



# AtheroRisk: An Integrated Computer Software System for Stroke Risk Stratification Utilizing Carotid Plaque Analysis in Ultrasound Videos

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## Abstract

In this study we propose and evaluate AtheroRisk, a standalone integrated computer software system for the analysis of carotid B-mode ultrasound (U/S) images and videos. Our goal was to provide a tool to help physicians stratify stroke risk. The presented system is based on outcomes from different research studies, as well as European guidelines for the evaluation and treatment of carotid artery disease. The goal is to enable reproducible analysis of atherosclerotic plaques in real time. AtheroRisk brings together analysis of U/S image and/or video of the carotid arteries facilitating anonymization, standardization, noise filtering and segmentation of plaques; followed by image and motion feature extraction to derive plaque-composition and stability. All the above steps are combined to determine the annual stroke risk rate and the 5-year stroke-free survival rate. The system is powered by an SQLite local database, in which the end user can save and manage data extracted from processing and analysis in an anonymized way. The first version of AtheroRisk was developed following an incremental software development process. The developed system was verified using 54 U/S videos (27 Asymptomatic, AS; 27 Symptomatic, SY cases) while the clinician's satisfaction and comments were collected through a questionnaire-based validation process. The results show that the integrated system proposed in this study can be successfully used for the automated image and video analysis of the CCA plaque in ultrasound videos.

**Keywords** Carotid plaque analysis · Plaque features · Ultrasound video · Motion analysis · Stroke risk stratification

## Introduction

Internal carotid artery (ICA) atherosclerosis constitutes an important ischemic stroke risk factor. For many years, carotid endarterectomy (CEA) was considered a solution to eliminate the risk of stroke [1, 2]. More specifically, it has been previously shown that in Asymptomatic (AS) patients with ICA stenosis > 60 to 70% (NASCET, The North American Symptomatic Carotid Endarterectomy Trial method), CEA limited the risk of stroke from 2 to 1%, per year [1, 2]. It is crucial to mention that among the findings of all above studies, a CEA-associated to a 2–3% perioperative stroke rate or death appeared, pertaining to an underlying danger, when attempting to support affected individuals (especially in AS patients). For doctors and clinicians, B-mode longitudinal ultrasound (U/S) has been a widely preferred method to derive the carotid stenosis degree, as well as characteristics of arterial wall and morphology. These may be useful in identifying possible carotid plaque growth in vivo,

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primarily due to their non-invasive (non-ionizing) nature and low cost [3]. A carotid atherosclerotic plaque is often characterized by a complex structure (composition such as fibrous cap, necrotic core, calcification, lipid core or ulcer) [4]. A B-mode U/S allows its overall identification by image and/or video texture and morphology analysis, methods holding notable potential in predicting the risk of stroke, as shown in [5, 6].

However, analysis of atherosclerotic carotid plaques in static image can only reveal a certain representation of its shape and composition, in a specific moment throughout the cardiac cycle (CC) [5, 6]. Notably, previous studies have suggested that the combination of inherent plaque rising strain and the excessive mechanical forces during the CC may lead to plaque rupture. More specifically, Murillo et al. [7], set forth a multiscale amplitude-modulation and frequency-modulation (AM-FM) approach to measure 2-D plaque motion, aiming to differentiate between AS and SY cases. Additionally, Golemati et al. [8], presented an adaptive block matching (ABM) method to identify and quantify asynchronous motion patterns, between the carotid plaque top and bottom surfaces (PTS and PBS, respectively), but also between PTS and the carotid wall, and between PBS and the carotid wall, in longitudinal carotid U/S videos. In essence, they calculated cross-correlations ( $CC_2$ ) of

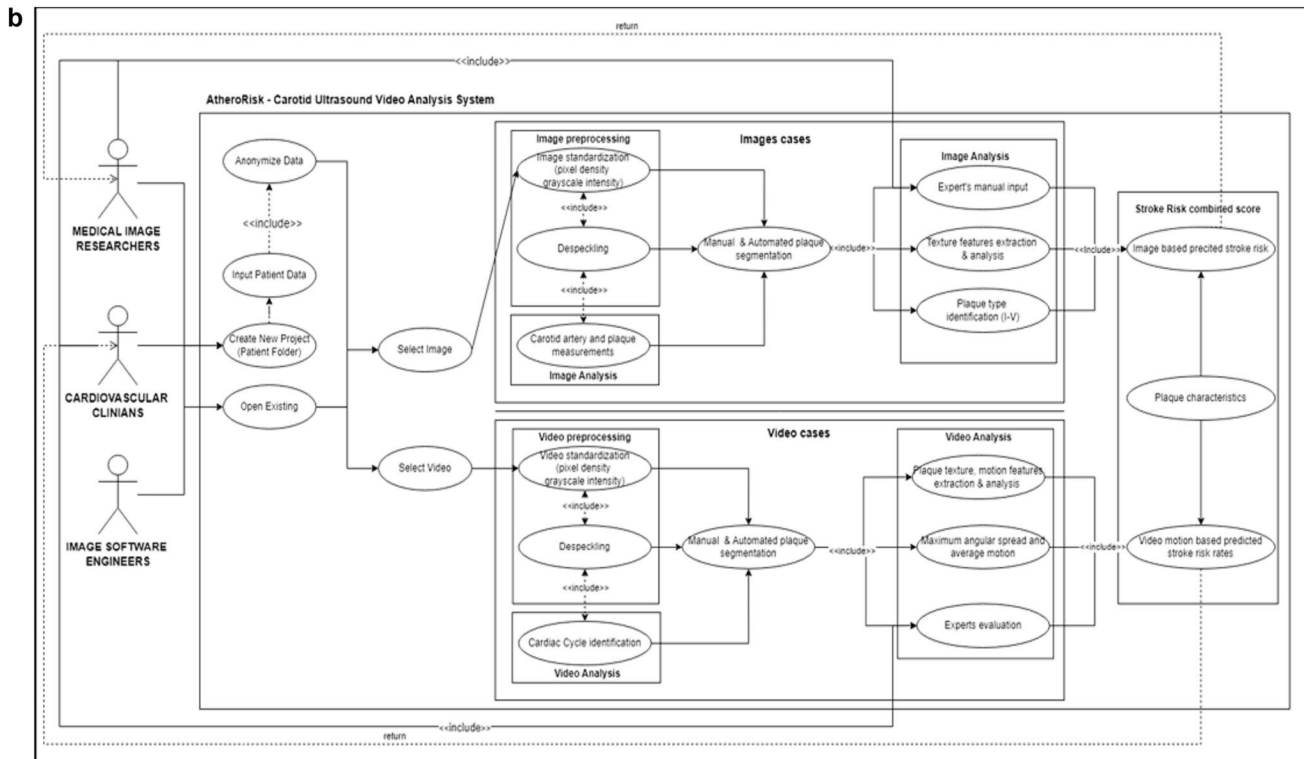
waveforms between PTS and PBS, reflecting intra-plaque kinematics, and showed that echolucent, high-stenosis and high-risk carotid plaques presented higher PTS and PBS radial displacement phase shifts ( $\text{mean}_{CC2}$  at  $0.26 \pm 0.15$  s;  $p=0.05$ ).

During the past decade, there was relatively limited research work done in the identification of carotid plaque motion configurations in U/S longitudinal videos, to detect patients in high risk of ischemic stroke. There have been two dominant U/S video-based methods for carotid plaque motion analysis, the ABM motion estimation and the Farnebäck's [9] optical flow method, as used and presented in [10]. Interestingly, only a few studies have concluded that carotid plaque motion characteristics can be used to stratify stroke risk based on reliable computer software design and statistical analysis, although larger datasets of AS-carotid U/S video recordings are needed in many cases. Support is needed before the results can be generalized. More importantly, no other study was found in the current literature that has addressed the motion in very complex carotid plaque examples, such as plaque with ulcers, acoustic shadowing, juxtaluminal black areas (JBAs) [11] or discrete white areas (DWAs) [5]. As also documented in [12], it is essential to automate the identification of JBAs (without a visible echogenic cap) and the DWAs, in carotid U/S videos, as these

**Fig. 1** **a** The class flow diagram for the first version of the AtheroRisk software as proposed in this study for carotid plaque processing and analysis in B-mode ultrasound longitudinal images and videos, **b** High-level architecture of the AtheroRisk software incorporating all the proposed software packages. ROI region of interest



Fig. 1 (continued)



constitute independent predictors of stroke. In addition, for experts to safely conclude on the existence or absence of both JBAs and DWAs in plaques of carotid U/S recordings, image intensity normalization is considered an indispensable factor in this computerized image analysis [12].

In this study, by building upon prior knowledge and computational tools developed by our group, we present the first version of AtheroRisk, an integrated computer software for atherosclerotic plaque analysis in carotid U/S longitudinal images and videos (see also Fig. 1a). This is particularly focused on image/video preprocessing and standardization, as well as in extraction and quantification of plaque-originating spatial and temporal features, specifically for individuals in the high-risk group. Our aim is to assist doctors and provide a research tool for stroke risk stratification and follow up, based on the derivation of unified stroke risk scores, combining atherosclerotic plaque features from carotid U/S image and video analysis.

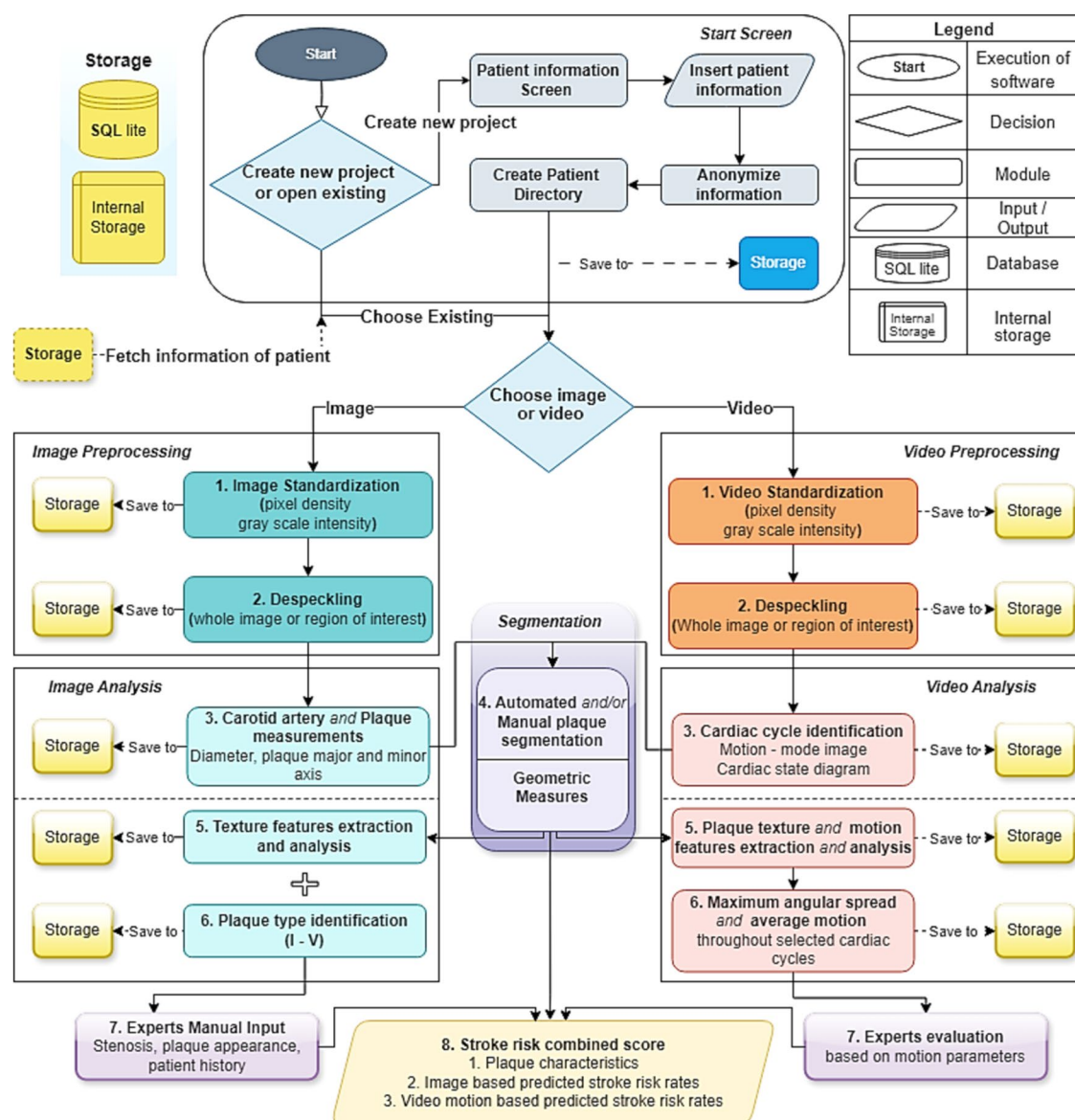
## Methodology

### The AtheroRisk Software Architecture and Computational Pathways

To develop the proposed software, we have utilized a plethora of digital images and video handling and processing

using Python (version 3.11) language [13]. The development followed an incremental approach, which involved building the software in small, manageable segments. This approach allowed for frequent testing and integration of new features, ensuring that each addition was stable and functional before moving on to the next. The incremental method enabled us to gather continuous feedback from end-users and incorporate it promptly into the development cycle, thus refining the software iteratively. In Fig. 1b, a representation of the high-level architecture of the software is illustrated, where all software packages used and developed are shown. This approach facilitated rapid prototyping and iterative improvements based on user feedback and performance evaluations. Additionally, a holistic view of all the carotid ultrasound image and video preprocessing and analysis pathways provided in the software is shown in Fig. 2. This method also allowed us to identify and resolve potential issues early in the development process, ensuring a robust and user-friendly final product.

The implemented computer software as proposed in this work, allows the user to create a patient analysis project, where anonymization of the patient information takes place automatically, producing a random name (see also Fig. 2, top). Upon project folder creation, the user may import and analyze either carotid U/S images or video recordings. In case a video analysis pathway is chosen, there is also the opportunity for



**Fig. 2** Flow diagram, demonstrating the available carotid B-mode ultrasound image and/or video preprocessing and analysis pathways for the proposed AtheroRisk software

the user to shift to image analysis for carotid plaque analysis. The software supports videos in 'AVI,' 'MOV' or 'AVC' containers, with 'Y800,' 'MPEG-4' or 'H264' transcoding. The developers highly recommend the use of images in 'tiff' format to secure lossless compression (LZW) and eliminate data loss. The software also allows for conversion of Digital Imaging and Communications in Medicine (DICOM) U/S image sequences into 'H264' 'MOV' or 'AVI' videos, to enable video visualizations and facilitate video analysis. Further details on the AtheroRisk software architecture are provided in Sect. 2.8.

## Carotid Ultrasound Video Dataset and Clinical Information

During the project, a carotid U/S video database was created, consisting of existing and newly acquired recordings (see also Fig. 2). A total of 339 patients were included (206 AS and 136 SY) with a total of 356 B-mode grayscale and 356 color doppler U/S longitudinal videos; in certain cases, there were U/S videos both from the right and left ICAs. The videos were captured at two different vascular



laboratories namely, at the University College London Hospital, Ealing Hospital, and at the Vascular Screening and Diagnostic Centre (United Kingdom). The new videos were recorded at the American Medical Center (Nicosia, Cyprus) and the Vascular Surgery Clinic of the National and Kapodistrian University of Athens (Attikon Hospital, Athens, Greece). The data acquisition took place upon approval by the London-Harrow national research ethics service committee (approval no. 11/LO/0299) and the Cyprus national bioethics committee and upon patients' written consent. The U/S videos were captured using the Philips iU22 U/S system (Philips Ultrasound, Bothell, Wash) with an L9-3 linear array probe or the Philips Affinity 70G system. Digital videos were resolution-normalized at 20 pixels/mm and were recorded digitally on with a resolution of  $768 \times 576$  pixels with 256 Gy levels. The majority of patients presented with carotid stenosis equal or higher than 50%, while some of them (assigned in the SY group) had already developed clinical symptoms, such as a stroke or a transient ischemic attack (TIA). Importantly, a patient had to be declared as AS, if there were no symptoms for the last six months.

In addition, a strict U/S video acquisition protocol was formulated by a highly experienced vascular surgeon to guide the ultrasonographers, followed by a patient information sheet, which allowed the documentation of the degree of carotid stenosis, the systolic and diastolic blood pressure, the age, the symptoms (history of amaurosis fugax, transient ischemic attack, major stroke, total occlusion) or previous surgical intervention (such as carotid artery stent or external carotid artery (ECA), for each patient. Manual carotid plaque regions of interest (ROIs) were provided by the vascular surgeon (coauthor Andrew Nicolaides, who produced one indicative ROI per video), defined with the help of color Doppler videos to approximate the plaque-to-lumen borders. Finally, the dataset includes some patient cases with more than one carotid plaque area in their video recordings; further analysis is needed to conclude on the existence of a single or multiple plaques, in these cases.

### Carotid Ultrasound Image and Video Preprocessing

In the AtheroRisk software, the first important step involves a conversion of the B-mode U/S recordings into an 8-bit grayscale representation (see Fig. 2, steps 1 and 2 image and video preprocessing). To proceed with reproducible data analysis, the user can normalize resolution in the selected image or video, at 20 pixels/mm (with bicubic interpolation-based upscaling), a process proved to enhance

plaque-originating image feature analysis [14]. Next, the user may select a blood area and a bright adventitia area near the plaque, on the given image or video, as reference pixel intensity values, to normalize the image intensity (with linear scaling), a step required to extract comparable plaque image features, as introduced in [12]. The user may also apply speckle noise removal, using among two different filters, namely the 'lsmv' (local statistics mean variance) or the hybrid-median filter, as proposed and evaluated in carotid U/S images from AS and SY cases in [15].

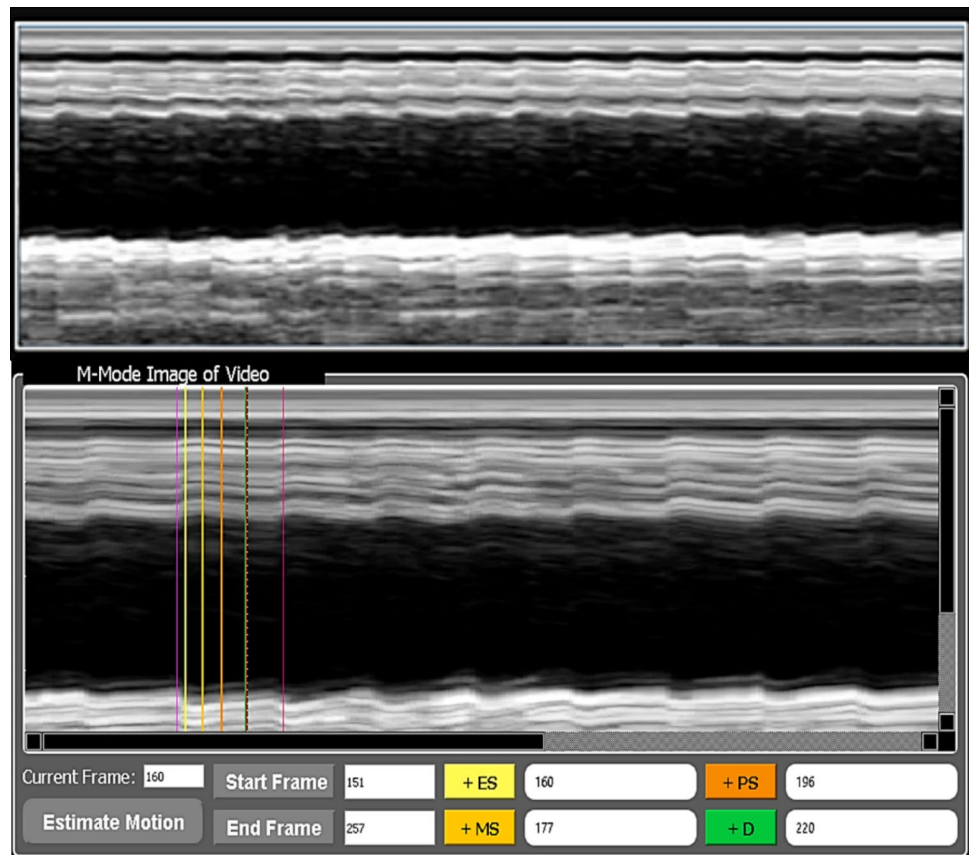
### Motion-Mode Image and Cardiac State Diagram Generation

In the proposed AtheroRisk software, the required next step is the identification of CCs and the U/S video states that correspond to cardiac early (ES), middle (MS), peak systole (PS) and/or cardiac diastole (D) respectively (see also Fig. 2, step 3 video analysis). It should be here also noted that the identification of the above states through the cardiac cycle is particularly important as also shown in previous studies presented by our group [16, 17]. More specifically, it was shown that the majority of plaque textural features are statistically significantly different at systolic and diastolic states and between AS and SY individuals [16]. To derive the CCs and CC states, AtheroRisk generates a Motion-mode image (M-mode, see also Fig. 3 top), which represents the movement of a perpendicular line selected manually by the user on the first VF of the video (see also Fig. 3a, yellow line) as proposed in [17]. By horizontally stacking the pixel intensity visualizations of the selected VF column for all the given VFs, we produce the M-Mode image (see Fig. 3, top). At this point the user can lead U/S video analysis within a confined number of consecutive CCs (see Fig. 3, bottom), by manually selecting ES, MS, PS and D-related VFs, as well as by setting a starting and an ending VF for the analysis.

### Manual and Automated Plaque Segmentation

In the AtheroRisk software, the user is able to manually select the area of interest (ROI) (see also Fig. 2, step 4), in pixel-level detail, but also use a deep learning method for automated plaque segmentation (model adapted by Lou et al. [18]), throughout all VFs, in a given U/S video. An example of an automated plaque segmentation is shown in Fig. 5 (top left; in green outline). Here, the user has access to ROI-originating geometrics metrics total plaque area (TPA), the minor (MinA) and major axes (MajA), the perimeter of the resulted ROI (P), as well as the intersection over union (IoU) between manual and automatic plaque segmentations (realized training and evaluation of the model in [19]).

**Fig. 3** Example of a motion-image (M-mode) image from an AS subject, aged 68 years, with carotid stenosis degree at 95%. Top: the initial M-mode image. Bottom: manual selection of the different cardiac phases for a given video, represented as colored lines; here, the user, can manually navigate on the M-mode image, to locate early, middle and peak systole-related video frames, as well as diastole-related frames, based on which the carotid plaque motion analysis will later be applied. The colored lines follow the colors of the corresponding cardiac phase selection buttons. *ES* early systole, *MS* middle systole, *PS* peak systole, *D* diastole



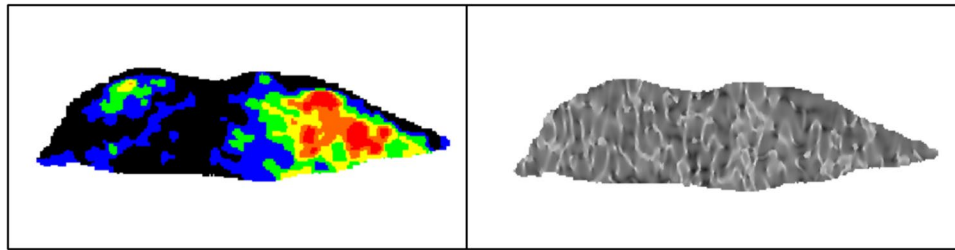
### Carotid Plaque Image Analysis and Image Features

Upon carotid plaque manual or automated segmentation in the whole U/S video, and the selection of the CCs (including ES, MS, PS, and D states), different groups of texture and morphological features from the plaque ROI may be automatically extracted across all VFs, and the corresponding statistics may be derived [6, 16]. AtheroRisk depicts alterations of plaque image features among ES, MS, PS, and D states, but also between all given states themselves (e.g., across PSs). These plaque-based features belong to the following groups: gray level dependence method (GLDM), spatial gray level dependence method (SGLDM), first order statistics (FOS), and run length features. In Table 1 of the Appendix, all individual carotid plaque-based textural features produced in AtheroRisk are shown. Importantly, certain carotid plaque characteristics, such as the presence or absence of JBAs or DWAs, are specified by the user manually.

*Echodensity-informed pseudo-coloring of carotid plaque to depict composition.* It is important to mention that different composition components of the carotid plaque result in different image and motion features (e.g. derivation of echodensity-based plaque types [20]). AtheroRisk is also equipped with a plaque contouring effect (developed in

close collaboration with an experienced vascular surgeon), where the color-to-composition mapping is as follows: pixel intensities in the 0–50 (black and blue), 51–100 (green and yellow), and 101–255 (orange and red), show lipid core, fibrous and calcified areas, respectively. A pseudo-colored plaque, with 10 identified composition contours, and a plaque depicting the medium-scale instantaneous frequency (IF) [19] representations, are shown in Fig. 4-left and Fig. 4-right, respectively.

*Amplitude-modulation and frequency-modulation (AM-FM) features.* AM-FM models offer a method to represent complex, non-stationary structures at the pixel-level resolution using multiple components characterized by physically meaningful descriptors [19, 22–24]. Instantaneous Amplitude (IA), for instance, captures variations in local image intensity, identifies edges, and quantifies component contributions. Instantaneous phase (IP) detects rapid changes in texture locally, while instantaneous frequency (IF) measures the local frequency content (see Fig. 4, Right). The magnitude of instantaneous frequency (IFI) offers a tangible measurement of local image texture and serves as a geometric measure of texture as well [19]. The angle of Instantaneous Frequency provides insight into directional structures. Additionally, employing multiple scales enables the visualization of otherwise imperceptible structures. AM-FM components



**Fig. 4** Different carotid ultrasound plaque representations, depicting the underlying compositions. Left: a pseudo-colored plaque, related to the analyzed video in Fig. 3 (highly dark areas represent lipid cores, while red areas portray calcifications. Right: an example of the

instantaneous frequency (IF) representations (medium scale), derived from the amplitude modulation-frequency modulation (AM-FM) analysis according to [19, 21]

can also be utilized to reconstruct textures. This model has a solid foundation, evident in its extensive applications in medical imaging [23]. Multiscale AM-FM analysis, utilizing difference of Gaussians (DoG) filterbanks [24] or Gabor filterbanks [23, 24], was used for the analysis of carotid plaque ultrasound images for the assessment of the risk of stroke via the discrimination between asymptomatic and symptomatic plaques. Histogram based AM-FM features were extracted from IA, IP and IIFl, across three scales (low, medium, and high), employing the methodology outlined in [19]. Statistically significant features were extracted for low, medium and high IA, IP and IIFl [24, 25]. Moreover, the statistically selected histogram-based AM-FM features were used to develop support vector machine (SVM) models to classify the features into two classes: asymptomatic plaques, or symptomatic plaques. The overall classification accuracy was in the region of 74–75% [23, 24].

### Carotid Plaque Motion Analysis and Motion Features

The AtheroRisk software, also introduces a carotid plaque motion analysis workflow, based on the derivation of optical flow, for all U/S VFs included in the consecutive CCs (selected by the user), as presented in [10], which is based on the Farnebäck's method [25]. The aim is to characterize the overall plaque motion as *concordant* (all plaque components simultaneously move towards the same direction throughout the CC) or *discordant* (plaque components move in different directions, at certain times of the CC). These motion configurations are associated with the risk of stroke [10]. Carotid plaque motion analysis in AtheroRisk can generate the following motion features: (1) the plaque's dominant orientation (DO) per CC state, (2) the maximum angular spread (MAXFW, the maximum fan-width, in degrees, per fixed motion magnitudes) per CC state, and (3) the average of the median motion magnitudes per angle degree (per CC state and across all types of CC states). For more explainable visualizations, we utilize

the polar directional diagrams and the scatterplots, shown later in Fig. 5 (middle bottom and bottom right, respectively), to depict the MAXFW<sub>20</sub> (for the first 20% of the analyzed plaque pixels) and the median motion magnitudes of the plaque per CC state. Our aim is to provide the average motion magnitudes and the angular spreads, across and between all CC states to dismantle plaque areas more susceptible to rupture, in specific CC moments [26, 27].

### Carotid Ultrasound Video Analysis Software Architecture

AtheroRisk is a standalone computer application, accompanied by a local SQLite database [28]. It is designed to support carotid U/S image and video analysis, including DICOM image sequences, allowing both patient clinical data and analysis results to be dynamically saved. Its architecture and high-level process are depicted in Fig. 1. All the above diagrams illustrate the comprehensive workflow, structural components, and functional interactions within the software. Its architecture consists of three main components the user interface (UI), the video and image analysis modules, and the database.

The UI, built using Python and PyQt5, supports functionalities such as loading images/videos, initiating analysis, displaying results, and managing patient information. It allows users to create new projects or open existing ones, standardize images and videos, and perform manual or automated plaque segmentation. The video and image analysis modules utilize key Python libraries including OpenCV [29], Keras [30], TensorFlow [31], Matplotlib [32], Scipy [33], Skimage [34], Sklearn [35], skvideo [36], and Numpy [37]. These modules perform tasks such as image and video reading and writing, preprocessing, ROI segmentation, and ROI-based feature extraction for motion analysis and stroke risk prediction, employing deep learning models such as the channel-wise feature pyramid network for medicine (CFPNet-M) [18]. The database, managed by SQLite, stores patient clinical data, analysis results, and anonymizes

patient information to ensure data security and privacy. It facilitates efficient data retrieval, modification, and storage, supporting the dynamic needs of clinical research.

The workflow of AtheroRisk begins with data input, where users load ultrasound images or videos via the user interface. The software then performs preprocessing steps, including image and video standardization [12, 14] and despeckling [15], to ensure consistency and remove noise. Segmentation follows, with both manual and automated methods [38] available to identify and analyze regions of interest. The software then extracts angular motion [26], and other features [16] for analysis, predicting stroke risk based on the extracted data. All patient information, images, videos, and analysis results are stored in the SQLite database for easy retrieval and further analysis. Figure 2 demonstrates all the various functionalities and interactions within AtheroRisk, including creating new projects, standardizing data, performing segmentation, extracting features, and predicting stroke risk.

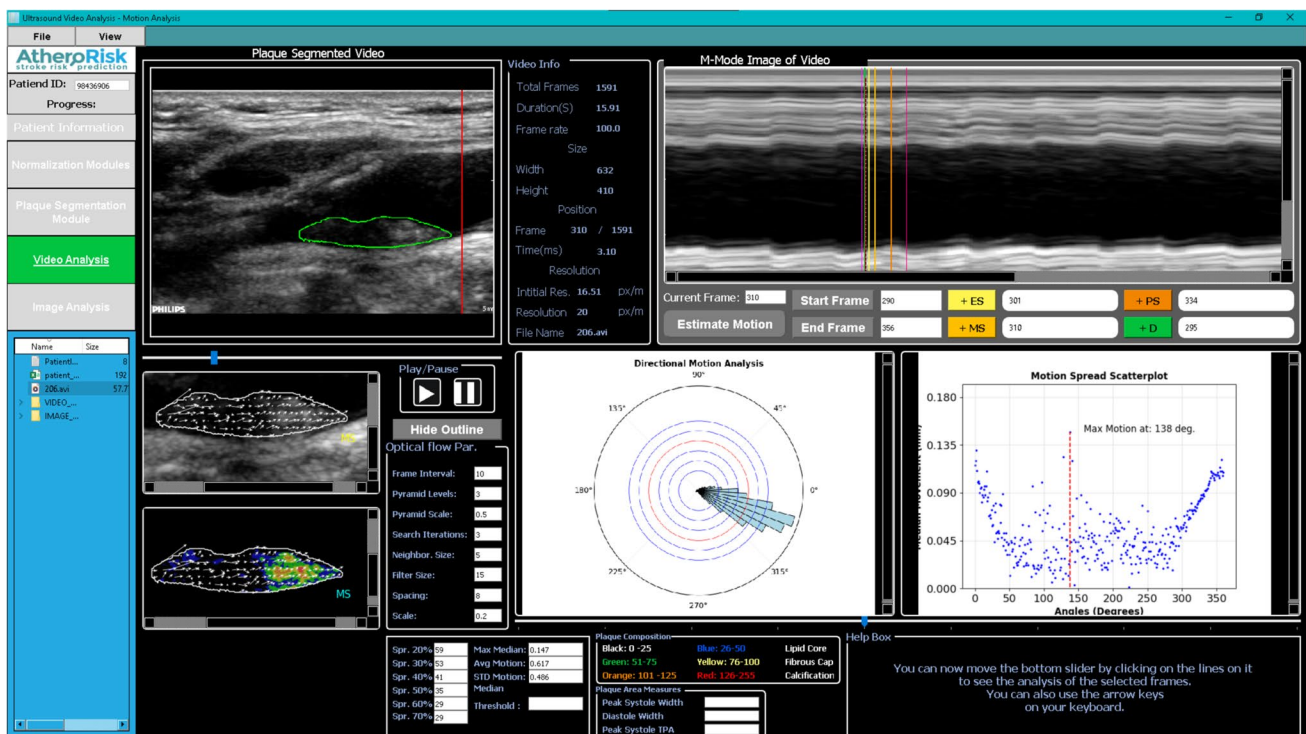
### Stroke Risk Stratification and Evaluation Metrics

As described above, the carotid U/S image and video analysis pathways in AtheroRisk serve to help us understand the severity of the carotid disease, with respect to the plaque's inherent (echodensity-informed composition, geometrical

measures, appearance) and induced features (plaque areas' motion magnitude and orientation). Our aim is to find the best combinations of clinical, textural, geometrical and motion features of the carotid plaque, to develop models that will confidently stratify carotid atherosclerosis patients (AS and SY) into low-, intermediate- and high-risk groups. In close collaboration with an experienced vascular surgeon, we have defined an assembly of the two following types of stroke risk estimation metrics.

**Plaque image feature classification.** Following the extraction of geometrical, morphological and textural carotid plaque features (including GSM), accompanied by carotid artery stenosis degree, and the specification (by the user) of the existence or absence of past contralateral symptoms, JBAs and/or DWAs, in a given case, the AtheroRisk Software extracts: (1) a 5-year stroke risk survival and (2) an average annual stroke rate.

**Plaque motion feature classification.** Concordant/low-risk plaques exist when we measure  $MAXFW < 70^\circ$ , moderately discordant/moderate-risk plaques exist when  $70^\circ < MAXFW < 120^\circ$  and discordant/high-risk plaques exist when  $MAXFW > 120^\circ$ . The derivation of these degree ranges confidently resulted from the analysis of 10 consecutive cardiac PSs (per video), in an existing dataset of 200 carotid B-mode U/S longitudinal videos [10].



**Fig. 5** Representation of a concordant carotid plaque, using the motion analysis computational pathway in the AtheroRisk Software, for an analysed video frame corresponding to cardiac middle systole (MS). Selection of the MS is given in an intermediate orange line



## Carotid Ultrasound Video Analysis Software Validation and Verification

**AtheroRisk software verification.** In the present study, we present AtheroRisk Version 1, which delivers carotid U/S image and video preprocessing, standardization and image and video analysis to stratify the risk of stroke (based on the studies in [10, 16, 26, 27, 39]), whose verification mainly refers to single plaque cases. The software was evaluated in this study by assessing 27 AS and 27 SY patient videos, from the AtheroRisk database. In a future version, the software will also perform analysis in more complex cases ( $> 1$  plaque areas/localizations will be present; more complex carotid artery anatomies will exist). Thirty-one different carotid plaque imaging features were extracted per AS and SY case, from a single selected VF as in [16], while for each AS and SY corresponding video, the carotid plaque MAXFW<sub>20</sub> was extracted, along with the average of the median motion magnitudes for the given plaque, as in [10]. In Sect. 3, value distributions for some of the above mentioned image features, will be shown, between the AS and SY cases, as well as a statistically significant difference and correlation test, accompanied by a regression line will be demonstrated for the carotid plaque MAXFW<sub>20</sub> and the median motion magnitudes per category.

**AtheroRisk software validation.** Close to the onset of the AtheroRisk project, we collected user requirements for the software development process, targeting cardiologists and dedicated vascular surgeons, experienced in carotid atherosclerosis assessment and patient management, as well as biomedical engineering experts. The AtheroRisk software has been used on site, by interested parties in the context of one of the most prestigious conferences on Biomedical Imaging in May 2024, during a software Demo process. There the clinicians and experts who interacted with the software were also encouraged to answer a User Experience Questionnaire (the standard UEQ) [40]. However, as the audience's background did not largely reflect clinicians and doctors, we plan to soon validate the 'AtheroRisk Version 1' standalone software, again, following the UEQ, upon a demonstration and hands-on tutorial, delivered to the end users in a Workshop. The end users will report their satisfaction level, with respect to the met software specifications. This questionnaire's results will lead to the upgrade of the current software version.

## Results

To the best of our knowledge, in this study, for the first time, we present results from carotid plaque image and motion feature analysis simultaneously (in 27 AS and 27 SY cases), as explained in Sect. 2.

Firstly, two paradigms of the software visual environment are given in Figs. 5 and 6, where a concordant

(MAXFW<sub>20</sub> = 59°) and a discordant carotid plaque (MAXFW<sub>20</sub> = 341°) are depicted, respectively. In Fig. 5, where the analysis took plaque on a MS-related VF, we may notice that the majority of the plaque pixels have a DO on the right bottom (see the polar diagram), close to the 350°, as depicted also in the scatterplot, on the bottom right. In the discordant case (see Fig. 6), focused also on MS, we see that different (mostly echolucent) parts of the plaque move to different orientations, yielding a DO close to the 90° and a MAXFW<sub>20</sub> = 341°.

Using the Mann Whitney rank sum test, we examined if there was a statistically significant difference at  $p < 0.05$ , between the MAXFW<sub>20</sub> and the averaged (for the 3 consecutive MS analyzed VFs per U/S video) median motion magnitudes of the AS and SY cases, respectively. We found statistically significant differences at  $p = 0.006$ , when comparing the MAXFW<sub>20</sub> of the AS versus the SY cases, and a  $p = 0.032$ , when comparing the averaged median motion magnitudes, respectively. In addition, we performed a Pearson correlation test, to examine if there was a statistically significant correlation between the MAXFW<sub>20</sub> and the median motion magnitudes of the AS and SY cases, in this study (see Fig. 7 left and right, respectively). We found a  $\rho = 0.170$  ( $p = 0.396$ ), when comparing the MAXFW<sub>20</sub> of the AS versus the SY cases, and a  $\rho = 0.015$  ( $p = 0.939$ ), when comparing the averaged median motion magnitudes, respectively. A regression analysis with a fitted line, for the MAXFW<sub>20</sub> and the averaged median motion magnitudes of the AS versus the SY cases, respectively are shown in Fig. 7 (left and right, respectively). The Pearson correlation analysis shows very low correlation between the two groups (AS and SY;  $\rho = 0.17$  and  $\rho = 0.015$ , respectively), when comparing the MAXFW<sub>20</sub> and the averaged median motion magnitudes, with strong  $p$ -values ( $p = 0.396$  and  $p = 0.939$ , respectively), suggesting reliable separation between the two carotid atherosclerosis patient groups.

Next, the image analysis process, where one VF selected by the carotid atherosclerosis such that the whole body of the plaque would be exposed, for each U/S video was used to extract a plethora of imaging features as in [16], showed that certain plaque echodensity-based features could be used to separate AS from SY cases. Figure 8 depicts how the value distributions of three different plaque imaging features differ between the AS and SY cases. More specifically, Fig. 8 illustrates boxplots, depicting the distributions for three different carotid plaque imaging features between all the AS and SY cases used in this study, where for all three features, the Pearson correlation analysis yielded low correlations ( $\rho = -0.34$ ,  $\rho = -0.06$ , and  $\rho = 0.19$ , for First Order Statistics Skewness, SGLDM Angular Second Moment, and the GDLM Mean, respectively), with  $p$  values  $> 0.05$  ( $p = 0.08$ ,  $p$  value = 0.7, and  $p$  value = 0.3, respectively), indicating reliable separation of the two disease groups.

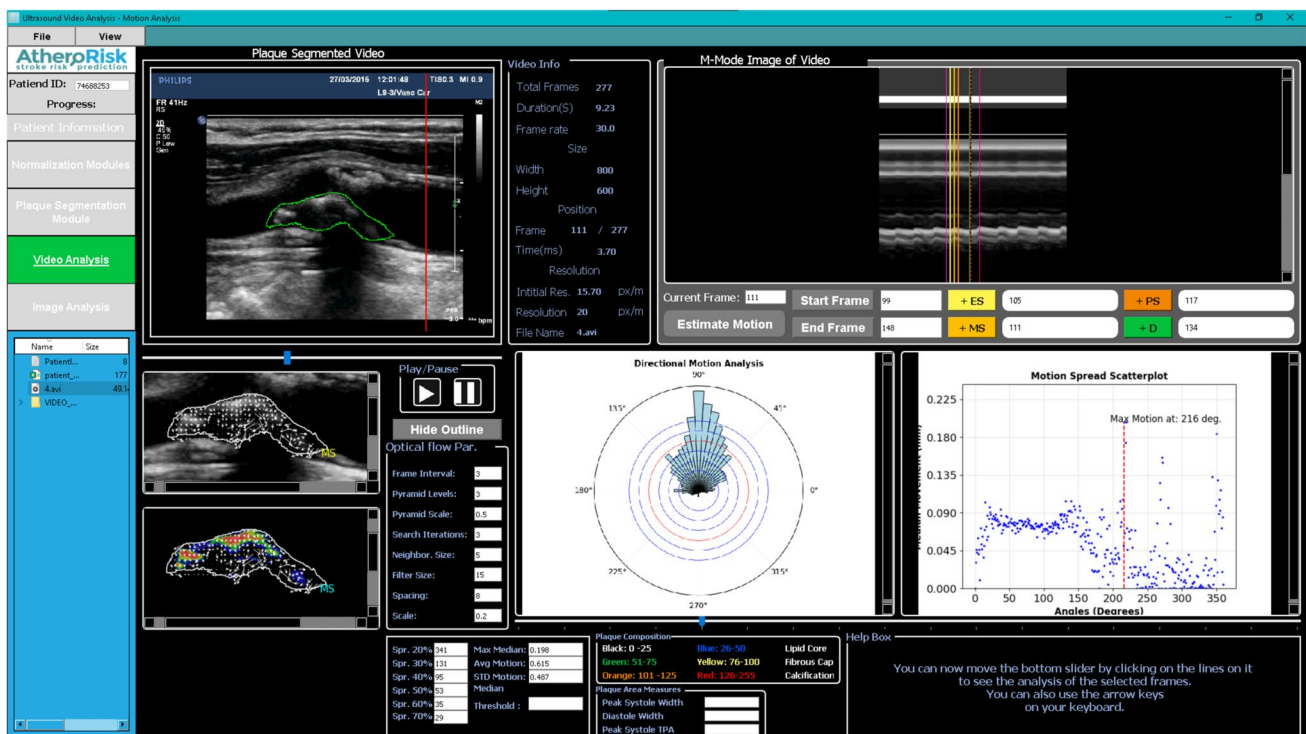
Overall, from the results of this study, evaluating the AtheroRisk Software, we may notice that the carotid U/S imaging and motion features hold capacity in distinguishing AS from SY cases. These results are in agreement with those derived in other related studies [10, 16].

## Discussion and Future Directions

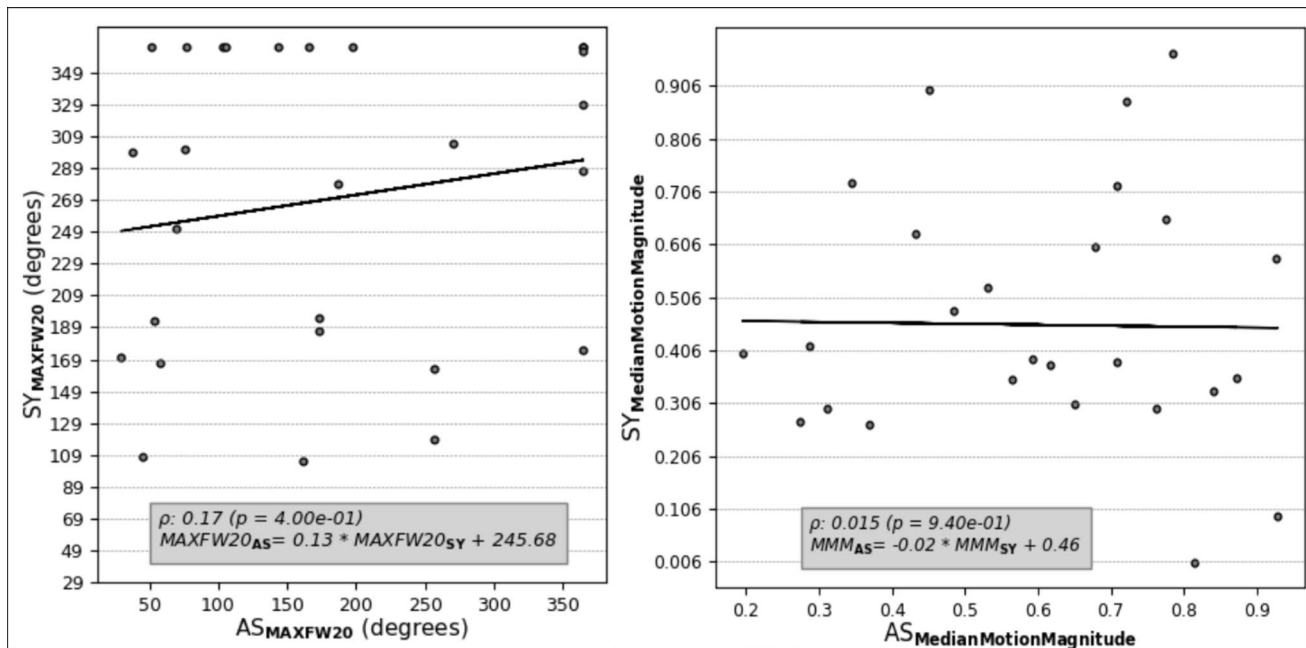
In the present study, we have introduced and described a new carotid B-mode longitudinal image and video analysis integrated computer software, with the aim to assist doctors in stroke risk stratification, for carotid atherosclerosis patients. This computer standalone application enables carotid plaque visualizations, through image preprocessing and automatic delineation, with submodules that were formally evaluated in previous studies [11, 12, 14–17]. Additionally, different meaningful echodensity-, geometry-, texture- and motion-based atherosclerotic plaque features can be extracted from a given U/S image or across multiple U/S VFs, preserving the information of the underlying plaque component composition and the identified cardiac states (cardiac ES, MS, PS and D), which combined with the reported patient clinical information (such as the degree of carotid stenosis or past symptoms) assemble an annual stroke rate and a 5-year stroke free survival rate.

AtheroRisk differs from previously proposed computational tools for carotid B-mode U/S image analysis, as it incorporates fast plaque automatic image and/or video segmentation and real-time analysis of plaque echodensity-derived composition, as well as motion, across different CC states, in which plaque image features have been found to change significantly [16], between AS and SY individuals, but also between different CC phases. Furthermore, one of the initial considerations for the development of ‘AtheroRisk’ was the high data *quality* and *integrity*, with respect to: a. the carotid U/S image and video capturing, entailing configuration of settings based on clinical recommendation (such as the use of maximum dynamic range, the use of low persistence and high frame rate, the Time Gain Compensation Curve sloping through tissues, while vertical through the blood vessel, and the use of a linear postprocessing curve), and b. the inclusion of truly AS patients according to the inclusion criteria in the ACSRS study [41, 42]. Until today, ACSRS consists the largest natural history study on patients with 50–99% AS carotid stenosis, including 1121 patients totally, with a follow-up ranging between 6 and 96 months; average: 48 months.

As shown from the results of the current study, image analysis and motion analysis of the carotid plaque in U/S videos (with a particular focus on the MS CC phase), can confidently distinguish AS from SY, and are in agreement

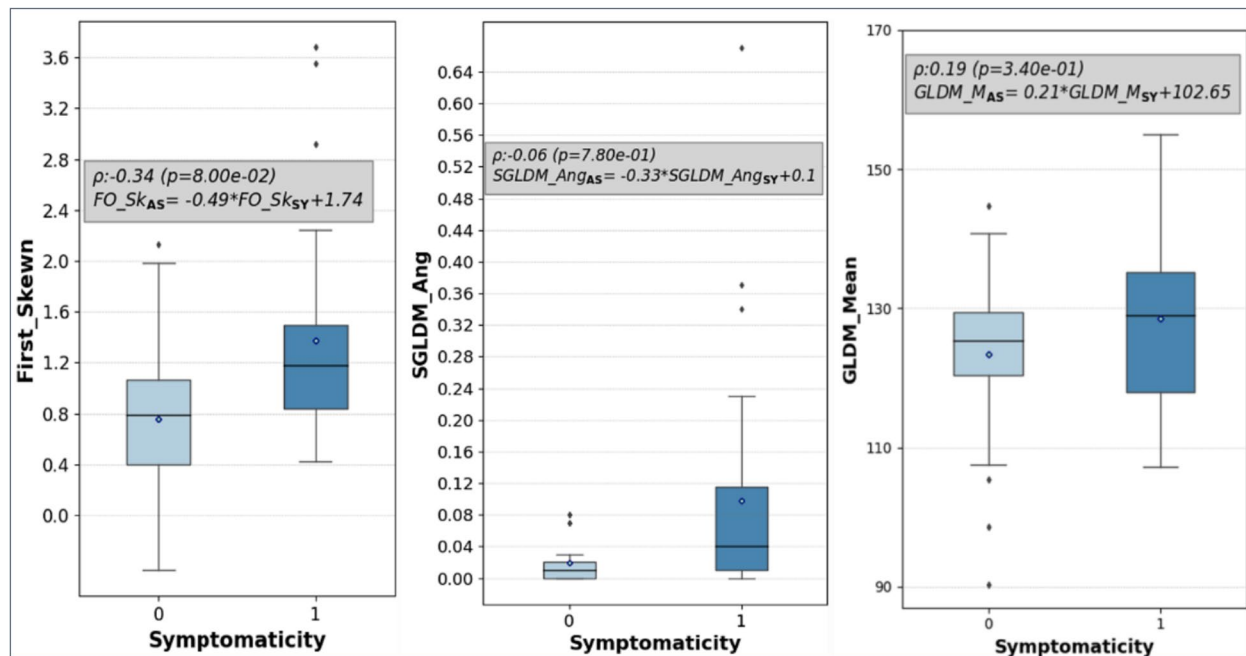


**Fig. 6** Representation of a highly discordant carotid plaque, using the motion analysis computational pathway in the AtheroRisk Software, for an analyzed video frame corresponding to cardiac middle systole. Selection of the middle systole is given in an intermediate orange line (top right)



**Fig. 7** Regression analysis with the Pearson correlation values, comparing the  $MAXFW_{20}$  of the 27 AS versus the 27 SY cases (on the left) for all subjects used in this study, and comparison of the aver-

aged median motion magnitudes (over 3 consecutive middle systoles) for these AS versus SY cases (on the right).  $MAXFW$  maximum fan width,  $MMM$  median motion magnitude



**Fig. 8** Boxplots depicting the distributions of three different carotid plaque imaging features, namely the first order statistics skewness (on the left), the spatial gray level dependence matrix (SGLDM) values for angular second moment (in the middle) and the gray level depend-

ence matrix (GLDM) values for mean (on the right), between the asymptomatic (given as '0') and symptomatic cases (given as '1') in this study ( $N_{AS} = 27$ ;  $N_{SY} = 27$ )

with previous findings [10, 16]. AtheroRisk can separate AS from SY individuals, both based on the  $MAXFW_{20}$  ( $p$  value = 0.006), when comparing the  $MAXFW_{20}$  of the AS versus the SY cases, but also based on the 3 MS-averaged median motion magnitude ( $p$  value = 0.032), respectively. However, the current findings will be further validated, by conducting complementary verification, using a larger number of AS and SY U/S video samples.

One key area where AtheroRisk can be evaluated against existing methods is in the automatic segmentation of carotid plaques using deep learning models. As highlighted in the study [43] the segmentation performance achieved with the AtheroRisk software demonstrates reliable accuracy across various plaque types. Specifically, the deep learning model achieved a dice similarity coefficient (DSC) of  $80.6 \pm 11\%$  for type I plaques,  $84.3 \pm 8\%$  for type II plaques,  $84.9 \pm 7\%$  for type III plaques,  $85.3 \pm 8\%$  for type IV plaques, and  $84.8 \pm 8\%$  for type V plaques when trained and tested with the standardized (RND) dataset. These results underscore the robustness of the segmentation approach, particularly for challenging plaque paradigms such as highly calcified or uniformly echolucent plaques. In contrast, most existing carotid ultrasound analysis tools focus exclusively on image-based analysis and do not extend to video-based motion analysis or the segmentation of complex plaque compositions. This positions AtheroRisk as a unique and innovative system, bridging this gap by providing automated segmentation coupled with motion and texture analysis for a more comprehensive evaluation of carotid plaques.

We foresee that AtheroRisk could assist in the management of carotid atherosclerosis patients in a clinical setting could positively impact the experts' workflow, but also the disease outcomes in the affected individuals, by minimizing potentially harmful invasive treatment approaches, such as CEAs. Although all modules in the 'AtheroRisk Version 1' software have been previously evaluated, there are two possible current limitations we identify when utilizing the software for ultrasound (U/S) video analysis. The first pertains to the complexity of cases where more than one atherosclerotic plaque is present, such as plaques localized on both the near and far carotid walls in a longitudinal view. In such scenarios, the AtheroRisk software remains effective in analysing the plaques, provided that the end-user (clinician) examines each plaque individually. This approach requires that all relevant preprocessing and analysis steps, such as plaque segmentation and motion analysis, are performed separately for each plaque. For example, if a clinician wishes to derive automated plaque annotations, the procedure must be applied independently to each plaque. Similarly, motion analysis throughout the entire U/S video can be conducted for each plaque separately. While a transverse view is not mandatory, it can complement the analysis by providing additional information to confirm the presence of one or

two plaques, particularly when different motion classes (e.g., concordant or discordant) are detected. The second limitation involves cases where carotid plaque ulcers are present, which are not always identifiable using U/S image features. This limitation is inherent to the nature of U/S imaging and highlights the need for further advancements in image acquisition and processing techniques to better capture such challenging cases.

In summary, the AtheroRisk software architecture ensures a seamless workflow from data input to analysis and result storage, supporting the clinical needs for carotid ultrasound analysis. Its design prioritizes user interaction, robust analysis capabilities, and secure data management, making it a valuable tool in medical image research and stroke risk prediction. This cohesive architecture, illustrated through the diagrams, provides a clear and detailed view of the software's structure and functionality, ensuring reproducibility and scalability in clinical settings.

Future work will focus on improving the video segmentation and motion analysis procedures such that it will process satisfactorily complex cases and difficult-to-analyze videos. Furthermore, the system proposed in this study will be incorporated into a computer-aided diagnostic system that supports the texture analysis of the segmented plaque as documented in [16, 26, 28], providing an automated system for the early diagnosis and the assessment of the risk of stroke. In the next version of the software, we will, among others, focus on carotid plaque ulcer identification based on intra-plaque component motion analysis, and analysis of cases presenting with multiple plaques. Finally, the authors aspire to embed the AtheroRisk software as a cornerstone of clinical workflows for stroke risk stratification in hospitals and healthcare systems. To achieve this, the refined version of the AtheroRisk software will be provided to a group of highly motivated clinicians who are well-versed in computational tools for carotid plaque analysis. Over a six-month period, the clinicians will utilize the software in high-paced clinical environments, analysing carotid plaques and generating stroke risk scores. During this period, their feedback will be systematically gathered through the user experience questionnaire (UEQ) to evaluate the practical usability and user experience of the software. This embedding process will also involve adherence to stringent security guidelines, including comprehensive data anonymization and encryption protocols to ensure data security and patient confidentiality. Furthermore, the final version of the software is expected to comply with regulatory standards, including patenting and CE marking, to facilitate its widespread use in clinical practice. These efforts aim to establish AtheroRisk as a reliable and indispensable tool for the automated segmentation, motion analysis, and risk assessment of carotid plaques, ultimately supporting clinicians in making early and accurate diagnoses to mitigate the risk of stroke.



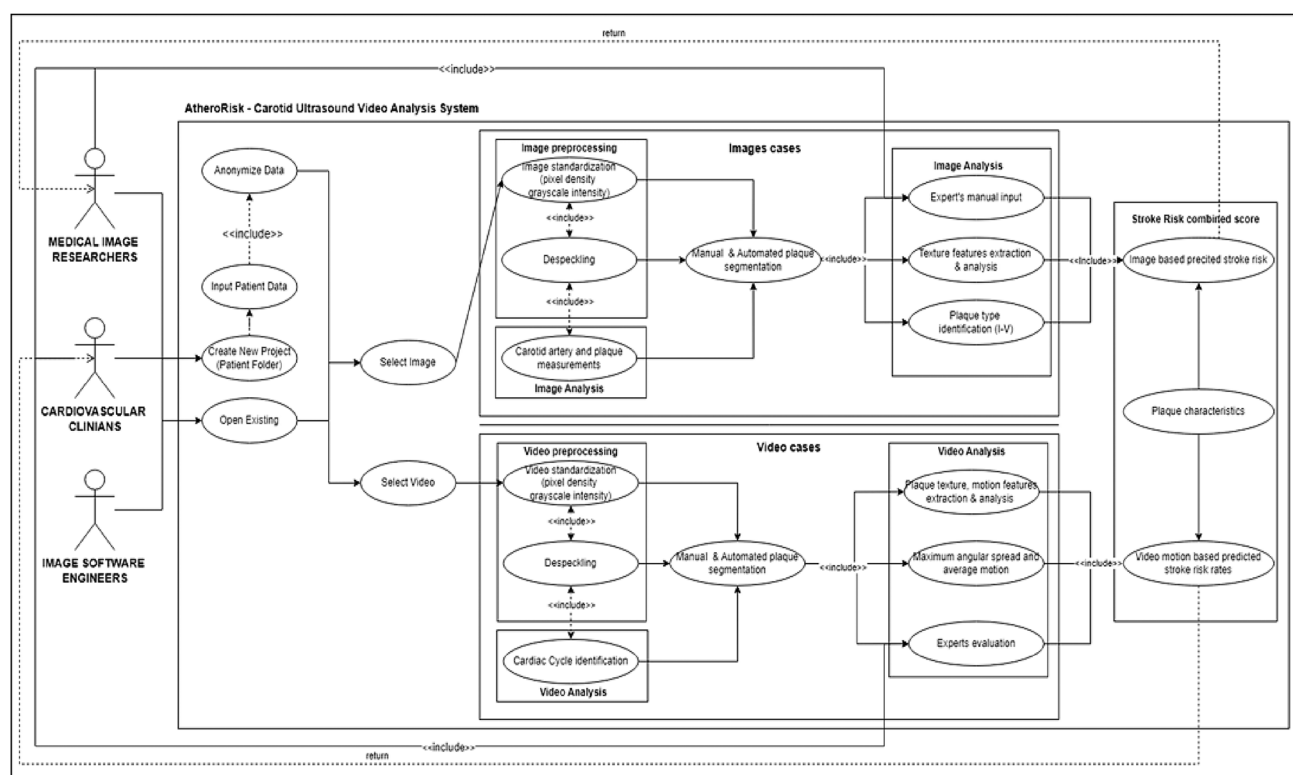
## Appendix

See Table 1 and Fig. 9.

**Table 1** Textural image and video features extracted from the manually segmented atherosclerotic carotid plaques, in the AtheroRisk ultrasound image analysis pathway

Feature group	Feature	Description
SGLDM	Angular second moment	Measures image homogeneity; higher values indicate more order or uniformity
	Contrast	Quantifies the amount of local variations present in the image
	Correlation	Assesses the linear dependency of the gray levels on those of neighboring pixels
	Variance	Measures the dispersion of the gray level distribution (GLD)
	Inverse difference moment	Reflects local homogeneity; higher values mean greater local homogeneity
	Sum average	The average sum of gray levels
	Sum variance	The variance of the sum of gray levels
	Sum entropy	Entropy of the sum of gray levels, indicating complexity
	Entropy	Overall complexity of the image texture
	Difference variance	Variance of the difference in gray levels
	Difference entropy	Complexity of the texture difference
	Information measures of correlation	Measures the complexity of texture
FOS	Mean	The average gray level intensity
	Variance	The variation of the gray level intensities
	Median	The middle value of gray level intensities
	Skewness	The asymmetry of gray level distribution around the mean
	Kurtosis	Peakedness or flatness of GLD compared to normal distribution
	Energy	The sum of squared elements in the GLCM; texture uniformity
	Entropy	The randomness in the distribution of the gray levels
GLDM	Homogeneity	The closeness of the distribution of elements in the GLCM to the GLCM diagonal
	Contrast	The intensity contrast between a pixel and its neighbor over the whole image
	Entropy	The degree of randomness of the GDL
RL	SRE	Gives higher values to homogeneous areas with short runs
	LRE	Gives higher values to homogeneous areas with longer runs
	GLN	Measures the non-uniformity of gray levels
	RP	Proportion of runs of a particular gray level and length in the image

*FOS* first order statistics, *GLCM* gray level co-occurrence matrix, *RL* run length, *GLD* gray level distribution, *GLN* gray level non-uniformity, *LRE* long run emphasis, *RP* run percentage, *SGLDM* spatial gray level dependence matrix, *SRE* short run emphasis



**Fig. 9** The class flow diagram for the first version of the AtheroRisk software as proposed in this study for carotid plaque processing and analysis in B-mode ultrasound longitudinal images and videos

**Author Contributions** Michalis Gemenaris: Software development of the AtheroRisk project, workflow development, manuscript writing. Georgia D. Liapi: Implementation of the carotid ultrasound preprocessing and motion analysis pathway/computational modules, Data statistical analysis, manuscript writing. Christos Markides: Project deliverables, Atherorisk workflow support, manuscript writing. Kyriacos Constantinou: AM-FM methods development. Christos P. Loizou: Project deliverables, Atherorisk workflow support, statistical analysis, manuscript writing. Michalis Neophytou: Ultrasound videos collection, clinical evaluation. Dimitrios Kardoulas: Ultrasound video collection. Marios S. Pattichis: Atherorisk workflow support, motion estimation techniques. Maura Griffin: Atherorisk workflow support, clinical evaluation. Andrew Nicolaides: Atherorisk workflow support, clinical evaluation. Constantinos S. Pattichis: Atherorisk workflow support, project conception. Efthymou Kyriacou: Principal investigator, project conception, Atherorisk workflow support, manuscript writing.

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**Data Availability Statement** Not applicable.

## Declarations

**Conflict of interest** Not applicable.

**Research involving human and/or animals** This study was conducted under an approval from the Cyprus Bioethics Committee (EEBK EP 2021.01.263). Each participant signed a consent form in order to be included in the study. Participants were patients visiting the participating physicians. No additional human experiments was carried out.

**Informed consent acknowledgement** This study was conducted under an approval from the Cyprus Bioethics Committee (EEBK EP 2021.01.263). According to the guidelines of the committee each participant signed a consent form in order to be included in the study.

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