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Μεταπτυχιακή Διπλωματική Εργασία

"CLINICAL APPLICATION OF DUPLEX IN PATIENTS WITH LOWER LIMB ATHEROSCLEROTIC DISEASE''

Υπό

ΣΤΥΛΙΑΝΗΣ Κ. ΣΤΟΥΚΗ

Ιατρού Ακτινολόγου

Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

Μεταπτυχιακού Διπλώματος Ειδίκευσης

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ΕΥΧΑΡΙΣΤΙΕΣ

Ολοκληρώνοντας την παρούσα διπλωματική εργασία στο πλαίσιο του Μεταπτυχιακού Προγράμματος «Υπερηχογραφική Λειτουργική Απεικόνιση για την πρόληψη & διάγνωση των αγγειακών παθήσεων» θα ήθελα να εκφράσω τις ειλικρινείς μου ευχαριστίες σε όλους όσους συνέβαλαν στην εκπόνησή της.

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ΣΤΥΛΙΑΝΗ Κ. ΣΤΟΥΚΗ

Abstract

Lower limb atherosclerotic disease or peripheral artery disease (PAD) or Lower Extremity Arterial Disease (LEAD) is the accumulation of atherosclerotic plaques in the lower extremities. There has been a recent interest in the use of ultrasonic imaging tools such as duplex ultrasound arterial mapping (DUAM) in PAD assessment. The aim of this research is: to explore and evaluate the clinical application of duplex ultrasonography in patients with lower limb atherosclerotic disease. A systematic review was undertaken across Google Scholar, where 11 studies exploring the application of duplex assessment were obtained. As per the findings, six themes examining the clinical application of duplex scanning for lower limb atherosclerotic disease found that it is associated with several advantages. These include: patient safety and clinical feasibility due to its non-invasive and cost effective nature; efficiency in timely determination in management of the PAD when combined with physiological assessments; ability to administer safe screening in patients with diabetes; ability to effectively determine the severity of lower limb PAD using specific stenosis screening; findings easily associated with standardized grading techniques as well as ability to be of equal value as traditional arteriogram techniques like CT. In contrast, some of the key disadvantages associated with clinical application of duplex scanning are: time consuming nature; limited knowledge of healthcare professionals concerning its effective application and advantages, as well as prevalence of resistance to change due to limited knowledge or preference towards traditional screening techniques. In conclusion, the clinical application of duplex scanning is effective for the assessment of patients with lower limb atherosclerotic disease if implemented considering some of its possible limitations.

Key words: Lower limb atherosclerosis, duplex, ultrasonography, application, effectiveness, peripheral artery disease, assessment, clinical application, traditional screening techniques.

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Chapter 1: Introduction

1.1. Introduction

Atherosclerosis is an adverse cardiovascular condition characterized by accumulation of plaque or fatty streaks in the blood vessels resulting in the disruption of normal blood circulation in the body. Lower limb atherosclerotic disease or peripheral artery disease (PAD) is the accumulation of such atherosclerotic plaques in the lower extremities. There has been a recent interest in the use of ultrasonic imaging tools such as duplex ultrasound arterial mapping (DUAM) in PAD assessment [1], [2]. The following chapter aims to discuss current background of existing research, the limited use of this diagnostic technique and the need for further research and exploration.

1.2. Research Background

Peripheral artery disease (PAD), also known as Peripheral Vascular disease (PVD) or lower limb atherosclerotic disease or Lower Extremity Arterial Disease (LEAD), is associated with accumulation of fatty streaks or atherosclerotic plaques in the lower limbs, resulting in narrowing of blood vessels and decreased blood circulation towards this region of the body [3]. PAD is associated with a range of symptoms and complications such as: claudication or excessive cramping across lower limb muscles after physical activity, weakness or numbness in the lower extremities, hypothermia or cold feet, discoloration and diminished pulse rate in the legs. If not assessed and controlled, PAD can cause complications such as erectile disruption, stroke and complete loss of blood flow in the lower limbs resulting in gangrene and amputation [3], [4]. Internationally it has been estimated that 236.62 million people across the world, aged 25 years and older, are residing with PAD. However, early diagnosis and alterations in lifestyle and diet have been evidenced to be useful in reversing or limiting the harmful consequences of PAD [5].

1.3. Research Rationale

Arteriography or arteriogram, have till date, been considered as the gold standard of PAD assessment and diagnosis. An arteriogram or arteriography, is a form of imaging procedure

comprising of radiological or X rays coupled with contrast dyes, for the purpose of examining blood circulation and detection of blockages in arteries and veins situated across organs and tissues [6]. However, while such procedures have been evidenced to provide an accurate insight of obstructive lesions in the blood vessels, arteriography is limited in its ability to estimate the hemodynamics associated with these lesions. For this reason, ultrasonic procedures like duplex scanning are considered as an effective replacement of arteriogram procedures [7]. The use of ultrasound has been evidenced to provide a non-invasive, non-radiological screening of the arterial vessels in the lower extremities. Images in grey scale assist in the identification of lower limb thrombus while ultrasonic Doppler techniques allow screening of the velocity of blood circulating through such vessels [8]. Recent technological advances in the form of colour flow mapping or colour Doppler imaging further enhance the localized identification of occlusions and stenosis across the arteries of the lower limbs. However, despite its effectiveness, there is limited research exploring the clinical application of duplex assessment of lower limb atherosclerotic disease, due to its time consuming nature, lack of adequate skill and training across the diagnostic workforce and prevalence of resistance from angiologists and surgeons due to preference towards the traditional arteriogram method [9], [10]. Thus, the serious adverse consequences of PAD, dearth of existing literature on clinical application of duplex assessments and its associated effectiveness, form the rationale for implementation of this research.

1.4. Research Aims, Objectives and Questions

In this respect, the aim of this research is: to explore and evaluate the clinical application of duplex ultrasonography in patients with lower limb atherosclerotic disease. This project will thus aim to explore existing research based on the following objectives:

1.4.1. Research Objectives

1. To explore and evaluate the clinical application of duplex ultrasonography in patients with lower limb atherosclerotic disease as compared to other radiological imaging methods.
2. To explore and evaluate the limitations associated with the clinical application of duplex ultrasonography in patients with lower limb atherosclerotic disease.
3. To recommend strategies of enhancing the clinical application of duplex ultrasonography in patients with lower limb atherosclerotic disease.

1.4.2. Research Questions

This research project, using existing studies, aims to resolve the following research questions:

1. What is the effectiveness of duplex ultrasonography in assessing patients with lower limb atherosclerotic disease as compared to other radiological imaging methods?
2. What are the limitations restricting the existing application of duplex ultrasonography in assessing patients with lower limb atherosclerotic disease as compared to other radiological imaging methods?
3. In what way such limitations can be mitigated so as to improve the effectiveness of duplex ultrasonography in assessing patients with lower limb atherosclerotic disease?

1.5. Research Significance

Colour mapping or duplex assessment studies, due to their non-invasive, non-radiological nature, have been evidenced to provide a safe and cost effective way in which patients with lower limb atherosclerotic disease can undergo early assessment, diagnosis and follow up,

resulting in improved health outcome. Its cost effectiveness and portability make it a feasible option for diagnostic implementation in small scale healthcare organizations with limited financial resources [11]. The ability to simultaneously detect arterial occlusions as well as hemodynamics, makes colour Doppler imaging an effective and precise way to quantify the severity of PAD. Consequently, the findings of this research will be useful in showing future radiologists and healthcare professionals the effectiveness of colour duplex and the correct use of this imaging modality in comparison to other radiological methods, which can then be used for implementing appropriate and timely clinical interventions in patients with PAD [12]. Thus, the significance of this research lies in its ability to provide cost effective, beneficial and feasible diagnostic strategies for patients with lower limb atherosclerotic disease, paving the way for achievement of positive health outcome in the future [11], [12].

1.6. Summary

This chapter provides a succinct yet comprehensive discussion on the adverse consequences of PAD, the importance of proper and effective screening and the limitations which have restricted the use of non-invasive ultrasonic scanning methods like DUAM in PAD assessment. Such evidence proved to be useful in encouraging the development of this research aims and goals, based on which the key tools of data collection were selected and applied, as discussed in the succeeding chapter.

Chapter 2: Methodology

2.1. Introduction

In order to obtain evidence based, reliable and credible answers to questions and objectives identified for a particular research, the implementation of valid and comprehensive data collection tools is of utmost importance [13]. Thus, the following chapter aims to provide a comprehensive discussion on the key qualitative methodologies which were used for the purpose of obtaining recent articles exploring the clinical application of duplex ultrasonography in the assessment of the PAD or lower limb atherosclerotic disease in adult patients. Additionally, this chapter will also provide insights concerning the relevant tools used for the purpose of analyzing and evaluating the characteristics and validity of the acquired existing research.

2.2. Research Philosophy

This study is based on the principle that the true operation of a clinical phenomenon within the environment can be understood via scientific methods such as experiments and statistical analysis [14]. This research does not rely on the direct implementation of primary research, but on the use of a systematic review of articles comprising of empirical, experimental as well as qualitative data on the clinical application of duplex ultrasonography.

2.3. Research Design and Methodology

A qualitative research design has been selected for this research, which comprises of the in-depth exploration of a wide range of secondary research, so as to provide a comprehensive overview of the issue in question [15]. Since this research is focused upon exploring multiple

aspects, such as the effectiveness and limitations of duplex ultrasonography, a qualitative research design proved to be useful in terms of comprehensiveness, which otherwise would not have been possible to capture by objective quantitative.

For the data collection and analysis, a qualitative methodology comprising of a systematic review was undertaken. A systematic review comprises of the structured collection of recent articles followed by thematically or systematically discussing their findings based on the objectives of the research. A systematic review is advantageous since it allows the inclusion of a large amount of existing secondary data within a short time period and in a cost effective manner, which otherwise would not have been possible via expensive and time consuming quantitative primary research methodologies [15], [16]. So, since this study aimed to enhance the existing research on characteristics associated with the clinical application of duplex ultrasonography, the use of a systematic review proved to be useful.

2.4. Data Sources

For the purpose of obtaining existing research exploring the clinical application of duplex ultrasonography in assessment of lower limb atherosclerotic disease, databases like Google Scholar were used. This is because of the ability of this database to provide a repertoire of multiple scholarly studies and papers across a wide variety of subjects and professions [17]. While obtaining articles from Google Scholar, care was taken to ensure the inclusion of studies comprising of a variety of both qualitative as well as quantitative research designs, such as systematic reviews, randomized controlled trials, cohort studies, observational studies and cross sectional studies. The inclusion of a variety of research designs was considered so as to obtain comprehensive, existing data on the clinical application of duplex ultrasonography in patients with lower limb atherosclerotic disease [18].

2.5. Search Strategy

For the purpose of obtaining recent articles for the systematic review, a search strategy was undertaken electronically using online databases such as Google Scholar. To ensure the same, keywords which were relevant to the research topic on focus, such as ‘duplex’, ‘ultrasonography’, ‘application’, ‘effectiveness’, ‘lower limb atherosclerosis’, ‘peripheral artery disease’, ‘peripheral vascular disease’, ‘examination’ and ‘assessment’ were used. To further expand the search via the inclusion of terms similar to the keywords, truncation symbols such as the asterisk (*) were used. For instance, to include articles containing both similar terms like ‘effective’ or ‘effectiveness’ and ‘atherosclerosis’ or ‘atherosclerotic’, the use of truncation such as, ‘effective*’ proved to be useful. To further enhance the search strategy via the inclusion of articles containing synonyms of the keywords, Boolean Operators like AND or OR were used.

For instance, to ensure that articles which contain similar terms like both ‘examination’ and ‘assessment’ are included, by typing ‘examination’ AND/OR ‘assessment’ in the search. In order to narrow down the search process, limitations in the form of setting the language to ‘English’ and the publication date to ‘2013 to 2020’ were established. This ensured the inclusion of articles which have been published recently in the English language, so that the most updated and current research is included in the systematic review of this study [17]–[19].

2.6. Data Collection

The electronic search strategy yielded a total of 795 results, out of which, a number of records had to be excluded due to reasons such as: lack of full text, prevalence of duplicates and irrelevance of the title and abstract in regards to the given research question and keywords. After

the exclusion, the articles were then selected for the final systematic review based on the following inclusion and exclusion criteria:

2.6.1. Inclusion Criteria

- Full text, academic, scholarly and peer reviewed articles, which have been published within the last 7 years, that is, from 2013 to 2020.
- Studies which explore the clinical application of duplex ultrasonography.
- Studies which explore the clinical application of duplex ultrasonography across patients with lower limb atherosclerotic disease or PAD or PVD.

2.6.2. Exclusion Criteria

- Grey literature or opinion editorials or studies which are not peer reviewed or have been published before 2013 [20].
- Studies which do not explore the clinical application of duplex ultrasonography or are only evaluating the application of other radiological or non-radiological methods such as arteriogram.
- Studies which do not explore the clinical application of duplex ultrasonography across patients with lower limb atherosclerotic disease or PAD or PVD or consider the application of duplex in the assessment of additional carotid arterial or vascular diseases.

Articles which appeared to the inclusion criteria were considered for further critical evaluation and selection. Grey literature or articles which did not assess the application of duplex or its use for assessing patients with lower limb atherosclerotic disease were excluded. The given search strategy yielded a total of 11 articles for

inclusion in the systematic review. The systematic review articles which were selected comprised of varied research designs such as systematic reviews, observational studies and cross sectional studies so as to ensure comprehensive existing data on the clinical application of duplex ultrasonography [21]. The details of the article selection process across databases as well as the key search strategy used have been both outlined diagrammatically in the form of a PRISMA as well in the form of table (Figure 1) (Appendix).

2.7. Data Extraction

The findings of the systematic review articles which were finally selected were extracted in the form of a data extraction table, comprising of sections like ‘author and country’, ‘aims/objectives’, ‘study participants’, ‘study design’, ‘findings’ and ‘recommendations’. These have then been discussed narratively in the form of themes in the succeeding chapters of ‘Results’ and ‘Discussion’. A narrative approach was undertaken while discussing and comparing the findings of the systematic review articles with existing literature.

2.8. Data Analysis

For the purpose of analyzing and evaluating the findings of each of the selected articles for the systematic review, in respect to the aims, objectives and questions of the research, the approach of thematic analysis was undertaken. Thematic or content analysis comprises of segregating and categorizing a large amount of secondary data into sections or ‘themes’ which are found to be relevant to the research question and objectives [22]. Since the focus of this research was centred on exploring multiple aspects underlying the clinical application duplex ultrasonography, such as effectiveness and limitations as compared to other assessment methods, a thematic analysis proved to be useful. After comparing and contrasting each of the systematic review articles, thematic analysis was performed by segregating similar characteristics and

findings into separate sections or themes in the succeeding chapter as per the research objectives. This is then followed by discussing the findings under each theme via critically comparing with existing research, so as to provide comprehensive information on the effectiveness of clinical application of duplex ultrasonography for assessing lower limb atherosclerotic disease in patients [23].

2.9. Research Validity

As discussed previously, systematic reviews are prone to limitations such as the inclusion of studies with poor methodological quality and inconclusive findings [16]. To prevent this, the application of a critical appraisal tool has proven to be useful as a comprehensive critique of the methods and results of a study. To ensure the inclusion of valid, recent articles exploring the clinical application of duplex ultrasonography in lower limb atherosclerotic disease, checklists available for the 'Critical Appraisal Skills Programme' (CASP) were used. CASP provides a range of checklists for a number of research designs, such as systematic reviews, qualitative studies, randomized controlled trials, cohort studies as well as case control and observational studies [24]. Since the articles selected for the systematic review were not limited to a single research design, use of CASP checklists for evaluating validity proved to be useful. Each CASP checklist comprises of 10 to 13 questions exploring the quality and validity of the design, methods and results underlying each study. Each question comprises of multiple choices of 'Yes', 'No' and 'Unclear'. Based on these checklist characteristics, only those articles which were able to score 6 to 9 'Yes' responses were included in the systematic review. Thus, this ensured the inclusion of articles which were valid and credible enough to provide conclusive findings concerning the clinical application of duplex ultrasonography in lower limb atherosclerotic disease [25].

2.10. Ethical Considerations

To guard ethical compliance, care was taken to ensure that the selected systematic review articles which comprised of human subjects had obtained ethical approval or ensured that participants' right to privacy and autonomy were maintained by obtaining informed consent and complying with participant confidentiality [26], [27]. Additionally, to prevent ethical issues with regards to plagiarism and copyrights, the findings from the selected systematic review articles were duly paraphrased along with acknowledging the work of the authors via addition of references [27].

2.11. Summary

This chapter provides an extensive and elaborate discussion on the comprehensive data collection tools which were used for the purpose of obtaining existing recent research, exploring the clinical application of duplex colour scanning or ultrasonography for the assessment of atherosclerotic disease in the lower extremities. The application of an electronic search strategy proved to be useful for the purpose of obtaining current research, exploring the topic on focus. The acquired articles proved to be useful for the purpose of comparing and discussing findings into themes. These findings have been collated in the succeeding chapters.

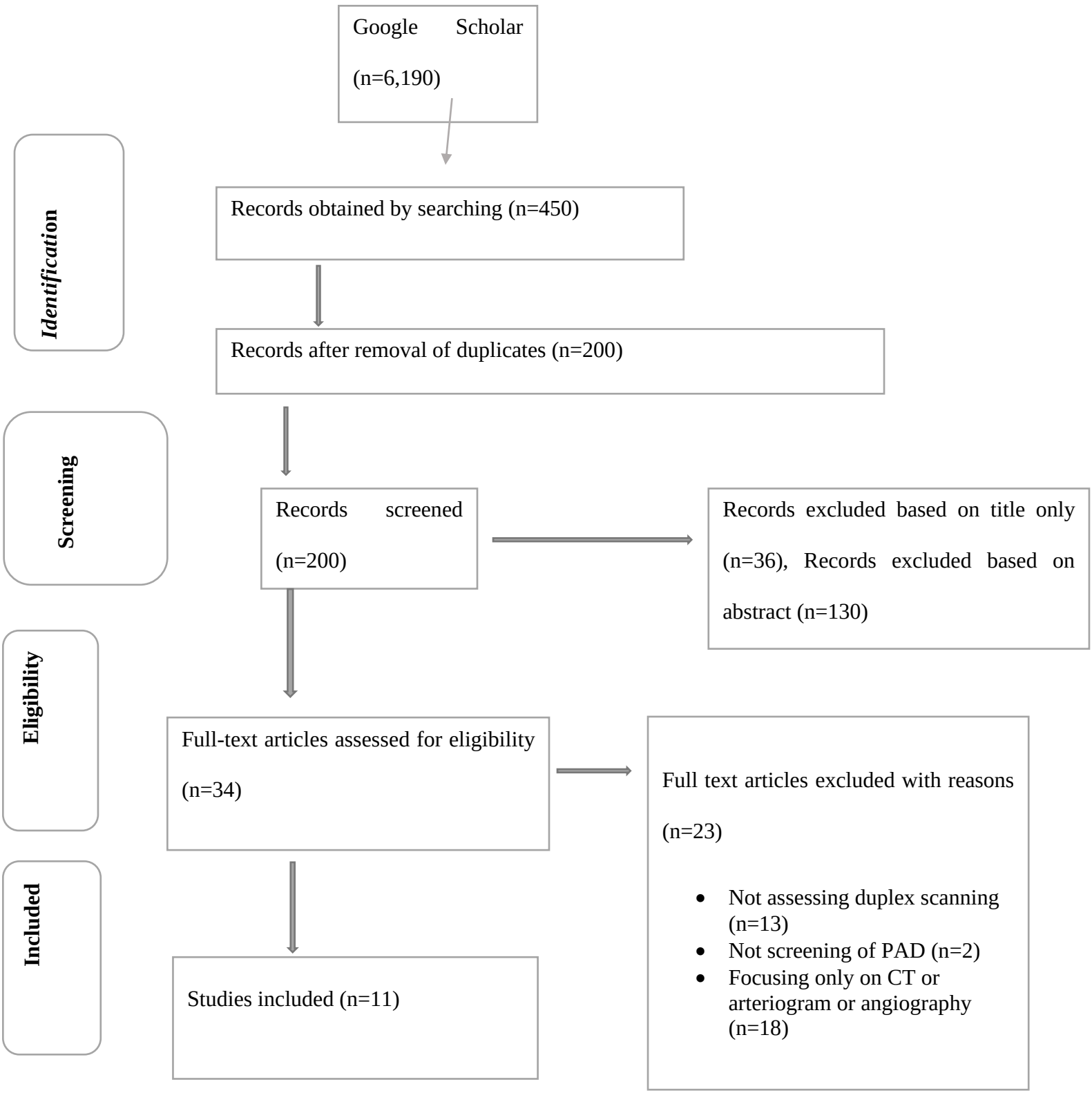

Figure 1: PRISMA diagram

Chapter 3: Results

3.1. Introduction

In order to systematically structure the outcomes of a research into themes relevant to the research objectives, it is essential to first obtain and examine the key findings underlying the articles selected for systematic reviewing [28]. The following chapter will provide a comprehensive discussion on the findings obtained from each of the eleven articles selected for the systematic review. This chapter will also draw upon a critical examination of the key limitations observed for each of the selected studies.

3.2. Overview of Selected Articles

A total of eleven articles discussing the clinical application of duplex in lower limb PAD were selected, 3 of which were narrative reviews [29]–[31]and the remaining 8 were based on cross sectional, comparative study designs [32], [33], [34], [35], [36], [37], [38], [39].Furthermore, 2 of the studies were published in the United States [29], [30], 1 article was published in Bangladesh [32], 3 articles were published in India [33]–[35],1 article was published in Egypt [36], 1 article was published in Australia [31], 1 article was published in Netherlands [37], 1 article was published in Italy [38] and1 article was published in the United Kingdom [39].

3.3. Findings of Selected Articles

3.3.1. Article 1

The qualitative study by Hodgkiss-Harlow and Bandyk [29] aimed to provide a comprehensive overview of the clinical application of arterial duplex testing in detecting and

interpreting aneurysmal and occlusive arterial disease in the lower limbs. According to the authors, duplex testing procedures have the potential to enhance clinical practice and care for lower limb atherosclerotic disease by providing comprehensive results, assessing the severity of existing occlusive symptoms and determining prognosis. However, the effectiveness of duplex testing in the management of lower limb atherosclerotic disease can be enhanced via undertaking blood pressure monitoring of the affected region. This in turn, as per the authors, allows efficient categorization of the severity of functional impairment and hemodynamics of the arteries. Such procedures when supplemented by colour scanning pave the way for the development of a comprehensive arterial map of various aneurysmal and occlusive lesions prevalent in the lower limbs of patients with atherosclerotic disease. Additional advantage of arterial duplex testing is its ability to accurately detect stenosis both prior to and after treatments like peripheral angioplasty or bypass grafting. Duplex testing methods estimate the risk of thrombosis during arterial repair treatments following stenosis, thus allowing long term positive health outcome across patients with lower limb atherosclerotic disease. Lastly, the authors concluded by stating that arterial duplex testing methods are an effective alternative to radiological or arteriogram methods in terms of portability, financial feasibility and non-invasive nature [29].

Upon critical examination of the above described study, it can be observed that its findings can be correlated well with the key objectives of this research, that is, the advantages associated with the application of duplex testing for patients with lower limb atherosclerotic disease. However, despite providing a comprehensive overview using standard diagnostic images and result criteria, this study does not shed light on the effectiveness of duplex scanning in comparison to existing ‘gold standard’ procedures, such as arteriogram or computer tomography in diagnosing lower limb atherosclerotic disease, or the limitations associated with this method of peripheral ultrasound testing [29]. Additionally, despite the study bearing resemblance to the study design of a scoping review, the authors have not provided any detail concerning strategies used to obtain and validate the articles which were used in covering the paper’s content. Such limitations raise doubts on quality, validity and credibility of this qualitative study and thus warrants the need for further research on the clinical question in focus [29], [40].

3.3.2. Article 2

Similarly, the review by Amrstrong, Carroll and Bandyk [30], narratively discusses the clinical advantages of duplex in assessing patients for lower limb atherosclerotic disease. By providing a detailed imaging of the physiology and anatomy of arteries across patients both with and without symptoms, duplex assessments enhance the clinical assessment and evaluation of stenosis severity in the lower limbs of patients with PAD. Integrating pulsed Doppler spectral analysis within duplex assessments further assists in determining the hemodynamics of arteries of the lower limbs with suspected occlusion. Such findings, in conjunction with the physiological assessments like monitoring of ankle-brachial systolic pressure, provide a cost effective, non-invasive measurement of PAD severity of the lower limbs, which can be implemented at the bedside and used for timely disease management. Such advantages indicate the potential of duplex assessment to conduct effective surveillance and follow up of patients who demonstrate progression of disease despite undergoing arterial and endovascular bypass procedures. However, the lack of outlining the methodology and strategy by which papers were reviewed in order to provide the content of this study can be considered as key limitation in terms of validity and reliability of the research [30], [41].

3.3.3. Article 3

The cross sectional study by Bhaduri et al. [32] aimed to assess the pattern and prevalence of PAD in the lower limbs of patients with a diagnosis of coronary artery disease (CAD) using duplex ultrasonography scanning methods. For the study, a total of 210 patients with an average age of 51.3±10.4 years, who were admitted with CAD in the cardiology department of a Bangladeshi hospital and diagnosed by using coronary catheter angiography, were recruited. Out of this group, 14 (6.7%) were female and 196 (93.3%) were male. Based on evaluation using duplex ultrasonography, approximately 90% of the patients were found to be

free from any clinical symptoms of PAD. However, prevalence of non-critical and critical stenosis across one or multiple arterial segments of the lower limbs was found to be 0.5% and 5.2%, out of the total group of patients. A lack of statistically significant correlation was observed between CAD severity and PAD occurrence [32].

The findings of this study proved to be useful in demonstrating the effectiveness of the clinical application of duplex in assessing the prevalence of lower limb atherosclerotic disease [32]. Such findings signify the importance of integrating duplex scanning in the routine practice for CAD management as a cost effective and non-invasive method for timely detection and mitigation of stenosis in the lower limbs. However, the cross sectional design of the study, restricted a comparative evaluation of duplex assessment findings with other methods like arteriogram which in turn, could have provided a more valid and reliable overview of the effectiveness of this method [32]. Furthermore, recruitment of primarily male patients and within a hospital of Bangladesh is further limitation in terms of transferability and applicability of findings to other patient settings or nationalities. Such limitations demonstrate the need to conduct further randomized controlled trials to validate the true effectiveness of duplex ultrasonography in lower limb atherosclerotic disease as compared to other methods [32], [42].

3.3.4. Article 4

In another cross sectional study, authors Das et al. [33] aimed to assess the value of duplex ultrasound in diabetic patients suspected with lower limb atherosclerotic disease. For this purpose, 60 patients aged 40 to 75 years, comprising of 25 females and 35 males, all diagnosed with diabetes were recruited. With the help of supine position of patients and variations in the position of equipment, the arteries of the lower limbs of the participants were assessed for narrowing of the lumen, atherosclerotic plaques, disturbances in blood flow and thickness of the intima-media, using SDU 1200 Diagnostic Ultrasound System and

a linear array transducer of 5-10 MHz. Based on the findings, narrowing of the lumen of the dorsalis pedis artery demonstrated the highest prevalence across patients (41%across the left and 36% across right side) followed by prevalence of atherosclerotic plaques across the femoral artery (44%). Twenty-eight out of the fifty plaques observed, demonstrated the prevalence of calcification. The prevalence of low peripheral resistance indicative of distal ischemia was found to be 25.5% in the dorsalis pedis artery, 23% in the anterior tibial artery and 21.5% in the posterior tibial artery [33].

Based on these findings, the authors concluded that duplex ultrasound was an effective assessment method by which the lesions and plaques across the lower limb blood vessels can be visualized and characterized in a cost effective and non-invasive manner. However, the key limitations of this assessment method, as identified by the author, are the extensive time required for implementation and the risk of variability in observations across practitioners [33]. Thus, the findings of this paper demonstrate relevance with regards to the objectives of this research, where the ability to distinguish between occlusions is a key advantage of duplex method in determining the severity of stenosis and PAD in diabetes [33]. Such findings hold future implications by necessitating the need to integrate duplex assessment in not just identifying, but also classifying the risk of lower limb atherosclerotic disease across diabetic patients, resulting in positive health outcome and preventive disease management [33]. However, the lack of randomization via inclusion of comparative analysis with additional assessment methods is a key limitation in terms of validity of the findings concerning duplex scanning. The relatively low sample size and inclusion of only diabetic patients are key limitations in terms of internal validity and applicability of findings. The study also did not provide any comprehensive insight concerning how the limitations of duplex assessment can be mitigated [33].

3.3.5. Article 5

The cross sectional observational study by Panda et al. aimed to evaluate the prevalence of PAD in the lower limbs across clinical suspected patients diagnosed with peripheral vascular insufficiency (PVI) using a duplex colour Doppler [34]. A total of 50 patients admitted with a

diagnosis of PVI at a hospital in Odisha, India, were recruited, 94% of which were males over 40 years old and with risk factors such as hypertension (50%), alcohol consumption (26%), hyperlipidaemia (50%) and diabetes (46%). B-Mode and Doppler were used to assess participants regarding contour and thickness of blood vessels, pattern and direction of blood flow, pulsation and associated pathology such as abscess, plaques, calcification, stenosis and aneurysm. Based on the findings, the prevalence of complete occlusion was observed in 38% whereas the prevalence of partial (49%) occlusion was observed in 30% of the recruited patients. Also, based on duplex assessment, the prevalence of intermittent claudication was observed in 60% of the patients out of which, 75% was prevalent in the femoropopliteal segment whereas 25% was observed in the infrapopliteal and iliac segments. The diagnosis of PAD based on duplex colour Doppler demonstrated a specificity and sensitivity of 96% and 92% respectively. Moreover, a Pulsatility Index ratio of less than 4 demonstrated the prevalence of stenosis in 80% of the patients [34].

Based on these findings, it can be stated that duplex assessment is a clinical effective method for evaluating the prevalence of atherosclerotic disease in the lower limbs. This is due to the ability of duplex methods, using colour Doppler mechanisms, to effectively detect the site as well as the extent of stenosis in the lower limbs [34]. The ability of duplex assessment methods to calculate Peak Systolic Velocity as well as waveforms of blood flow, make it an effective and non-invasive method by which the hemodynamic status of patients with lower limb PAD can be evaluated, resulting in timely detection, management and positive health outcome [34]. However, the lack of randomization or comparative analysis with other assessment methods such as a control group demonstrates the risk of inconclusiveness and invalidity of findings with regard to duplex effectiveness. The inclusion of a small sample size comprising of only elderly males admitted in an Indian hospital further contributes to limitations in terms of applicability and transferability to other patient groups [34], [43].

3.3.6. Article 6

The cross sectional, comparative study by Hiremath et al. [35] aimed to validate the feasibility of a diagnostic scoring system for PAD in the lower limbs based on Doppler

sonographic features of duplex assessment across patients with diabetes and smokers. A total of 106 patients with suspected symptoms of PAD were categorized across three groups: those who smoked, those with diabetes and those with diabetes who smoked. The patients were examined clinically and depending on severity of PAD, a scoring system was developed, according to which they were grouped as ’severe’, ‘moderate’ and ‘mild’ailing. The participants were then assessed by duplex ultrasound, based on the findings of which they are grouped as having, ‘severe illness’, ‘moderate illness’ or ‘mild illness’. To evaluate the agreement between the two scoring systems, the Cohen kappa value was used [35]. A kappa value of 0.83 was demonstrated by the inter-observer agreement between the duplex scoring system and traditionally used Rutherford clinical scoring for PAD, hence demonstrating the prevalence of significance of agreement ($p < 0.001$). Its relevance to existing standardized systems of scoring, as per the findings of this study, thus demonstrates that duplex imaging procedures are a clinical effective way in which the PAD in the lower limbs can be diagnosed as well as graded and staged based on clinical severity [35]. However, a number of limitations identified in this study demonstrate the need to further validate duplex assessment in future research. These were: the absence of arteriography or angiography procedures such as MRI or CT scans to substantiate the findings, the small sample size of participants, lack of evaluating variability in observations and absence of follow up assessments due to the cross sectional design of the study [35].

3.3.7. Article 7

The cross sectional, comparative study by Gamal El Dein et al. [36] aimed to assess the effectiveness of duplex ultrasonography as compared to multi-detector computed tomography angiography (MDCT) for the assessment of ischemia in the lower limbs. Participants comprised of 54 patients (30 males and 24 females, aged 33 to 75 years) who visited the radiology department for assessment of lower limb, chronic ischemic disease, using MDCT. They had also duplex ultrasonography assessment to correlate the findings. In terms of comparing between MDCT and duplex ultrasonography, the kappa agreement for assessment of the external iliac artery was 0.87, for the common femoral artery was 0.88, for the superficial femoral artery was 0.82, 0.76 and 0.86 for the upper, middle and lower

third, for the popliteal artery was 0.87, for the peroneal artery was 0.88, for the posterior tibial artery 0.93 and for the anterior tibial artery 0.88 ($p< 0.001$)[36]. These findings demonstrate significance in terms of agreement and reliability of duplex ultrasonography with MDCT, thus implying accuracy in diagnosis. However, the lack of follow up assessments due to cross sectional design as well as the implementation of research across a small sample size of only Egyptians demonstrate limitations in terms of reliability, transferability and applicability [36], [44].

3.3.8. Article 8

A retrospective cohort study was conducted by Janssen et al. [37] among 124 patients with chronic limb-threatening ischemia (CLI) to determine whether duplex ultrasound (DUS) and physical examination results could be used to help predict the best degree of lower limb amputation in CLI patients. The mean age of the patients was 70 years, and 67% were male. Out of the 124 patients, 120 had unilateral amputation, 2 had bilateral amputation during the same treatment, and 54% had below-knee amputation (BKA). There was no significant impact of demographic characteristics and comorbidity on revision, conversion or reoperation rates. Thirty-nine reoperations were carried out, out of which 17 stump revisions were performed and 22 conversions were amputated from below to above the knee. In this study, three major findings were reported by the authors. Firstly, a difference was observed in 25 percent for the femoral artery and 34 percent for the popliteal artery between physical examination results and DUS. Secondly, with more proximal occlusions on DUS, reoperation and conversion rates increased. Thirdly, no significant effect on conversion or reoperation rates of patient characteristics or comorbidities was found. This study demonstrated that physical examination results are inaccurate, while DUS findings have been shown to be useful in assessing the extent of lower CLI extremity amputation. Patients with aortoiliac trajectory occlusion or deep femoral artery on DUS can benefit from primary above-knee amputation (AKA) on the basis of the results of this study. Finally, the authors concluded that as compared to DUS test findings, results from physical analysis of the femoral and popliteal pulsations are inaccurate. Due to the retrospective nature of the study, it was not possible to collect data on each variable for all patients in this study [37].

3.3.9. Article 9

A study was performed by Martinelli et al. [38] among 94 patients with peripheral arterial disease (PAD) to evaluate the duplex sonography (DUS) diagnostic accuracy compared to computed tomography angiography (CTA) in PAD occlusion and stenosis detection in candidate patients with intraprocedural digital subtraction angiography (DSA) for endovascular revascularization. The agreement between findings of CTA and DUS using DSA as a reference modality was expressed as a statistical agreement of Cohen's kappa (κ). The mean age of the patients was 68.2 years, and 64.2% were male. Among the 94 patients, 30 patients had tissue loss or gangrene (Fontaine's classification (FC) stage 4), 46 patients had rest pain (FC stage 3) and 18 patients complained of disabling intermittent claudication (FC stage 2B). The findings indicate that when assessed against DSA, DUS was less effective than CTA in measuring iliac arterial diseases (Cohen's κ agreement of 0.91 and 1.0, respectively). In the detection of hemodynamic stenosis and femoro-popliteal axis occlusion, the authors found strong diagnostic concordance between DUS and DSA (Cohen's κ agreement between 0.96 and 0.93).CTA showed much less concordance with DSA below the knee (Cohen's κ 0.75). Finally, the authors concluded that in testing PAD, DUS has proved to have high diagnostic precision. A primary benefit of ultrasound testing methods is that it offers Doppler measurements and generates arterial disease images simultaneously to estimate the quality of inflow and outflow and the degree of stenosis. Also, the lack of a panoramic view, high interobserver variability and operator-interpretation dependency at the various lower-limb levels are the main limitations of DUS [38].

3.3.10. Article 10

A review by Varaki et al. [31] evaluated the available diagnostic methods for peripheral arterial disease (PAD), deep vein thrombosis (DVT) and chronic venous insufficiency (CVI) with a focus on non-invasive modalities. The authors critically evaluated each method in terms of ease of use, accuracy, specificity, sensitivity, procedural time duration and training criteria. The authors demonstrated that to detect both venous and arterial disorders, including deep vein thrombosis, chronic venous insufficiency and occlusions, plethysmographic methods are most useful. Plethysmography devices, however, are bulky and require limitations on their use by a highly qualified practitioner. It also takes a significant amount of time to complete the evaluation

of plethysmography, and usually lacks the ability to localize the occlusion/stenosis site. Details about the location of vascular dysfunction can be given by Doppler techniques. Duplex ultrasound is the gold standard approach for the diagnosis of peripheral vascular disease (PVD) and is currently the most sensitive non-invasive procedure. Similar to plethysmographic methods, however, highly skilled practitioners and expensive equipment are required. Doppler vascular evaluation also takes much longer than plethysmography. As such, for PVD screening or regular use in the clinic, plethysmography and Doppler techniques have limited use [31].

3.3.11. Article 11

A study by Normahani et al. [39] assessed the association between vessel wall calcification severity, number of vessels at the ankle of the patient, features of the arterial spectral waveform, as evaluated on a centred ankle Duplex ultrasound (DUS) and 12-month healing in a cohort of patients who had conservatively treated their diabetic foot ulcers. The study included scans conducted on 50 limbs in 48 patients. For 12 months, patient health records were prospectively checked to determine the outcome of ulcer healing. As noted by the trend towards statistical significance, the authors found that the number of waveform components, peak systolic velocity, systolic rise time and long forward flow, as well as the number of patent vessels at the ankle on DUS, can be useful independent predictors of healing [39].

3.4. Summary

This chapter provides an extensive array of information concerning the key findings which were obtained from each of the articles used for the systematic review. In addition to discussing the relevance of the findings according to the objectives of this research, this chapter also provides an overview of the key results and methodological limitations which were observed in each of the selected articles. Such findings proved to be useful in conducting a thematic analysis using a critical discussion of other existing research, which have been discussed in the succeeding chapters [45].

Chapter 4: Discussion

4.1. Introduction

For the purpose of drawing relevant conclusions according to the objectives and aims of a research, the implementation of thematic analysis proves to be beneficial [30]. In this respect, the following chapter will provide an extensive overview of the major themes which emerged, indicative of the clinical application of duplex scanning in the assessment of patients with lower limb atherosclerotic disease, as per the findings of the selected articles discussed in the previous chapter. In doing so, the key themes of this chapter proved to be useful in determining conclusions and recommendations for future evidence based research regarding this clinical topic [46].

4.2. Key Themes as per Article Findings

4.2.1. Continued Care when Combined with Physiological Screening

One of the key themes which emerged pertaining to the clinical effectiveness and advantages of duplex scanning for assessing patients with lower limb atherosclerotic disease, is its efficiency in regulating long term PAD care management when combined with physiological assessments like blood pressure screening [29]–[31], [38]. Such findings were extensively demonstrated in the qualitative study by Hodgkiss-Harlow and Bandyk [29] aimed to provide a comprehensive overview of the clinical application of arterial duplex testing for the purpose of detecting and interpreting aneurysmal disease outcomes and prevalence of occlusive arterial symptoms in the lower limbs. Non-invasive screening methods such as duplex scanning and Doppler assessments are associated with the use of ultrasonography to screen the nature of hemodynamic function or circulation of blood in the lower limbs blood vessels [30]. This feature of duplex scanning makes this screening method an effective option for early detection of even

minute lesions, occlusions or aneurysms within the lower limb blood vessels – key risk factors for PAD which often go undetected when using traditional radiological assessments such as arteriogram and computed tomography (CT) [29]. Additionally, arteriograms and CT scans are useful in detecting the prevalence of lower limb occlusions, although cannot assess the hemodynamics of blood circulation in the lower extremities, such as rate of blood flow or blood velocity across arteries – which are equally essential parameters and far more sensitive biomarkers or lower limb atherosclerotic disease [29]. When combined with colour scanning methods as well as physiological assessments such as blood pressure screening, duplex scanning methods have the potential to create an arterial map – a detailed colour coded image demonstrating the various aneurysmal and occlusive lesions prevalent in the lower limbs of patients with atherosclerotic disease [29]. The efficiency of such PAD-associated assessments can further be enhanced with the inclusion of specific screening such as ankle-brachial systolic pressure. The latter reflects blood flow rate in the lower extremities, as demonstrated in the review by Amrstrong, Carroll and Bandyk [30], which narratively discusses the clinical advantages of duplex in assessing patients for lower limb atherosclerotic disease. If not detected and managed in a timely manner, lower limb atherosclerotic disease like PAD is associated with a range of complications such as pain, swelling, impaired mobility, possible limb loss or the risk of thromboembolism in organs such as brain or lungs, thus resulting in long term hindrances to wellbeing and quality time [47]. Such advantages of duplex assessment over CT are useful in terms of timely detection, management and prevention of adverse consequences associated with lower limb atherosclerotic disease such as PAD. This in turn, implies that the integration of duplex scanning based assessments in continued care management of lower limb atherosclerotic disease has the potential to enhance the quality of life and wellbeing for such patients [29], [30].

An additional advantage of the clinical application of duplex assessments in lower limb atherosclerotic disease is its ability to conduct effective surveillance and follow up of patients demonstrating progression of the disease despite undergoing arterial and endovascular bypass procedures [30]. While invasive coronary angiography (ICA) has been considered the gold standard for assessing the risk of graft-related occlusions in patients with bypass surgery, the technique is expensive as well as risky due to its invasive nature to the potential risk of disrupting cardiac motion [48]. However, non-invasive techniques such as duplex scanning, due to its efficient hemodynamic screening, relatively feasible application and lack of invasiveness

has been evidenced to be useful as routine, bed side care strategy for such patients who are at risk of experiencing arterial narrowing or stenosis after complex cardiovascular surgery [29], [30]. Thus, as per such findings, duplex assessments in combination with the examination of specific blood pressure measures, enhance the clinical assessment and evaluation of stenosis severity in the lower limbs of patients with PAD, by providing a detailed imaging of the physiology and anatomy of arteries across patients both with and without risk factors of lower limb atherosclerotic disease [29], [30].

4.2.2. Cost-effectiveness and Clinical Feasibility

One of the major advantages which has recently emerged in existing research concerning the clinical application of duplex scanning for assessing patients with lower limb atherosclerotic disease, is the cost effectiveness, safety and feasibility associated with this screening method [29], [30], [33]. Till date, radiological and invasive procedures, such as CT scans or ICA have been regarded as the gold standards of assessing the prevalence of lower limb atherosclerotic disease. However, radiological procedures such as CT scans may be associated with symptoms like diarrhea, constipation, vomiting, nausea and cramps in the abdomen for at-risk populations like the elderly, women who are pregnant and children [49]. Furthermore, the use of radiation - X-rays may also render CT scans to be a risky option for patients demonstrating abnormal tissue growth, such as in the case of cancer. As mentioned previously, additional invasive assessment procedures like ICA may also impair cardiac motion and vascular damage, which in turn, may pave the way for cardiac injury or adverse health consequences for individuals undergoing bypass grafting [43]. Patients undergoing an ICA may also be prone to bleeding in the region of insertion and may experience cardiac arrhythmia [50]. Due to the use of ultrasonography technology, duplex assessment is devoid of the risks associated with invasive, radiological procedures, thus making it a safer option for assessing lower limb atherosclerotic disease in patients. The portable nature of equipment further enhances the feasibility of duplex assessment thus making it easier to be included in routine bedside assessments, which would not be possible with the techniques considered as gold standard [29], [30].Moreover, as mentioned previously, the effectiveness of traditional PAD assessment methods lie in their ability to detect endothelial

occlusions and lesions after injury – which may not facilitate timely clinical management of adverse consequences of lower limb atherosclerotic disease. Duplex colour scanning, when combined with blood pressure assessments have the potential to detect even minute changes in the circulation and flow rate of blood in blood vessels, making it a more sensitive and clinically feasible option for the timely detection and management of lower limb atherosclerotic disease [29], [30], [33].

However, despite such advantages, duplex assessments continue not to be regarded as the first line method in detecting lower limb atherosclerotic disease in patients. Since limited research has been conducted concerning this issue, there currently lays insufficient evidence regarding the key technical or clinical issues which may be associated with the limitations of duplex scanning procedures. Nevertheless, as per limited recent research, a key limitation associated with the clinical application of duplex methods is its relatively time consuming nature since combining it in routine PAD care management will comprise of multiple and repeated combined sessions of ultrasonography, colour scanning as well as lower limb blood pressure assessments [51]. Further, due to its relatively recent emergence as a potentially beneficial screening method, healthcare professionals may lack knowledge or find its use and application in lower limb atherosclerotic care management as difficult [35]. Another limitation is general demonstration of resistance towards change practices associated with the inclusion of duplex scanning as a standardized and routine procedure for lower limb atherosclerotic management, since healthcare organizations have continued to rely on traditional scanning techniques like CT and ICA for many years [36]. However, due to limited existence of current research, the scope of this systematic review in exploring possible solutions to such limitations was also restrictive. Nevertheless, one of the key solutions which have been evidenced to be useful in adequate management of such limitations is the implementation of comprehensive training sessions [32]. Educational and training sessions implemented in healthcare organizations can be useful in managing doubt as well as improving skills in staff concerning the effective clinical application of duplex ultrasonography. The effectiveness of such training sessions can be enhanced if, in addition to educating on recent research on duplex effectiveness, healthcare organizations also provide staff the opportunity to share feedback concerning their difficulties [52]. This will be useful in directing staff training using a need based approach, resulting in greater levels of staff motivation, efficiency and compliance towards the clinical application of duplex assessments. In

criticism, however, it must be noted that continuous training and staff assessments can be prone to higher organizational expenditures, thus defeating the previously identified cost effectiveness of the clinical application of duplex assessments [53]. It also must be noted that the cost associated with the training sessions coupled with staff feedback, needs assessment and performance monitoring, although it is outweighed by the benefits which healthcare organizations are likely to experience in the long run. For example, improved efficiency and confidence of duplex application, reduced likelihood of errors, timely detection and management of lower limb atherosclerotic disease in at-risk patients, reduced expenditures and increased patient satisfaction associated with management of adverse consequences of PAD prognosis, as well as overall improvement in long term wellbeing, health and quality of life patients [54]. In criticism, simply training sessions may not be enough to ensure long term change in PAD care practice – it is suggested that alterations in healthcare policies, standardized treatment plans and grading measures, by both healthcare organizations, international organizations as well as the government, can also be useful for the purpose of initiating long term clinical application of duplex scanning for lower limb atherosclerotic disease [55].

4.2.3. Effective Stenosis Screening for CAD

An additional key theme of benefits associated with the clinical application of duplex scanning in the assessment of lower limb atherosclerosis disease is its ability to accurately and specifically locate regions of stenosis as well as disrupted blood circulation across patients with CAD [32], [33]. Such findings were demonstrated in the cross sectional study by Bhaduri et al. [32]which aimed to assess the pattern and prevalence of PAD in the lower limbs of patients with a diagnosis of coronary artery disease (CAD) using duplex ultrasonography scanning methods. Based on evaluation using duplex ultrasonography, approximately 90% of patients were found to be free from any clinical symptoms of PAD. However, prevalence of non-critical and critical stenosis across one or multiple arterial segments of the lower limbs was found to be 0.5% and 5.2%, out of the total group of patients. A lack of statistically significant correlation was observed between CAD severity and PAD occurrence. Thus, the findings of this study proved to be useful in demonstrating the effectiveness associated with the clinical application of duplex in

assessing the prevalence of lower limb atherosclerotic disease [32]. As per the findings underlying this theme, it can be implied that the application of duplex ultrasonography will be useful in encouraging timely care assessment and long term health and wellbeing for patients. CAD has been associated with an increased risk of stenosis, occlusions and lesions in the lower limb blood vessels resulting in PAD and the need for continued care and screening which can be provided by the inclusion of routine duplex based screening [32].

Additionally, the effectiveness of duplex scanning in stenosis risk assessment may also be demonstrated for patients at risk of CAD, lower limb atherosclerotic diseases, peripheral vascular insufficiency (PVI), and patients with additional risks such as smoking, alcohol intake and old age [34]. Such findings were obtained in the cross sectional observational study by Panda et al. aimed to evaluate the prevalence of PAD in the lower limb across clinical suspected patients diagnosed with peripheral vascular insufficiency (PVI) using a duplex colour Doppler [34]. Participants were assessed using B-Mode and Doppler for contour and thickness of blood vessels, pattern and direction of blood flow, pulsation and associated lesions such as abscess, plaques, calcification, aneurysm and stenosis. Based on the findings, the prevalence of complete occlusion was observed in 38% whereas the prevalence of partial (49%) occlusion was observed in 30% of the recruited patients. In addition, based on duplex assessment, the prevalence of intermittent claudication was observed in 60% of the patients, 75% was prevalent in the femoropopliteal segment whereas 25% was observed in the infrapopliteal and iliac segments. The diagnosis of PAD based on duplex colour Doppler demonstrated a specificity and sensitivity of 96% and 92% respectively. Further, a Pulsatility Index ratio of less than 4 demonstrated the prevalence of stenosis in 80% of the patients [34]. Thus, based on these findings, it can be stated that duplex assessment is a clinical effective method by which the prevalence of atherosclerotic disease in the lower limbs can be evaluated. This is due to the ability of duplex methods, using colour Doppler mechanisms, to effectively detect the site as well as the extent of stenosis of the lower limb [34]. Hence, as per this theme, the long term care and management of patients at risk of lower limb stenosis and atherosclerotic disease, such as those with CAD, PVI and additional risks like old age, alcohol intake and smoking, can be improved via non-invasive techniques like duplex scanning, due to its ability to comprehensively evaluate the hemodynamic status of patients using circulatory details like Peak Systolic Velocity as well as waveforms of blood flow [32], [34].

4.2.4. Safe Screening for Diabetics

Another key theme underlying the clinical effectiveness of duplex scanning is its safety in PAD or lower limb atherosclerotic disease assessment for patients with diabetes [33]. Such findings were extensively demonstrated in the cross sectional study, by authors Das et al.[33], which aimed to examine the value of duplex ultrasound in evaluating the status of diabetes patients suspected with atherosclerotic disease in the lower limbs. Based on the findings, narrowing of the lumen of the dorsalis pedis artery demonstrated the highest prevalence across patients (41% and 36% across the left and right sides) followed by prevalence of atherosclerotic plaques across the femoral artery (44%). Out of the fifty plaques observed, twenty eight demonstrated the prevalence of calcification. The prevalence of low peripheral resistance indicative of distal ischemia was estimated to be 25.5% in the dorsalis pedis artery, 23% in the anterior tibial artery and 21.5% in the posterior tibial artery [33]. Thus, as per these findings, it can be implied that duplex ultrasound is an effective and safe method for the assessment of lesions and plaques across the lower limb blood vessels which can be visualized in a cost effective and non-invasive manner across patients with diabetes [33]. The prevalence of diabetes is one of the key risk factors of lower limb atherosclerotic disease in individuals. This is because impairment in glucose and lipid metabolism, as a result of diabetes, often increases the risk of excess free fatty acids circulation, resulting in increased likelihood of endothelial fatty streak deposition, plague formation, thromboembolism and PAD [56]. Additionally, due to the damaging effects of uncontrollable hyperglycaemia, individuals with diabetes are often prone to a range of chronic risk factors such as delayed wound healing, excessive bleeding and diabetic nephropathy. Such risk factors are a concerning issue in patients with both diabetes and lower limb atherosclerosis disease. This is because it has been evidenced that the contrast dye injected during implementation of CT scanning methods, may cause kidney damage, aggravating the risk of diabetic nephropathy in patients with both diabetes and lower limb atherosclerotic disease [57]. Additionally, as discussed previously, invasive procedures such as ICA are often associated with a range of complications such as: excessive bleeding which in turn may result in delayed wound healing and ulcers in diabetic patients with lower limb atherosclerotic disease. Consequently, it can be implied that one of the key advantages associated with the clinical application of duplex assessment, due to its non-invasive, non-radiological nature, is to

encourage safe and effective assessment of PAD, free of the risks associated with diabetes [58]. Thus, in addition to patients undergoing bypass grafting, the clinical application of duplex assessment is also associated with timely, effective and safe screening and management of lower limb atherosclerotic disease and improved health, wellbeing, quality of life and positive healthcare outcome for patients with risk factors like diabetes [33].

4.2.5. Effective Grading and Staging

Another possible advantage of the clinical application of duplex assessment for patients with lower limb atherosclerotic disease is its ability to diagnose stage and grade PAD [35]. Such findings were demonstrated in cross sectional, comparative study by Hiremath et al. [35] aimed to validate the feasibility of a diagnostic scoring system for PAD in the lower limbs based on the Doppler sonographic features of duplex assessment across diabetic patients and smokers. A kappa value of 0.83 was demonstrated by the inter-observer agreement between the duplex scoring system and traditionally used Rutherford clinical scoring for PAD, hence demonstrating the prevalence of significance of agreement ($p < 0.001$). Its relevance to existing standardized systems of scoring, as per the findings of this study, demonstrates that duplex imaging procedures are a clinical effective way in which PAD in the lower limbs can be diagnosed as well as graded and staged based on clinical severity [35]. A prevalent reason for limited use of duplex assessment is the absence of grades or standards based on which, its findings can be categorized to diagnose PAD in patients based on severity. However, according to these findings, the results obtained from duplex scanning have the potential to be replicated into traditionally used scoring mechanisms, rendering it to be a convenient technique by which, not just the presence but also the severity of lower limb atherosclerotic disease can be understood in patients at risk of the same [59]. Such ease in grading and scaling render duplex scanning as an effective method by which at-risk patients can be kept informed regarding the state and progression of their disease, resulting in delivery of high quality, patient centred treatments [35].

4.2.6. Comparative Effectiveness with CT

An essential theme which emerged as an indicator of the effectiveness associated with clinical application of duplex scanning for assessing patients with lower limb atherosclerotic disease is its ability to be at par with other gold standard PAD assessment techniques, such as, multi-detector computed tomography angiography (MDCT) [36]. Such findings were obtained from the cross sectional, comparative study by Gamal El Dein et al. [36] which aimed to assess the effectiveness of duplex ultrasonography as compared to multi-detector computed tomography angiography (MDCT) for the assessment of ischemia in the lower limbs. In terms of comparing between MDCT and duplex ultrasonography, the kappa agreement for assessment of the external iliac artery was 0.87, for the common femoral artery was 0.88, for the superficial femoral artery was 0.82, 0.76 and 0.86 for the upper, middle and lower third, for the popliteal artery was 0.87, for the peroneal artery was 0.88, for the posterior tibial artery 0.93 and for the anterior tibial artery 0.88 ($p< 0.001$) [36]. Such findings demonstrate significance in terms of agreement and reliability of duplex ultrasonography with MDCT, thus implying the prevalence of accuracy in diagnosis [36]. One of the key reasons which contribute to avoidance of duplex assessment use across healthcare organizations is the perception that it will not be as effective as gold standard or traditional techniques such as MDCT. However, such findings not only demonstrate the fact that duplex assessments can be effective as MDCT but also serve as a guide by which, healthcare professionals can be educated on the use of this method as a part of effective, safe and routine care PAD management. There is, however, a need to conduct further research on comparative effectiveness of duplex scanning and prevalent invasive techniques like ICA [50], [36].

4.2.7. Predict the Best Level of Lower Limb Amputation

Lower limb amputations have a large impact on patients' quality of life because of loss of mobility. A retrospective cohort study was conducted by Janssen et al. [37] to determine whether duplex ultrasound (DUS) and physical examination results could be used to help predict the best degree of lower limb amputation in CLI patients. Out of 124 patients, 120 had unilateral amputation, 2 had bilateral amputation during the same treatment, and 54% had below-knee amputation (BKA).There was no significant impact of demographic characteristics and co

morbidity on revision, conversion or reoperation rates. Thirty-nine reoperations were carried out, out of which 17 stump revisions were performed and 22 conversions were amputated from below to above the knee. In this study, three major findings were reported by the authors. Firstly, a difference was observed in 25 percent for the femoral artery and 34 percent for the popliteal artery between physical examination results and DUS. Secondly, with more proximal occlusions on DUS, reoperation and conversion rates increased. Thirdly, no significant effect on conversion or reoperation rates of patient characteristics or co morbidities was found. This study demonstrated that physical examination results are inaccurate, while DUS findings have been shown to be useful in assessing the extent of lower CLI extremity amputation. Patients with aortoiliac trajectory occlusion or deep femoral artery on DUS can benefit from primary above-knee amputation (AKA) on the basis of the results of this study [37]. In patients with PAD and CLI, DUS was shown to have high sensitivity and specificity: a median sensitivity of 92 percent and a specificity of 96 percent were found for the aortoiliac trajectory. In addition, 89 percent of all patients have shown that the recommendations for surgical intervention based on DUS alone are right. It was therefore proposed that DUS could be used as a single preoperative imaging procedure for aortoiliac trajectory occlusive vascular disease [60].

4.2.8. DUS versus CT angiography (CTA)

For assessing the lower-extremity arterial system, DUS is an extremely reliable non-invasive imaging tool. Without resorting to more invasive and expensive approaches such as CTA, it may be regarded as a pre-interventional diagnostic modality of PAD [61]. A study by Martinelli et al. [38] evaluated the duplex sonography (DUS) diagnostic accuracy compared to computed tomography angiography (CTA) in PAD occlusion and stenosis detection in candidate patients with intraprocedural digital subtraction angiography (DSA) for endovascular revascularization. The agreement between findings of CTA and DUS using DSA as a reference modality was expressed as a statistical agreement of Cohen's kappa (κ). The mean age of the patients was 68.2 years, and 64.2% were male. Among the 94 patients, 30 patients had tissue loss or gangrene (Fontaine’s classification (FC) stage 4), 46 patients had rest pain (FC stage 3) and 18 patients complained of disabling intermittent claudication (FC stage 2B). The findings indicate that when assessed against DSA, DUS was less effective than CTA in measuring iliac arterial

diseases (Cohen's κ agreement of 0.91 and 1.0, respectively). In the detection of hemodynamic stenosis and femoro-popliteal axis occlusion, the authors found strong diagnostic concordance between DUS and DSA (Cohen's κ agreement between 0.96 and 0.93).CTA showed much less concordance with DSA below the knee (Cohen's κ 0.75). Finally, the authors concluded that in testing PAD, DUS has proved to have high diagnostic precision [38]. Recently, Wong et al. confirmed that DUS is accurate enough to guide the initial clinical management of patients with PAD [62].

4.2.9. Emerging non‑invasive diagnostic methods

The available diagnostic methods for peripheral arterial disease (PAD), deep vein thrombosis (DVT) and chronic venous insufficiency (CVI) with a focus on non-invasive modalities were evaluated by Varaki et al.[31]. The authors critically evaluated each method in terms of ease of use, accuracy, specificity, sensitivity, time duration for procedure and where appropriate, training criteria. The authors demonstrated that to detect both venous and arterial disorders, including deep vein thrombosis, chronic venous insufficiency and occlusions, plethysmographic methods are most useful. Plethysmography device, however, are bulky and require limitations on their use by a highly qualified practitioner. It also takes a significant amount of time to complete the evaluation of plethysmography, and usually lacks the ability to localize the occlusion/stenosis site. Details about the location of vascular dysfunction can be given by Doppler techniques. Duplex ultrasound is the gold standard approach for the diagnosis of peripheral vascular disease (PVD) and is currently the most sensitive non-invasive procedure. Similar to plethysmographic methods, however, highly skilled practitioners and expensive equipment are important. Doppler vascular evaluation also takes much longer than plethysmography [31].Despite attempts to create an optimal non-invasive diagnostic tool for PVDs, underdiagnosis in primary care remains an ongoing issue, requiring the development of new unobtrusive screening techniques[63].

4.2.10. Arterial spectral waveform analysis

The association between vessel wall calcification severity, number of vessels at the ankle of the patient, features of the arterial spectral waveform, as evaluated on a centred ankle Duplex ultrasound (DUS) and 12-month healing in a cohort of patients who had conservatively treated their diabetic foot ulcers were assessed by Normahani et al. [39]. The study included scans conducted on 50 limbs in 48 patients. For 12 months, patient health records were prospectively checked to determine the outcome of ulcer healing. As noted by the trend towards statistical significance, the authors found that the number of waveform components, peak systolic velocity, systolic rise time and long forward flow as well as the number of patent vessels at the ankle on DUS, can be useful independent predictors of healing [39].There is also evidence that careful wound treatment, including daily debridement, dressing and offloading, are also major predictors of healing [39].

4.3. Summary

This chapter proved to be useful in obtaining themes which were relevant to the objectives previously outlined in this research. Such themes demonstrate several aspects underlying the clinical application of duplex scanning assessment in patients with lower limb atherosclerotic disease, such as its effectiveness, feasibility, possible limitations and mitigation strategies and its ability to match the efficiency demonstrated by additional screening technologies regarded traditionally as ‘gold standard’ for PAD screening. Such findings were useful in drawing key conclusions and making recommendations for future research and clinical practice regarding this clinical issue, which have been discussed in the succeeding chapter.

Chapter 5: Conclusion and Recommendations

5.1. Conclusion

As per the findings and themes obtained after the systematic review of the articles, it can be observed that the clinical application of duplex scanning for lower limb atherosclerotic disease assessment is associated with several advantages. These include: patient safety and clinical feasibility due to its non-invasive and cost effective nature; efficiency in timely determination in management of the PAD when combined with physiological assessments; ability to administer safe screening in patients with diabetes; ability to effectively determine the severity of lower limb CAD using specific stenosis screening; ease in associating findings with standardized grading techniques as well as ability to be at par with traditional arteriogram techniques like CT. Furthermore, despite the limited evidence, some of the key disadvantages associated with clinical application of duplex scanning are: time consuming nature; limited knowledge of healthcare professionals concerning its effective application and advantages as well as prevalence of organizational resistance to change due to limited knowledge or preference towards traditional screening techniques. To conclude, according to these findings, the clinical application of duplex scanning is effective for the assessment of patients with lower limb atherosclerotic disease if implemented considering some of its possible limitations.

5.2. Future Recommendations

Based on the findings, it is recommended that healthcare organizations integrate the clinical application of duplex scanning as a part of routine and follow up assessment for patients with lower limb atherosclerotic disease as well as for patients with risk factors such as old age, diabetes, CAD, smoking and alcohol consumption. In doing so, healthcare professionals and

organizations are likely to pave the way for timely detection of patients in risk of PAD resulting in improved healthcare management, positive health outcome, prevention of adverse PAD consequences, prevention of extensive medical expenditures for patients, families and organizations, improved patient trust and recovery and lastly, overall improvement in patient satisfaction and quality of healthcare services. Additionally, prior to its implementation, it is recommended that healthcare organizations obtain both subjective and objective feedback from staff, so as to develop a comprehensive training plan for effective duplex application compliant with the needs of the workforce. This will ensure improved staff compliance and time management as well as reduced likelihood of errors. It is further recommended that public health and governmental organizations develop improved healthcare policies for PAD management that include duplex application, so as to encourage practice and acceptance across healthcare organizations. Last recommendation would be for researchers to conduct further evaluation concerning the effectiveness of duplex application so as to comprehensively compare its advantages with gold standard methods like arteriogram.

5.3. Strengths and Limitations

Despite the comprehensive nature of these findings, this research project was also prone to several limitations which must be taken into consideration. It is worthwhile to note that the key data collection and data analysis methods adopted by this research were based on systematically reviewing existing research using a narrative approach. While such a form of unstructured, narrative approach proved to be useful in providing a broad exploration of the clinical application of the duplex scanning, the lack of any form of statistical analysis using meta-analysis or confidence intervals is indicative of limited precision of the suggested strategies [42]. Additionally, systematic reviews are often prone to publication bias and inclusion of inconclusive studies [38]. While critical appraisal tools were used to assess the validity of the findings, it was difficult to include studies of exceptionally high quality and validity due to dearth of recent research conducted concerning this issue [25]. Furthermore, several issues concerning the validity, reliability and applicability in methods and findings of the selected studies were also identified. For instance, three studies [29]–[31], despite adopting a narrative

approach of reviewed findings, demonstrated little insights into their methodological and analytical framework, raising concerns of issues in reliability. Moreover, most of the studies included in this systematic review relied upon the use of cross sectional or comparative studies designed with limited follow ups or any form of randomizations which could have been useful in determining a cause-effect relationship between duplex scanning and effective screening of lower limb atherosclerotic disease in patients. A number of studies were also specific to developing countries or inclusive of participants with specific characteristics, such as old age, diabetes or chronic illnesses, demonstrating issues in terms of applicability, generalizability and transferability of the findings. The scarcity of recent evidence concerning the clinical topic, also made it difficult to produce comprehensive findings on the key limitations associated with currently restrictive practice of duplex as well as ways in which the same can be mitigated [32]–[39]. Nevertheless, it is worthwhile to note that despite such limitations, this current research demonstrated the effectiveness of duplex ultrasonography in lower limb atherosclerotic disease, which will help clinicians in decision making in patients with lower limb atherosclerotic disease. The key limitations and issues identified by this paper in existing research is useful in paving the way for future studies with more robust methodologies and data evaluation frameworks. The key benefits and aspects identified by this research concerning the clinical application of duplex scanning also prove to be useful in guiding future researchers on implementing further analysis regarding the advantages of duplex screening in lower limb atherosclerotic disease compared to other traditionally used techniques. The benefits, challenges and possible management requirements associated with the clinical application of duplex scanning in PAD assessment as discussed in this research, also demonstrate future implications They might manifest in the form of guiding healthcare professionals and healthcare organizations on the importance of, as well as the impact of, barriers and improvement solutions associated with implementation of this practice in routine atherosclerotic disease management.

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Appendices

Table 1: Search Strategy for Article Selection (as per Google Scholar)

Search Terms	Search Results
application AND duplex scanning AND effectiveness OR efficiency OR advantages AND lower limb atherosclerosis OR peripheral arterial disease	15,800
application AND duplex scanning AND effectiveness OR efficiency OR advantages AND lower limb atherosclerosis OR peripheral arterial disease (Limiters: Publication: 2013 to 2020)	6,190
application AND duplex scanning AND effectiveness OR efficiency OR advantages AND lower limb atherosclerosis OR peripheral arterial disease (Limiters: Publication: Last 5 years)	3,480

Table 2: Data Extraction of Selected Articles

Authors	Research Aim	Study Design	Participants	Results
Hodgkiss-Harlow and Bandyk[29]	To provide a comprehensive overview of the clinical application of arterial duplex testing for the purpose of detecting and interpreting aneurysmal disease outcomes and prevalence of occlusive arterial symptoms in the lower limbs.	Unclear, possibly scoping/narrative review	Unclear	Duplex testing procedures have the potential to enable clinical practice and care for lower limb atherosclerotic disease by providing a comprehensive, prognosis and severity of existing occlusive symptoms. However, the effectiveness of duplex testing in the management of lower limb atherosclerotic disease can be enhanced via undertaking blood pressure monitoring of the affected region. This is in turn, as researched by the authors, allow efficient

				categorization of the severity of functional impairment and hemodynamics of the arteries. Such procedures when supplemented by colour scanning paves the way for the development of a comprehensive arterial map of the various aneurysmal and occlusive lesions prevalent in the lower limbs of patients with atherosclerotic disease. Additional advantages of arterial duplex testing is its ability to provide accurately detect stenosis both prior to and after treatments like peripheral angioplasty or bypass grafting. Such advantages allow duplex testing methods to produce a timely diagnosis of the risk of thrombosis during arterial repair treatments following stenosis thus allowing for maintenance of long term positive health outcomes across with lower limb atherosclerotic disease.
Armstrong et al., [30]	To discuss the clinical advantages of duplex in assessing patients	Unclear, possibly scoping/narrative review	Unclear	By providing a detailed imaging of the physiology and anatomy of arteries

	for lower limb atherosclerotic disease.			across patients both with and without symptoms, duplex assessments enhance the clinical assessment and evaluation of stenosis severity in the lower limbs of patients with PAD. Integrating pulsed Doppler spectral analysis within duplex assessments further assist in determining the hemodynamics of arteries of the lower limbs with suspected occlusion. Such findings in conjunction with the physiological assessments like monitoring of ankle-brachial systolic pressure provides a cost effective, non-invasive measurement of PAD severity of the lower limbs which can be implemented at the bedside and used for timely disease management. Such advantages thus imply the potential of duplex assessment to conduct effective surveillance and follow up of patients demonstrating progression of disease despite undergoing arterial and endovascular bypass procedures.
Bhaduri et al.	To assess the	Cross sectional	For the study, a	Based on evaluation

[32]	pattern and prevalence of PAD in the lower limbs of patients with a diagnosis of coronary artery disease (CAD) using duplex ultrasonography scanning methods.	study	total of 210 patients who were admitted with CAD in the cardiology department of a Bangladeshi hospital, as evidenced by a diagnosis using coronary catheter angiography were recruited, with an average age of 51.3±10.4 years. Out of this group, 14 (6.7%) and 196 (93.3%) were female and male.	using duplex ultrasonography, approximately 90% of patients were found to be free from any clinical symptoms of PAD. However, prevalence of non-critical and critical stenosis across one or multiple arterial segments of the lower limbs, was found to be 0.5% and 5.2%, out of the total group of patients. A lack of statistically significant correlation was observed between CAD severity and PAD occurrence.
Das et al[33]	To evaluate the value of duplex ultrasound in evaluating the status of diabetes patients suspected with atherosclerotic disease in the lower limbs.	Cross sectional study	For this purpose, 60 patients aged 40 to 75 years 25 comprising of 25 females and 35 males and with a diagnosis of diabetes were recruited. With the help of supine positions of patients and variations in the position of equipment, the arteries of the lower limbs of the participants were assessed for the presence of narrowing of the lumen, atherosclerotic plaques, disturbances in blood flow and thickness of the	Narrowing of the lumen of the dorsalispedis artery demonstrated the highest prevalence across patients (41% and 36% across the left and right sides) followed by prevalence of atherosclerotic plaques across the femoral artery (44%). Of the fifty plaques observed, twenty eight of them demonstrated the prevalence of calcification. The prevalence of low peripheral resistance indicative of distal ischemia was found to be 25.5% in the dorsalispedis artery, 23% in the anterior tibial artery and

			intima media, using SDU 1200 Diagnostic Ultrasound System and a linear array transducer of 5-10 MHz.	21.5% in the posterior tibial artery.
Panda [34]	To evaluate the prevalence of PAD in the lower limb across clinical suspected patients diagnosed with peripheral vascular insufficiency (PVI) using a duplex colour Doppler [34].	Cross sectional study	A total of 50 patients admitted with a diagnosis of PVI at a hospital in Odisha, India, were recruited, of which 94% were males aged more than 40 years and with risk factors like hypertension (50%), alcohol consumption (26%), hyperlipidemia (50%) and diabetes (46%). Participants were assessed using B-Mode and Doppler for contour and thickness of blood vessels, pattern and direction of blood flow, pulsation and thus associated concerns like abscess, plaques, calcification, stenosis and aneurysm.	The prevalence of complete occlusion was observed in 38% whereas the prevalence of partial (49%) occlusion of observed in 30% of the recruited patients. Further, based on duplex assessment, the prevalence of intermittent claudication was observed in 60% of the patients of which, 75% was prevalent in the femoropopliteal segment whereas 25% was observed in the infrapopliteal and iliac segments. The diagnosis of PAD based on duplex color Doppler demonstrated a specificity and sensitivity of 96% and 92% respectively. Further, a Pulsatility Index ratio of less than 4 demonstrated the prevalence of stenosis at a significantly critical stage across 80% of the patients
Hiremath et al. [35]	To validate the feasibility of a diagnostic scoring	Cross sectional study	A total of 106 patients with suspected	A kappa value of 0.83 was demonstrated by the

	system for PAD in the lower limbs based on the Doppler sonographic features of duplex assessment across patients with diabetes and smokers.		symptoms of PAD were categorized across three groups: those who were only smoking, those with only diabetes and those with diabetes who smoked.	inter-observer agreement between the duplex scoring system and traditionally used Rutherford clinical scoring for PAD, hence demonstrating the prevalence of significance of agreement ($p < 0.001$). Its relevance to existing standardized systems of scoring, as per the findings of this study, thus demonstrates that duplex imaging procedures are a clinical effective way in which the PAD in the lower limbs can be diagnosed as well as graded and staged based on clinical severity.
Gam El Diel et al. [36]	To assess the effectiveness of duplex ultrasonography as compared to multi-detector computed tomography angiography (MDCT) for the assessment of ischemia in the lower limbs.	Cross sectional, comparative study	Participants comprised of 54 patients (30 males ad 24 females, aged 33 to 75 years) who had visited the radiology department for the assessment of lower limb, chronic ischemic disease, using either MDCT or duplex ultrasonography for comparing.	In terms of comparing between MDCT and duplex ultrasonography, the kappa agreement for assessment of the external iliac artery was 0.87, for the common femoral artery was 0.88, for the superficial femoral artery was 0.82, 0.76 and 086 for the upper, middle and lower third, for the popliteal artery was 0.87, for the peroneal artery was 0.88, for the posterior tibial artery 0.93 and for the anterior tibial

				artery 0.88 ($p< 0.001$)
Janssen et al. [37]	To determine whether duplex ultrasound (DUS) and physical examination results could be used to help predict the best degree of lower limb amputation in CLI patients	A retrospective cohort study	124 patients with chronic limb-threatening ischemia (CLI). The mean age of the patients was 70 years, and 67% were male.Of the 124 patients, 120 had unilateral amputation, 2 had bilateral amputation during the same treatment, and 54% had below-knee amputation (BKA).	Three major findings were reported by the authors. Firstly, a difference was observed in 25 percent for the femoral artery and 34 percent for the popliteal artery between physical examination results and DUS.Secondly, with more proximal occlusions on DUS, reoperation and conversion rates increased.Thirdly, no significant effect on conversion or reoperation rates of patient characteristics or comorbidities was found.
Martinelli et al.[38]	To evaluate the duplex sonography (DUS) diagnostic accuracy compared to computed tomography angiography (CTA) in PAD occlusion and stenosis detection in candidate patients with intraprocedural digital subtraction angiography (DSA)for endovascular revascularization	Unclear	94 patients with peripheral arterial disease (PAD). The mean age of the patients was 68.2 years, and 64.2% were male. Among the 94 patients, 30 patients had tissue loss or gangrene (Fontaine's classification(FC) stage 4), 46 patients had rest pain (FC stage 3) and 18 patients complained of disabling intermittent claudication (FC stage 2B)	When assessed against DSA, DUS was less effective than CTA in measuring iliac arterial diseases (Cohen's κ agreement of 0.91 and 1.0, respectively). In the detection of hemodynamic stenosis and femoro-popliteal axis occlusion, the authors found strong diagnostic concordance between DUS and DSA (Cohen's κ agreement between 0.96 and 0.93).CTA showed much less concordance with

				DSA below the knee (Cohen's κ 0.75).
Varaki et al. [31]	To evaluated the available diagnostic methods for peripheral arterial disease (PAD), deep vein thrombosis (DVT) and chronic venousinsufficiency (CVI) with a focus on non-invasive modalities	Review	Unclear	Duplex ultrasound is the gold standard approach for the diagnosis of peripheral vascular disease (PVD) and is currently the most sensitive non-invasive procedure.Similar to plethysmographic methods, however, highly skilled practitioners and expensive equipment are important.Doppler vascular evaluation also takes much longer than plethysmography.As such, for PVD screening or regular use in the clinic, plethysmography and Doppler techniques have limited use.
Normahani et al.[39]	To assessed the association between vessel wall calcification severity, number of vessels at the ankle of the patent, features of the arterial spectral waveform, as evaluated on a centred ankle Duplex ultrasound (DUS) and 12-month healing in a cohort of patients who had conservatively treated their diabetic foot ulcers	Unclear	50 limbs in 48 patients	As noted by the trend towards statistical significance, the authors found that the number of waveform components, peak systolic velocity, systolic rise time and long forward flow, as well as the number of vessels patented at the ankle on DUS, can be useful independent predictors of healing.

Table 3: Critical Appraisal of Qualitative Studies (CASP)

Checklist Questions	**Responses (Yes/No/Unclear)**		
	Hodgkiss-Harlow and Bandyk[29]	**Amrstrong et al.,** [30],	**Varaki et al.,** [31]
Was there a clear statement of the aims of the research?	Yes	Yes	Yes
Is a qualitative methodology appropriate?	No	Yes	Yes
Was the research design appropriate to address the aims of the research?	No	Yes	Yes
Was the recruitment strategy appropriate to the aims of the research?	Unclear	Unclear	Unclear
Was the data collected in a way that addressed the research issue?	Unclear	Unclear	Unclear
Has the relationship between researcher and participants been adequately considered?	Unclear	Unclear	Unclear
Have ethical issues been taken into consideration?	No	No	No
Was the data analysis sufficiently rigorous?	No	No	No
Is there a clear statement of findings?	Yes	Yes	Yes

Table 4: Critical Appraisal of Cross sectional/Case Control Studies (CASP)

Checklist Questions	Responses (Yes/No/Unclear)							
	Bhaduri et al. [32]	**Das et al.** [33]	**Panda** [34],	**Hiremath et al.** [35]	**Gam El Diel et al.** [36]	**Janssen et al.** [37])	**Martinelli et al.** [38]	**Normahani et al.** [39]
Are the results of the trial valid?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the authors use an appropriate method to answer their question?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the cases recruited in an acceptable way?	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Were the controls selected in an acceptable way?	Unclear	Unclear	Yes	Unclear	Yes	Unclear	Unclear	Unclear
Was the exposure accurately measured to minimise bias?	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Have the authors taken account of the potential confounding	No	Yes	No	Yes	Yes	Yes	Yes	Yes

factors in the design and/or in their analysis?								
Do you believe the results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Can the results be applied to the local population?	No	No	No	No	No	No	No	No
Do the results of this study fit with other available evidence?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes