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Article

Bubbles help in troubles: Contrast-enhanced ultrasound (CEUS) as a predictor of recurrence for TIA/stroke in low-grade internal carotid artery stenosis

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Abstract: Introduction: Contrast-enhanced ultrasound (CEUS) allows the visualization of atherosclerotic plaque neovessels, which are the hallmark of carotid plaque instability. **Aim:** The purpose of our prospective study was to check the correlation between carotid CEUS analysis and the recurrence of TIA/stroke in patients with a previous recent TIA/stroke and neurological impairment congruent with vascular stenosis. **Materials and methods:** From November 2021 to May 2023, 62 consecutive patients (mean age 73.8 ± 12.2, 51 female) with a TIA/stroke in the previous 30 days underwent carotid ultrasound and carotid CEUS in an outpatient setting after 10 days from the acute event. The inclusion criteria were one atherosclerotic plaque inside the internal carotid artery, congruent with symptoms, which was causing a stenosis of less than 50% (low-grade stenosis). The carotid plaque neovascularization scoring method was score 0: no visible microbubbles within the plaque (A); score 1: minimal microbubbles confined to periadventitial (B); and score 2: microbubbles present throughout the plaque core (C). During the 6-month, 12-month, and 18-month follow-ups, we checked TIA/stroke recurrences. A multivariable logistic regression analysis was performed. $P < 0.05$ was considered significant. **Results:** In our series, 22% of patients have a CEUS score of 0, 35% have a CEUS score of 1, and 43% have a CEUS score of 2. At six-month follow-up, we found 21% TIA/stroke recurrences in CEUS score 2, despite the ongoing best medical therapy as per guidelines. At 12-month follow-up, we did not find any recurrence of cerebrovascular events. In Cox regression analysis, CEUS-detected neovascularization was independently associated with TIA/stroke recurrence (hazard ratio, 5.37; 95% confidence interval, 1.36–2.31). **Conclusions:** Plaque neovascularization, detected by CEUS, is an independent predictor of TIA/stroke recurrence at six-month follow-up in patients with carotid atherosclerosis despite low-grade stenosis. This diagnostic method can guide the best surgical vs. medical choice in the treatment of low-grade carotid stenosis, which is determined by soft atherosclerotic plaque.

Keywords: CEUS; TIA stroke; carotid stenosis; ultrasound; doppler; echography

1. Introduction

Atherosclerosis is an inflammatory disease caused by lipoproteins. The rupture of vulnerable atherosclerotic plaques and thrombosis are the main contributors to the development of acute cardiovascular events [1]. Despite various advances in the treatment of atherosclerosis, there has been no satisfaction in the assessment and evolution of atherosclerotic vascular disease. The identification and classification of vulnerable plaques at an early stage, as well as research of new treatments, remain a challenge [2]. The precocious identification of specific morphological features of vulnerable plaques (including 1) intraplaque hemorrhage, 2) large lipid necrotic cores, 3) thin fibrous caps, 4) inflammation, and 5) neovascularization) is fundamental. Notably, the development of novel ultrasound techniques has introduced the traditional assessment of plaque echogenicity and luminal stenosis to a deeper assessment of plaque composition [3]. In recent years, the implementation of contrast-enhanced ultrasound (CEUS) in clinical practice has opened new horizons in arterial pathologies research, since this technique is able to supply new sets of data that can be crucial in patients' management. The main applications of CEUS in the arterial system are the detection, characterization, and follow-up of carotid plaques and the endoleak after endovascular aortic repair. Other clinical conditions in which CEUS was demonstrated to be a useful tool are large vessel vasculitis, dissections, and untreated aneurysms. In carotid atherosclerosis, CEUS is not only able to acquire quantitative data about stenosis but also to perform a qualitative assessment of the plaque. The most important plaque features that CEUS is able to depict are ulceration and neovascularization. CEUS is also a good tool to highlight the presence of inflammatory infiltrates. Thus, CEUS is crucial in order to allow better risk stratification and management of patients, because ulceration, neovascularization, and inflammatory infiltrates contribute to plaque vulnerability. International guidelines for carotid artery atherosclerosis treatment (surgical and/or endovascular) are clear and strictly related to 1) patients' symptoms, 2) grade of vascular stenosis, and 3) measured velocity [4,5]. In case of not significant stenosis caused by soft plaque, which may determine TIA/stroke and its recurrence due to embolism, surgeons are keen to remove it [6]. This prudential orientation may cause an overtreatment of patients. In regard to this perceived feeling of surgical overdoing and aiming to move towards increasingly precise medicine, we started a prospective observational trial with the purpose of identifying possible diagnostic strategies to better orient surgical decision-making in this grey zone. To meet our commitment to reducing not only surgical overtreatment but also patients' X-ray exposure, we find that carotid CEUS may be the method to adopt in our research program, and we try to elaborate an image-based surgical decision score system.

2. Material and methods

The aim of our prospective study was to check the correlation between carotid CEUS analysis and the recurrence of TIA/stroke in patients with a previous recent TIA/stroke and neurological impairment congruent with vascular stenosis. From November 2021 to May 2023, 62 consecutive patients (mean age 73.8 ± 12.2, 51 female) with a TIA/stroke in the previous 30 days underwent carotid ultrasound and carotid CEUS using 3 mL of intravenous sulfur hexafluoride solution (SonoVue®, Bracco, Milan, Italy) in an outpatient setting 10 days after the acute event. The demography of the population is summarized in **Table 1**. Inclusion criteria were one atherosclerotic plaque inside the internal carotid artery, congruent with symptoms, which was causing a stenosis less than 50% (low-grade stenosis), while exclusion criteria were previous history of cerebrovascular diseases due to cardioembolic accident; history of any other neurological disease; presence of infections, malignancies, cardiopulmonary dysfunction, hepatic dysfunction, kidney failure (any degree), or respiratory failure; or hyperechoic or uniformly hyperechoic plaque. The research topic is important, addressing the prediction of recurrence for TIA/stroke in patients with low-grade internal carotid artery stenosis using CEUS. In literature, it is well shown that high plaque neovascularization and microvascularization are associated with a higher risk of symptomatic stenosis despite their degree, but the Duplex ultrasound scan, which is routinely used as a diagnostic method, has some limitations in detection, such as microvascularization and neovascularization. On the other hand, CEUS is an imaging technique that involves the use of contrast agents (e.g., saline solution bubbles or sulfur hexafluoride solution) to enhance the visualization of blood flow within the carotid arteries using ultrasound technology. During a carotid CEUS procedure, the contrast agent is injected into the bloodstream. It highlights the blood vessels and improves the clarity of the ultrasound images. This allows us to more accurately evaluate the structure and function of the carotid arteries, aiding in the diagnosis and management of conditions such as carotid artery disease and stroke risk assessment [7,8]. Carotid artery CEUS is a complementary part of the multiparametric ultrasound technique, which shows promising results and provides additional characterization of soft- and high-risk atherosclerotic plaques. The added value of CEUS in the characterization of atherosclerotic plaque is that this method can clearly indicate regions with high neovascularization, and it visualizes ulcerations on the plaque surfaces, suggesting the increased instability risk. The only limitation is the extensive calcinosis with important acoustic shadows in carotid atherosclerotic plaque neovascularization, but calcium indicates stability, so it rules out the softness of plaque and its related risk. Despite the promising performance of CEUS and its relatively limited expenditure in terms of time and cost, in clinical practice and in literature, CEUS is not so represented; in fact, in 2024, only 29 studies are mentioned in the most recent review [9]. Feinstein [10] in 2006 and Schinkel et al. [11] in 2020 reported the feasibility of using contrast-enhanced ultrasound to identify intraplaque neovascularization, but only in 2022 have many studies shown that the CEUS method can significantly improve the imaging effect of this neo-revascularization and microvascularization [12]. In 2020, Zhu et al. showed that there is a correlation between the grade of plaque enhancement and the risk of ischemic stroke. The data suggested that the presence of neovascularization is a marker for unstable plaque [13]. Overall, carotid artery plaque contrast-enhanced ultrasound can play an important role in the diagnosis and management of carotid artery disease, helping cardiovascular surgeons to make informed decisions about treatment and reduce the risk of stroke and/or futile risk of overtreatment. Aware of the above, we have arbitrarily chosen the intra-plaque neovascularization (IPN) score as indicated in the existing literature [14]. The utility of CEUS in the evaluation of carotid IPN to reclassify patients into more accurate risk categories has been confirmed by several studies [15,16]. Based on the existence and location of ultrasound microbubbles within each plaque, IPN is typically graded into three levels in CEUS: grade 0: no visible microbubbles in the plaque; grade 1: minimal microbubbles confined to the shoulder or adventitial side of the plaque; and grade 2: plentiful microbubbles throughout the plaque. We adopt a carotid IPN scoring method in which score 0 means no visible microbubbles within the plaque; score 1 is when minimal microbubbles are confined to peri-adventitial; and score 2 consists of microbubbles that are present throughout the plaque core. We checked

TIA/stroke recurrences at 6- and 12-month follow-ups, and no patient was lost at follow-up. We have also performed 18-month follow-up by phone call: no patient was lost, and no one reported having experienced any TIA/stroke recurrence during this extra frame time follow-up. We used a Philips EPIQ CVx® with its linear probe and its vascular setting program for each ultrasound examination. Multivariable logistic regression analysis for ischemic stroke and recurrent TIA was performed, checking the correlation between TIA/stroke recurrence and gender, age, hypertension, hyperlipidemia, diabetes (any type), chronic obstructive lung disease (COPD), smoking status (active or previous), obesity, stress, atrial fibrillation, plaque velocity (peak systolic velocity), internal carotid kinking, CEUS score 0, CEUS score 1, and CEUS score 2. The internal ethical committee approved the study and produced a specific informed consent form for patients. This study complies with ethical standards; each patient signed the specific informed consent (in accordance with the Declaration of Helsinki) to be enrolled in this research and authorized to publish the data in the anonymous mode for search purposes only. Additional informed consent for personal data collection, treatment, post-processing analysis, and publishing purposes was collected and signed by each patient as per the institutional internal ethical committee. No sponsor or external fund was used to conduct this independent search. Statistical analysis was performed using SPSS Statistics 17.0 software. Frequencies and percentages (%) were used for categorical variables, whereas mean ± SD was employed for continuous variables. Continuous variables were compared between three groups using the independent *t*-test. Proportions were compared using the chi-square test. To determine the association between variables and ischemic stroke or recurrent TIA after TIA, a multivariate logistic regression analysis was performed. Receiver operation curve (ROC) was generated to examine the efficacy of the resulting model. The level of significance was set at a P value < 0.05.

Table 1. Patients' demography.

Variable	***N* (%)/Mean ± SD**	**Variable**	***N* (%)/Mean ± SD**
Female	51 (82)	Antiplatelet therapy	60 (97)
Male	11 (18)	Antihypertensive therapy	62 (97)
Age	73.8 ± 12.2	Statin	58 (94)
Hypertension	60 (97)	New oral anticoagulant	22 (35)
Hyperlipidaemia	58 (94)	Atrial fibrillation	8 (13)
Diabetes (any type)	24 (39)	Coronary artery disease	2 (3)
COPD	21 (34)	Peripheral artery disease	14 (23)
Active smoker	41 (66)	Internal carotid artery stenosis (%)	52 ± 10
Previous smoker	21 (34)	Peak systolic velocity (cm/s)	162 ± 104
Stress	32 (52)	End diastolic velocity (cm/s)	62 ± 12

3. Results

CEUS generally makes up for the deficiency of conventional B-mode and color-Doppler ultrasound, which have long been challenged by their insufficient value to identify components and neovascularization within the plaque. In order to circulate freely in the bloodstream like red blood cells through capillaries, these microbubbles are designed into core-shell inflatable microspheres typically smaller than 7 μm in diameter [17]. The shell is usually composed of lipids, proteins, polymers, and surfactants. This makes a barrier between the surrounding environment and the encapsulated gas inside. The composition of the shell determines the hardness of microbubbles, their susceptibility to recognition by the reticuloendothelial system, and their resistance in high-intensity ultrasonic fields. In addition, the air core encased inside the microbubble considerably enhances the backward scattered acoustic signal [18]. Several types of microbubbles, such as the SonoVue® (Bracco, Milan, Italy, EU) series, are the main ultrasound contrast agents currently approved and recommended for clinical use. In clinical practice, conventional diagnostic ultrasound imaging frequency is usually less than 7.5 MHz, but higher spatial and temporal resolution is needed for the detection of fine vascular structures in preclinical applications, so 15–55 MHz is generally recommended. Penetration depth of CEUS is relatively poor compared with standard B-mode imaging. Lower imaging frequencies improve penetration, but spatial resolution gets worse. Gas-filled microbubbles can stay at the site of the capillary bed and oscillate upon interacting with the ultrasound wave, enhancing the reflected ultrasound signal and improving the visualization of small vascular beds. As is strongly recommended by the European Federation of Societies for Ultrasound in Medicine and Biology, CEUS has opened a new field of vision for the study of arterial pathology, for it can not only quantitatively assess the degree of atherosclerosis stenosis but also qualitatively assess the vulnerability of plaque based on the presence of ulceration, neovascularization, and inflammatory infiltration [14–19]. In literature, it is proven that the extent of intra-plaque neovascularization (IPN) displayed on CEUS has a good correlation with histology; in fact, in areas where plaques presented a larger degree of contrast enhancement, the corresponding region on histology also had increased density [14,15]. Based on those previous considerations, we used a Philips EPIQ CVx® with its linear probe and its vascular setting program. We have arbitrarily chosen the IPN score in harmony with the existing literature. Several studies have confirmed the utility of CEUS in the evaluation of carotid IPN to reclassify patients into more accurate risk categories. In CEUS, based on the existence and localization of the ultrasound microbubbles within plaque, IPN is typically graded into three levels: grade 0: no visible microbubbles in the plaque; grade 1: minimal microbubbles confined to the shoulder or adventitial side of the plaque; and grade 2: plentiful microbubbles throughout the plaque [15,16]. In our series, 22% of patients have a CEUS score of 0 (as shown in A), 35% of patients have a CEUS score of 1 (B), and 43% of patients have a CEUS score of 2 (C), as it is shown in **Figure 1**.

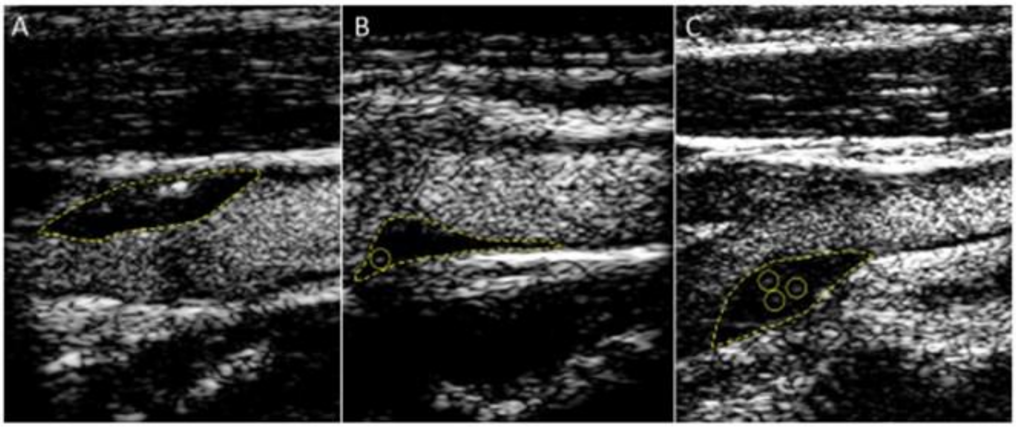

Figure 1. Carotid plaque neovascularization scoring: score 0: **(A)** no visible microbubbles within the plaque; **(B)** score 1: minimal microbubbles confined to periadventitial; **(C)** score 2: microbubbles present throughout the plaque core.

At six-month follow-up, we found 21% TIA/stroke recurrences in patients with CEUS score 2, despite the ongoing best medical therapy (antiplatelet, anti-hypertensive, and statin) as per guidelines. At 12-month and 18-month follow-up, we did not find any recurrence of cerebrovascular events. The multivariable logistic regression analysis for ischemic stroke and recurrent TIA shows that CEUS-detected neovascularization was independently associated with TIA/stroke recurrence (hazard ratio, 5.37; 95% confidence interval, 1.36–2.31). No other considered factors appeared to be significant predictors of the recurrence of TIA/stroke, as is reported in **Table 2**. The ROC of the multivariate logistic regression analysis model for CEUS score 2 is shown in **Figure 2**.

Table 2. Multivariable logistic regression analysis for ischemic stroke/TIA recurrence.

Variable	***P* value**	**Hazard ratio**	**Confidence interval 95%**
Female	0.21	0.07	0.67–0.87
Male	0.11	0.04	0.57–0.98
Age	0.89	0.02	0.76–0.89
Hypertension	0.98	0.32	0.57–0.98
Hyperlipidaemia	0.92	1.2	0.26–0.29
Diabetes (any type)	0.76	1.8	0.76–0.89
COPD	0.09	0.5	0.06–0.89
Active smoker	0.78	0.7	0.23–9.87
Previous smoker	0.43	0.3	0.57–12.48
Obesity	0.08	1.3	0.05–11.28
Stress	0.68	0.2	0.26–0.98
Atrial fibrillation	0.89	1.8	0.76–0.89
Peak systolic velocity	0.25	1.98	0.22–0.34
Vessel kinking	0.82	1.72	0.52–9.48
CEUS score 0	0.23	1.02	0.21–1.28
CEUS score 1	0.08	1.32	1.28–1.98
CEUS score 2	0.002	5.37	1.36–2.31

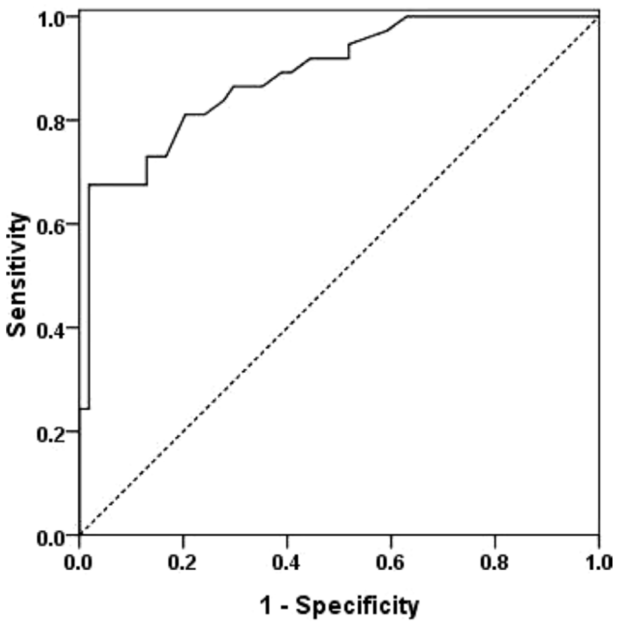

Figure 2. Receiver operation curve (ROC) of the multivariate logistic regression analysis model for CEUS2 score.

4. Discussion

Carotid CEUS is often used as a non-invasive alternative to other imaging techniques such as computed tomography angiography (CTA) and/or magnetic resonance angiography (MRA) for evaluating extracranial carotid artery disease [20]. It offers advantages such as real-time imaging, lack of ionizing radiation, and the ability to assess blood flow dynamics. Carotid plaque instability refers to a condition where the atherosclerotic plaque becomes particularly prone to rupture or erosion. When plaque becomes unstable, it can lead to the formation of blood clots (thrombosis) or embolism. These clots or particles can then travel to smaller blood vessels in the brain, leading to blockages and potentially causing a stroke or transient ischemic attack (TIA) [6]. Several factors contribute to carotid plaque instability, including the composition of the plaque, because plaque that contains a large amount of soft, lipid-rich material is more prone to rupture than stable, calcified plaque. Other factors for instability are the plaque size and shape; in fact, large, irregularly shaped plaques are more likely to be unstable compared to smaller, smoother plaques. Underlying medical conditions like hypertension, diabetes, hyperlipidemia, and smoking can contribute to plaque instability by promoting inflammation and atherosclerosis; finally, hemodynamic factors, due to turbulent blood flow, can increase stress on the plaque, potentially leading to its rupture [21]. All these factors were entered in our propensity score and Cox regression analysis, as reported in **Table 2**, but only CEUS-detected neovascularization was independently associated with TIA/stroke recurrence (hazard ratio, 5.37; 95% confidence interval, 1.36–2.31). Identifying carotid plaque instability is important because it indicates an increased risk of stroke or other cardiovascular events. Imaging techniques such as ultrasound, MRA, or CTA can help assess plaque stability by evaluating plaque composition, size, and characteristics [11]. Management of carotid plaque instability typically involves aggressive risk factor modification, including lifestyle changes (such as diet, exercise, and smoking cessation) and medications such as statins, single (or double) antiplatelet agents, and/or anticoagulants to stabilize the plaque and reduce the risk of thrombosis and/or embolism [22]. In some cases, surgical intervention, such as carotid endarterectomy or carotid artery stenting, may be considered to remove or stabilize the unstable plaque and restore proper blood flow. Atherosclerotic plaque vascularization, also known as neovascularization, refers to the formation of new blood vessels within or around an atherosclerotic plaque. This process occurs in response to the inadequate blood supply to the growing plaque and the hypoxic conditions within it. Neovascularization is the body's attempt to supply oxygen and nutrients to the hypoxic areas within or around the plaque. However, the newly formed blood vessels are often fragile and leaky, leading to increased inflammation and plaque instability. Neovascularization is commonly observed in advanced atherosclerosis and is associated with vulnerable plaques that have a higher risk of rupture and causing cardiovascular events such as heart attack or stroke. Detecting neovascularization within atherosclerotic plaques can be challenging but can be achieved through advanced imaging techniques such as contrast-enhanced ultrasound, MRA, or CTA [22]. These imaging examinations are expensive and time-consuming. In the case of CTA, it exposes patients to X-rays. On the other side, MRA identifying neovascularization within plaques may help in risk assessment and guiding treatment decisions in individuals with advanced atherosclerosis, but it is not adaptable for each patient (e.g., claustrophobia, intracorporeal metal splinters, or intracorporeal devices not MR compatible). Transient ischemic attack (TIA) can occur in individuals with low-grade carotid artery stenosis, although the risk is generally lower compared to cases of more severe stenosis. In low-grade carotid artery stenosis, the narrowing of the artery is typically less than 50% [23]. As it is described in the latest European guidelines, it is essential to recognize that even low-grade stenosis can contribute to TIA under certain circumstances, first of all, plaque vulnerability [5,24]. As mentioned above, IPN was usually graded by a semiquantitative image analysis relying on the visual assessment, which lacks internal standards, nor is IPN suitable for assessing highly calcified plaques, so divergence about the objectivity of CEUS simply employing IPN to evaluate vulnerable plaque still exists [25]. Notably, Boswell-Patterson et al. employed a new measurement parameter, neovascularized enhancement ratio (NER), to analyze complex atherosclerotic plaque models, which allows highly calcified plaques to be analyzed. The formula of NER is $(AP \times PER) - (AC \times CER)/(AP - AC)$, where AP equals plaque area, AC equals calcified area, PER equals plaque enhancement rate, and CER equals calcified area enhancement rate. NER in this study also shows a positive relationship with IPN volume [26]. Recently, Lyu et al. [27] proposed that the direction of contrast agent diffusion may be severe as another complementary method for the prediction of unstable atherosclerotic plaques. Apart from the characteristic contrast filling of the depressions at the plaque-lumen boundary, microbubbles spreading from the arterial lumen and into the plaque in the form of rotating, moving bright spots or lines can also be a complementary method of detecting plaque rupture [27]. Another study reported that incorporating the analysis of stress and strain distribution apart from IPN can also improve the accuracy in the assessment of plaque rupture with neovascularization and IPN [28]. Furthermore, the current CEUS-assessed plaque is mainly based on 2-D imaging, which is prone to being interfered with by acoustic shadowing [29]. The newer three-dimensional CEUS requires more validation studies on its function of further improving visualization and grading the unstable plaques [11]. All of these studies pave the way for a more objective measurement of vulnerable plaque and clinical identification of the plaque progression. In the study of Školoudík et al. [30], they divided asymptomatic plaques into stable and progressive groups; the results of this study clearly showed that there were significant differences between stable and progressive plaque elasticity, therefore, shear wave elastography (SWE) measurements of plaque elasticity can be used as an adjunct parameter for the indication of carotid endarterectomy or angioplasty and stenting when asymptomatic carotid stenosis of >50% is first detected [30]. However, the complex composition of atherosclerotic plaques strongly requires a combination of other parameters to distinguish. In vitro studies have shown that a combination of space-temporal and frequency-dependent shear wave analysis can be used to non-invasively assess the characteristics of atherosclerotic plaques in vivo [31]. Recently, Marlevi et al. further showed in an in vivo study that vulnerable plaques have significant group velocities and frequency-dependent phase velocities compared to other types of plaques. More interestingly, this parameter was also used in the study to classify specific components within the plaque, including thin fibrous caps, lipid-rich necrotic cores, and intraplaque hemorrhages [32]. In addition, Torres et al. combine signal correlation and signal-to-noise ratio (SNR), expressed as a decimal logarithm of the acceleration variance, either directly or through displacement variance, called “log (Vo A)” to successfully describe the composition and structure of human carotid atherosclerotic plaque [33]. Overall, these results are all clinically useful for predicting stroke risk and facilitating medical management. As such, elastography provides a more in-depth assessment of plaques by bringing a novel dimension—analyzing tissue displacement—to clinical use. Still, it remains a challenge to reach intra/inter-observer reproducibility and agreement on standardized cutoff values. Based on this previous knowledge and the results of our study, the presence of minimal microbubbles, which are confined to the peri-adventitial zone, and microbubbles throughout the plaque core appear to be predictive risk factors for TIA/stroke. Instead, the absence of microbubbles in our series was not related to TIA/stroke recurrence, so the best medical therapy (statin, antihypertensive drugs, and single/dual antiplatelet) appears to be efficient enough to prevent further neurological episodes over time [5,25]. It is useful to expand this type of study because the technique is not yet widespread in the routine practice of vascular Doppler ultrasound imaging. The tendency is to prescribe diagnostic tests such as CTA or MRA, which have prohibitive costs and times, while a routine carotid CEUS would save a lot of time in diagnostics and would guarantee greater precision in the prescription of the most suitable pharmacological/surgical therapy for the individual patient with its carotid plaque pattern.

5. Conclusions

The rupture of vulnerable atherosclerotic plaques and thrombosis are major contributors to the development of acute cardiovascular events. Despite various advances in the treatment of atherosclerosis, there has been no satisfaction in the prevention and assessment of atherosclerotic vascular disease. The identification and classification of vulnerable plaques at an early stage, as well as research of new treatments, remain a challenge and the ultimate goal in the management of atherosclerosis and cardiovascular disease. While ultrasound-based imaging currently is regarded as a first-line technique in clinical practice, the use of other techniques such as computed tomography angiography or magnetic resonance angiography needs to be considered in the presence of significant stenosis with or without symptoms. Advancements in these two modalities, as well as in positron emission tomography imaging, are increasingly moving toward a better understanding of the risk stratification and pre-interventional monitoring of patients at risk of plaque rupture, as well as early identification of plaque development and better understanding of plaque composition. However, these methods are expensive, time-consuming, and not always available in all diagnostic contexts, and therefore have significant logistical limitations. Neovascularization is commonly observed in advanced atherosclerosis and is associated with vulnerable plaques that have a higher risk of rupture and causing cardiovascular events such as heart attack or stroke. So, to date, no consensus on the best predictive IPN score detected by CEUS capable of predicting significant carotid stenosis has been reached when taking IPN as an independent predictor of carotid stenosis. To sum up, although it remains challenging to reach a consensus on the diagnostic standards and is limited by some intrinsic factors such as artifacts and rather short enhancement time, contrast-enhanced ultrasound has obvious advantages over conventional ultrasound in providing quantifiable data and better image quality for identifying intraplaque neovascularization in rupture-prone vulnerable plaques and formulating a more accurate risk stratification strategy. In our series, plaque neovascularization, detected by CEUS, is an independent predictor of TIA/stroke recurrence at six-month follow-up in patients with carotid atherosclerosis despite low-grade stenosis. This finding may guide the decision between medical therapy and surgical/interventional treatment in the decision-making and management of low-grade carotid artery stenosis that is symptomatic for a single episode of TIA/stroke. We present the preliminary data of diagnostic methods through which we discriminate if patients with an embolic carotid plaque should be subjected to conservative pharmacological treatment (best medical therapy with antiplatelet, statin, and anti-hypertensive drugs) or sent to surgery. This method is simple, safe, feasible, and reproducible also in an outpatient setting, without having to resort to magnetic resonance imaging. Carotid CEUS is useful to guide healthcare practitioners to prescribe the best medical or surgical therapy in case of low-grade soft plaque stenosis. In conclusion, CEUS appears to be cost-effective and positive in carotid diagnosis and may be helpful both in hospital and outpatient settings. The major limitations of the present study are represented by the paucity of the sample, so these preliminary data need to be confirmed by a large sample of patients and a longer follow-up period.

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Institutional review board statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of the Cardiovascular Outpatients Clinic, Università degli Studi di Salerno, 84084 Salerno, IT (protocol code:2021_10_04_CVOPC_UNISA) on October 4th, 2021.

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

Conflict of interest: The authors declare no conflict of interest.

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