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Review

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Usefulness of Carotid Ultrasonography for Risk Stratification of Cerebral and Cardiovascular Disease

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Carotid ultrasonography is useful for the assessments of the risk stratification for stroke or coronary artery disease, because it is a simple, repeatable, and noninvasive procedure. The carotid intima-media thickness (IMT), which is assessed using carotid ultrasonography, is a widely used surrogate marker for the severity of atherosclerosis. Several large clinical studies showed that increased carotid IMT is associated with the future stroke or cardiovascular events. In addition, in many clinical trials, it has been adopted for surrogate markers of clinical endpoints of medical intervention. Moreover, carotid ultrasonography allows the measurement of the presence and characteristics of plaques and the severity of carotid artery stenosis. The unstable morphology of plaque, such as hypoechoic, ulcer, and mobility, is associated with future ischemic stroke events. The screening tool of asymptomatic carotid artery stenosis is also important, although whether routine carotid ultrasonography assessment is recommended in the general population remains controversial. The screening of carotid artery stenosis using ultrasonography is essential for not only daily clinical settings but also management of patients with acute ischemic stroke. The patients with atherothrombotic stroke with severe internal carotid artery stenosis should be considered to surgical intervention, and duplex ultrasound approach is important to estimate for the severity of carotid stenosis. Physicians should keep in mind the usefulness of carotid ultrasonography for risk stratification of cerebral and cardiovascular disease based on various aspects. In addition, visual assessment or dynamic changes using carotid ultrasonography could provide the various and valuable insights in clinical settings.

Key words: **Intima-media thickness, Review, Atherosclerosis, Carotid ultrasonography**

1. Introduction

Carotid ultrasonography became widespread worldwide because it can be simply, reproducibly, and noninvasively used. Because the severity of atherosclerosis can be evaluated, the main reason of measurements is risk stratification of future cerebral and cardiovascular events. Carotid intima-media thickness (IMT), which can be used by carotid ultrasonography, was adopted as a surrogate marker for the presence and progression of atherosclerosis[1-4]. Many studies reported that carotid IMT measurements are useful for evaluating the risk and incidence of cerebral and cardiovascular disease[5-9]. Even though increased carotid IMT was associated with future cardiovascular events, the addition of the carotid IMT to traditional vascular risk prediction models did not significantly increase the performance of the models[10, 11]. Clinicians should consider the region used for the measurement of the different carotid segments (common carotid artery [CCA] or internal carotid artery [ICA]) and the use of the mean or maximum IMT.

As well as carotid IMT, assessments of carotid plaque are essential to predict the ischemic stroke events. Whether the plaque is included in the carotid IMT and how the plaque is defined is not unified worldwide. Plaque morphology with ultrasonography is also important. The severity of carotid stenosis also should be evaluated, because surgical intervention such as carotid endarterectomy (CEA) or carotid

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artery stenting (CAS) might be considered for the patients with high-risk of stroke. Although it remains controversial whether routine carotid IMT measurement or screening for asymptomatic carotid artery stenosis are recommended in general population[12, 13], comprehensive interpretation of ultrasonography is very essential for daily clinical settings. In this review, we discuss the clinical utility and perspective of carotid ultrasonography for the risk stratification tool of the cerebral and cardiovascular disease.

2. Carotid IMT

The carotid IMT is measured between the intimal-luminal and the medial-adventitial interfaces of the carotid artery. Although carotid IMT generally means CCA-IMT, which is located in the 1-cm straight segment of the extracranial carotid artery proximal to the bifurcation[14, 15], the definitions of the measurements of CCA-IMT segments were not unified between various studies. Several observational studies measured the CCA-IMT according to the Mannheim consensus using the same ultrasound protocol[16].

Many studies showed that the carotid IMT is associated with aging, vascular risk factors, and the prevalence of cardiovascular disease[2, 17-20]. In addition, many large cohort studies found that increased carotid IMT is associated with the future cerebral and cardiovascular events[6, 17, 21]. However, the USE-IMT collaboration, a global meta-analysis project using individual participant data from prospective cohort studies, found that the addition of the mean CCA-IMT to traditional vascular risk prediction models did not significantly increase the performance of the models[11]. Therefore, whether the mean CCA-IMT is useful in cardiovascular risk stratification in the general population remains controversial[12]. We presented the summary of those studies and issues of interpretation for carotid IMT in previous review[22]. One of issues was that the regions of the carotid segments used for the measurements (CCA or ICA) varied among the studies. Researchers should keep in mind the difference for measurement segments, definition of IMT such as mean or maximum, and the carotid plaque. Different etiology of the atherosclerotic process between mean IMT, maximum IMT, and carotid plaque were reported[23, 24]. The CCA-IMT is mainly affected by age and blood pressure[25], whereas the ICA-IMT probably reflects the presence of focal plaques and may be more representative of exposure to cardiovascular risk factors. The Framingham Offspring cohort found that maximum ICA-IMT is associated with the prevalent cardiovascular disease and future cardiovascular events compared to mean CCA-IMT[26, 27]. Those findings might indicate that ICA, especially maximum IMT, is a suitable screening point for the risk stratification of cerebral or cardiovascular disease. Conversely, Toyota *et al.* reported that carotid bifurcation in Japanese subjects were higher by almost one cervical vertebra compared with Western subjects[28]. Therefore, routine assessments of ICA-IMT might be relatively difficult for screening of atherosclerosis in Japanese population. Kokubo *et al.* found that maximum CCA-IMT can be easily measured and adopted as a promising risk factor for future cardiovascular disease in the Japanese large cohort study (Suita Study)[29]. In this study, a maximum CCA-IMT >1.1 mm was revealed to be associated with increased risks of cerebral and cardiovascular disease by the C statistic improvement of the current risk prediction model (Suita Risk Score)[29, 30]. In addition, several studies also showed that carotid plaque was a more suitable indicator to predict the future cardiovascular disease compared to the mean CCA-IMT[31-33]. At least, physicians should not only focus on the mean CCA-IMT for management of risk stratification. Considering the maximum carotid IMT or carotid plaque is essential for the prediction of cerebral and cardiovascular disease.

Carotid IMT was also considered as a surrogate clinical endpoint for several clinical trials using lipid-lowering, antihypertensive, and/or antidiabetic drugs[34-43]. A systematic review and meta-analysis showed that low density lipoprotein cholesterol reduction by a statin treatment and carotid IMT change reduction strongly correlated[44]. Most previous studies referred in this meta-analysis were reported from Western countries, and a higher statin dose exists in Western countries than those in Japan. In addition, limited evidence exists for the association between statin treatment and carotid IMT reduction among Asian population. We recently found several novel findings for the association between carotid IMT and statin treatment using pravastatin (10 mg daily, usual dose in Japan) from Japan Statin Treatment Against Recurrent Stroke (J-STARS) study. The J-STARS study was conducted to examine whether pravastatin reduces stroke recurrence in patients with noncardioembolic ischemic stroke, and the J-STARS Echo Study was planned to determine the preventive effect of pravastatin on progression of carotid IMT[42, 45-47]. In brief, pravastatin treatment could significantly reduce the progression of mean CCA-IMT after long-term treatment (5 years)[48]. In addition, pravastatin treatment may prevent the occurrence of atherothrombotic brain infarction in patients with noncardioembolic infarction with the baseline highest-tertile mean CCA-

IMT[49]. Those findings might support that carotid IMT is considered as a surrogate marker of medical intervention and useful for risk stratification of future cerebral and cardiovascular events. The PROG-IMT collaborative project found that mean CCA-IMT progression was not associated with cerebral and cardiovascular events, although baseline CCA-IMT was strongly associated with those[50, 51]. However, a more recent meta-analysis of 119 clinical trials showed that the extent of medical intervention effects on CCA-IMT progression was associated with the reduction of cardiovascular events[52]. In this meta-analysis, mean CCA-IMT was available in 74,891 patients and maximum CCA-IMT in 41,841 patients. No significant difference was found in the predictive power for risk reduction between the change of mean CCA-IMT and the change of maximum CCA-IMT. To guide future development for cardiovascular drugs, both CCA-IMT parameters (mean or maximum) might be useful as surrogate markers.

3. Carotid Plaque

The definition of carotid plaque varies by country. The Mannheim consensus advocates that carotid plaques are focal structures that either encroach the arterial lumen by at least 0.5 mm or 50% of the surrounding IMT value or exhibit a thickness from the intimal-luminal to the medial-adventitial interface greater than 1.5 mm[53]. American Society of Echocardiography defined carotid plaques as a focal region with a carotid IMT greater than 1.5 mm that protrudes into the lumen[15]. Although the size of carotid plaque (>1.5 mm) is the same, whether the plaque is included in the carotid IMT between those groups is different. Japanese guidelines showed that carotid plaques are included in carotid IMT, but the definition of plaque size (>1.0 mm or ≥ 1.1 mm) is less than those according to European or American guidelines[54, 55]. Maximum CCA-IMT (>1.1 mm), which was adopted as carotid plaque according to Japanese guidelines, adding to the traditional risk prediction models, is useful to predict the future cerebral and cardiovascular events in Japanese general population[29]. In addition, the plaque score by adding the maximum thickness of plaques (>1.0 mm) on the near and far walls at each of four divisions of both sides of the carotid artery, which was developed in Japan, is also useful. This semi-quantified scoring system was associated with cardiovascular risk factors, cerebral white matter lesions, and future cardiovascular events[18, 56-59]. However, whether increased the numbers of carotid plaque is useful for prediction of future cerebral and cardiovascular disease compared to carotid IMT remains unclear. To discuss the issue, considering the different definitions of carotid plaque, as mentioned above, is important.

The characteristics of carotid plaque is also essential. The description for assessment of plaque is not unified, but it is generally is carried out based on the following points: (i) echogenicity; (ii) heterogeneity; and (iii) structure (surface morphology). The echogenicity is classified as following as hypoechoic (low echoic or echo lucent), isoechoic (echogenic), and hyperechoic (high echoic or echodense). In general, hyperechoic plaque means fibrous tissue or calcification changes and sometimes exhibits an acoustic shadow[60]. The heterogeneity is divided into "homogeneous" and "heterogeneous." The heterogeneous plaque is sometimes represented as "mixed" plaque[61]. The surface morphology is classified as smooth, irregular, and ulceration[62]. The definition of carotid plaque ulceration varies depending on the different modality and different studies. De Bray *et al.* proposed that a plaque ulceration should measure as according to the following points: (1) at least 2 mm in depth and 2 mm in length; (2) with a well-defined back wall at its base shown by B-mode; and (3) with an internal flow reversal on color Doppler imaging[63]. Although the size of cavities was adopted as 1 mm in some studies[64, 65], the size as 2 mm seem to be the most widely used[66-69]. A thin fibrous cap, hypoechoic plaque, or ulcerated plaque suggests vulnerable plaque, which leads to the possibility of plaque rupture and ischemic stroke events[64, 65, 70]. The mobile component of carotid plaque can be detected by using carotid ultrasonography, and it is also considered as a vulnerable plaque[71]. Although the vulnerable plaque is sometimes represented as "unstable" plaque, the definition of both terms is also not clear. Several characteristics of carotid plaque are presented in **Fig. 1**. More detail or quantitative assessments of vulnerable plaque are gray-scale median (GSM) approach, integrated backscatter (IBS) approach, and contrast-enhanced ultrasound (CEUS) approach. The GSM approach indicates that the frequency of gray values of the pixels within the plaque is used to quantify their echogenicity[72]. The IBS approach is based on an analysis of unprocessed radiofrequency signals to derive quantitative ultrasonic indexes[73]. Accumulating evidences that those approaches are useful for predictions of cerebral or cardiovascular events have existed[70, 74]. CEUS can be used to improve visualization of carotid plaque surface delineation and highlighting features of vulnerability of plaque including ulceration and intraplaque neovascularization[75, 76]. This approach can provide the useful information for selection of patients with surgical intervention. However, performing as

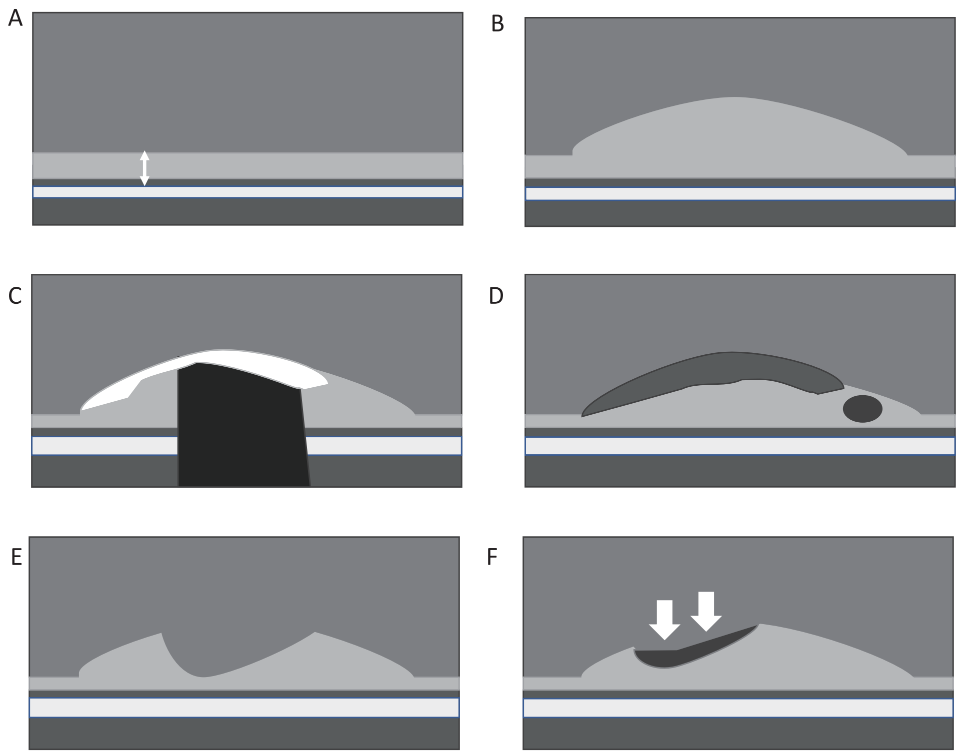


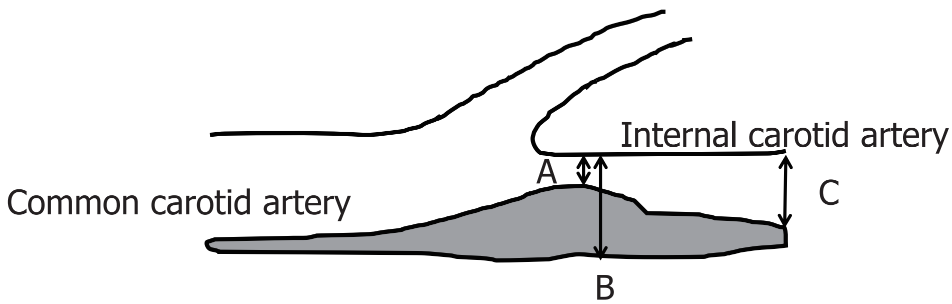
Fig. 1. The characteristics of carotid plaque are carried out based on following points; (i) echogenicity; (ii) heterogeneity; and (iii) structure (surface morphology)

A; normal intima-media thickness (two-way arrow) B; the characteristics of carotid plaque show that iso echoic, homogeneous, and surface smooth. C; the characteristics of carotid plaque show that high echoic with acoustic shadow, heterogeneous. D; the characteristics of carotid plaque show that iso or low echoic and heterogeneous. E; the surface of carotid plaque shows ulceration. F; the surface of carotid plaque shows low echoic and with mobile components (arrow).

routine assessments by using those approaches may be difficult. Those are regarded as advanced technic for risk stratification of future ischemic stroke events. Next, assessing the vulnerable plaque not only by using carotid echography but also other modalities, such as multi-detector computed tomography angiography and magnetic resonance imaging (fast spin echo, black-blood technique, time of flight MR images, and so on), is also important[77, 78]. Although the strong points of carotid ultrasonography compared with those modality might be simple or noninvasive, physicians should pay attention for some pitfalls of artifacts when evaluating the plaque ulceration in carotid ultrasonography, and sometimes they need to add the comprehensive approach using those different modalities.

4. Carotid Stenosis

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST), which were published in 1991, showed the benefits of surgical intervention in certain subgroups of patients with symptomatic ICA stenosis[79, 80]. In general, the degree of carotid stenosis is described as NASECT criteria or ECST criteria, and both are based on digital subtraction angiography. Clinicians should keep in mind the differences according to those criteria, e.g., NASCET criteria of 50% stenosis is roughly equal to 75% stenosis by ECST criteria (**Fig. 2**)[81]. The patients with symptomatic ICA stenosis, especially severe stenosis such as greater than NASCET 70%, should be considered for treatment of surgical intervention (CEA or CAS)[82]. Duplex ultrasound (DUS) approach is very important to estimate the severity of carotid stenosis. The assessments of DUS should be performed by the recommended angulation (insonation angle less than or equal to 60 degrees). In 2001, Koga *et al.* showed that peak systolic velocity (PSV) of ICA greater than 200 cm/s was a reliable predictor of ICA stenosis greater than NASCET 70%[83].



$$\text{NASCET} = (C\text{-}A)/C \times 100$$
$$\text{ECST} = (B\text{-}A)/B \times 100$$

NASCET (%)	ECST (%)
30	65
50	75
70	85
90	97

Fig. 2. The association between the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) measurements

Approximate equivalent degrees of internal carotid artery stenosis assessed in NASCET criteria and ECST criteria according to resent direct comparisons[81].

In 2012, the neurosonology research group of the world federation of neurology proposed the methods of grading carotid stenosis using carotid ultrasonography[84]. This paper reported that PSV was a suitable parameter to estimate for the degrees of ICA stenosis but also indicated that it alone was also insufficient. They reported that the threshold of PSV for the moderate stenosis as greater than NASCET 50% indicated more than 120 cm/s. The threshold of PSV for the severe stenosis as greater than NASCET 70% was adopted as more than 230 cm/s. Conversely, they referred that the increased velocities in stenosis fall in situations of near occlusion, moreover the presence/absence of collateral flows may affect the PSV values. Poststenotic PSV on ICA ≥ 50 cm/s indicated that the less than NASCET 70% stenosis and poststenotic PSV on ICA were considered as <30 cm/s in cases where diameter reduction was almost NASCET 90% (the residual lumen is <1 mm, irrespective of the PSV in the stenosis). Also, the ICA/CCA velocity ratio was considered as a criterion to estimate for the degree of ICA stenosis. The ICA/CCA velocity ratio ≥ 2 indicated the more than NASCET 50% stenosis, and >4 indicated the more than NASCET 70% stenosis. This consensus also recommended that a search for collateral flow was made in the ophthalmic artery branches (continuous wave Doppler) or the anterior cerebral artery (transcranial Doppler or color-coded duplex sonography). However, using those approaches to assess the collateral flow in daily clinical settings may be difficult because of technical issues or taking a lot of time. Additionally, physicians should keep in mind that usual criteria for the threshold of PSV for carotid stenosis are not applied for restenosis assessments among patients who treated with CEA or CAS[85-87].

The patients with symptomatic ICA stenosis (especially more than NASCET 70%) should be considered for the surgical intervention as mentioned above[79]. Conversely, whether the patients with asymptomatic carotid artery stenosis could have a benefit of surgical intervention still remains controversial[88]. At present, a lot of risk stratification models are proposed and used in clinical settings[89]. An update of the 2007 U.S. Preventive Services Task Force (USPSTF) found no evidence that screening for carotid artery stenosis leads to additional treatment and benefit beyond standard preventive treatments based on traditional cardiovascular risk factors[13]. Therefore, the USPSTF recommends against screening for asymptomatic carotid artery stenosis in the general adult population[13]. Similar recommendations were proposed in other research groups or guidelines[90, 91]. Although physicians should not examine the screening of carotid artery using echography vaguely, those guidelines are not denied the usefulness of carotid ultrasonography for the medical or surgical managements among patients with vascular risk factors. Promising risk stratification models considering both the traditional vascular risk factors and the suitable carotid ultrasonography parameters would be expected.

5. Other Aspects of Assessments Using Carotid Ultrasonography

5.1. Vertebral Artery

The diameter or flow velocity of vertebral artery (VA) are measured using carotid ultrasonography. The several patterns of VA occlusion or VA hypoplasia are divided based on some indicators such as the diameter-ratio (diameter of contralateral VA divided by that of target VA), mean flow velocity (MV)-ratio (MV of contralateral VA divided by that of target VA), and end-diastolic flow velocity[92)]. Although the clinical significance of VA occlusion or hypoplasia for predictor of future ischemic stroke events is under discussion, the findings of VA obtained by carotid ultrasonography could provide several insights for mechanisms of acute ischemic stroke or neurological symptoms including vertigo or dizziness. First, they have been used to diagnose or follow-up to change the VA dissection among patients with acute stroke[93, 94)]. For those cases, the strong point of carotid ultrasonography is that detection of blood flow velocity change can be easily performed in a short time and bedside. Second, it can be applied to diagnose the Bow hunter's syndrome. Bow hunter's syndrome is known as vertebrobasilar insufficiency resulting from mechanical occlusion or stenosis of the VA during head and neck rotation or extension[95)]. The changes of VA blood flow using carotid ultrasonography on neck rotation can be detected easily and noninvasively[96, 97)]. Third, the reversal blood flow on VA can play an important role in the diagnosis of subclavian steal phenomenon[98, 99]. Next, the waveform patterns of the ipsilateral VA with the subclavian artery stenosis are classified into several types. The associations between the increasing waveform type and the increasing degree of subclavian stenosis have been reported[99, 100)].

5.2. Common Carotid Interadventitial Diameter

The common carotid interadventitial diameter (IAD) can be easily measured as well as carotid IMT by using carotid ultrasonography. It is associated with vascular risk factors, carotid IMT, plaque scores, left ventricular mass, and myocardial infarction[26, 101-103)]. It was reported that the presence of both increased IAD, and increased IMT was the strongest predictor of stroke incidence in the general population[104)]. Interestingly, carotid IAD was a stronger predictor of ischemic stroke than carotid IMT from the results of the Multi-Ethnic Study of Atherosclerosis (MESA)[105)]. However, few studies exist on whether carotid IAD is more suitable screening point than carotid IMT for risk stratification of future cerebral or cardiovascular events. Carotid IAD might be decreased by several medications such as antihypertensive agents[43)]. Although it also may be considered as a surrogate clinical endpoint using several medical intervention, few investigations to assess those associations exist. Future observational or clinical studies are needed to clarify the usefulness of carotid IAD.

5.3. The Assessments of Collagen Disease

A diffuse circumferential mild hypoechoic thickening of the intima-media complex resulting from granulomatous inflammatory changes, termed the "macaroni sign," was detected by carotid ultrasonography in patients with Takayasu disease[106)]. This "macaroni sign" has been used not only for the diagnosis for Takayasu disease but also in the evaluation of inflammatory activity. Serial changes of "macaroni sign" might be detected as the disease activity or treatment response[107)]. Ultrasound of temporal arteries, not carotid artery, is a useful for diagnosis of giant cell arteries. It can detect vessel wall edema, termed as the "halo sign," throughout the length of the vessel[108)]. Although the diagnostic properties of temporal artery ultrasound may be more useful compared to temporal artery biopsy, for the diagnosis of giant cell arteries, physicians should be keep in mind to the potential pitfalls (transducer pressure, gray-scale settings, color Doppler settings, and so on)[109, 110)].

5.4. Carotid Web

Carotid webs are nonatherosclerotic fibrous bands (pathologically defined as an intimal variant of fibromuscular dysplasia) that are along the posterior margin of the carotid bulb or ICA[111)]. Recently, accumulating evidences that carotid webs are considered as one possible cause of cryptogenic stroke exist[112-114)]. Hemodynamic changes such as blood flow stagnation or turbulence in the rostral aspect of the carotid web result in thrombus formation, which can be considered as an embolic source of ischemic stroke[115)]. Although detection of carotid webs using carotid ultrasonography sometimes might be difficult[116)], serial examinations by ultrasonography can reveal the dynamic imaging features of carotid web and provide the insights of etiology for thrombosis[117)].

5.5. Flip-Flop Phenomenon

The hyoid bone was implicated in focal carotid vasculopathy, including carotid artery dissection and occlusion, due to mechanical pressure on the ICA[118-120)]. Carotid ultrasonography could be detected the dynamic changes of association between the carotid artery and hyoid bone. Kinoshita *et al.* reported on a patient with stroke with repeated positional changes of the carotid arteries to and from a retropharyngeal position with interference of the hyoid bone during swallowing, and they named it the "flip-flop phenomenon (FFP)"[121]. Patients with FFP exhibited a higher prevalence of internal carotid stenosis than those without[122]. Although FFP might be a potential indicator of ischemic stroke, a lack of evidence on whether the presence of FFP is predictor of ischemic stroke exists.

6. Conclusion

Assessment of carotid ultrasonography is very useful for the risk stratification of future cerebral or cardiovascular events. Apart from that, a lot of risk stratification models are also proposed and used in clinical settings[89]. Additionally, we need to develop easy and useful risk stratification models considering both the traditional risk stratification models and the several carotid parameters. The visual assessment or dynamic changes for the severity of atherosclerosis, plaque characteristics, and several other aspects that are available from carotid ultrasonography can provide the valuable insights for managements for patients receiving carotid ultrasonography. Carotid ultrasonography should be used as a tool for not only risk stratification of vascular events but also comprehensive interpretation of atherosclerosis or etiology of stroke.

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Conflicts of Interest/Disclosures

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