administration, reduce total plaque area, which results in a decline in clinical adverse events. Newer ultrasonographic techniques have also emerged, such as superb microvascular imaging (SMI), contrast-enhanced ultrasound (CEUS), and carotid plaque elasticity [42]. Preliminary data have suggested the association of statin therapy with less IPN, based on SMI and CEUS, but their diagnostic accuracy should be further tested [40]. Regarding the underlying mechanisms of statin-induced carotid plaque echogenicity (a higher GSM score), this probably derives from increased plaque calcification, usually observed with statins [10]. Hence, carotid ultrasound has the potential to easily assess changes in plaque composition, but more studies are required to validate the impact of statin therapy on ultrasound-based "vulnerable" plaques and clinical outcomes.

Effects of statins on fluorodeoxyglucose-positron emission tomography/computed tomography--based assessment of carotid plaque vulnerability

PET/computed tomography (CT) has been proposed as a useful tool for the detection of arterial wall inflammation implicating atherosclerotic plaque vulnerability [43]. In assessing the noninvasive quantification of inflammation--related plaque metabolism, 18-fluorodeoxyglucose (FDG) radiotracer accumulates in plaque macrophages, depicting the severity of atherosclerotic plaque inflammation [44]. In other words, PET/CT can detect even small changes in arterial wall inflammation, which is a unique property among other imaging techniques or biomarkers. So far, seven prospective studies have used scintigraphy to evaluate the impact of statins on carotid plaque inflammation by measuring target-to-background ratio (TBR) (n = 5 studies) [45–48] and/or standardized uptake value (SUV) (n = 3 studies) [39, 49, 50]. Most of them supported a significant reduction of arterial wall inflammation after either 3-month atorvastatin (10–80 mg/d) [46, 48–50] therapy, or 1-month atorvastatin (20 mg/d) [45] administration, or 6-month therapy with either simvastatin (10 mg/d), rosuvastatin (10 mg/d) [39], pitavastatin (2 mg/d), or pravastatin (10 mg/d) [39]. Only one study failed to show such an effect [46]. Although none of those studies co-evaluated the clinical outcomes along FDG-PET/CT scan findings, the results indirectly suggest that statin administration favorably changes plaque texture by suppressing intraplaque inflammation [48]. This could decide unambiguously the dosage of statins.

Table 1 summarizes the up-to-date data on statin--induced effects on novel imaging markers of carotid plaque vulnerability based on imaging modalities.

Limitation of imaging markers

Overall, the absence of cut-off values remains the great disadvantage of novel imaging markers for their clinical application in patients with carotid atherosclerosis. The favorable statin-induced changes in imaging parameters should be graded based on validation studies. Unambiguously, carotid ultrasound seems to be the most cost-effective among all imaging techniques; and it is also superior in terms of saving time, feasibility, and reproducibility. There is a plethora of prospective data supporting its accuracy, which makes it a first-line choice for monitoring patients with asymptomatic carotid atherosclerosis.

EFFECTS OF STATINS ON BIOMARKERS OF CAROTID PLAQUE VULNERABILITY

Inflammatory biomarkers

Inflammatory biomarkers play a key role in carotid artery disease, mediating plaque progression and vulnerability. In parallel, statins exert anti-inflammatory properties with potential stabilizing effects on atherosclerotic plaques [51]. Twenty-four prospective clinical trials have assessed the influence of statins on carotid plaque vulnerability concomitantly with the modulation of circulating inflammatory biomarkers. Based on imaging indices of plaque vulnerability, such as PET scans [47, 48–50, 52] and carotid plaque echogenicity [53, 54], most of those studies suggested an improvement in plaque stability after statin administration, accompanied by a significant reduction in inflammatory biomarkers. Those studies used the most known inflammatory biomarkers, like CRP [47–49, 53–59], interleukin (IL)-6 [53, 55–57, 59], tumor necrosis factor (TNF)-a [49, 54, 56, 59], and monocyte chemoattractant protein-1 [49]. Nevertheless, two studies [52,58] failed to demonstrate the stabilizing effects of statins despite their anti-inflammatory action while other studies failed to find any effect of statins on the aforementioned anti-inflammatory biomarkers at all. Using less-known inflammatory biomarkers such as tumor necrosis factor receptor (TNFR)-I and II [58], IL-2, -8, -10, -18, -23, interferon-γ, transforming growth factor (TGF)-β [59], pentraxin-3 [49], and others, statins have shown anti-inflammatory impact as well. The association

Table 1. Studies investigating the effects of statins on carotid plaque vulnerability based on novel imaging modalities

Authors	Population (number, underlying disease)	Protocol design (type, duration, groups, dose)	Novel imaging markers
MRI			
Feng T 2017 [22]	50 patients with carotid atherosclerosis	Randomized (48 weeks) • 26 patients PITA (2 mg/d) • 24 patients PITA (4 mg/d)	↓ Lipid core area ↓ Plaque thickness ↓ Wall area ↓ Normalized wall index ↓ Lumen area (dose-dependent effect of PITA)
Brinjikji W 2017 [31]	Systematic review: 7 studies (8 treatment arms), 361 patients with carotid atherosclerosis	Non-randomized (3–24 months) Various statins	↔ Wall volume ↔ Lumen volume ↓ LRNC volume
Alkhalil M 2018 [33]	21 statin-naive patients with ACS	Non-randomized (3 months) ATOR (80 mg/d)	↓ Carotid lipid (%) ↑ Carotid fibrous (%)
Du R 2019 [34]	43 statin-naive patients with asymptomatic carotid atherosclerosis underwent	Non-randomized (3, 12 and 24 months) ROSU (5–20 mg/d) & DCE-MRI	↓ Adventitial & plaque vascularity ↔ Adventitial & plaque vascular permeability
Carotid ultrasound			
Ibrahimi P 2015 [37]	Systematic review: 9 studies (11 treatment arms), 566 participants with carotid atherosclerosis	5 prospective open-label studies and 4 RCTs Mean follow up: 7.2 months ATOR, SIMVA, PRAVA, PITA, and ROSU	↑ Plaque echogenicity ↓ hs-CRP (dose-dependent statin effect)
Marchione P 2015 [38]	210 patients with recent symptomatic ischemic cerebrovascular event (TIA, minor stroke, major stroke)	Randomized (12 months) • 68 patients ATOR (80 mg/d) • 69 patients ATOR (40 mg/d) • 73 patients no statin	↑ Plaque echogenicity ↑ GSM score ↔ Plaque thickness ↔ Degree of stenosis ↓ hs-CRP
Zhu Y 2019 [40]	82 patients with carotid atherosclerosis	Randomized (6 months) • 39 patients ATOR (20 mg/d) • 43 patients control group	↓ Intraplaque neovascularization (CEUS and SMI)
F^{18}-FDG-PET			
Kim CJ 2020 [45]	Statin-naive patients with ACS and non-calcified carotid plaques	Non-randomized (1 month) ATOR (20 mg/d)	↓ TBR
Hoogeveen RM 2021 [46]	14 patients with CKD stage 3 or 4 (eGFR = 15–60 ml/min/1.73 m^2)	Non-randomized (12 weeks) ATOR (40 mg/d)	↔ TBR
Oh M 2019 [47]	50 patients with ACS	Randomized (6 months) • 25 patients Ezetimibe/SIMVA (10/10 mg/d) • 25 patients ROSU (10 mg/d)	↓ Plaque inflammation ↓ TBR
Tawakol A 2013 [48]	67 subjects with risk factors or established carotid atherosclerosis	Randomized (4 weeks and 12 weeks) • ATOR (10 mg/d) • ATOR (80 mg/d)	↓ TBR (dose-dependent reduction)
Komatsu T 2021 [49]	31 statin-naive patients w/ carotid atherosclerosis	Randomized (12 weeks) • 15 patients dietary management • 16 patients ATOR (10 mg/d)	↓ Arterial inflammation (carotid and thoracic aorta) ↓ 18-FDG uptake
Van der Valk F 2016 [50]	24 patients with AS 20 controls age- and sex-matched	Non-randomized (3 months) ATOR (40 mg/d)	↓ Carotid arterial wall inflammation ↓ 18-FDG uptake
F^{18}-FDG-PET + carotid ultrasound			
Watanabe T 2015 [39]	20 patients high risk of atherosclerosis or in need of statin treatment	Randomized (6 months) • 10 patients PITA (2 mg/d) • 10 patients PRAVA (10 mg/d)	↓ TBR (in the PITA group) ↓ CIMT (PITA group) ↑ CIMT (PRAVA group) ↓ SUV ↑ Plaque echogenicity

Abbreviations: ACS, acute coronary syndrome; AS, ankylosing spondylitis; ATOR, atorvastatin; CEUS, contrast enhanced ultrasound; CIMT, carotid intima-media thickness; DCE-MRI, dynamic contrast-enhanced MRI; FDG, fluorodeoxyglucose; GSM, gray scale median; hs-CRP, high-sensitivity C-reactive protein; LRNC, lipid-rich necrotic core; MRI, magnetic resonance imaging; PET, positron emission tomography; PITA, pitavastatin; PRAVA, pravastatin; RCTs, randomized controlled trials; ROSU, Rosuvastatin; SIMVA, simvastatin; SMI, superb microvascular imaging; SUV, standardized uptake value; TBR, target-to-background ratio; TIA, transient ischemic attack

between carotid plaque stabilization and suppressed inflammation after statins was observed across heterogeneous studies using a wide spectrum of statins, doses, and therapy duration. Nevertheless, the inhibition of inflammatory pathways remains among the predominant pleiotropic mechanisms of intensive statin therapy, leading to histopathologically stable carotid plaques and fewer cardiovascular events [60–62]. Provisionally, close monitoring of those biomarkers in statin-treated patients could predict atherosclerotic plaque destabilization and cardiovascular disease progression (Figure 2).

Neovascularization

Intraplaque neovascularization is a characteristic feature of vulnerable plaques, associated with carotid plaque rupture and stroke recurrence [63]. Unfortunately, only small-cohort studies have examined the impact of statins on IPN. Four previous studies have assessed IPN using

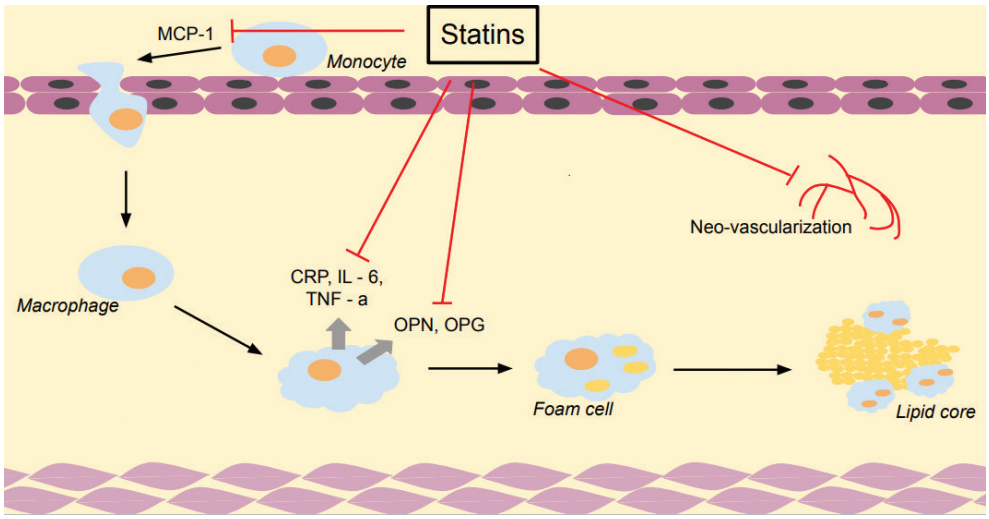

Figure 2. Stabilizing effects of statins on the carotid atherosclerotic plaque by suppressing inflammation and neovascularization

Abbreviations: CRP, C-reactive protein; IL, interleukin; MCP, monocyte chemoattractant protein; OPG, osteoprotegerin; OPN, osteopontin; TNF-a, tumor necrosis factor-a

CEUS. All of them suggested reduced IPN after either 6-month statin therapy [40, 64], or 24-month atorvastatin administration (20 mg/d) [65], or angiotensin-converting enzyme inhibitors and statins treatment [66]. Similarly, in 45 statin-naive patients with asymptomatic carotid atherosclerosis, 24-month rosuvastatin therapy (5–20 mg/d) reduced the MRI-based IPN [34]. The main limitations of the existing studies are the small number of participants and short duration of therapy [34]. To our knowledge, a single study [67] has reported an inverse relationship between the statin-induced regression of IPN within carotid plaques and stroke incidence. Those atheroprotective mechanisms of statins may be attributed to their favorable effects on endothelial cell proliferation and nitric oxide (NO) bioavailability [68–70]. Therefore, larger studies are needed to confirm the negative impact of statins on IPN, the underlying mechanisms, and the clinical relevance.

Calcification

Osteopontin (OPN) and osteoprotegerin (OPG) constitute potent inhibitors of osteoclastogenesis and vascular calcification and are secreted by a plethora of tissues, including endothelial cells, vascular smooth muscle cells, and macrophages [71–72]. OPN is a multifunctional phosphoprotein, and OPG is a member of the TNF-related family and part of the receptor activator of nuclear factor-B ligand (RANKL). Both of them have been involved in several inflammatory conditions, such as autoimmune diseases, atherosclerosis, and vascular calcification [73], and they have been associated with cardiovascular mortality [74, 75].

Scarce data support the influence of statins on blood regulators of vascular calcification [76].So far, only three studies have investigated the effect of statins on circulating levels of OPN and OPG in patients with carotid artery disease [77–79]. In particular, patients with symptomatic or asymptomatic established carotid atherosclerosis were treated with atorvastatin 10–80 mg/d for 6 to 12 months. Statin administration significantly reduced OPN and OPG levels in a dose-dependent manner. Simultaneously, the GSM score was inversely correlated to the atorvastatin-induced changes in OPN and OPG levels [77, 78]. That led to a mechanistic explanation of an inverse relationship between atherosclerotic calcification triggered by statins and carotid plaque vulnerability. Although this hypothesis seems attractive, it has two important drawbacks. First, it should be further tested in studies evaluating clinical outcomes and not only surrogate markers, like the GSM [10]. Second, the interplay between statins and vascular calcification is more complex. The latter comprises an essential part of atherosclerosis development but is a less common characteristic in advanced, vulnerable atherosclerotic plaques. Statins seem to exert a dual action. On the one hand, in developing atherosclerotic plaques, they can slow down or even inhibit atherogenic mechanisms, like calcium deposition [80]. On the other hand, in established and advanced atherosclerotic lesions, they may increase the calcification density [81]. This working hypothesis has been derived from extensive research about the interpretation of higher calcium scores in the coronary artery tree among statin users [82]. The calcium score is an unambiguous index of atherosclerosis progression, but the clinical meaning of its modification by statins is still complex. Extrapolating those results to carotid artery disease, more studies with a larger number of patients need to be conducted to verify the interplay between statin use, the serum levels of vascular calcification inhibitors, the stabilization process via calcification, and the net effect on the overall cardiovascular risk. Table 2 depicts the combined application of biomarkers and imaging techniques for the assessment of carotid plaque vulnerability.

Table 2. Studies investigating the effects of statins on carotid plaque vulnerability based on a combined assessment of biomarkers and imaging markers

Authors	Population (number, underlying disease)	Protocol design (type, duration, groups, dose)	Biomarkers	Novel imaging markers
Komatsu T 2021 [49]	31 statin-naive patients carotid atherosclerosis	Randomized (12 weeks): 15 patients dietary management 16 patients ATOR (10 mg/d)	↓ CRP ↓ S100A12 ↔ TNF-a ↔ MCP-1 ↔ Pentraxin 3	↓ Arterial inflammation (carotid and thoracic aorta) by FDG-PET/CT ↑ FMD
Oh M 2020 [52]	48 patients ACS	Randomized (6 months) ROSU (20 mg/d) Ezetimibe/ROSU (10 mg/5 mg/d)	↓ hs-CRP (ezetimibe/ /ROSU group)	↔ TBR (PET)
Oh M 2019 [47]	50 patients ACS	Randomized (6 months) 25 patients Ezetimibe /SIMVA (10/10 mg/d) 25 patients ROSU (10 mg/d)	↔ hs-CRP	↓ Atherosclerotic plaque inflammation ↓ TBR
Van der Valk F 2016 [50]	24 patients AS 20 age-, sex- matched controls	Non-randomized (3 months) ATOR (40 mg/d)	↓ CRP	↓ Carotid arterial wall inflammation (by FDG-PET/CT)
Watanabe T 2015 [39]	20 patients	Randomized (6 months) 10 patients PITA (2 mg/d) 10 patients PRAVA (10 mg/d)	↔ -CRP	↓ TBR (PITA group)
Tawakol A 2013 [48]	67 patients cardiovascular risk factors or established atherosclerosis	Randomized (4 weeks and 12 weeks) ATOR (10 mg/d) ATOR (80 mg/d)	↔ hs-CRP	↓ TBR (dose-dependent reduction)
Yamagami H 2008 [53]	81 patients hypercholesterolemia + carotid atherosclerosis	Non-randomized (12 months): 41 patients no statin 24 patients SIMVA (10 mg/d) 16 patients ATOR (5 mg/d)	↓ hs-CRP ↓ IL-18 ↔ IL-6	↓ Plaque thickness ↑ Plaque echogenicity
Nakamura T 2008 [54]	65 patients ACS + echolucent carotid plaque	Randomized (1 month): 33 patients PITA (4 mg/d) 32 patients placebo	↓ CRP ↓ VEGF ↓ TNF-a ↓ Total cholesterol ↓ Triglycerides ↓ LDL-C	↑ Plaque echogenicity
Kadoglou N 2008 [77]	97 patients with carotid atherosclerosis mot requiring intervention 52 age- and sex-matched controls	Non-randomized (6 months) 97 patients ATOR (10–80 mg/d) target LDL-C <100 mg/dl 52 controls no treatment	↓ hs-CRP ↓ OPG ↓ OPN	↑ GSM
Kadoglou N 2010 [79]	140 patients with symptomatic or asymptomatic moderate carotid atherosclerosis not requiring intervention	Randomized (12 months) 70 patients moderate therapy: ATOR (10–20 mg/d) target LDL-C <100 mg/dl 70 patients aggressive therapy: ATOR (80 mg/d) target LDL-C <70 mg/dl	↓ hsCRP ↓ OPG ↓ OPN (dose-dependent manner)	↑ GSM (significant increase after aggressive therapy)

Abbreviations: AS, ankylosing spondylitis; CT, computed tomography; FMD, flow-mediated dilatation; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; MCP, monocyte chemoattractant protein; OPG, osteoprotegerin; OPN, osteopontin; TBR, target-to-background ratio; TNF-a, tumor necrosis factor-a; VEGF, vascular endothelial growth factor; other — see Table 1

Thrombosis

A few other biomarkers have been targeted by statin interventions with regard to their correlation to carotid plaque vulnerability and cardiovascular morbidity and mortality. Tissue factor (TF) is a glycoprotein, derived from activated macrophages and T cells. It is highly expressed in unstable atheromatous plaques and relates to the coagulation cascade [83]. Two studies have examined the effect of statin use on TF expression in carotid plaques extracted from patients undergoing CEA. Both of them found less TF protein expression within carotid plaques from statin-treated patients, without any influence on tissue factor pathway inhibitor [84, 85]. Perhaps, this may lead to a suppressed thrombotic response to plaque rupture, and consequently to a reduced incidence of ipsilateral stroke.

Limitations of biomarkers

Biomarkers are easy to use, accessible, relatively cheap, and repeatable tools for the surveillance of many diseases and monitoring the efficacy of their therapeutic regimens. Numerous biomarkers can be easily assayed in blood samples, but their levels may be affected by co-morbidities or medications while their circulating levels do not exclusively express the local plaque destabilization process, confounding the interpretation of their changes. Moreover, their use at the moment is limited to research purposes.

PERIOPERATIVE TREATMENT WITH STATINS OF PATIENTS WITH CAROTID ATHEROSCLEROSIS

The systematic use of statins is increasing during the perioperative period of carotid revascularization, either CEA or CAS. Substantial evidence supports using statins before major vascular operations as a measure to reduce the perioperative incidence of major complications/death [86]. A meta-analysis of six studies (7 053 patients) undergoing CEA demonstrated a lower periprocedural death rate in statin-treated patients compared to statin-naive

patients, without affecting the risk of stroke [87]. A more recent systematic review analyzed seven studies of 21 387 CEA-treated patients and confirmed reduced mortality associated with statin treatment persistent for a longer mean follow-up period (62 months) [88]. That meta-analysis described also a lower incidence of periprocedural stroke as a result of statin administration. Lastly, a similar meta-analysis (four studies of 4 978 patients) showed better survival rates and decreased risk of stroke when statins were used before CEA [89]. In conclusion, in patients undergoing CEA, the early prescription of statins unambiguously reduces mortality and, possibly, stroke incidence, but more studies are needed.

In the case of patients undergoing CAS, a single meta-analysis including 11 studies and 4 088 patients documented lower rates of perioperative ischemic stroke and death in patients treated with statins before intervention [90]. However, the risk of perioperative TIAs was not affected by statins. Since then, one randomized control trial (RCT) and three retrospective studies have been published with controversial results. In particular, the RCT confirmed that patients receiving statins had a lower incidence of post-operative TIAs and stroke in comparison to placebo receivers [91]. However, the latest three retrospective studies did not detect any benefit from statin administration in terms of stroke incidence [92–94]. Thus, the evidence about the advantages of statins' use in patients undergoing CAS is still controversial. Further data, especially from powered RCTs are needed.

AGGRESSIVE VS. CONVENTIONAL STATIN THERAPY

The benefits of aggressive over conventional statin treatment in patients with carotid stenosis is a highly challenging topic. The term "aggressive" describes the prescription of the highest dose of statins independent of LDL-C levels, while the "conventional" approach determines the dose based on the achievement of LDL-C targets. We have previously demonstrated a dose-dependent increase in carotid plaque stability expressed by the GSM score in patients with carotid atherosclerosis receiving statins and not requiring revascularization [81]. Growing evidence supports the aggressive statin therapy over the conventional one with regard to its impact on plaque stability in asymptomatic patients with carotid atherosclerosis without the need for revascularization [95]. Most importantly, the higher doses of statins have been extensively shown as an effective measure to reduce morbidity and mortality in patients with other atherosclerotic manifestations at very low risk of adverse events [96, 97].

On the other hand, only a few retrospective and observational studies have comparatively evaluated aggressive versus conventional perioperative statin therapies in patients undergoing either CEA or CAS. The results regarding the perioperative stroke rates were contradictory [94, 98, 99]. Interestingly, the higher the dose of statins, the lower the frequency of new lesions on MRI after 48 hours of CAS. In a retrospective study of 21 277 individuals undergoing CEA, aggressive statin therapy did not further reduce the perioperative stroke rates [100]. As a result, RCTs with larger populations need to be conducted to clarify whether higher statin doses confer greater cardiovascular and cerebrovascular protection on patients with carotid stenosis undergoing revascularization. After aggressive statin therapy, a further decrease in LDL-C levels is expected. This is in line with the current recommendations of the scientific societies for very low LDL-C targets in patients with significant carotid atherosclerosis. However, the bottom LDL-C limit has not been yet established, maintaining "the lower LDL-C, the better for the patient" as a general rule. In this case, the therapeutic target should be re-considered from lipid-lowering to other indices of plaque vulnerability.

CONCLUSION

The current literature review recommends a multi-level guided statin therapy based on blood LDL-C levels, novel imaging modalities, and systematic biomarkers in patients with established asymptomatic carotid atherosclerosis not requiring revascularization. Such an approach, in addition to lipid-lowering, will assist in patient risk stratification and guide an aggressive statin therapy, with favorable effects on the clinical course. On the other hand, perioperative statin usage has not shown consistently beneficial results. Only the pre-operative commencement of statins in patients undergoing CEA has been shown to be beneficial independently of the dose. More unambiguous data are needed to alter the therapeutic targets of statins in patients with carotid atherosclerosis undergoing, or not, carotid revascularization.

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