Chapter 1

Introduction

Summary

The present study reviewed the different causes of stroke and cardiovascular diseases (CVDs). Atherosclerosis is a disease of the arteries that causes stenosis, which can subsequently lead to stroke and other CVDs. Stroke and CVDs have a massive impact on people's health worldwide. Early detection of atherosclerosis may reduce the risk of death and diminish treatment costs. Lumen diameter and carotid intima-media thickness are the two parameters that are used as markers for atherosclerosis. Given the rising number of strokes due to CVDs, we need a robust computer-aided diagnosis system. Many automated techniques, such as methods based on machine learning (ML), can diagnose CVDs at an early stage. Still, attention is shifting toward developing diagnostic systems based on deep learning (DL). Therefore, the current review explores DL-based strategies in a competitive environment. The major drawback of ML strategies is their self-correction capability, which requires the system designer's input. DL strategies, on the other hand, provide a robust solution for the problem of self-correction.

ML strategies are based on extracting custom-built features from the region of interest in ultrasound images of the carotid artery and classifying those using supervised algorithms, such as support vector machines, artificial neural networks, and AdaBoost classifiers. However, in modern DL techniques, convolutional features replace custom-built features. The depth of the neural network refines these convolutional features, a process that is dependent on CPU speed. Fortunately, the advent of modern graphics processing units (GPUs) has accelerated CPU operations. We have studied the different applications of DL systems in medical image diagnosis of stroke and CVDs.

ML and DL strategies have their pros and cons, so the system designer may need to select the best method for a given application. Overall, we find that DL strategies prove to be more competent than ML strategies.

1.1 Introduction

In a report published by the WHO, cardiovascular diseases (CVDs) were declared the primary cause of death in the United States in 2016 (43.2%), with stroke in second place with 16.9% [1-3]. CVDs significantly impact human life and cause 17.9 million deaths worldwide in the year 2019, where heart attack and stroke were responsible for 85% of reported deaths [3]. CVDs lead to high costs in treatment, productivity, and mortality; therefore, the total direct expenditure on CVDs is projected to increase to $1.1 trillion in 2035 [4]. Low- and middle-income group countries are also affected by CVDs. CVDs have gained more importance in India due to rising fatality rates [5-7]. Prabhakaran *et al.* reported that the urban population of India is likely to be more susceptible to CVDs (1-13.2%) than its rural population (1.6-7.4%) [7].

The WHO estimated an age-standardized CVD mortality rate in India among males and females of 363-443 and 181-281 (per 1,00,000), respectively. Atherosclerosis in carotid arteries is the primary cause of stroke. Atherosclerosis narrows the arteries and blocks blood flow into the cardiovascular and cerebrovascular systems [8-10]. Severe-risk patients are primarily advised for carotid endarterectomy, which is a costly invasive procedure [11]. Early detection of CVDs may reduce mortality rates and treatment expenditure.

Atherosclerosis is an inflammatory process that develops with age. Different stages of the development of the disease are subsequently endothelial dysfunction, fatty streak formation, and complicated lesion formation [8, 12-15]. The chemical, mechanical, or immunological changes damage the endothelium and lead to endothelial dysfunction, which starts atherosclerosis. Endothelial permeability, leukocyte migration, endothelial adhesion, and leukocyte adhesion are the factors responsible for endothelium dysfunction [13]. Under normal physiological conditions, the endothelial layers prevent penetration of leucocytes into intimal layers. Thus, the endothelial layer is a barrier to the blood and the intima layers. However, a state of low shear stress and flow turbulence is built due to adverse conditions such as abnormal arteries (tortuosity, kinking, and coiling) [16]. Therefore, large molecules such as low-density lipoproteins penetrate the endothelium layers and accumulate beneath the intimal layer. This process is known as atheroma formation and increases with enhanced LDL cholesterol levels. Growth factors such as VCAM-1 and ICAM-1 (macrophage colony-stimulating factors) are responsible for atheroma formation. Phagocytosis by monocyte-derived macrophages oxidizes LDL, and foam cells appear, which is the first appearance of plaques in the form of fatty streaks [12, 14, 15].

Figure 1.1 shows the schematic diagram of the progression of the disease in arteries. Cardiologists and cardiovascular pathologists found that culprit plaques are responsible for cardiovascular events. In the clinical practice, these culprit plaques also termed as vulnerable, high-risk, or unstable plaques. Naghavi *et al.* have reviewed and explored various categories of vulnerable plaques [14]. Vulnerable plaques render people prone to thrombosis, and patients are at risk of cardiovascular events, stroke, or sudden death [17, 18].

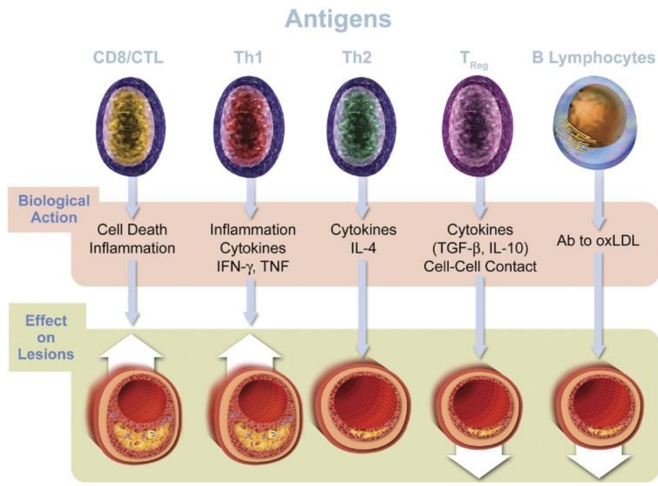

Figure 1.1 A schematic view of the atherogenesis courtesy of Libby *et al.* [19]

1.2 PRISMA Model and Article Search strategy

Our work started with a rigorous search on academic websites, such as Google Scholar, PubMed, and Web of Science Arxiv, and non-academic websites, such as Github, Kaggle, and stack overflow. For automated cIMT, LD, and plaque segmentation we confined our research only to articles published within the past ten years in high impact factor and peer-reviewed journals. Since we focused on the segmentation of ICA images based on a DL strategy, we used keywords related to the title of this review. Figure 1.2 shows the PRISMA distribution of the articles. Table 1.1 represents the sector-wise representation of "School of Thoughts" (SOTs). SOT1 is based on the biology of atherosclerosis and the acquisition of B-mode ultrasound (BUS) images of carotid arteries. SOT2 is based on the DL strategies for CCA and its cIMT, LD and plaque area measurement. Similarly, SOT3 is based on DL strategies used for ICA plaque segmentation. Table 1.2 lists the articles studied for statistics of CVDs, atherosclerosis and plaque formation, plaque tissue characterization, carotid imaging modalities, carotid artery subsections and biomarker

A total of 328 articles came into view after rigorous searching, and nearly half were selected based on relevance. The keywords we used for searching are segmentation of carotid arteries, "carotid arteries ultrasound image", "cIMT segmentation", "common carotid artery plaque segmentation", "automated method of segmentation", "internal carotid artery plaque segmentation", and "deep-learning-based segmentation". Cardiologists and radiologists from our team reviewed the papers related to the anatomy of the cardiovascular system. Computer science and electrical engineering experts inspected whether the articles were worth including from a technical point of view. Finally, we prepared a consolidated list of references based on the advice of our team members. Articles were selected using these criteria; however, the selection was not limited to the above criteria.

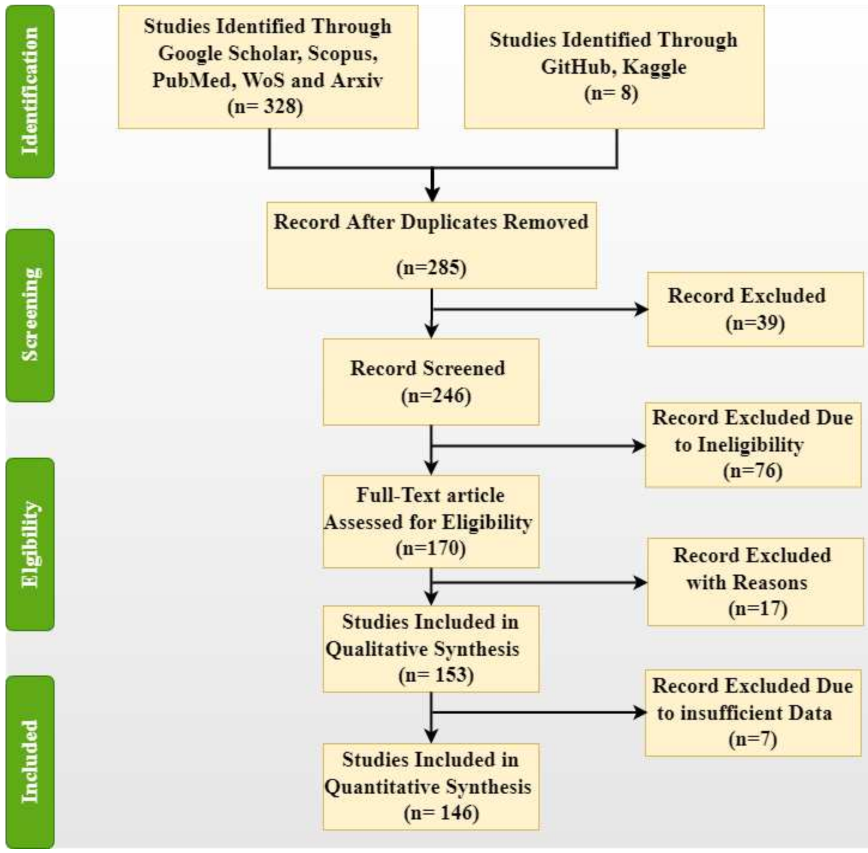

Figure 1.2 PRISMA Model for CVD risk biomarker measurement.

Table 1.1 Sector-wise subjects of the articles studied.

Sr.#	Sector	Subject
1	Sector 1	Statistics of CVDs, atherosclerosis and plaque formation, plaque tissue characterization, carotid imaging modalities, carotid artery subsections and biomarker
2	Sector 2	DL based methods for CCA biomarker Segmentation
3	Sector 3	DL based methods for ICA biomarker Segmentation

1.3 Plaque morphology

The atherosclerotic plaque results in thrombotic occlusion of the carotid arteries, which causes CVDs such as myocardial infarction (MI) and unstable angina [1, 2, 5, 7, 8, 12, 20, 21]. Furthermore, the embolization of the carotid arteries results in stroke and ischemic attack [22-24]. Both thrombosis and embolization may sometimes lead to death or permanent disability. Thus, atherosclerotic plaque is identified as a high-risk or vulnerable plaque [25]. As the age of the plaque increases, various plaque components are produced. Depending on which imaging modalities are used, these plaque components are visible in the images [26]. Plaques can be classified into three categories based on their echolucency in US images: hyperechoic, hypo-echoic, and moderately echoic plaques [27-29]. However, US imaging is mostly operator-dependent; hence, the reproduction of images is expected to be affected primarily by the operator's skills [9, 30-32]. We further classify plaques into low- (asymptomatic) and high-risk (symptomatic) plaques. In the past, researchers studied various parameters other than LD and cIMT related to the carotid arteries, e.g., pulse wave velocity (PWV), total plaque area (TPA), total plaque volume (TPV), bifurcation angle, tortuosity, and bulb diameter [18, 33]. Recently, Saba *et al.* [34] reviewed certain characteristics of the vulnerable plaque such as ulceration, fibrous cap separating necrotic core from lumen, calcification, and intra-plaque haemorrhage by studying histopathological, MRI, CT, and US images.

1.4 Carotid Artery Subsections and Biomarkers

Significant parts of the carotid arteries include the internal carotid artery (ICA), common carotid artery (CCA), external carotid artery (ECA), and bulb, which are all affected by atherosclerosis. The CCA has been studied extensively, but the ICA and the bulb have not. The ICA is deeply embedded and covered with flesh in the neck; hence, anterior to posterior manoeuvring is very difficult [22]. The ECA supplies blood to the face and the scalp, whereas the ICA supplies blood to the brain. The plaque growth inside the ICA and the bulb has no pattern; however, the focal thickening around the lumen region can be viewed in a 3D cross-sectional slice of the carotid artery. As shown in Figure 1.3, the unidirectional plaque can be quantified using conventional carotid intima-media thickness (cIMT) measurement methods. The bidirectional stenotic plaques shown in Figure 1.3 can be quantified using North American Symptomatic Carotid Endarterectomy Trial (NASCET) or European Carotid Surgery Trial (ECST) criteria by utilizing various tools of lumen diameter (LD) measurements [35]. Saba *et al.* discussed the guidelines for cIMT and carotid plaque measurement based on the NASCET and ECST criteria and the factors needed to revise these guidelines [35].

The cIMT- or LD-quantified measurements are conventionally used as gold standards for stroke risk assessments [30, 31, 36-42]. Researchers have suggested the carotid intima-media thickness as a surrogate marker of cardiovascular diseases [42]. Recently geometric and total plaque areas have also emerged as leading biomarkers of CVD [43, 44]. In some studies [23, 45, 46] researchers have found that the CVD risk factors such as smoking, total cholesterol, and systolic blood pressure have strong correlation with TPA compared to cIMT. Also, they have found that the plaque area is a better predictor of CVD than the cIMT. Thus, the association of the risk factors among the non-invasive biomarkers [47] of the CVDs, such as cIMT, carotid stenosis, and TPA have different associations.

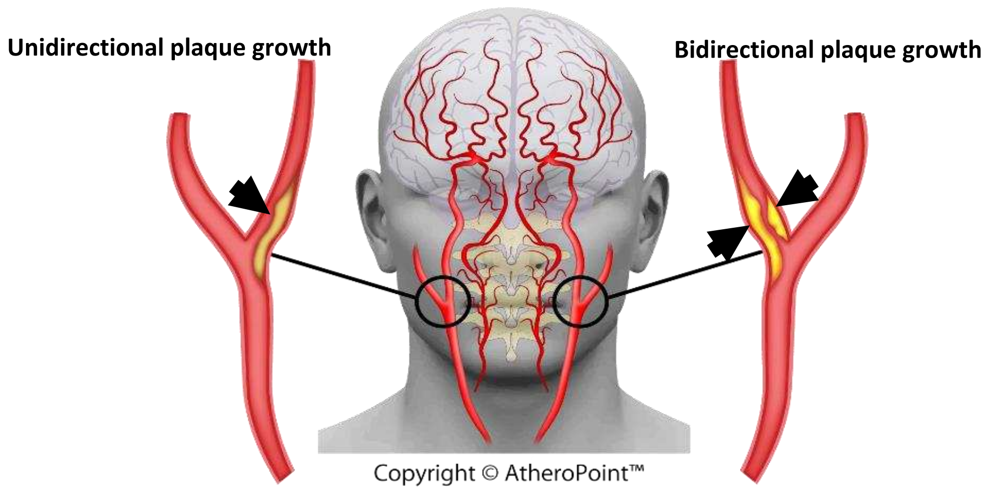

Figure 1.3 Anatomy of the human cerebrovascular system. Atherosclerotic plaque growth in carotid arteries (left) unidirectional growth (right) bidirectional growth)

1.5 Carotid Imaging Modalities

Different imaging modalities, such as magnetic resonance imaging (MRI), computed tomography (CT) angiography, and ultrasound (US) scans, are available to locate and identify atherosclerosis in the arteries, as shown in Figure 1.3 [12, 24, 48]. The B-mode US are preferred over the other imaging modalities as it does not use a contrast agent and is radiation-free and non-invasive. Therefore, the diagnosis with ultrasound is better than the diagnosis based on MRI or CT scans. The ICA is posterior and lateral to the ECA and is slightly larger than the ECA; therefore, ICA scanning is a complicated job. The sonographer can identify the ECA by tapping a finger on the ipsilateral temporal artery, which produces a serration-like artefact in the Doppler spectrum [49]. Figure 1.4 shows the carotid artery B-mode ultrasound images and its external, internal and common carotid artery subsections.

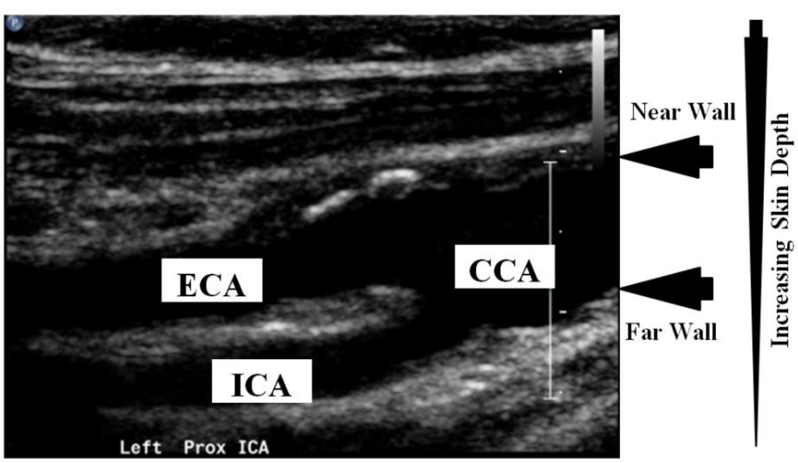

Figure 1.4 Carotid artery subsections CCA, ICA, and ECA in B-mode US image.

1.6 Discussion

This study aimed at discovering the data related to the causes of cardiovascular and cerebrovascular diseases, and we identified atherosclerosis as the leading cause of these diseases. Atherosclerosis is the cause of enhanced IMT and LD. However, previous studies describe other causes for the enhancement of LD and IMT.

1.6.1 Association of CVD Risk factors with cIMT, LD and plaque

In a recent report published by AHA, Virani *et al.* have suggested 7 factor associated with the CVDs. These factors are healthy and active life style, low BMI, low cholesterol, no smoking or tobacco consumption, healthy diet, controlled blood pressure, and controlled diabetes [2]. Previously researchers have found these factors associated with the CVDs. Ozdemir *et al.* identified obesity (high body mass index, or BMI) as one of the causes of enhanced LD and IMT in a group of 71 people [50]. People with a BMI of 23 found to have an average RCCA LD of 6.90±0.93 mm, whereas people with a BMI of 27.62±1.72 had an enhanced LD of 7.40 ± 0.79 mm, which shows that there is a relationship between BMI and increased LD. Llyod *et al.* [51] performed a similar study on obese or overweight postmenopausal women. They found that women undergoing current hormone therapy had an LD of 5.31 mm and an IAD of 6.79 mm, whereas former hormone therapy users had an LD of 5.44 mm and an IAD of 6.94mm. Another gender-based study by Kreja *et al.* on 500 patients found a difference in lumen diameter between men and women [52]. The mean LD in 305 women was found to be 4.66 ± 0.78 mm, whereas in men, the mean was 5.11±0.87 mm. Figure 1.5 shows a chart of 7 simple factors of life to avoid chances of stroke.

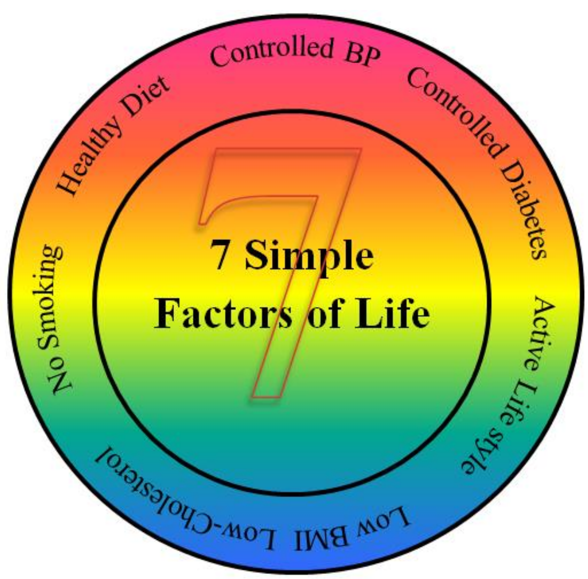

Figure 1.5 Seven factors to avoid CVDs in life.

Apart from gender-based studies, Ruan *et al.* also studied the relation between LD and cIMT among a cohort of 1,040 persons, of whom 306 were of the Black race and 734 of the White race [53]. Persons of the White race had a mean LD of 5.72±0.53, whereas persons of the Black race had a mean LD of 5.81±0.65 (106). Mirek *et al.* presented a multivariate logistic regression model using LD, age, and MI as parameters to find the correlation between LD and three-vessel disease (3VD) [54]. With AUC = 0.8, their model found a significant correlation between the LD and IMT of the right carotid and left femoral arteries in patients with 3VD compared to those without 3VD (53). Detecting abnormalities in the arteries, Togay *et al.* found a relation between the abnormalities and the reduced LD in 345 patients [16]. The LD at the origin of the ICA and the carotid abnormality in patients with tortuosity are 6.45 and 4.55 mm, in patients with kinking 6.30 and 3.75 mm, and in patients with coiling 6.08 and 2.80 mm. Patients with kinking and coiling have a higher maximum systolic velocity (MSV) (103 and 120 cm/s) than patients with tortuosity (84.5 cm/s).

1.6.2 Future of the CVD Risk in Deep Learning

Most of the reviewed studies used still images for experiments. Some studies converted motion data into still images. However, none of the studies used motion US data for plaque segmentation. Also reported studies used 2D data for plaque area segmentation, however, 3D images can also be used for plaque volume analysis. Further, all methods used supervised learning algorithm where binary plaque images (mask) are used as the labelled information. However, considering the cases where number of training images are very large (>5000), preparation and verification of binary mask will be close to impossible. In such scenario unsupervised learning algorithms may be useful. Recently, unsupervised learning algorithms are not explored for medical image classification and segmentation by the researchers. But, we can see many applications of such algorithms in medical imaging very soon.

1.6.3 Extension for the NextGen System

Previous CVD risk studies can be majorly classified in three categories. Category one comprises CVD risk studies based on conventional methods. ML based semi-automated methods fall under category two. Previous DL-based studies fall under category three where automated methods are used as classification and segmentation. These DL-based studies involve CNN, VGG-16, ResNet50, GoogleNet, Xception, Inception, and UNet, UNet++ etc. for classification and segmentation task. These methods are state-of-the art methods deployed in many other medical imaging tasks. Another category of modern DL is emerging as fourth category where DL-based studies are merged with some conventional methods, recently developed HDL models for classification and segmentation tasks. Further, DL-based methods can combine metaheuristic algorithms such as Ant colony, particle swarm optimization (PSO), genetic algorithm etc. Lastly, multi-ethnic, multi-centre, multi-race, and scientifically validated CVD risk assessment can be designed.

Table 1.2 Biological Phenomenon of atherosclerosis disease.

Author	Summary
Benjamin *et al.* [55]	A WHO report on statistics of the stroke and cardiovascular disease published in 2019
Suri *et al.* [8]	Cause of atherosclerosis and preventive measures
Park *et al.* [9]	Carotid plaque imaging using US
Togay Ishikay *et al.* [16]	Carotid artery abnormalities its association with stroke risk.
Teng *et al.* [56]	Different properties of the atherosclerotic plaque in carotid arteries
Patel *et al.* [10]	Mechanical properties of the atherosclerotic plaque studied via US.
Rothwell *et al.* [22]	Study of ischemic stroke in patients with reduced ICA LD
Kim and Youn [32]	US based study for atherosclerosis detection
Naim *et al.* [12]	Atherosclerotic plaque study based on US, MRI and CT scans
Naghavi *et al.* [14]	Clinical trial of the patients with atherosclerotic plaque
Hopkins E.[15]	Biology of the atherosclerosis
Mohebali *et al.* [28]	Plaque characterization using acoustic shadowing in US images
Pedro *et al.* [17]	Characterization of symptomatic and asymptomatic carotid plaque using enhance activity index (EAI) based system
Ho *et al.* [18]	A review of the carotid US in atherosclerosis diagnosis
Mirek *et al.* [54]	Peripheral artery disease LD biomarker relation with coronary atherosclerosis
Nambi *et al.* [57]	Role of cIMT and plaque in CVD prediction
Picano *et al.* [20]	Vulnerable Plaque tissue characterization in US images
Cuadrado-Godia *et al.* [21]	CSVD review using pathophysiology, biomarkers and ML strategies.
Gupta *et al.* [27]	Echolucency based Plaque characterization for stroke risk in US images
Hunt *et al.* [29]	ARIC study: Prediction of ischemic stroke using acoustic shadowing in BUS images of carotid arteries
Kamensk iy *et al.* [33]	Age and disease related structural remodelling in carotid arteries
Remington and Goodwin [58]	Clinical anatomy and physiology of ICA
Londhe and Suri [59]	Effect of super harmonic frequency in US image formation
Jashari *et al.* [60]	Echogeneicity-based plaque tissue characterization and cerebrovascular symptoms
Barnett *et al.* [11]	Carotid endarterectomy performed in patients with symptomatic moderate or severe stenosis
Ozdemir *et al.* [50]	Effect of overweight on LD, PSV and cIMT
Lloyd *et al.* [51]	CCA diameter and CVD risk factor on obese postmenopausal women
Kreja *et al.* [52]	Sex based study of CCA LD
Polak *et al.* [42]	Study of cIMT biomarker for prediction of CVD risk
Ruan *et al.* [53]	Race based study of CCA LD
Mancini *et al.* [61]	Study of structural markers in relation with CVD
Cohn *et al.* [62]	Study of functional markers in relation with CVD
Amato *et al.* [63]	Relation of cIMT and coronary atherosclerosis.

Hong *et al.* [64]	Relation between age and ICA
Bartlett *et al.* [65]	Relation between carotid stenosis diameter and cross sectional areas
Hyde *et al.* [66]	ICA stenosis measurement in 3D CTA and digital subtraction angiography

1.7 Objectives of the Thesis

The main objective of the thesis is to provide an artificial intelligence based solution for carotid artery plaque segmentation and quantification. Under artificial intelligence based methods, deep learning are the most suitable choice to provide automated segmentation [67-72]. Thus, primary objective is to develop some deep learning based algorithms for automated plaque detection and segmentation in internal carotid arteries. Further, the same algorithms should be applicable to other segments of carotid artery such as common carotid artery. These algorithms should overcome the systems based on previous generation algorithms such AtheroEdge™ 2.0. The developed algorithm should be generalized for multicentre, multi-ethnic databases. Therefore, the algorithms should be tested on diversified database and overcome the performance (e.g. accuracy, precision, recall, dice similarity coefficient etc.) of previous methods. Finally, the algorithms must be suitable for fast and low memory (small size) applications. Thus, we objectify these goals as following:

(1) To develop some hybrid deep learning models for atherosclerotic plaque segmentation in internal and common carotid artery. Where hybrid model stands for amalgamation of two CNNs or arangement of layers in such a way that the developed hybrid model carries different properties then traditional models.

(2) To develop unseen deep learning models for segmentation of atherosclerotic plaque from common carotid arteries of patients from different geographic locations. Unseen model should be developed by training on database-1 and testing on database-2 and viceversa.

(3) To develop advanced U-series deep learning architectures for atherosclerotic plaque segmentation in ICA and CCA sections. The advanced DL architecture should be compuatationally inexpensive, fast, and attract developer for wider application areas.

(4) To apply attention module on basic deep learning model to enhance the feature extraction capability of the segmentation model.

(5) To develop Fast RCNN based model for localization of common carotid artery transverse section in ultrasound images.

1.8 Thesis Organization

All objective are fulfilled sequentially and arranged in this thesis chapter wise. Every chapter describes the idea of each objective in detail. The chapters are organized in the following manner.

Chapter 1 provides the description of the disease, global statistics, biomarkers, imaging modality, and CVD risk factors. Then we discuss the objectives of the thesis and its organization. This chapter also introduces the PRISMA model for literature survey. Chapter 2 discusses the CVD risk biomarker measurement systems from previous and present generations. This chapter briefly discusses the cIMT, plaque and LD measurement by conventional, machine learning, and deep learning based methods. Further, emergence of deep learning based method in other medical imaging applications gives wide view of the technology.

The implementation of the ideas discussed in the previous section begins from Chapter 3. This chapter introduces the concept of merging two solo deep learning models to form a hybrid deep learning model. Three SDLs and two HDLs are proposed in this chapter to segment the moderate to high risk plaque in ICA ultrasound images. Further, we validated our results by performing series of statistical tests.

Chapter 4 uses one SDL and one HDL to check the system feasibility for low to moderate plaque images of CCA ultrasound. A commercially available system AtheroEdge 2.0 (AtheroPoint LLP, Roseville, CA, USA) is used as benchmark for plaque segmentation. The AtheroEdge 2.0 system is based on level set methods which fall under second generation methods of segmentation. Chapter 5 uses two kinds of databases (Japanese and Hong Kong) for generating unseen deep learning system. The proposed system in this chapter uses one database for training and other for testing and vice-versa. A further, combined database experiment is compared against the unseen database experiments. Chapter 6 introduces some novel deep learning architecture for plaque segmentation. These architectures are small in size, faster and have low training parameters. All models are tested on ICA and CCA images. Also, an unseen experiment makes the system more robust and bias free.

Chapter 7 introduces a novel concept of attention block in UNet architecture. The attention block has better feature modification capability in shallow feature zone. The combined architecture captures the plaque area in critical ultrasound images. Chapter 8 uses a Faster RCNN method for common carotid artery cross section localization in transverse ultrasound images. Two different datasets are combined and used for training and testing which shows the bias free ability of the system towards databases.