Online version at http://www.minervamedica.it

International Angiology 2019 December;38(6):451-65
DOI: 10.23736/S0392-9590.19.04267-6

REVIEW

CAROTID DISEASE

EDITOR'S CHOICE

Global perspective on carotid intima-media thickness and plaque: should the current measurement guidelines be revisited?

Luca SABA [1], Ankush JAMTHIKAR [2], Deep GUPTA [2], Narendra N. KHANNA [3], Klaudija VISKOVIC [4], Harman S. SURI [5], Ajay GUPTA [6], Sophie MAVROGENI [7], Monika TURK [8], John R. LAIRD [9], Gyan PAREEK [10], Martin MINER [11], Petros P. SFIKAKIS [12], Athanasios PROTOGEROU [13], George D. KITAS [14], Vijay VISWANATHAN [15], Andrew NICOLAIDES [16], Deepak L. BHATT [17], Jasjit S. SURI [18] *

[1]Department of Radiology, University of Cagliari, Cagliari, Italy; [2]Department of Electronics and Communication Engineering, Visvesvaraya National Institute of Technology, Nagpur, India; [3]Department of Cardiology, Indraprastha APOLLO Hospitals, New Delhi, India; [4]Department of Radiology and Ultrasound, University Hospital for Infectious Diseases, Zagreb, Croatia; [5]Brown University, Providence, RI, USA; [6]Department of Radiology, Weill Cornell Medicine, New York, NY, USA; [7]Cardiology Clinic, Onassis Cardiac Surgery Center, Athens, Greece; [8]Department of Neurology, University Medical Center Maribor, Maribor, Slovenia; [9]Heart and Vascular Institute, Adventist Health St. Helena, St Helena, CA, USA; [10]Minimally Invasive Urology Institute, Brown University, Providence, RI, USA; [11]Men's Health Center, Miriam Hospital, Providence, RI, USA; [12]Unit of Rheumatology, National Kapodistrian University of Athens, Athens, Greece; [13]Department of Cardiovascular Prevention and Research, Clinic and Laboratory of Pathophysiology, National and Kapodistrian, University of Athens, Athens, Greece; [14]R and D Academic Affairs, Dudley Group NHS Foundation Trust, Dudley, UK; [15]MV Hospital for Diabete, Professor M Viswanathan Diabetes Research Center, Chennai, India; [16]Vascular Screening and Diagnostic Center, University of Nicosia Medical School, Nicosia, Cyprus; [17]Brigham and Women's Hospital Heart, Vascular Center, Harvard Medical School, Boston, MA, USA; [18]Stroke Monitoring and Diagnostic Division, AtheroPoint™, Roseville, CA, USA

*Corresponding author: Jasjit S. Suri, Stroke Monitoring and Diagnostic Division, AtheroPoint™, Roseville, CA, USA.
E-mail: jasjit.suri@atheropoint.com

ABSTRACT

Carotid intima-media thickness (cIMT) and carotid plaque (CP) currently act as risk predictors for CVD/Stroke risk assessment. Over 2000 articles have been published that cover either use cIMT/CP or alterations of cIMT/CP and additional image-based phenotypes to associate cIMT related markers with CVD/Stroke risk. These articles have shown variable results, which likely reflect a lack of standardization in the tools for measurement, risk stratification, and risk assessment. Guidelines for cIMT/CP measurement are influenced by major factors like the atherosclerosis disease itself, conventional risk factors, 10-year measurement tools, types of CVD/Stroke risk calculators, incomplete validation of measurement tools, and the fast pace of computer technology advancements. This review discusses the following major points: 1) the American Society of Echocardiography and Mannheim guidelines for cIMT/CP measurements; 2) forces that influence the guidelines; and 3) calculators for risk stratification and assessment under the influence of advanced intelligence methods. The review also

presents the knowledge-based learning strategies such as machine and deep learning which may play a future role in CVD/stroke risk assessment. We conclude that both machine learning and non-machine learning strategies will flourish for current and 10-year CVD/Stroke risk prediction as long as they integrate image-based phenotypes with conventional risk factors.

(*Cite this article as:* Saba L, Jamthikar A, Gupta D, Khanna NN, Viskovic K, Suri HS, *et al.* Global perspective on carotid intima-media thickness and plaque: should the current measurement guidelines be revisited? Int Angiol 2019;38:451-65. DOI: 10.23736/S0392-9590.19.04267-6)

Key words: Ultrasonography; Carotid arteries; Cardiovascular diseases; Stroke.

Cardiovascular diseases (CVD) including myocardial infarction (MI) and stroke are the leading causes of both regional and global mortalities.[1] Atherosclerosis is the prominent contributor of such mortalities.[2, 3] Thus, there is a need to develop a set of preventive tools that can monitor atherosclerosis. In the last four decades, carotid intima-media thickness (cIMT) and carotid plaque (CP) measured using the B-mode carotid ultrasound (CUS) imaging technique has been considered as non-invasive, quantitative, and preventive tools for the assessment of CVD and stroke risk.[4-6] There exists a plethora of evidence that indicates a strong association between these CUS image-based phenotypes (CUSIP) and cardiovascular (CV)/stroke events.[7-20] Furthermore, cIMT acts as a cost-effective surrogate endpoint of CVD and stroke in situations when the accurate CV and stroke endpoints need longitudinal trials.[5, 21, 22] Despite all this, the use of CUSIP for routine CVD/stroke risk assessment still remains a debatable topic[23] due to several reasons such as variations in the measurement protocols, types of measurement tools, different ways of 10-year risk computation, specific carotid segment to be analyzed (common, bulb or internal), scientific validation protocols used, and the type of the study utilized.[23]

In order to maintain uniformity in the measurement protocols of CUSIP, several guidelines have been reported.[19, 24, 25] Based on these guidelines, in 2010, the American College of Cardiology (ACC)/American Heart Association (AHA) supported the use of cIMT for CVD/stroke risk assessment. Similarly, the National Cholesterol Education Program-Adults Treatment Panel (NCEP-ATP) III[26] and the European Society of Hypertension[27] had also recommended the use of cIMT for CVD/stroke risk assessment. However, in 2012, Ruijter *et al.*[28] presented a meta-analysis with 11 years of follow-up that measured the cIMT within the 10 mm distance of the far wall of the common carotid artery (CCA), without considering the plaque in the bulb and internal carotid artery.[29] Ruijter *et al.*[28] indicated minimal improvement in the 10-year risk of CVD after adding cIMT (as measured in the 10 mm region, free of plaque) to the Framingham risk score (FRS).[30] They also noted that the improvement was of little clinical importance. This study presented by Ruijter *et al.*[28] had a strong impact in modifying the CVD/stroke risk assessment guidelines recommended by ACC/AHA which reported against the use of cIMT for routine risk assessment.[31] It should be noted that atherosclerotic plaques are uncommon in the CCA and practically start at the carotid bifurcation *i.e.*, the origins of the internal and external carotid arteries. This may also be the reason for little improvement in the CVD risk when cIMT was considered with FRS.

In the past decade, with the advancement in technology, full-length measurement of cIMT, *i.e.*, measurement of cIMT all along the length of CUS scans of three arterial segments (CCA, carotid bulb, and ICA) have been used for CVD and stroke risk stratification.[32-35] The automated full-length measurements have also been used as covariates in a CVD/stroke risk prediction model to estimate the 10-year risk of patients.[36-38] Such types of full-length measurements were not considered while framing the guidelines.[19, 24, 25] These studies demonstrated that plaque thickness had a stronger association with future CVD/stroke events. Recently, the European Society of Cardiology/European Atherosclerosis Society guidelines stated that the presence of coronary calcium on CT or carotid plaque on ultrasound unequivocally identifies individuals at high risk of myocardial infarction or stroke.[39]

Our efforts in this review are to understand various forces (or factors) that link and impact the guidelines and potentially be considered in future guidelines. Figure 1 shows the influencing factors on the American Society of Echocardiography (ASE)/Mannheim measurement guide-

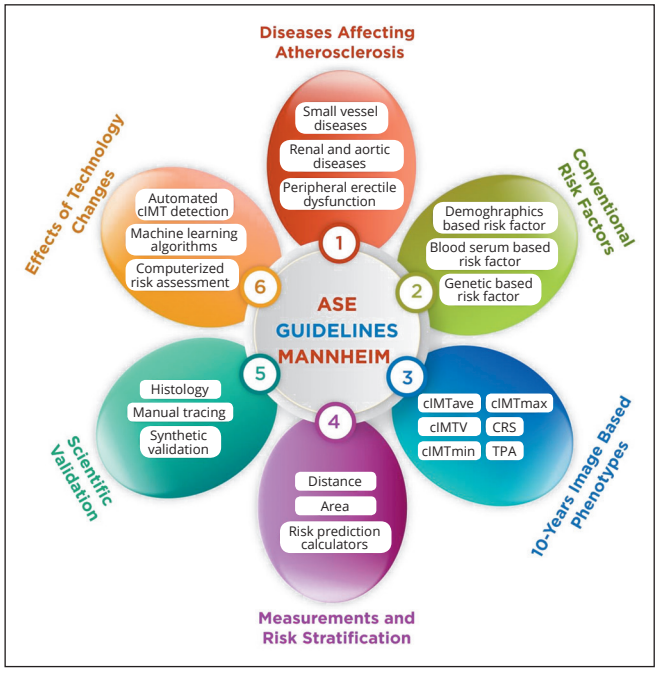

Figure 1.—Various forces that interact and influence the guidelines. ASE: American Society of Echocardiography; TPA: Total Plaque Area; CRS: Composite Risk Score; cIMTave: Average Carotid Intima-Media Thickness; cIMTmax: Maximum Carotid Intima-Media Thickness; cIMTV: Variability in Carotid Intima-Media Thickness; cIMTmin: Minimum Carotid Intima-Media Thickness.

lines (from here on we will use the word "guidelines" implying the "ASE/Mannheim measurement guidelines"-represented as the central circle). Figure 1 shows six elliptical petals representing the factors which are directly linked to the guidelines. This includes the diseases that affect atherosclerosis,[22, 40-42] conventional risk factors (CRF) which affects the atherosclerosis disease,[43-47] current and 10-year image-based phenotypes for quantifying the atherosclerosis disease,[37] measurements tools and techniques for risk stratification,[32-35] scientific validation,[48-50] and effect of technology changes. The intent of this review is to summarize improvements made in the area of CUSIP measurement and to identify the factors which can impact the measurement guidelines in the future. It is important to note that the focus of this paper is to investigate the tools and techniques solely dedicated to 2D carotid longitudinal scans. Since 90% of the adaptability for atherosclerotic risk assessment uses 2D ultrasound, we, therefore, focus on the key advantages and further, the pitfalls, challenges for CVD/stroke risk assessment. As a result, this review does not focus on 3D imaging for the carotid artery. Measurement of 3-D ultrasound image-based phenotypes from

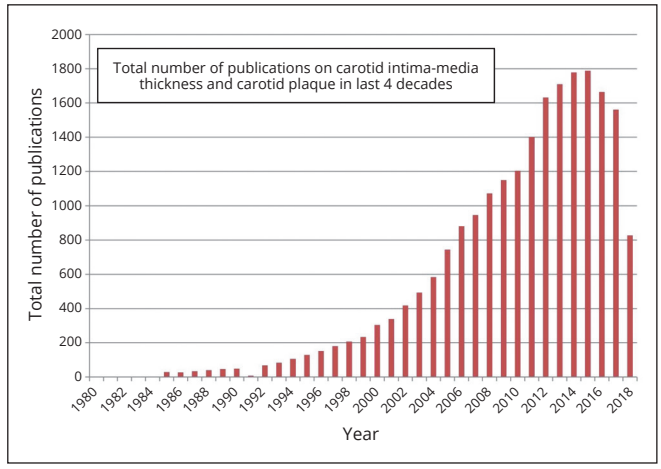

Figure 2.—The overall trend of publications on cIMT and on CP in the past four decades.

the carotid artery using automated tools is a wider topic and has already been discussed in detail in the previous literature published by our group.[51-54]

Search strategy

The cIMT and CP have received significant attention from the research communities which reflects the total number of studies published in the last four decades, depicted in Figure 2. Our review is the outcome of searches in PubMed to investigate various relevant articles published in peer-reviewed journals. Figure 3 shows the flow diagram for the search strategy followed in this review. Articles published within the last 15 years were given greater preference. The initial search in PubMed was started by using the keywords such as: "carotid intima-media thickness," "intima-media thickness variability," "carotid wall motion," "carotid plaque," "Consensus" AND "Intima-media thickness," "Consensus" AND "carotid plaque," "Carotid-intima Media thickness" AND "cardiovascular risk prediction," total carotid plaque area, "carotid plaque burden," "carotid plaque characterization," "automated cIMT," "carotid artery calcium," "Cardiovascular risk stratification," "Cardiovascular risk assessment," "vascular ultrasound," "Cardiovascular risk calculators," small vessel disease AND "atherosclerosis," "neurological diseases," "large vessel disease" AND "atherosclerosis," "neurological diseases" AND "atherosclerosis" "vascular disease and atherosclerosis," "preventive cardiology," "carotid artery disease" AND "management," machine learning AND Carotid Artery, "deep learning and carotid artery," "carotid intima media thickness progression," and "carotid intima

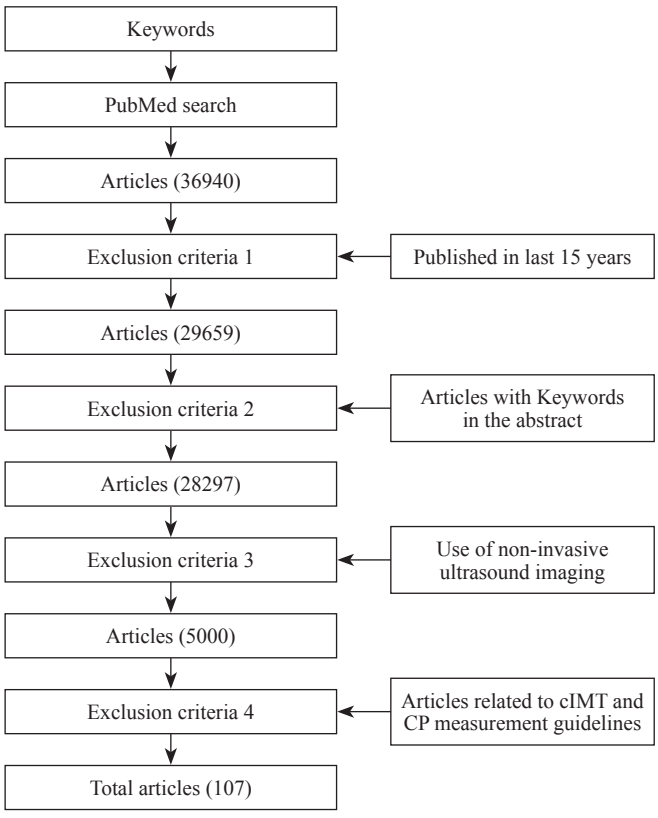

Figure 3.—Fundamental flow-diagram for the search strategy.

media thickness regression." The citations from the published articles were also shortlisted for the design of this review. This review is the outcome of 107 articles which were scrutinized using four exclusion criteria depicted in Figure 3.

Guidelines for cIMT and CP measurement

In the last decade, Touboul *et al.*[24, 25] and Stein *et al.*[19] presented the CUS-based guidelines that provided recommendations for the measurement of cIMT and CP. Furthermore, these guidelines presented the clinical use of cIMT and CP for the risk assessment of CVD/stroke events. In order to perform the risk assessment, Stein *et al.*[19] recommended a two-step process: 1) identification of CP by thorough scanning of the carotid artery; and 2) measurement of the cIMT within the 10 mm plaque-free segment in the far wall of the CCA. It has also been reported that the majority of CP lies within the distal end of the common carotid artery, carotid bulb (sinus and flow divider area) and the internal carotid artery.[19] For this reason, the guideline mentions scanning of the carotid bifurcation thoroughly.

Touboul *et al.*[24, 25] recommended the measurement of cIMT in the 10 mm plaque-free segment of CCA or ICA or carotid bifurcation (and sinus bulb). The idea behind considering the plaque-free region was to perform a reproducible measurement of the cIMT. The definitions of CP were also quite similar to the ASE guidelines.[19] Stein *et al.*[19] defined CP as the focal wall thickening of 50% greater than surrounding cIMT of the vessel wall or a focal region with cIMT greater than 1.5 mm protruding into the lumen. In addition, Touboul *et al.*[24, 25] added one additional measure for the CP measurement and defined the CP as a focal thickening region encroaching into the lumen by at least 0.5 mm or 50% of surrounding cIMT or a focal thickening region with cIMT value greater than 1.5 mm. The type of cIMT measurement is another point reported in both guidelines. Different types of cIMT measurement include: 1) mean of cIMT values along the 10 mm segment of CCA; 2) maximum of cIMT values along the 10 mm segment of CCA; 3) mean of mean measurement in which first mean of cIMT values along the 10 mm length of both left and right CCA is computed. The average of these two mean cIMT values provides the final cIMT measurement. Besides these, a composite measurement of cIMT along with all three segments (CCA, bulb, and ICA) and for both sides of the neck can also be considered as a type of measurement.

The guidelines discussed above[19, 24, 25] have tried to bring all the aspects of CUSIP measurements on a single platform. However, in the majority of routine practice, the CUSIP measurement protocols or the recommendations provided in the guidelines are followed to a limited extent and with great diversity. In the last decade, the researchers have identified multiple loose-endpoints in the current guidelines and have suggested several improvements in the CUSIP measurements to consider such unanswered issues. Figure 1 indicates the missing links between the current guidelines and several factors that influence the guidelines. All such missing links between the current guidelines and the influential forces that affect the guidelines will be discussed in the following sections.

Factors that affect the central guidelines

Figure 1 shows various factors that influence the current guidelines. The first elliptical petal of Figure 1 indicates three categories of diseases that primarily impact the complex nature of atherosclerosis: 1) conventional systemic diseases; 2) local arterial vascular diseases; and 3) neurological diseases. Conventional diseases are further divided

into diabetes,[55] hypertension, hyperlipidemia, obesity, and autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. All these diseases exhibit a higher risk of CVD and stroke. Vascular diseases are further divided into carotid artery diseases, coronary artery diseases,[42] renal artery diseases,[40] aortic diseases,[56] peripheral artery diseases,[41] and brachial artery diseases. These are further divided into small vessel diseases, large vessel diseases, leukoaraiosis, Alzheimer's disease,[57] thyroid disease,[58] and erectile dysfunction[59] since all are accelerated by the atherosclerotic process leading to the formation of more calcium, fibrin, fibrosis, and macrophages.[2, 3]

The second set of factors that influence the guidelines includes CRF which includes age, height, and weight of the patient, serum and lipid biomarkers.[43-47] The third set of factors influencing the guidelines includes the current measurements of the image-based phenotypes and 10-year prediction of the image-based phenotypes.[18, 37] Recently, five types of current and five types of 10-year CUSIP have been proposed based on the morphological variations in the atherosclerotic plaque.[18, 37] These image-based phenotypes are average cIMT, maximum cIMT, minimum cIMT, variations in cIMT, and morphological plaque area, responsible for the progression of plaque. Khanna *et al.*[37] computed the 10-year predictions of these five current CUSIP. Furthermore, a composite risk score (CRS) has been proposed recently by Godia *et al.*[17] that combines the effect of five current CUSIP to provide a real-valued percentage risk in patients.

Figure 1 explicitly shows the tools and techniques for CP burden measurements and 10-year risk calculators for risk stratification.[32-35] This includes centerline, polyline, shortest distance, Mahalanobis distances.[60] Tools also include the calculators like Framingham Risk Score (FRS),[30] United Kingdom Prospective Diabetes Study (UKPDS),[56, 61] UKPDS60,[62] Reynolds's Risk Score (RRS),[63] Systemic coronary risk evaluation (SCORE),[64] NIPPON,[65] a World Health Organization (WHO) calculator,[66] QRISK3,[67] and the ACC/AHA ASCVD risk score. Note that all the above interacting factors are affected by the evolution of technologies such as automated method, machine learning (ML) methods, or deep learning (DL) methods.

Conventional risk factors and image-based phenotypes

Conventional risk factors

Both of the CRF and CUSIP are strongly associated with each other.[43-45, 47] However, in the current guidelines, a little emphasis was given on the association between CUSIP and the CRF. In Figure 1, the second ellipse titled "Conventional Risk Factors" indicates a direct link to the guidelines for risk assessment. Since almost 90% of patients with CVD/Stroke mortalities have at least one type of CRF,[68, 69] it is essential to investigate the behavior of CUSIP in conjunction with CRF when making a determination of CVD risk. Annual progression CUSIP is influenced by the traditional risk factors such as age,[45] gender,[43] smoking,[44] Body Mass Index,[47] diabetes,[46] low-density lipoprotein cholesterol,[46] and hypertension.[46] It should be noted that it is extremely important to track the increase in CUSIP since it increases the risk of stroke.[70] Furthermore, as discussed in the previous section (*i.e.*, in section link between cIMT and atherosclerosis in other vascular beds) the increase in cIMT is also associated with abnormalities in other vascular beds that result in endothelial dysfunction, renal diseases, coronary heart diseases, and erectile dysfunction.[71] Recommendations of CUSIP measurement provide vital information about the morphology and growth of atherosclerotic plaque. This may support the physician while recommending the treatment plans to prevent the onset of CVD/stroke events. The association of CUSIP measurement with CRF also enables researchers to predict the long-term variations in cIMT and CP. Using this information one can reliably execute the prevention plans for controlling and managing the CRF.

Current and 10-year image-based phenotypes as risk factors

Figure 1 shows the third elliptical petal indicating the measurement of current image-based phenotypes and prediction of 10-year image-based phenotypes. In the current of CUSIP measurement guidelines, the average measurement of cIMT has been proposed within a 10 mm segment of the CCA.[19, 24, 25] However, in the past decade, five types of CUSIP were used to capture plaque variations in the carotid wall. The set of five CUSIP included four different types of full-length cIMT measurements (average cIMT or $cIMTave_{curr}$, maximum cIMT or $cIMTmax_{curr}$, minimum cIMT or $cIMTmin_{curr}$, and variability in cIMT or $cIMTV_{curr}$) and a total area of CP which was also termed as total plaque area or TPA_{curr}.[18, 72, 73] Here, "full-length" indicates the measurement of cIMT or TPA_{curr} all along the length CUS scan of CCA (Figure 4A-D for CCA). The full-length measurement for CCA was performed from the edge of the bulb or flow dividers. A set of 100 sample equidistant points (or vertices) were

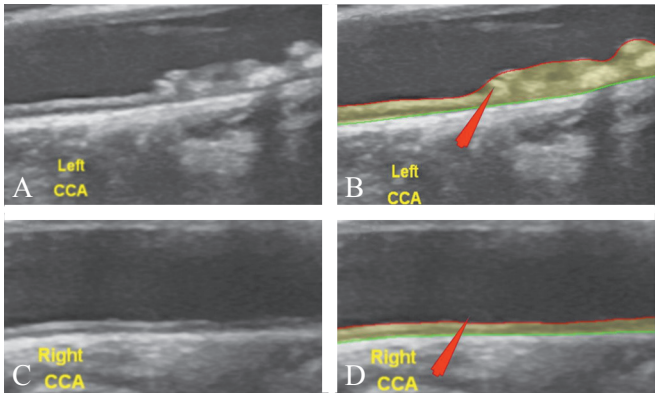

Figure 4.—Full-length scanning of the carotid ultrasound image in the far wall of the CCA segment. (A) Original Image and (B) processed image using AtheroEdge™ 2.0 for the left side of the neck; (C) original Image and (D) processed image using AtheroEdge™ 2.0 for the right side of the neck.

collected throughout the length of the CUS scan for the measurement of cIMT or TPA_{curr}. Figure 4B, D show the variation in carotid wall thickness throughout the length of the CUS scan for the far wall of the left and right CCA. If the CUS scan is for bulb or an ICA scan, then full-length still implies a measurement of cIMT in the bulb's eye and its surrounding far wall region (Figure 5A-D for bulb and Figure 6A-D for ICA).

$cIMTave_{curr}$ is the average distance between two sets of observation points measured on the lumen-intima (LI) and media-adventitia (MA) interfaces when the patient visits the radiological ultrasound laboratory, and the readings are taken instantaneously.[74, 75] Similarly, $cIMTmax_{curr}$ and $cIMTmin_{curr}$ were the maximum and minimum values computed within the full-length scan of cIMT values. Suri *et al.*[76] proposed another important phenotype called $cIMTV_{curr}$. Variability in the carotid artery wall ($cIMTV_{curr}$), is associated with cerebrovascular events[76] and thus has a bearing on the guideline. The atherosclerotic plaque can cause inflammation in both directions (towards the lumen region and towards the adventitia region) of the carotid artery wall as it does not follow any defined morphology. This indicates that the atherosclerotic plaque of the media wall can protrude in both the lumen zone and the adventitia zone forming a balloon-like structure. Thus, there is a need to quantify this bidirectional morphological variation in the carotid wall. Recently developed CUS image-based phenotype called *IMT variability* (IMTV) measures the variation in carotid wall thickness in both directions and has been successfully tested for risk stratification in patients.[72, 76, 77]

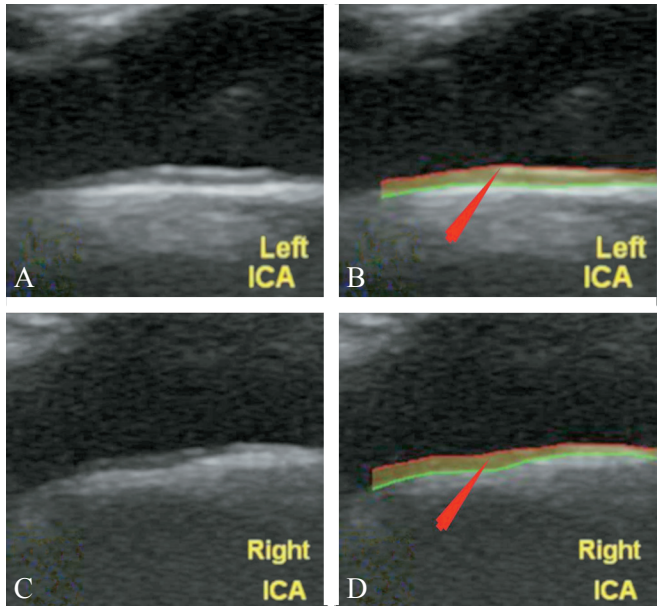

Figure 5.—Full-length scanning of the carotid ultrasound image in the far wall of the carotid ICA segment. A) Original image and (B) processed image using AtheroEdge™ 2.0 for the left side of the neck; C) original image and (D) processed image using AtheroEdge™ 2.0 for the right side of the neck.

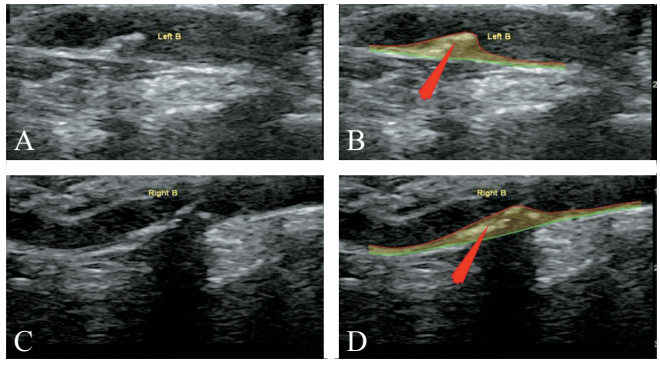

Figure 6.—Full-length scanning of the carotid ultrasound image in the far wall of the carotid bulb segment. A) Original image and (B) processed image using AtheroEdge™ 2.0 for the left side of the neck; C) original image and (D) processed image using AtheroEdge™ 2.0 for the right side of the neck.

The TPA_{curr} included the focal thickening region which was above the one mm average baseline distance between LI and MA interfaces.[78, 79] In order to compute the TPA_{curr}, all the pixels within the focal thickening region were accumulated and further converted into a square millimeter (mm^2) scale.[78, 79] The subscript 'curr' indicated the current measurement of CUSIP. All five CUSIP depicted the ma-

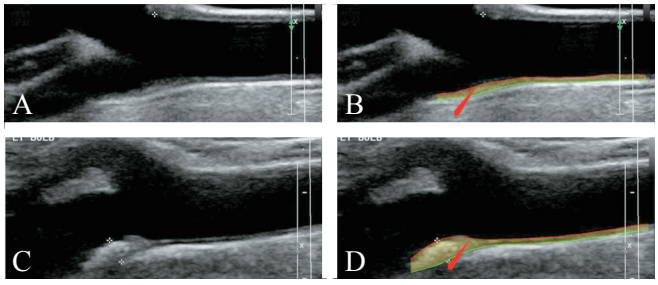

Figure 7.—Full-length scanning of the carotid ultrasound image in the far wall of the carotid bulb and ICA segments. A) Original image and (B) processed image using AtheroEdge™ 2.0 without the CP at the entrance of bulb/ICA lesion; C) original image and (D) processed image using AtheroEdge™ 2.0 with the CP at the entrance of bulb/ICA lesion.

jority of morphological variations within the carotid wall. Furthermore, these phenotypes had also been used for the risk stratification in patients.[18] Thus, it would be more interesting to consider all the five CUSIP while assessing the risk of CVD/Stroke in future measurement protocols. The association between CRF and the progression of cIMT has already been discussed in the previous section. Based on this, Khanna *et al.*[37] modeled the five 10-year CUSIP ($cIMTave_{10yr,}$ $cIMTmax_{10yr,}$ $cIMTmin_{10yr,}$ $cIMTV_{10yr,}$ and TPA_{10yr}) by using the well-established annual progression rates of cIMT and CP. The 10-year predictions of CUSIP are important because they provide the extent by which the CUSIP can be increased if the corresponding CRF are well-controlled. The subscript '10yr' indicated the 10-year prediction of the CUSIP.

Measurements and risk stratification

Full-length measurement of cIMT with equidistant points

The variations in the LI and MA interfaces of the carotid wall can happen due to morphological changes in the artery, the so-called Glagov phenomenon.[80] These morphological variations can extend outside the 10 mm length of the carotid artery segment and typically missed in routine mode during real-time screening. Figure 4, 5, 6, 7 showed variations in carotid wall thickness throughout the length of the grayscale region in the CUS scan (*i.e.*, in the region beyond the 10 mm region indicated by the current guidelines). Figure 7A-D indicates the variations in cIMT and CP in the carotid bifurcation region and ICA region. The elevated wall thickness at the eye of the carotid bulb is shown in Figure 7D may not be captured using the recommendations by the current guidelines.[19, 24, 25] Thus, by restricting the wall thickness measurement within the confined 10 mm carotid artery segment is not viable in explaining the CVD/stroke risk. One must, therefore, look for the measurements to be taken all along the length of the carotid artery segment or bifurcation segment in the CUS scans (or full-length cIMT)[48, 73] during the routine mode measurements. Note that during the measurement of the segments, the neighboring region of the segment may also be present in the CUS scan. For example, during the plaque measurement in the bulb's eye, the distal end of the CCA segment might also be present in the CUS scan, hence it is part of the full-length measurement. By undergoing the full-length measurements, it gives further advantage to the neuroradiologist while capturing the morphological changes in the atherosclerotic plaque due to the shape of the artery (convex, concave, down-slope, and up-slope). Since the system is fully automated and reproducible, the results are unbiased.

Along with the full-length cIMT measurement, a sufficiently large number of equidistant sample points (or vertices of the line) on both LI and MA interface needs to be considered for providing an accurate measurement of the mean cIMT. This is because atherosclerotic plaque does not have any specific distribution, thus, the true morphological variations in cIMT may not be captured if limited observations are considered. The current guidelines provide little attention towards the total number of equidistant observation points on the LI and MA interfaces. However, the approach of measuring the full-length cIMT with a large number of equidistant sample points has been recently demonstrated[32-35] for the stroke risk assessment. Recently, Saba *et al.*[60, 81] and Suri *et al.*[82, 83] followed a well-known polyline distance measurement method for the accurate computation of cIMT. Furthermore, Suri and his team have used an equidistant B-spline interpolation technique to smooth-out both the LI and MA borders giving equidistant points normalized to 100.[83] This equidistant protocol was beneficial in computing perpendicular distances from the LI border point to MA polyline and vice-versa.[32] Instead of using the manual or semi-automated approach (which was followed by guidelines), Suri and his team have employed fully automated methods for measuring the full-length cIMT.[49]

Morphologic total plaque area

Computation of total plaque area (TPA) as suggested by the some conventional studies[16, 78, 79, 84] includes follow-

ing steps: 1) identification of the CP lesion with focal thickening region >1 mm; 2) counting all the pixels within the manually traced region-of-interest; 3) converting the count of all the pixels to millimeter domain by multiplying with image-resolution factor; and 4) finally, repeating step (1) to (2) throughout the carotid scan and accumulating all the areas to obtain TPA. The common challenge in measuring the TPA in all these studies is the involvement of manual analysis of plaque region[17, 18] which further leads to the intra- or inter-operator variability.[17, 18] In order to avoid this variability, recently, an automated method of TPA computation has been proposed.[17, 18] In automated TPA measurement, the first step was to identify the LI and MA borders using a fully-automated measurement tool.[73] Then, the envelope between the LI and MA borders which follows the morphology of atherosclerotic plaque was delineated. Finally, all the pixels within an envelope were accumulated and converted into the millimeter domain to obtain the TPA. Since this TPA follows the morphology of atherosclerotic plaque, it was also termed as the morphologic TPA or mTPA. It is an interesting point to note that, the mTPA is not only the area within the LI and MA borders but also the area above the baseline, which is along with the guidelines, however completely automated. Note that, both cIMT region and focal thickening as recommended by previous studies have been considered, hence TPA fully covers the CP area. These automated plaque area measurements have been associated with patients with CVD outcomes.[17, 18] Thus, such advanced metrics can be useful for the design of future guidelines.

Far and near wall measurements

Another major focus of the current guidelines was to assess the cIMT in the far wall of the carotid artery. The main idea behind considering the far wall of the CCA was to provide reproducible results. Both the inter- and intra-operator reproducibility of cIMT measurements is a crucial task. One of the main factors which cause the challenge in the inter- and intra-operator reproducibility is the image resolution or image quality in conjunction with the type of delineation method (auto *vs*. semi-auto). Low-resolution images (having low signal to noise ratio), not meeting the criteria such as: 1) bright (hyper-echoic) adventitia; 2) dark gray media wall; 3) bright gray intima wall; 4) dark (hypo-echoic) lumen region; and 5) automated measurement technique, increases the inter- and intra-operator error which further poses a challenge in reproducibility analysis.[32, 85, 86] Furthermore, if the image is of high-resolution and meets all the above-mentioned criteria, then the question of inter- and intra-operator reproducibility does not arise.[32, 85, 86] This is because the automated algorithms are very successful as demonstrated in the recent studies by our group.[32, 85, 86] Recent studies have also shown inter- and intra-operator reproducibility analysis to measure the cIMT along both the far and near the wall of the carotid artery.[32, 50] Due to such recent advancements, cIMT can also be measured from the near wall with a high degree of reproducibility.

cIMT threshold for risk stratification

Currently, there exists a lack of concurrence between multiple studies to decide the cIMT and CP cut-off values for risk stratification.[87] Clinical studies have adopted a wide variety of cIMT thresholds ranging from 0.7 mm to 1.2 mm. It has been observed that the risk stratification cut-off points for cIMT depend upon the baseline characteristics of the patients. This cut-off value affects the area-under-the-curve when computing the performance of the system using receiver operating characteristics curve analysis.[28, 87, 88]

From the above discussions, it is clear that there is a set of points that have been answered by the recently published studies that directly link to the guidelines, and therefore can potentially reshape the design of the next set of guidelines for CUSIP measurements.

Scientific validation

Validation is the most crucial part of any kind of clinical parameter measurement and risk assessment system. Figure 1 shows ellipse number 5 that represents the essential link between scientific validation and the CUSIP measurement guidelines. Measurement of CUSIP such as cIMT and CP from any automated or semi-automated algorithms needs to be validated against the gold standard. The definition of the gold standard varies with the type of study. In general three types of gold standards have been used in the clinical settings: 1) manual tracings from expert physicians who have spent a sufficiently large amount of time in the relevant medical domain; 2) the histological findings to validate the CUSIP measurements values; and 3) events (such as cerebrovascular or cardiovascular) obtained from longitudinal clinical trials.

Several studies have used the manual tracings made by an expert physician as a gold standard to validate the LI and MA interfaces, lumen diameters (LD), cIMT values, and CP area.[73, 89] Manual analysis is the most feasible

and economical process, however tedious. Furthermore, it compares the measurements against human knowledge which is always considered superior compared to the automated systems. Although histological analysis is costly and not feasible, few studies have performed histological validations that reported the high-degree of correlation between CUS measurements and histological findings.[90, 91]

The CUS measurements validated using the longitudinal trials with considerable follow-up time has proved to be a better choice amongst the physicians. In the last decade, multiple longitudinal studies have been used to validate the measurements of cIMT and CP against the events resulted in the longitudinal follow-up.[8-14] A total of 17 follow-up studies (in chronological order) from the 10 most popular longitudinal trials (column C2) are presented in Table I[7-14, 28, 70, 92-96, 98] that indicate the significant association between both cIMT and CP with the onset of CV and stroke events. Out of 17 follow-up studies in Table I, 9 studies were in targeted the patients with middle age group (~ 40 to 60 years), 6 studies were targeted for higher age-group patients (>60 years), and remaining two studies by Lorenz *et al.*[11, 96] (rows R10 and R14) considered all the three categories of the age groups (younger age, middle age, and older age). Irrespective of the varying age-groups, the cIMT and CP were indicated to show a significant association with the onset of CV and stroke events.[8, 9, 11-14, 28, 70, 96-99] Although there is variation in cIMT measurement protocol followed by all these studies, nearly all of them indicated a significant association between CUSIP and the vascular events (column C10).

Another type of validation method is to analyze and compare the composition of the atherosclerotic plaque using multiple imaging modalities. That means the plaque composition observed using CUS can be validated using CT or MRI. Recently, Saba *et al.*[100] showed a multimodality validation approach where the authors used pairs of CT and CUS images.

Another important component of scientific validation is to not overlook the intra- and inter-operator variability analysis.[86] Readings taken by the same operator at different times is considered as intra-operator variability analysis. Another way of evaluating the intra-operator performance is to take multiple images of the same patient at different orientations (anterior, posterior and anterolateral) and then measure cIMT in all orientations. The readings (or CUSIP measurements) taken between two different operators (novice operator or experienced operator) are considered as inter-operator variability 73. Since the CUSIP measurements are computed only for one patient at a time, the error in measurements by both operators must be less.[86] Similarly, there should be a high degree of correlation between the CUSIP measurements of both the operators.[73]

Besides all the validation methods, different results derived from performance evaluation metrics such as accuracy, figure-of-merit, and precision-of-merit needs to be highlighted.[32, 50] All such performance evaluation metrics indicate the closeness or preciseness between the observed readings and ground truth readings. Apart from all the techniques for the validation and performance evaluation, it is also interesting to finalize the results by benchmarking the measurements against some previously established automated software.[50]

Effect of technology changes

The advancements in the technology have assisted in generating more accurate and consistent measurements of the image-based phenotypes. Computation intelligence technologies such as machine learning (ML) and deep learning (DL) approaches have been widely adopted for the CVD/stroke risk assessment.[33, 35, 101-106] In terms of the measurement of cIMT, both the ML and DL techniques have shown efficient and reliable results compared to statistical conventional techniques or manual approaches.[107-110] Furthermore, such intelligence-based paradigms have facilitated the assessment in CUS images to provide the risk stratification with higher accuracy.[33, 35, 101-106] The ML algorithms are generally used for risk prediction or risk stratification.[111] Such algorithms need prior input labels to train the ML system by performing the CVD/stroke risk stratification.[111] The input labels can be derived from an expert physician or as an endpoint during the longitudinal trials.[111] In the last decade, multiple cohort studies were used in the ML systems to perform the CVD and stroke risk assessment using cIMT and CP as the surrogate markers.[33, 35, 101-106] Looking at the wide scope of the ML systems, the newer measurement guidelines can also take the aid of such developed techniques that can provide reliable and accurate information for performing the CVD/stroke risk assessment using CUS.

Conclusions

This review is the first of its kind which elaborates on the role of various factors that influences the atherosclerotic

TABLE I.—*Studies that indicate the association between carotid ultrasound image-based phenotypes and CVD/stroke risk assessment.*

Author (year)	Study/trial	FU (years)	Ethnicity	#Patients	Image phenotype
Salonen *et al.*[7] (1991)	The KIHD Study	-	Finnish	1288	cIMT and CP
Bots *et al.*[8] (1997)	The Rotterdam Study	2.7	Dutch	7983	cIMT and CP
Chambless *et al.*[9] (1997)	The ARIC Study	5.2	American	12841	cIMT
O'Leary *et al.*[12] (1999)	The CHS Study	6.2	American	5858	cIMT
Chambless *et al.*[10] (2000)	The ARIC Study	7.2	American	14214	cIMT
Iglesias *et al.*[92] (2002)	The Rotterdam Study	4.6	Dutch	5854	cIMT
Hollender *et al.*[93] (2003)	The Rotterdam Study	6.1	Dutch	6913	cIMT and CP
Kitamura *et al.*[94] (2004)	-	4.5	Japanese	1289	cIMT and CP
Rosvall *et al.*[14] (2005)	The MDCS Study	7	Finnish	5163	cIMT and CP
Lorenz *et al.*[11] (2006)	CAPS Study	4.2	German	5056	cIMT
Nambi *et al.*[95] (2010)	The ARIC Study	15.1	American	13145	cIMT and CP
Polak *et al.*[13] (2011)	FHS	7.2	Non-Hispanic white	2965	cIMT and CP
Polak *et al.*[70] (2011)	MESA	3.22	White, black, Hispanic, and Chinese	5028	cIMT
Lorenz *et al.*[96] (2012)	PROG-IMT Study	7	White, Afric-an American, Hispanic	36984	cIMT
Ruijter *et al.*[28] (2012)	The USE-IMT study	11	-	45858	cIMT
Ruijter *et al.*[97] (2013)	The USE-IMT study	8.7	-	4220	cIMT
Bots *et al.*[98] (2014)	The USE-IMT study	9.9	-	17254	cIMT

measurement guidelines. It examines important factors influencing guideline design. They are atherosclerosis disease itself, conventional risk factors, 10-year CUSIP prediction tools, types of CVD/stroke risk calculators, incomplete validation of measurement tools, and the fast pace of computer technology advancements.

The technological advances in software and hardware engineering have prompted new methods for the measurements of cIMT and CP. As a result, one can now detect the full-length measurements along the carotid artery, which detects both subclinical atherosclerosis and CP. This eases the measurement process.

Reproducibility of the CUSIP measurements has always been a challenging task in low-resolution images. Recent advancements in software technology (*i.e.* AtheroEdge, AtheroPoint™, Roseville, USA) has shown a high inter-and intra-operator reproducibility in moderate to high-resolution carotid scans. Still, a large reproducibility follow-up study with a multi-ethnicity database of the CUSIP measurements must be warranted in the future for low contrast carotid scans, that use the semi-automated methods."

Several non-communicable diseases which are more prevalent causes the atherosclerosis disease to accelerate, therefore segments like bulb and ICA must be taken into consideration. Further, the risk prediction can be more accurately measured using integrated calculators and in the future, we anticipate the role of artificial intelligence-base techniques for penetrating CV risk prediction.

We conclude that both ML and non-ML strategies will flourish for current and 10-year CVD/Stroke risk prediction as long as they integrate image-based phenotypes with CRF. We believe that it will be important for new and evolving evidence to continue to influence clinical practice guidelines for CVD/stroke risk to improve patient outcomes.

AT	Age (years)	Endpoints	#Events	Main findings
CCA and Carotid bulb	40 to 60	CHD	-	A strong association exists between carotid artery wall morphology and coronary heart disease.
CCA	>55	MI and Strokes	MI: 98 Stroke: 95	Increased common cIMT is associated with an increased risk of MI and stroke.
CCA, ICA, and bifurcation	45 to 60	CHD	CHD:290	Mean of mean cIMT has a strong association with CHD events
CCA and ICA	>65	MI and stroke	MI: 267 Stroke: 284	cIMT of CCA and ICA have strong predictive power of MI.
CCA, ICA, and bifurcation	45 to 64	Stroke	Stroke:199	Mean of mean cIMT has a strong association with stroke events.
CCA, ICA, and bifurcation	70 to 72	MI	MI: 194	cIMTs from all segments of the carotid artery are predictors of MI.
CCA	≥55	Stroke	Stroke: 378	cIMT and aortic calcification is a strong predictor of stroke events.
CCA and ICA	60 to 74	Stroke	Stroke: 34	CCA IMT and ICA plaque are important phenotype of stroke events.
CCA and Carotid plaque	57.4	-	-	Common cIMT is associated with coronary events.
CCA, ICA, Bifurcation	19 to 90	MI, stroke, and deaths	MI: 228 Stroke: 107	cIMT is biomarker of vascular events even at younger age.
CCA, ICA, and bifurcation	45 to 64	CHD	CHD events: 1812	Addition of cIMT and CP to CRF improve the CHD event prediction
CCA and ICA	57.3±9.5 (Ave)	CV event	Deaths: 296	Maximum ICA has been considered as the gold standard.
CCA	64.2 (Ave)	Stroke	Stroke: 42	CCA IMT progression is strongly associated with stroke.
CCA, ICA, and bifurcation	15 to 95	MI, stroke, and Deaths	MI: 1519 Stroke: 1339 Deaths: 2028	Association between cIMT progression and CVD risk remains unproven
CCA	45 to 75	MI and stroke	MI and stroke: 4007	Addition of common cIMT resulted in less improvement in 10-year risk of MI.
CCA	45 to 75	MI and stroke	MI and stroke: 684	Less improvement in 10-year risk prediction while adding the common cIMT for diabetes patients.
CCA	45 to 75	MI and Stroke	MI and Stroke: 2014	Addition of common cIMT resulted in less improvement in the 10-year risk of MI.

References

1. Organization WH. 2017; [Internet]. Available from: http://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) [cited 2019, Oct 18].

2. Libby P. Vascular biology of atherosclerosis: overview and state of the art. Am J Cardiol 2003;91(3A):3A–6A.

3. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135–43.

4. O'Leary DH, Bots ML. Imaging of atherosclerosis: carotid intima-media thickness. Eur Heart J 2010;31:1682–9.

5. Bots ML, Sutton-Tyrrell K. Lessons from the past and promises for the future for carotid intima-media thickness. J Am Coll Cardiol 2012;60:1599–604.

6. Nicolaides A, Panayiotou AG. Screening for atherosclerotic cardiovascular risk using ultrasound. J Am Coll Cardiol 2016;67:1275–7.

7. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991;11:1245–9.

8. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation 1997;96:1432–7.

9. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, *et al.* Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. Am J Epidemiol 1997;146:483–94.

10. Chambless LE, Folsom AR, Clegg LX, Sharrett AR, Shahar E, Nieto FJ, *et al.* Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol 2000;151:478–87.

11. Lorenz MW, von Kegler S, Steinmetz H, Markus HS, Sitzer M. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). Stroke 2006;37:87–92.

12. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr; Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med 1999;340:14–22.

13. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB Sr. Carotid-wall intima-media thickness and cardiovascular events. N Engl J Med 2011;365:213–21.

14. Rosvall M, Janzon L, Berglund G, Engström G, Hedblad B. Incident coronary events and case fatality in relation to common carotid intima-media thickness. J Intern Med 2005;257:430–7.

15. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction

of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007;115:459–67.

16. Spence JD, Eliasziw M, DiCicco M, Hackam DG, Galil R, Lohmann T. Carotid plaque area: a tool for targeting and evaluating vascular preventive therapy. Stroke 2002;33:2916–22.

17. Cuadrado-Godia E, Srivastava SK, Saba L, Araki T, Suri HS, Giannopolulos A, *et al.* Geometric Total Plaque Area Is an Equally Powerful Phenotype Compared With Carotid Intima-Media Thickness for Stroke Risk Assessment: A Deep Learning Approach. Journal for Vascular Ultrasound 2018;42:162–88.

18. Cuadrado-Godia E, Maniruzzaman M, Araki T, Puvvula A, Jahanur Rahman M, Saba L, *et al.*; Fellow AIMBE. Morphologic TPA (mTPA) and composite risk score for moderate carotid atherosclerotic plaque is strongly associated with HbA1c in diabetes cohort. Comput Biol Med 2018;101:128–45.

19. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, *et al.*; American Society of Echocardiography Carotid Intima-Media Thickness Task Force; Endorsed by the Society for Vascular Medicine. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. J Am Soc Echocardiogr 2008;21:93–111, quiz 189–90.

20. Inaba Y, Chen JA, Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. Atherosclerosis 2012;220:128–33.

21. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH, *et al.* The role of carotid arterial intima-media thickness in predicting clinical coronary events. Ann Intern Med 1998;128:262–9.

22. Bots ML, Evans GW, Tegeler CH, Meijer R. Carotid Intima-media Thickness Measurements: Relations with Atherosclerosis, Risk of Cardiovascular Disease and Application in Randomized Controlled Trials. Chin Med J (Engl) 2016;129:215–26.

23. Kim GH, Youn HJ. Is Carotid Artery Ultrasound Still Useful Method for Evaluation of Atherosclerosis? Korean Circ J 2017;47:1–8.

24. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, *et al.* Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Cerebrovasc Dis 2007;23:75–80.

25. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, *et al.* Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis 2012;34:290–6.

26. Grundy SM, Bilheimer D, Chait A, Clark LT, Denke M, Havel RJ, *et al.* Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). JAMA 1993;269:3015–23.

27. de la Sierra A, Zamorano JL, Ruilope LM. Application of hypertension guidelines in clinical practice: implementation of the 2007 ESH/ESC European practice Guidelines in Spain. J Hypertens Suppl 2009;27:S27–32.

28. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, *et al.* Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA 2012;308:796–803.

29. Stein JH, Tattersall MC. Carotid intima-media thickness and cardiovascular disease risk prediction. J Am Coll Cardiol 2014;63:2301–2.

30. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, *et al.* General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743–53.

31. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, *et al.* 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63(25 Pt B):2935–59.

32. Saba L, Banchhor SK, Suri HS, Londhe ND, Araki T, Ikeda N, *et al.* Accurate cloud-based smart IMT measurement, its validation and stroke risk stratification in carotid ultrasound: A web-based point-of-care tool for multicenter clinical trial. Comput Biol Med 2016;75:217–34.

33. Acharya UR, Mookiah MR, Vinitha Sree S, Afonso D, Sanches J, Shafique S, *et al.* Atherosclerotic plaque tissue characterization in 2D ultrasound longitudinal carotid scans for automated classification: a paradigm for stroke risk assessment. Med Biol Eng Comput 2013;51:513–23.

34. Saba L, Araki T, Kumar PK, Rajan J, Lavra F, Ikeda N, *et al.* Carotid inter-adventitial diameter is more strongly related to plaque score than lumen diameter: an automated tool for stroke analysis. J Clin Ultrasound 2016;44:210–20.

35. Araki T, Jain PK, Suri HS, Londhe ND, Ikeda N, El-Baz A, *et al.* Stroke risk stratification and its validation using ultrasonic Echolucent Carotid Wall plaque morphology: a machine learning paradigm. Comput Biol Med 2017;80:77–96.

36. Khanna NN, Jamthikar AD, Gupta D, Nicolaides A, Araki T, Saba L, *et al.* Performance evaluation of 10-year ultrasound image-based stroke/cardiovascular (CV) risk calculator by comparing against ten conventional CV risk calculators: A diabetic study. Comput Biol Med 2019;105:125–43.

37. Khanna NN, Jamthikar AD, Araki T, Gupta D, Piga M, Saba L, *et al.* Nonlinear model for the carotid artery disease 10-year risk prediction by fusing conventional cardiovascular factors to carotid ultrasound image phenotypes: A Japanese diabetes cohort study. Echocardiography 2019;36:345–61.

38. Khanna NN, Jamthikar AD, Gupta D, Araki T, Piga M, Saba L, *et al.* Effect of carotid image-based phenotypes on cardiovascular risk calculator: AECRS1.0. Med Biol Eng Comput 2019;57:1553–66.

39. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, *et al.*; ESC Scientific Document Group. 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J 2016;37:2999–3058.

40. Leskinen Y, Lehtimäki T, Loimaala A, Lautamatti V, Kallio T, Huhtala H, *et al.* Carotid atherosclerosis in chronic renal failure-the central role of increased plaque burden. Atherosclerosis 2003;171:295–302.

41. Razzouk L, Rockman CB, Patel MR, Guo Y, Adelman MA, Riles TS, *et al.* Co-existence of vascular disease in different arterial beds: peripheral artery disease and carotid artery stenosis. Data from Life Line Screening®. Atherosclerosis 2015;241:687–91.

42. Bots ML, Baldassarre D, Simon A, de Groot E, O'Leary DH, Riley W, *et al.* Carotid intima-media thickness and coronary atherosclerosis: weak or strong relations? Eur Heart J 2007;28:398–406.

43. Johnson HM, Douglas PS, Srinivasan SR, Bond MG, Tang R, Li S, *et al.* Predictors of carotid intima-media thickness progression in young adults: the Bogalusa Heart Study. Stroke 2007;38:900–5.

44. Hansen K, Östling G, Persson M, Nilsson PM, Melander O, Engström G, *et al.* The effect of smoking on carotid intima-media thickness progression rate and rate of lumen diameter reduction. Eur J Intern Med 2016;28:74–9.

45. Howard G, Sharrett AR, Heiss G, Evans GW, Chambless LE, Riley WA, *et al.*; ARIC Investigators. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. Stroke 1993;24:1297–304.

46. Rosvall M, Persson M, Östling G, Nilsson PM, Melander O, Hedblad B, *et al.* Risk factors for the progression of carotid intima-media thickness over a 16-year follow-up period: the Malmö Diet and Cancer Study. Atherosclerosis 2015;239:615–21.

47. Rashid SA, Mahmud SA. Correlation between carotid artery inti-

ma-media thickness and luminal diameter with body mass index and other cardiovascular risk factors in adults. Sultan Qaboos Univ Med J 2015;15:e344–50.

48. Molinari F, Meiburger KM, Zeng G, Saba L, Rajendra Acharya U, Famiglietti L, *et al.* Automated carotid IMT measurement and its validation in low contrast ultrasound database of 885 patient Indian population epidemiological study: results of AtheroEdge™ Software. Int Angiol 2012;31:42–53.

49. Molinari F, Zeng G, Suri JS. Intima-media thickness: setting a standard for a completely automated method of ultrasound measurement. IEEE Trans Ultrason Ferroelectr Freq Control 2010;57:1112–24.

50. Saba L, Molinari F, Meiburger KM, Acharya UR, Nicolaides A, Suri JS. Inter- and intra-observer variability analysis of completely automated cIMT measurement software (AtheroEdge™) and its benchmarking against commercial ultrasound scanner and expert Readers. Comput Biol Med 2013;43:1261–72.

51. Rikin Trivedi LS, Jasjit S. Suri. 3D Imaging Technologies in Atherosclerosis. In: Rikin Trivedi LS, Suri JS, editors. Berlin: Springer; 2015.

52. Suri JS. Advances in diagnostic and therapeutic ultrasound imaging. Norwood, MA: Artech House; 2008.

53. Saba L, Sanches JM, Pedro LM, Suri JS. Multi-modality atherosclerosis imaging and diagnosis. Berlin: Springer; 2014.

54. Laine A, Sanches JM, Suri JS. Ultrasound Imaging: Advances and Applications. Berlin: Springer; 2012.

55. Brohall G, Odén A, Fagerberg B. Carotid artery intima-media thickness in patients with Type 2 diabetes mellitus and impaired glucose tolerance: a systematic review. Diabet Med 2006;23:609–16.

56. Bots ML, Witteman JC, Grobbee DE. Carotid intima-media wall thickness in elderly women with and without atherosclerosis of the abdominal aorta. Atherosclerosis 1993;102:99–105.

57. Lathe R, Sapronova A, Kotelevtsev Y. Atherosclerosis and Alzheimer—diseases with a common cause? Inflammation, oxysterols, vasculature. BMC Geriatr 2014;14:36.

58. Ichiki T. Thyroid hormone and atherosclerosis. Vascul Pharmacol 2010;52:151–6.

59. Kloner RA, Speakman M. Erectile dysfunction and atherosclerosis. Curr Atheroscler Rep 2002;4:397–401.

60. Saba L, Molinari F, Meiburger K, Piga M, Zeng G, Rajendra UA, *et al.* What is the correct distance measurement metric when measuring carotid ultrasound intima-media thickness automatically? International angiology 2012;31:483-9.

61. Stevens RJ, Kothari V, Adler AI, Stratton IM; United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). Clin Sci (Lond) 2001;101:671–9.

62. Kothari V, Stevens RJ, Adler AI, Stratton IM, Manley SE, Neil HA, *et al.* UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. Stroke 2002;33:1776–81.

63. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA 2007;297:611–9.

64. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, *et al.*; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987–1003.

65. Group ND; NIPPON DATA80 Research Group. Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a Japanese representative population. Circ J 2006;70:1249–55.

66. Mendis S, Lindholm LH, Mancia G, Whitworth J, Alderman M, Lim S, *et al.* World Health Organization (WHO) and International Society of Hypertension (ISH) risk prediction charts: assessment of cardiovascular risk for prevention and control of cardiovascular disease in low and middle-income countries. J Hypertens 2007;25:1578–82.

67. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ 2017;357:j2099.

68. Rosengren A, Hawken S, Ôunpuu S, Sliwa K, Zubaid M, Almahmeed WA, *et al.*; INTERHEART investigators. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:953–62.

69. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, *et al.*; INTERSTROKE investigators. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet 2016;388:761–75.

70. Polak JF, Pencina MJ, O'Leary DH, D'Agostino RB. Common carotid artery intima-media thickness progression as a predictor of stroke in multi-ethnic study of atherosclerosis. Stroke 2011;42:3017–21.

71. Osondu CU, Vo B, Oni ET, Blaha MJ, Veledar E, Feldman T, *et al.* The relationship of erectile dysfunction and subclinical cardiovascular disease: A systematic review and meta-analysis. Vasc Med 2018;23:9–20.

72. Saba L, Meiburger KM, Molinari F, Ledda G, Anzidei M, Acharya UR, *et al.* Carotid IMT variability (IMTV) and its validation in symptomatic versus asymptomatic Italian population: can this be a useful index for studying symptomaticity? Echocardiography 2012;29:1111–9.

73. Molinari F, Pattichis CS, Zeng G, Saba L, Acharya UR, Sanfilippo R, *et al.* Completely automated multiresolution edge snapper—a new technique for an accurate carotid ultrasound IMT measurement: clinical validation and benchmarking on a multi-institutional database. IEEE Trans Image Process 2012;21:1211–22.

74. Suri JS, Haralick RM, Sheehan FH. Greedy algorithm for error correction in automatically produced boundaries from low contrast ventriculograms. Pattern Anal Appl 2000;3:39–60.

75. Molinari F, Zeng G, Suri JS. Greedy technique and its validation for fusion of two segmentation paradigms leads to an accurate intima–media thickness measure in plaque carotid arterial ultrasound. Journal for Vascular Ultrasound 2010;34:63–73.

76. Saba L, Mallarini G, Sanfilippo R, Zeng G, Montisci R, Suri J. Intima Media Thickness Variability (IMTV) and its association with cerebrovascular events: a novel marker of carotid therosclerosis? Cardiovasc Diagn Ther 2012;2:10–8.

77. Lucatelli P, Raz E, Saba L, Argiolas GM, Montisci R, Wintermark M, *et al.* Relationship between leukoaraiosis, carotid intima-media thickness and intima-media thickness variability: preliminary results. Eur Radiol 2016;26:4423–31.

78. Spence JD, Solo K. Resistant Atherosclerosis: The Need for Monitoring of Plaque Burden. Stroke 2017;48:1624–9.

79. Rundek T, Spence JD. Ultrasonographic measure of carotid plaque burden. JACC Cardiovasc Imaging 2013;6:129–30.

80. Korshunov VA, Schwartz SM, Berk BC. Vascular remodeling: hemodynamic and biochemical mechanisms underlying Glagov's phenomenon. Arterioscler Thromb Vasc Biol 2007;27:1722–8.

81. Huttenlocher DP, Klanderman GA, Rucklidge WJ. Comparing images using the Hausdorff distance. IEEE Trans Pattern Anal Mach Intell 1993;15:850–63.

82. Molinari F, Meiburger KM, Saba L, Acharya UR, Famiglietti L, Georgiou N, *et al.* Automated Carotid IMT Measurement and Its Validation in Low Contrast Ultrasound Database of 885 Patient Indian Population Epidemiological Study: Results of AtheroEdge® Software. Multi-Modality Atherosclerosis Imaging and Diagnosis. Berlin: Springer; 2014. p. 209-19.

83. Molinari F, Meiburger KM, Saba L, Zeng G, Acharya UR, Ledda M, *et al.* Fully automated dual-snake formulation for carotid intima-media thickness measurement. A new approach. J Ultrasound Med 2012;31:1123–36.

84. Mathiesen EB, Johnsen SH, Wilsgaard T, Bønaa KH, Løchen ML, Njølstad I. Carotid plaque area and intima-media thickness in prediction

of first-ever ischemic stroke: a 10-year follow-up of 6584 men and women: the Tromsø Study. Stroke 2011;42:972–8.

85. Saba L, Banchhor SK, Araki T, Viskovic K, Londhe ND, Laird JR, *et al.* Intra- and inter-operator reproducibility of automated cloud-based carotid lumen diameter ultrasound measurement. Indian Heart J 2018;70:649–64.

86. Saba L, Banchhor SK, Araki T, Suri HS, Londhe ND, Laird JR, *et al.* Intra- and Inter-operator Reproducibility Analysis of Automated Cloud-based Carotid Intima Media Thickness Ultrasound Measurement. J Clin Diagn Res 2018;12:KC01–11.

87. Araki T, Ikeda N, Dey N, Acharjee S, Molinari F, Saba L, *et al.* Shape-based approach for coronary calcium lesion volume measurement on intravascular ultrasound imaging and its association with carotid intima-media thickness. J Ultrasound Med 2015;34:469–82.

88. Kao AH, Lertratanakul A, Elliott JR, Sattar A, Santelices L, Shaw P, *et al.* Relation of carotid intima-media thickness and plaque with incident cardiovascular events in women with systemic lupus erythematosus. Am J Cardiol 2013;112:1025–32.

89. Krishna Kumar P, Araki T, Rajan J, Saba L, Lavra F, Ikeda N, *et al.* Accurate lumen diameter measurement in curved vessels in carotid ultrasound: an iterative scale-space and spatial transformation approach. Med Biol Eng Comput 2017;55:1415–34.

90. Farkas S, Molnár S, Nagy K, Hortobágyi T, Csiba L. Comparative in vivo and in vitro postmortem ultrasound assessment of intima-media thickness with additional histological analysis in human carotid arteries. Perspectives in Medicine 2012;1:170–6.

91. Gamble G, Beaumont B, Smith H, Zorn J, Sanders G, Merrilees M, *et al.* B-mode ultrasound images of the carotid artery wall: correlation of ultrasound with histological measurements. Atherosclerosis 1993;102:163–73.

92. Iglesias del Sol A, Bots ML, Grobbee DE, Hofman A, Witteman JC. Carotid intima-media thickness at different sites: relation to incident myocardial infarction; The Rotterdam Study. Eur Heart J 2002;23:934–40.

93. Hollander M, Hak AE, Koudstaal PJ, Bots ML, Grobbee DE, Hofman A, *et al.* Comparison between measures of atherosclerosis and risk of stroke: the Rotterdam Study. Stroke 2003;34:2367–72.

94. Kitamura A, Iso H, Imano H, Ohira T, Okada T, Sato S, *et al.* Carotid intima-media thickness and plaque characteristics as a risk factor for stroke in Japanese elderly men. Stroke 2004;35:2788–94.

95. Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, *et al.* Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. J Am Coll Cardiol 2010;55:1600–7.

96. Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Völzke H, Tuomainen TP, *et al.*; PROG-IMT Study Group. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. Lancet 2012;379:2053–62.

97. den Ruijter HM, Peters SA, Groenewegen KA, Anderson TJ, Britton AR, Dekker JM, *et al.* Common carotid intima-media thickness does not add to Framingham risk score in individuals with diabetes mellitus: the USE-IMT initiative. Diabetologia 2013;56:1494–502.

98. Bots ML, Groenewegen KA, Anderson TJ, Britton AR, Dekker JM, Engström G, *et al.* Common carotid intima-media thickness measurements do not improve cardiovascular risk prediction in individuals with elevated blood pressure: the USE-IMT collaboration. Hypertension 2014;63:1173–81.

99. Øygarden H. Carotid Intima-Media Thickness and Prediction of Cardiovascular Disease. J Am Heart Assoc 2017;6:e005313.

100. Saba L, Montisci R, Molinari F, Tallapally N, Zeng G, Mallarini G, *et al.* Comparison between manual and automated analysis for the quantification of carotid wall by using sonography. A validation study with CT. Eur J Radiol 2012;81:911–8.

101. Kyriacou EC, Petroudi S, Pattichis CS, Pattichis MS, Griffin M, Kakkos S, *et al.* Prediction of high-risk asymptomatic carotid plaques based on ultrasonic image features. IEEE Trans Inf Technol Biomed 2012;16:966–73.

102. Gastounioti A, Makrodimitris S, Golemati S, Kadoglou NP, Liapis CD, Nikita KS. A novel computerized tool to stratify risk in carotid atherosclerosis using kinematic features of the arterial wall. IEEE J Biomed Health Inform 2015;19:1137–45.

103. Saba L, Jain PK, Suri HS, Ikeda N, Araki T, Singh BK, *et al.* Plaque Tissue Morphology-Based Stroke Risk Stratification Using Carotid Ultrasound: A Polling-Based PCA Learning Paradigm. J Med Syst 2017;41:98.

104. Weng SF, Reps J, Kai J, Garibaldi JM, Qureshi N. Can machine-learning improve cardiovascular risk prediction using routine clinical data? PLoS One 2017;12:e0174944.

105. Kakadiaris IA, Vrigkas M, Yen AA, Kuznetsova T, Budoff M, Naghavi M. Machine Learning Outperforms ACC / AHA CVD Risk Calculator in MESA. J Am Heart Assoc 2018;7:e009476.

106. Lekadir K, Galimzianova A, Betriu A, Del Mar Vila M, Igual L, Rubin DL, *et al.* A Convolutional Neural Network for Automatic Characterization of Plaque Composition in Carotid Ultrasound. IEEE J Biomed Health Inform 2017;21:48–55.

107. Biswas M, Kuppili V, Araki T, Edla DR, Godia EC, Saba L, *et al.* Deep learning strategy for accurate carotid intima-media thickness measurement: an ultrasound study on Japanese diabetic cohort. Comput Biol Med 2018;98:100–17.

108. Menchón-Lara RM, Bastida-Jumilla MC, Larrey-Ruiz J, Verdú-Monedero R, Morales-Sánchez J, Sancho-Gómez JL. Measurement of Carotid Intima-Media Thickness in ultrasound images by means of an automatic segmentation process based on machine learning. Eurocon 2013, 2013. IEEE: 2086-93.

109. Menchón-Lara RM, Sancho-Gómez JL. Ultrasound image processing based on machine learning for the fully automatic evaluation of the Carotid Intima-Media Thickness. 2014 12th International Workshop on Content-Based Multimedia Indexing (CBMI), 2014. IEEE: 1-4.

110. Shin J, Tajbakhsh N, Todd Hurst R, Kendall CB, Liang J. Automating carotid intima-media thickness video interpretation with convolutional neural networks. Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition, 2016. 2526-35.

111. Jamthikar A, Gupta D, Khanna NN, Araki T, Saba L, Nicolaides A, *et al.* A Special Report on Changing Trends in Preventive Stroke/Cardiovascular Risk Assessment Via B-Mode Ultrasonography. Curr Atheroscler Rep 2019;21:25.

Conflicts of interest.—Jasjit S. Suri is affiliated to AtheroPoint™, focused in the area of stroke and cardiovascular imaging.

Authors' contributions.— Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology

(Guest Editor; Associate Editor), Medtelligence/ReachMD (CME steering committees), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Fractyl, Merck, Novo Nordisk, PLx Pharma, Takeda. Luca Saba: design and support of radiology component such as CT and carotid ultrasound; Ankush D. Jamthikar: design of the manuscript, proofreading many iterations, researching PubMed and other research sites for article search; Deep Gupta, Tadashi Araki, Ajay Gupta, Monika Turk, Petros P. Sfikakis, Athanasios Protogerou, Vijay Viswanathan: resources, imaging contribution and proofreading the manuscript; Narendra N. Khanna: vision of cardiac risk assessment and proofreading the manuscript, final approval of the manuscript; Klaudija Viskovic, Tomaz Omerzu, John R. Laird, Gyan Pareek, Martin Miner, Deepak Bhatt: proofreading and guidance of cardiology and vascular components; Harman S. Suri: machine learning, deep learning ideas and proofreading the manuscript; Sophie Mavrogeni: proofreading and guidance of cardiology imaging components of the manuscript; George D. Kitas: design and solid proofreading of the manuscript, especially rheumatology component, revising it critically for important intellectual content; Andrew Nicolaides: vascular tissue characterization and proofreading of the manuscript; Jasjit S. Suri: principal investigator-design, proofreading of the manuscript and management.

Article first published online: November 25, 2019. - Manuscript accepted: October 7, 2019. - Manuscript revised: October 4, 2019. - Manuscript received: August 2, 2019.