THE IMPACT OF NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE CLINICAL GUIDELINE 168 ON THE MANAGEMENT OF SUPERFICIAL VENOUS DISEASE

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ABSTRACT

INTRODUCTION

In 2013, NICE published new guidance (CG168) for the management of lower limb venous disease; these guidelines sought to improve access to secondary care and recognised newer endovenous treatment modalities sufficiently robust to recommend. No formal study had evaluated the effect of the introduction of Guideline CG168 on venous disease management; this prompted the research project embodying this thesis.

METHODS

The management of venous disease was investigated locally at a secondary care level with primary care management being studied via the Health Improvement Network Database

RESULTS

Local secondary care has improved significantly since the introduction of CG168, demonstrating an increased use of endovenous treatments at earlier stage of venous disease. A significantly higher number of patients are being referred for specialist review with leg ulceration.

An improvement in referral and management of varicose veins in the community setting was noted, however the increase in referral for leg ulceration was more modest, with

patients often not referred at all for secondary care assessment.

CONCLUSION

Whilst current data presented here suggests enhanced management of superficial venous disease, nationwide primary care improvements have been less marked. Further efforts will be required to continue to publicise the importance of NICE Guideline CG168 in order to extend its beneficial effects on patient care.

DEDICATION

I would like to dedicate this work to my parents, brother and wife for their support and love.

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I would like to thank my supervisors Prof A Bradbury, Mr M Claridge and Mr R. Singhal for their support and kindness; with their help this work has improved my understanding of the topic of this thesis and enthused me in trying to obtain a wider knowledge of research methodology.

Professor Bradbury's mentorship has introduced me to the delights of the inquisitive researcher's mind and developed my fledgling critical thinking. I hope this will enhance my ability to help future patients by ensuring that I understand and question available evidence to optimise their healthcare in partnership. Additionally I hope that I will be able to continue to seek to add to the evidence base and improve it for the remainder of my surgical career.

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LIST OF ABBREVIATIONS

AVF	American Venous Forum
AVVQ	Aberdeen Varicose Vein Questionnaire
BMI	Body Mass Index
CCGS	Clinical Commissioning Groups
CEAP	Clinical, Etiological, Anatomic, Pathophysiological
CI	Confidence Interval
CIVIQ	Chronic Venous Insufficiency Quality Of Life Questionnaire
CG	Clinical Guideline
CKS	Clinical Knowledge Summary
CS	Conventional Surgery
CT	Computer Tomography
DUS	Duplex Ultrasonography
DVI	Deep Venous Insufficiency
DVT	Deep Vein Thrombosis
ETA	Endothermal Ablation
EQ-5D	Euroqol-5d
ESCHAR	Comparison Of Surgery And Compression With Compression Alone In
TRIAL	Chronic Venous Ulceration Trial
EVLA	Endovenous Laser Ablation
EVRA	Early Endovenous Reflux Ablation Trial
FVI	Functional Venous Insufficiency

GP	General Practitioner
GPP	General Practitioner Practice
GSV	Great Saphenous Vein
HEFT	Heart Of England NHS Foundation Trust
HES	Hospital Episode Statistics
HR	Hazard Ratio
HSE	Health Survey England
IAP	Intra-Abdominal Pressure
ICD	International Classification of Disease
IL	Interleukin
IMD	Index of Multiple Deprivation
ISTCS	Independent Sector Treatment Centres
LLVD	Lower Limb Venous Disease
LU	Leg Ulcer
MRI	Magnetic Resonance Imaging
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NOO	National Obesity Observatory
PMI	Private Medical Insurers
PROMS	Patient Reported Outcome Measures
Q	Quintile
QALY	Quality Adjusted Life Year
QoL	Quality of Life
QS	Quality Standard

RCN	Royal College Of Nursing
RCS	Royal College Of Surgeons
RCT	Randomised Controlled Trial
RFA	Radio Frequency Ablation
SD	Standard Deviation
SIGN	Scottish Intercollegiate Network
SF-36	Short Form-36
SFJ	Sapheno-Femoral Junction
STS	Sodium Tetradecyl Sulphate
SVI	Superficial Venous Insufficiency
THIN	The Health Improvement Network
TNF-α	Tumour Necrosis Factor-α
UGFS	Ultrasound-Guided Foam Sclerotherapy
UK	United Kingdom
VAS	Visual Analogue Score
VCSS	Venous Clinical Severity Score
VTE	Venous Thromboembolism
VSGBI	Vascular Society Of Great Britain And Ireland
VV	Varicose Veins
WHO	World Health Organisation

LIST OF PUBLICATIONS ARISING FROM THIS THESIS

- A review of randomised controlled trials comparing ultrasound-guided foam sclerotherapy with endothermal ablation for the treatment of great saphenous varicose veins. Huw OB Davies, Matthew Popplewell, Katy Darvall, Gareth Bate and Andrew W Bradbury. *Phlebology*. 2016; 31 (4): 234-40

- Obesity and lower limb venous disease – The epidemic of plebesity. Huw OB Davies, Matthew Popplewell, Rishi Singhal, Neil Smith and Andrew W Bradbury. *Phlebology*. 2017, 32 (4): 227-33

- The impact of 2013 UK NICE guidelines on the management of varicose veins at the Heart of England NHS Foundation Trust, Birmingham, UK. Huw OB Davies, Matthew Popplewell, Gareth Bate, Lisa Kelly, Katy Darvall, Andrew W Bradbury. *Phlebology*. 2016; 31 (9): 612-6

- Impact of UK NICE Clinical Guidelines 168 and social deprivation on access to interventional treatment for symptomatic varicose vein and specialist referral for leg ulceration. Huw OB Davies, Matthew Popplewell, Gareth Bate, Lisa Kelly, Andreas Koutsoumpelis and Andrew W Bradbury. *Phlebology*. 2017; 32 (8): 548-5

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- Analysis of Effect of NICE Clinical Guideline CG168 on Management of Varicose Veins in Primary Care Using The Health Improvement Network Database. Huw OB Davies, Matthew Popplewell, Gareth Bate, Ronan P Ryan, Tom P Marshall, Andrew W Bradbury. *Eur J Vasc Endovasc Surg* 2018; 56 (6) 880-884

- Publication of UK NICE Clinical Guidelines 168 has not significantly changed the management of leg ulcers in primary care: An analysis of The Health Improvement Network database. Huw OB Davies, Matthew Popplewell, Gareth Bate, Ronan P Ryan, Tom P Marshall, Andrew W Bradbury. *Phlebology* 2018 (October – epub ahead of print)

LIST OF PRESENTATIONS ARISING

- Impact of New NICE Guidelines on the Management of Venous Lower Limb Disease in East Birmingham UK. Royal Society of Medicine, Venous Forum, London, UK. 2015

- Effect of New National Guidelines in Treatment of Varicose Veins in East Birmingham. European Venous Forum, St Petersburg, Russia. 2015

- Prospective Study of 385 Patients Presenting to a Specialist Leg Ulcer Service Following Publication of NICE Clinical Guidelines. Vascular Society of Great Britain and Ireland. Annual Scientific Meeting, Bournemouth, UK. 2015

- Impact of UK National Institute of Health and Care Excellence (NICE) Clinical Guidelines (CG168) on the Referral and Management of Leg Ulcers. American Venous Forum, Orlando, USA. 2016

- The Relationship Between Social Deprivation and Referral to Vascular Surgery for the Assessment and Diagnosis of Varicose Veins and Leg Ulcer before and after Publication of NICE CG168. European Venous Forum, London, UK. 2016

- Analysis of The Health Improvement Network Database for The Incidence and Referral of Leg Ulceration Before and After NICE CG168. Vascular Society of Great Britain and Ireland Annual Scientific Meeting, Manchester, UK. 2016

- The Impact of 2013 UK NICE Clinical Guideline CG168 on Family Doctor Management of Varicose Veins based on the Health Improvement Network UK Database. American Venous Forum, New Orleans, USA 2017 (Poster)

- The Relationship Between Social Deprivation and Referral to Vascular Surgery for the Assessment and Diagnosis of Varicose Veins and Leg Ulcer before and after Publication of NICE CG168. American Venous Forum, New Orleans, USA 2017

- The Relationship Between Social Deprivation and Referral to Vascular Surgery for the Assessment and Diagnosis of Varicose Veins and Leg Ulcer before and after Publication of NICE CG168. Japanese Society of Phlebology Annual Meeting, Tokushima, Japan. 2017

- Utilisation of The Health Improvement Network (THIN) UK Database to Assesse the Impact of 2013 UK NICE Clinical Guideline CG168 on The General Practitioner Management of Varicose Veins. European Venous Forum, Porto, Portugal. 2017

Chapter 1

INTRODUCTION

1.1 THE PROBLEM OF CHRONIC VENOUS DISEASE:

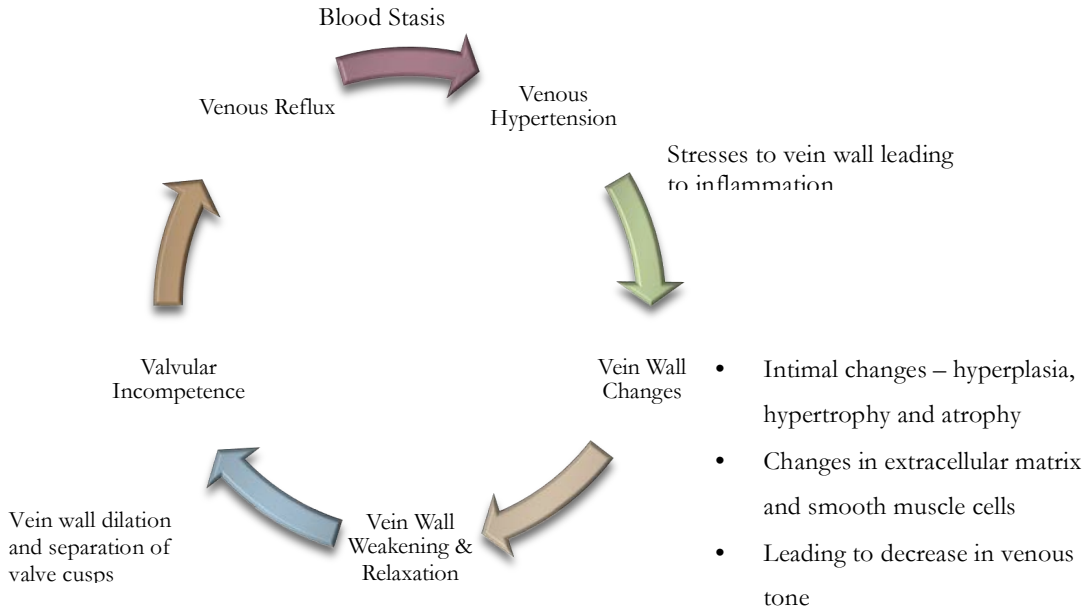
1.1.1 Pathophysiology of Venous Disease

Varicose veins are defined as dilated, tortuous veins of the superficial venous system. They are most commonly found in the lower limb. These veins exhibit reversed venous blood flow (reflux), which results in venous hypertension of the lower limb.

The venous system of the lower limb is divided into two components, the deep and superficial systems, separated by a fascial layer. Deep veins situated in the calf muscles converge to form the popliteal vein, this in turn becomes the femoral, common femoral and finally the external iliac vein before the right and left common iliac veins combine to form the inferior vena cava. The superficial system comprises of the small and great saphenous veins, both veins are connected through the fascia of the leg to the deep system at the sapheno-popliteal and sapheno-femoral junctions respectively. There are further anastomoses from superficial to deep systems from perforating veins along the length of the lower limb. In the normal physiological state, blood flows proximally along the deep system and from superficial to deep systems as a result of contraction of the calf muscle pump. Reverse flow from proximal to distal and from deep to superficial systems is prevented by a system of valves.

Chronic venous insufficiency occurs as a result of disturbance to normal flow. This may be primary or secondary (e.g. venous incompetence from deep vein thrombosis). Three factors are responsible for the development of chronic venous insufficiency: failure of the calf muscle pump (inactivity), failure of valves and obstruction to venous flow (e.g. deep vein thrombosis). Any combination of these results in venous hypertension, forcing fluid and protein out of the vein resulting in the skin changes associated with chronic venous insufficiency. In spite of the general acceptance of the previously mentioned features, the exact aetiology of the pathogenesis of varicose veins remains uncertain. A systematic review by Lim [1] suggests several methods for venous insufficiency – however, once venous reflux is detectable clinically and with duplex ultrasonography, all of these processes have begun and therefore it is difficult to elucidate the initiating cause or causes (Figure 1.1.1).

Figure 1.1.1 Pathogenesis of Venous Insufficiency, Adapted From Lim et al[1]



The most common presentations of chronic venous disease are reticular veins, telangiectasia and varicose veins. This progresses to chronic venous insufficiency resulting in venous hypertension of the lower limbs. The consequences of chronic venous insufficiencies are patient symptoms, e.g., pain, leg swelling, skin changes (venous eczema, haemosiderin deposition and lipodermatosclerosis) and venous leg ulceration.

1.1.2 Epidemiology of Venous Disease

In 1999 the Edinburgh Vein Study found an age-adjusted prevalence of venous disease (trunk varices) of 40% and 32% in men and women respectively [2]. The United States has approximately 25 million inhabitants suffering from simple varicose veins and around 6 million suffering from more advanced venous disorders [3] (superimposed skin changes and ulceration). The increasing awareness of the high incidence and prevalence of venous disease and its associated morbidity, led the American Venous Forum to conduct the National Venous Screening Programme, publishing the results of the second survey in 2008. This identified varicose veins in >30% of it's 2234 participants and more advanced venous disease in >10% [4]. In 2010 rates of 25% were found by the BONN vein study II [5]. Follow up to the Edinburgh Vein study found over a 13 year period, an incidence of around 1% of the population developing venous reflux per year [6]; this was comparable to the annual incidence described in the Framingham study in 1988 (1.9% for males and 2.6% for females) [7]. Prevalence, appears to vary with the geographical location of studied patients and appears higher in more developed countries. Mekky et al [8] found the prevalence of varicose veins in England was five times that in Egypt although they

concluded that environmental factors probably played a more important role than ethnic/genetic differences.

Geographical and/or environmental influences were also suggested by a study of different populations in the South-Pacific; higher rates of varicose veins were seen in New Zealand compared with atoll-dwelling islanders [9, 10]. In Jerusalem, the country of birth appeared to affect the prevalence, it was found to be reduced in people from North Africa when compared to those born in America, Asia and Europe [11]. In Europe it has been noted that the prevalence was lower in Southern European women (e.g. Italy and Spain) compared to other European countries (e.g. Switzerland, France and countries of central Europe) [12]. The San Diego Population Study demonstrated a higher prevalence of visible varicose veins in Hispanics (26.3%) and non-Hispanic whites (24.0%), compared to African-Americans (20.8%) and Asians (18.7%). Similarly a higher proportion of non-Hispanic whites and Hispanics suffered from duplex identified superficial venous disease [13].

Variation of the reported prevalence of varicose veins exists throughout all the major epidemiological studies. Robertson et al reviewed seven population studies and found a variation in prevalence from 6.8-39.7% in men and 24.6-41.7% in women [14]. It is likely that a proportion of this variability could be accounted for by analysing the differing methods of reporting venous disease. Some studies included all evidence of disease from spider and reticular veins through to venous ulceration and some only included people with visible varicose veins. The methods of assessment of venous disease also varied; some

studies relied on self-assessment, others used questionnaires or examination by medical professionals. In spite of the variation in prevalence and geographical, ethnic or environmental factors, these studies demonstrated that varicose veins and venous reflux are a significant health issue throughout the world, especially when viewed at a population level.

The sequelae of chronic venous insufficiency to the lower limb comprise of skin changes including venous eczema, haemosiderin deposition, lipodermatosclerosis and ulceration. The prevalence of ulceration, the most severe and difficult to treat form of chronic venous disease, is thought to be around 1% [15] ; this represents a significant number of affected individuals when considering the prevalence of venous disease in the whole population.

1.1.3 Financial Implications of Venous Disease

Healthcare providers often underestimate the magnitude and importance of chronic venous disease. Chronic venous disease is widespread and the treatment of more complex sequelae of chronic venous insufficiency, like venous leg ulcers, is not straightforward and requires long–term strategies. This results in a significant cost implication for healthcare providers and is estimated to command around 1% of western European healthcare budgets [16]. There are approximately 2.5 million Americans suffering from venous ulceration with an annual calculated treatment cost of 1.6 billion dollars [17]. A review of the burden of venous disease in Europe predicted that, in the United Kingdom (UK), approximately 77,000 varicose vein procedures should be performed annually in 2010 if aiming to treat all those with C2-6

CEAP classification [18,19] (please see Section 1.1.5 and Table 1.1.5.1 for the CEAP Classification); in fact less than half this number of procedures were carried out. There has been a trend toward performing lessening numbers of venous procedures in the UK for some time [19]. Previous National Institute for Health and Care Excellence (NICE) guidelines [20] recommended referral of patients with varicose veins causing troublesome symptoms or affecting quality of life along with those with more severe venous disease (old/current ulceration or bleeding). In spite of these recommendations, National Health Service (NHS) funding bodies commonly only reimburse treatment for patients with severe skin changes or a failure to respond to 6 months of compression treatment. It is the author/candidate's expectation that the number of treatments in the NHS will slowly begin to increase in response to the more recent guidelines of 2013 [21]; the latter emphasise the importance of earlier intervention for venous disease to prevent onset of the more costly and difficult to treat skin complications, thereby reducing overall costs to the NHS.

1.1.4 Patient Perspectives of Varicose Veins – symptoms and quality of life

Commonly described symptoms by sufferers of venous insufficiency are heaviness, swelling, itching, aching, restless legs, cramps and tingling [22]. Several authors have noted that varicose veins are associated with poorer quality of life measures, both generic and disease specific[23-25]. Increasing scores in the clinical component of the CEAP classification (Section 1.1.5 and Table 1.1.5.1, below) relate to the proportion of people with any of the above-mentioned symptoms and correlate with symptom severity and quality of life [18 26 27]. Although recent work by Darvall et al, agrees with the principle that both physical and psychological measures of generic quality of life are worsened by symptomatic lower limb

varicosities, this relationship did not correlate with increasing clinical severity as defined by CEAP [28]. Chronic venous insufficiency is a degenerative, progressive condition and it is estimated that 2% of sufferers per annum progress from C2 to C3-6 disease [29], thereby suggesting that the quality of life of a significant proportion of the population will worsen and will involve a significant number of patients developing venous leg ulceration.

1.1.5 Defining the Severity of Varicose Vein Symptoms and Using Symptoms to Commission Varicose Vein Interventions

The symptoms as described above in 1.1.4 are often vague and difficult for the clinician to define. There are multiple tools to assess quality of life for completion by the patient, clinician or both. These can be generic (such as EuroQol-5D (EuroQol, Rotterdam, Netherlands) or Short Form-36 (Quality Metric, Lincoln, Rhode Island, USA)), with ability to assess the patient as a whole, but may underestimate the impact of specific disease states[30, 31]. These can be better assessed by disease-specific quality of life instruments (such as the Aberdeen Varicose Veins Questionnaire[30] or Chronic Venous Insufficiency Quality of Life questionnaire[32]) however this does not allow direct comparison between different diseases. This ability to directly compare how a disease impacts on quality of life and measure the improvements after an intervention is important at a national health economic level where budgets are fixed and require rationing of interventions to maximise the improvement of the general population's health.

Whilst there is good evidence for varicose veins negatively impacting quality of life as referenced in 1.1.4, it is difficult for the clinician (within the confines of an NHS consultation) to objectively and accurately assess the severity of symptoms upon a patient and compare patient to patient without recourse to time and resource heavy quality of life questionnaires.

Varicose vein intervention commissioning occurs at a local/regional level with clinical commissioning groups. There are 195 such groups across the UK, these are responsible for two thirds of the NHS budget and are independent of one another (www.nhscc.org). Pre- NICE Clinical Guideline 168 commissioning varied widely across the country[33]. Griffin's work[33] demonstrated that interventions were being rationed with differing groups commissioning interventions depending on whether varicose veins were mild, moderate or severe. This was defined using the CEAP classification (see section 1.1.6) – a classification tool unable to account for disease progression[18]. A significant proportion of commissioners therefore utilised simple objective signs such as skin changes, to ration treatments and ensure treatments are not given to those misperceived to have a 'cosmetic' problem[34]. Sadly this approach would disadvantage a considerable number of patients whose venous symptoms were significantly affecting their quality of life, ignoring evidence that quality of life improvement after treatment is greater before skin damage develops and reduces recurrence[35].

1.1.6 Classification of Chronic Venous Disease

The classification of venous disease has developed significantly from the Basle Classification described in 1978 [36]. In 1994 the Clinical, Etiological, Anatomic, Pathophysiological (CEAP) classification was developed. This produced a score based on the severity of disease and was established to incorporate duplex ultrasonography assessment and allow comparison of outcomes across clinical studies [37]. The system was revised in 2004 by Eklof [18] and has become the most widely used classification for venous disease. The CEAP classification is summarised in Table 1.1.5.1.

Table 1.1.6.1 ***CEAP Classification (revised)***

Clinical Classification	Etiological Classification	Anatomical Classification	Pathological Classification
C0: Nil visible/palpable venous disease	Ec: congenital	As: superficial veins	Pr: reflux
C1: Telangiectasia or reticular veins	Ep: primary	Ap: perforator veins	Po: obstruction
C2: Varicose veins	Es: secondary (post-thrombotic)	Ad: deep veins	Pr,o: reflux and obstruction
C3: Oedema			Pn: no venous pathology identifiable
C4a: Pigmentation and eczema			
C4b: Lipodermatosclerosis and atrophie blanche			
C5: Healed venous ulcer			
C6: Active venous ulcer			
S: symptomatic: aching, pain, tightness, heaviness, skin irritation, muscle cramps etc. **A:** Asymptomatic			

The CEAP classification is a useful means of assessment of venous disease at presentation, however, it correlates poorly with changes after treatment, particularly in C4-6 disease [38-41]. The simplicity of CEAP allows its widespread adoption in healthcare since patient assessment is rapid and associates with little inter-observer variability. The Venous Clinical Severity Score (VCSS) [38] was developed by Rutherford and adapted by Vasquez [42] as a supplement to clinical assessment by CEAP thereby allowing greater differentiation between disease states (particularly C4-6). The revised VCSS is shown in Table 1.1.5.2.

Table 1.1.6.2: ***Venous Clinical Severity Score (revised)***

	None: 0	Mild: 1	Moderate: 2	Severe: 3
Venous pain/discomfort		Occasional	Daily-non limiting	Daily-limiting
Varicose Veins (diameter ≥3mm)		Few scattered or corona phlebectatica	Confined to calf or thigh	Involving calf and thigh
Oedema of venous origin		Confined to foot/ankle	Extends above ankle, below knee	Extends to knee and above
Skin pigmentation	None/focal	Limited to peri-malleolar area	Diffuse over lower 1/3 of calf	Widespread above lower 1/3 of calf
Inflammation (e.g. venous eczema, cellulitis)		Limited to peri-malleolar area	Diffuse over lower 1/3 of calf	Widespread above lower 1/3 of calf
Active ulcer number	0	1	2	≥3
Active ulcer duration	N/A	<3 months	>3months, <1 year	>1 year
Active ulcer size (largest)(diameter in cm.)	N/A	<2	2-6	>6
Use of compression therapy	Not used	Intermittent compliance	Wears most days	Full compliance

1.2 NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE GUIDELINES

1.2.1 Purpose of National Institute for Health and Care Excellence Guidelines

The National Institute for Health and Care Excellence (NICE) is an executive body of the Department of Health functioning independently of the Department. It has responsibilities in four areas:

- Health technology use
- Clinical guidelines
- Public sector worker guidance on health promotion and ill-health avoidance
- Social care service and user guidance

Appraisals are evidence based and examine efficacy and cost-effectiveness of interventions. Internationally, NICE guideline recommendations are highly regarded and influence health care systems worldwide. The guidance is designed to aid effective and cost-effective health care delivery to patients suffering from a variety of conditions.

1.2.2 Development and Cost of Producing NICE Clinical Guidelines

There are 172 currently extant clinical guidelines. Subjects for review are referred to NICE by NHS England. Production of each guideline involves a number of groups and individuals [43]. The major groups and their tasks comprise:

- **NICE**
    - Commissions guidelines

    - Organises guideline development
    - Signs off of completed guidance
- **National Collaborating Centre**
    - Drafts scope and review questions of guidelines (revised as each guideline is developed)
    - Provides technical and managerial support
    - Prepares draft and finalised guidelines
    - Advises NICE on publishing, dissemination, implementation and updating of guidelines
- **Guideline Development Group**
    - Contributes to the scope of each guideline
    - Refines and agrees review questions
    - Discusses evidence leading to appropriate conclusions
    - Develops guideline recommendations
    - Supports and promotes guideline dissemination to clinicians
- **Patient and Public Consultation Group**
    - Advises on patient and carer matters
    - Comments on draft guidelines from the patient/carer perspective
    - Aids with drafting public information sections of guidelines

Guideline development is an exhaustive process and the above groups include managerial staff, public health staff, medical/healthcare professionals, statisticians, information technology experts and patient/carer groups. The process not only ensures that all available literature is reviewed and recommendations are clinically sound but also aims to

ensure guideline cost effectiveness. NICE measures cost effectiveness with 'quality-adjusted life years' (QALY), a generic measure of disease burden in terms of quantity of life adjusted for quality of life. At present NICE recommends interventions (excluding cancer) at an incremental cost ceiling of <£20 000/QALY, although this may be raised if the available evidence is strong [44].

The extensive and comprehensive process, along with the resources required predict that the development of NICE guidelines is likely to be expensive, at present there is no published data referencing the cost of producing each NICE clinical guideline.

A 'Freedom of Information Act' (2000) enquiry as to the cost of producing NICE CG168 was made (Appendix 1); however, NICE cannot provide an exact costing of guideline production. The corresponding information from NICE indicated that CG168 took 24 months to produce (on average a guideline requires 26 months). NICE provided the National Collaborating Centre with £424 080 for the production of CG168, this figure does not include internal NICE costs, committee expenses or communication/press costs. Therefore the final figure is likely to be considerably higher than the approximately £0.42 million for which NICE was able to account.

The current and likely enduring climate of financial constraint makes it extremely important that NICE guidelines are useful to health professionals and to patients/families/carers in aiding decision-making and optimising care. Presently NICE

does not have the ability to measure the impact of its guidelines and specifically for NICE Clinical Guideline 168, assessment of the impact upon venous disease management has been entirely lacking. The work programme for this thesis included an attempt to assess the impact of NICE Clinical Guideline 168 on venous disease management at local and national levels in both primary and secondary care.

1.3 COMPARISON OF INTERNATIONAL GUIDELINES ON VENOUS DISEASE

1.3.1 Summary of National Institute for Health and Care Excellence Clinical Guideline 168

The National Institute for Health and Care Excellence (NICE) Clinical Guideline (CG) 168 was published in July 2013 and differed considerably from various sources of previous guidance for managing venous insufficiency. CG 168 recommended that adults (aged over 18 years) be referred to a vascular specialist and undergo duplex ultrasound assessment if they suffered from symptomatic CEAP C2 varicose veins or worse. There was also a recommendation to refer patients suffering from leg ulceration that had not healed within a 2 week period [21]. Treatment guidelines also recognised that significant advances had been made in endovenous treatment modalities and that the treatment hierarchy should be amended to:

1. Endothermal ablation
2. Ultrasound-guided foam sclerotherapy (UGFS)
3. Conventional surgery

Individual tailoring of treatment strategies (e.g., simultaneous or delayed treatment of tributaries or perforator treatments), is left to the specialist's discretion, as evidence levels were not considered strong enough to produce 'blanket' guidance for treatment strategies – in any event NICE has stated that their guidelines are meant to be appropriate for 'most' patients but need individualised application [37]. CG168 specified compression hosiery as not considered adequate management for varicose veins unless 'active' interventional treatment was unsuitable.

1.3.1.1 Venous Disease Guidance Prior to NICE CG168

Prior to publication of CG 168 in July 2013 guidance on venous disease was limited [20]. In general, it was recommended that patients with simple varicose veins (CEAP C2-3) (Table 1.1.5.1) be treated conservatively with lifestyle advice and compression hosiery. If symptoms were very severe and affecting quality of life, then application could be made for special funding to allow further treatment. Only those patients with bleeding from varicose veins, skin damage (venous eczema, lipodermatosclerosis, haemosiderin deposition, healed or active ulceration) were thought to be suitable for referral to secondary care for vascular specialist review, interventional treatment funding was limited and variable across the UK as varicose vein surgery was seen as a 'procedure of low clinical priority.' This opinion prevailed in spite of clear evidence that symptomatic varicose veins significantly and negatively impact on patients' quality of life.

Conventional surgery was recommended as first line treatment for superficial venous reflux as evidence for newer endovenous techniques was limited although these procedures

could be performed providing special audit arrangements were in place to ensure their effectiveness.

No recommendations were made regarding referral times for leg ulceration, which was primarily managed in the community by district nurses and general practitioners.

1.3.2 Summary of European Venous Forum Guidelines

The European Society for Vascular Surgery published guidelines on the management of chronic venous disease in 2015 [45]; these recommendations for diagnosis and assessment centred on clinical examination and duplex ultrasound. No guidance was offered on referral to vascular specialists from primary care or who should be treated for superficial venous disease. These considerations were left to attendant medical practitioners.

Treatment recommendations suggested compression as the cornerstone of conservative management; there was limited evidence for veno-tonic medications their use being regarded as optional. Intervention was recommended for those with uncomplicated (CEAP C2-3) varicose veins. Reflux ablation recommendations were similar to NICE CG168, with a hierarchy of endothermal ablation, foam sclerotherapy and finally, surgery. The guidelines go slightly further than CG168 in recommending the consideration of foam sclerotherapy as a first line treatment in the elderly or frail.

In venous ulceration, compression bandages/hosiery were recommended as initial treatment, further investigation being required before superficial venous ablation could be considered as an aid to ulcer healing.

1.3.3 Summary of American Venous Forum Guidelines

American Venous Forum (AVF) guidelines were published in 2011 [46]. These did not address referral guidelines for specialist review as these are determined by medical insurance companies and are regularly reviewed and modified.

In similarity with NICE, the AVF recommends all patients with varicose veins or more severe venous disease, should be assessed by a specialist and undergo duplex ultrasound. The AVF also recognises that compression alone is inadequate as a primary treatment of VVs in the presence of treatable superficial venous insufficiency. Medical treatment (e.g. with micronized purified flavonoid fraction) is suggested in those countries were this preparation is available.

Recommendations for interventional treatment hierarchy are endothermal ablation over UGFS or surgical ligation/stripping. The AVF recommended either UGFS or phlebectomy as treatment for tributaries. Treatment of pathological perforating veins was advocated by the AVF if underlying healed or active ulceration were present.

Table 1.3.1: ***Comparison of NICE vs EVF vs AVF Guidelines***

	NICE CG168	EVF	AVF
Community Referral Advice	Yes	No	No
Recommend Specialist Review For VV	Yes	Yes	Yes
Primary Imaging Recommendations	Ultrasound duplex	Ultrasound duplex	Ultrasound duplex
Compression	Only if not suitable for intervention	Only for conservative management	Only if not suitable for intervention
Medical Treatment	Not recommended/available in UK	Use is optional	Can consider
Intervention	1) Endothermal ablation 2) UGFS 3) Conventional surgery	1) Endothernal ablation 2) UGFS (consider as first line in elderly) 3) Conventional surgery	1) Endothermal ablation 2) UGFS or conventional surgery Use phlebectomy of UGFS for tributaries

1.4 PREDICTED CHANGES IN VENOUS TREATMENT ACTIVITY/COST AFTER INTRODUCTION OF NICE CG168

As part of the development of NICE CG168, NICE produced a costing report [47], estimating the expense of changing practice in contrast to the previous approach which restricted the use of superficial venous interventions. The costing report predicted an increase in referral rates by 25% and correspondingly, an increase in interventional procedures by 25%. This increased activity was equated with an additional £9000 per annum per 100 000 population. This increase in NHS expenditure was expected to be offset by the move to endovenous

procedures from conventional surgery with an expected cost saving of £7800 per annum per 100 000 population.

The costing report predicted further benefits, including a reduction in incidence of venous leg ulcers. NICE calculated the resulting average cost of venous leg ulceration as £1872/elective in-patient admission. Further savings were predicted for primary care by the reduction of use of compression hosiery (estimated at £182 per year per patient).

The savings anticipated from leg ulcer prevention and reduced use of compression hosiery were difficult to predict and were excluded from the overall conclusion that CG168 would result in increased expenditure of £1200 per annum per 100 000 population.

The costing report differs from the health economic analysis where the cost-effectiveness compares costs in monetary units with outcomes in terms of their utility, usually to the patient, measured, e.g., in QALYs. This ensures treatments meet the willingness to pay threshold and allows measurement of the impact of the intervention on health and permits differing interventions in healthcare to be compared so that resources may be allocated more efficiently.

NICE CG168 considered 4 treatments to be analysed for cost-effectiveness:

1) Conventional surgery
2) Endothermal ablation

3) Ultrasound-guided foam sclerotherapy

4) Conservative management

NICE found all treatments to be cost-effective compared to conservative treatment with lifestyle advice. Endothermal ablation provided the most improvement in quality associated life years but was associated with increased cost compared to UGFS. The incremental cost-effectiveness ratio of endothermal compared to UGFS was £3161 per QALY gained, both endothermal ablation and UGFS were considerably below the threshold to pay of £20 000 per QALY recommended by NICE[21].

1.5 Geographical Variation In Commissioning Of Varicose Vein Interventions

With current budget constraints and need to save money, commissioners have often resorted to rationing treatment depending upon local financial plans. Three main strategies are employed to this end[48] – rationing by:

1. Withholding treatment until later disease state
2. Rationing by delay
3. Introduction of lifestyle criteria (e.g. BMI or smoking status)

Differing CCGs are employing none, one or more of these strategies in attempts to save costs. This has resulted in significant geographical variation, related to differing commissioning policies across the UK[49-52].

Chapter 2

REVIEW OF EVIDENCE RELATING TO RECOMMENDATIONS OF NICE CG168

NICE CG168 made several recommendations predicted to improve the management of venous disease in the UK; however, some aspects of CG168 were controversial especially the treatment hierarchy for VV: endothermal ablation (ETA), ultrasound-guided foam sclerotherapy (UGFS), surgery and compression hosiery [53]. Here the evidence justifying this hierarchy and its support by the Vascular Society of Great Britain and Ireland (VSGBI) and the UK Royal Colleges of Surgeons (RCS) is examined.

2.1 REVIEW OF LEVEL[1] EVIDENCE FOR ENDOVENOUS TREATMENTS OF VARICOSE VEINS

Search Strategy

PubMed and OVID literature searches were performed from 1900 - April 2018 using the terms: RCT, sclerotherapy, radiofrequency ablation, laser ablation, endovenous and endothermal linked with varicose veins. Abstracts were screened and the full papers obtained if they compared UGFS with ETA for the treatment of VV.

Inclusion/Exclusion criteria

Papers were included within the review if they were classified as randomised controlled trials, all other study types were excluded.

Analysis

ETA and UGFS RCT data were analysed in terms of endovenous methodology, technical success, clinical success, morbidity, complication rates, costs and time to return to work.

PubMed and Ovid cite nine publications of data from five RCTs. The RCTs included Rasmussen *et al* [54-56], Lattimer *et al* [57, 58], Biemans *et al* [59, 60], Brittenden *et al* [61] and Venermo *et al* [62]), all of which studied only great saphenous (GSV) VV. Only Rasmussen allowed recurrent GSV VV, provided the GSV was still present in the groin. Three papers described initial results [54, 57, 59] and were followed by further publications reporting longer-term outcomes [55, 56, 58, 60]. Rasmussen compared EVLA, RFA, UGFS and conventional surgery (CS) in 580 legs, Lattimer compared EVLA and UGFS in 100 legs, Biemans compared EVLA, UGFS and CS in 240 legs, Brittenden compared EVLA, UGFS and CS in 798 legs and Venermo studied EVLA and UGFS in 214 legs (Table 2.1.1).

Table 2.1.1*: Comparison of RCT Allocated Treatments*

Trial	Legs Randomised				
	EVLA	RFA	UGFS	CS	**Total**
Rasmussen 2011	144	148	125 (124 received treatment)	125 (124 received treatment)	**580**
Lattimer 2012	50 (4 lost to follow up)	-	50 (5 lost to follow up)	-	**100**
Biemans 2013	80 (2 procedure failed)	-	80 (1 lost to follow up, 2 other intervention)	80 (3 procedure failed, 4 other intervention, 8 no intervention)	**240**
Brittenden 2015	292 (251 completed follow up)	-	212 (183 completed follow up)	294 (236 completed follow up)	**798**
Venermo 2016	73	-	76 (72 completed follow up)	65 (61 completed follow up)	**214**

EVLA-endovenous laser ablation, RFA-radiofrequency ablation, UGFS-ultrasound-guided foam sclerotherapy, CS-conventional surgery

The details of treatment methods differed and are summarised for the controlled studies in Table 2.1.2. Brittenden's multi-centre trial did not specify laser manufacturer, wavelength or fibre type presumably as these varied across hospitals. All of the other RCTs use bare-

tipped fibres and lasers of varying wavelength: Rasmussen and Venermo used 980 and 1470nm (Ceralas D, Biolitec, Jena Germany); Lattimer 1470nm (ELVeS Painless diode laser, Biolitec Inc, East Long Meadow, MA, 01028, USA); Biemans 940nm (manufacturer not specified). For most treatments the laser fibre appears to have been inserted into the GSV under ultrasound-guidance at approximately the level of the knee, or at the level of lowest incompetence in the thigh. The laser fibre tip was then advanced to within 2cm of the sapheno-femoral junction (SFJ) after which the GSV was ablated by slow withdrawal of the catheter. Rasmussen achieved a median of 69J/cm; Lattimer delivered a median of 69J/cm, Biemans aimed for at least 60J/cm and Brittenden and Venermo's studies aimed for at least 70J/cm energy delivery. This was in accord with previous work suggesting that at least 60J/cm energy delivery is required for satisfactory vein closure [63]. All of the RCTs used tumescence anaesthesia and some patients received light sedation. Rasmussen [54], Lattimer [57] and Venermo [62] performed EVLA with concurrent phlebectomies; Biemans [59] with either concurrent or delayed (3 months) phlebectomies; and Brittenden [61] with UGFS to tributaries at 6 weeks (except one site that performed concurrent phlebectomies) [64].

Only Rasmussen evaluated RFA and used a VNUS ClosureFAST catheter (Covidien, Mansfield, Mass, USA) inserted under ultrasound-guidance into the GSV just below the knee or at the lowest point of reflux in the thigh. This was performed using tumescent anaesthesia with light sedation and tributaries were removed with concurrent phlebectomies [54].

UGFS techniques varied considerably. Rasmussen inserted a single cannula into the GSV just below the knee and injected 3% polidocanol foam (volume not specified) until the foam was visualised by ultrasound at the SFJ and the GSV was contracted (in spasm) throughout its length [54]. Lattimer inserted a single cannula into the GSV at knee level and injected 1% sodium tetradecyl sulphate (STS) using a median of 12ml/session. If the GSV was ≥8mm in diameter, tumescence anaesthesia was used to compress the vein before introduction of STS foam. Lattimer performed further foam treatments in 4.6% of patients who initially received EVLA and in 56% of the patients who had been randomised to foam. Biemans performed UGFS as per the Second European Consensus guidance [65] using 3% polidocanol with a maximum of 10ml/session. Six patients (4.6%) in the UGFS group had further foam treatment in the first six months. Brittenden did not provide information on use of cannulas (numbers and sites) but stipulated that 3% STS be used on truncal veins and 1% STS on varicosities [64], with a maximum of 12ml/session. At 6 weeks, 38% UGFS and 31% EVLA patients underwent a further UGFS treatment. Finally Venermo inserted a cannula in the proximal thigh and immediately below the knee and instilled either 1% polidocanol or 1/3% STS in unspecified volumes, allowing a further treatment at 4 weeks. All trials used foam volumes in accordance with manufacturers' licences. For the RCTs including CS, SFJ ligation was performed and the GSV stripped to the knee, or just below, with concurrent phlebectomies. Rasmussen performed CS using tumescence anaesthesia under light sedation; Biemans used general anaesthetic; and Brittenden did not specify the type of anaesthesia.

Table 2.1.2: ***Comparison of Treatment Techniques***

Intervention		Study				
		Rasmussen 2011	**Lattimer 2012**	**Biemans 2013**	**Brittenden 2015**	**Venermo 2016**
EVLA	Fibre	Bare tipped 980-1470nm (Ceralas D)	Bare tipped 1470nm (ELVeS)	Bare tipped 940nm (Manufacturer not specified)	No specification	Bare tipped 980nm Radial 1470nm (Ceralas and ELVes)
	Cannulation	All studies – GSV under ultrasound guidance at level of knee or lowest point of reflux, advanced to 2cm from SFJ				
	Energy	69J/cm	69J/cm	>60J/cm	>70J/cm	70J/cm
	Anaesthesia	All studies – tumescence analgesia +/- light sedation				
	Tributaries	Concurrent phlebectomies	Concurrent phlebectomies	Concurrent or delayed (3 months) phlebectomies	UGFS at 6 weeks (1 centre concurrent phlebectomies)	Concurrent phlebectomies
RFA		VNUS, cannulation just below knee GSV or lowest point of reflux with concurrent phlebectomies, under tumescence analgesia	-	-	-	
UGFS	Sclerosant	Polidocanol	Sodium Tetradecyl Sulphate	Polidocanol	Sodium Tetradecyl Sulphate	Polidocanol and Sodium Tetradecyl Sulphate
	Concentration	3%	1%	3%	3% truncal, 1% to varicosites	PD 1% STS 1 and 3%
	Volume	Not specified	Median 12ml/session	Maximum 10ml/session	Maximum 12ml/session	Not specified
	Technique	Single cannula just below knee. Continue injection until foam visualised at SFJ and GSV contracted	Single cannula at knee level. If GSV≥8mm then tumescence to reduce diameter	As per 2nd European Consensus	No specifications regarding number of injections/sites	Cannula proximal thigh and immediately below knee

2.1.1 Technical Success

Rasmussen defined technical success as a closed or absent GSV without reflux and failure as an open segment of GSV >10cm in length or GSV unsuccessfully stripped. Five GSVs were open after one month in the UGFS group and these were re-treated. At one year (2011), the technical failures rates were 16.3% for UGFS, 5.8% for EVLA and 4.8% for RFA ($p<0.001$, χ^2) [54]; and at 3 years (2013) they were 26.4% for UGFS, 6.8% for EVLA and 7% RFA ($p <0.0001$, statistical test not stated) [55].

Lattimer defined technical success as complete ablation of GSV reflux (occlusion not required) and failure as reflux anywhere in the above knee GSV. At 3 months (2012), the technical success rate, as defined by absence of above knee GSV reflux on duplex, was 80% in both the EVLA and UGFS groups; at 15 months (2013), global absence of reflux was 41% for EVLA and 43% for UGFS. At 15 months (2013), however, complete GSV occlusion was observed in 95.5% of the EVLA, and 67.4% of the UGFS, patients ($p=0.001$, Fisher exact probability test).

Biemans defined technical success as complete obliteration, without flow or reflux, of the mid-thigh GSV. At 12 months (2013), the technical success rate was 88.5% for EVLA and 72.7% for UGFS ($p <0.001$, χ^2).

Brittenden (2015) defined technical success according to Kundu [66] as ‘successful ablation of the target vein as demonstrated by a complete lack of flow or disappearance of vein by

duplex ultrasound imaging in the entire treated segment.' At 6 weeks, the technical success rate was 83% for EVLA and 54.6% for UGFS ($p \leq 0.01$, statistical test not stated). Venermo (2016) measured 1-year occlusion rates (no further information) and diameter of GSV 20cm below the groin pre and post treatments; one-year results were 97% for EVLA and 51% for UGFS ($p<0.001$).

2.1.2 Clinical Success

Rasmussen reported clinical success using the Venous Clinical Severity Score (VCSS) [42], Aberdeen Varicose Vein Questionnaire (AVVQ) [30], Short Form-36 (SF-36®) (Quality Metric, Lincoln, Rhode Island, USA) and visual analogue scores (VAS) for pain. All three improved significantly in all four patients groups and there was no difference between EVLA, RFA, UGFS and CS at 1 (2011) or 3 years (2013).

Lattimer (2013) reported clinical success using the VCSS, AVVQ, and the Saphenous Treatment Score [67]. All three improved significantly in both groups and there was no difference between EVLA and UGFS recorded to 15 months; although 7-day pain scores were significantly higher with EVLA.

Biemans (2013) reported clinical success using the Chronic Venous Insufficiency Quality-of-Life Questionnaire (CIVIQ) [32] and EuroQoL 5D (EQ-5D) (EuroQol, Rotterdam, Netherlands). These both improved at 3 months and there was no difference between EVLA and UGFS recorded to one year.

Brittenden (2015) reported clinical success using AVVQ, VCSS, EQ-5D, SF-36 and clinical vein appearance. At 6 months both EVLA and UGFS showed improvement in AVVQ and VCSS, with no statistical difference between EVLA and UGFS reported. Both EQ-5D and the physical component of SF-36 showed improvement in all groups, with no statistical difference between groups. The SF-36 mental component was slightly better in EVLA vs. UGFS (p=0.048, using general linear model with adjustments for covariates used in minimisation algorithm) and all groups improved. Patient and nurses reported no difference between UGFS and EVLA in terms of residual veins at 6 weeks but fewer residual veins were reported by patients (not by nurses) in EVLA compared to UGFS at 6 months. Venermo's (2016) clinical success was measured using AVVQ and showed improvements in all groups with no statistical differences between groups.

2.1.3 Morbidity and Complication Rates

Morbidity and complication rates were very low in all RCTs in all treatment groups. Rasmussen (2011) reported one iliac vein thrombosis with pulmonary embolus one week after UGFS. Lattimer (2012) reported no serious complications except one EVLA patient who developed a common femoral vein thrombosis. Biemans (2013) noted a low frequency of minor morbidity (such as hyperpigmentation, thrombophlebitis and paraesthesiae), which was not statistically significant between groups. Brittenden (2015) reported no difference between groups in terms of serious adverse events (these included deep vein thrombosis and pain). Venermo (2016) noted no serious complications but recorded haematoma in 42% EVLA and 20% UGFS (p=0.001) and 4% superficial wound

infection rate with EVLA. Skin pigmentation and palpable lumps were seen more commonly in UGFS than EVLA at 4 weeks.

2.1.4 Costs and Return to Work

Only Rasmussen (2011), Lattimer (2012), Brittenden (2015) (reported by Tassie [68]) and Venermo (2016) looked at these outcomes. Rasmussen reported a quicker return to work after UGFS and RFA when compared to EVLA and Venermo found UGFS resulted in a faster return to work than EVLA. Treatment costs were €994 for UGFS, €1360 EVLA and €1436 RFA (cost of catheter higher than for EVLA). If time lost from work is included overall costs were €1554 UGFS, €2200 EVLA and €1996 RFA. Lattimer also found a cost advantage with UGFS (£230.24) compared to EVLA (£724.72), even if further foam treatments were required. Brittenden's trial demonstrated treatment costs of £245 for UGFS and £737 for EVLA (the difference appears to be due in part, to increased consumable costs). At 6 months total health service costs (including follow up and unplanned use of health service), UGFS costs were £465 and EVLA were £975.

2.1.5 Five-Year Results

Both Rasmussen's (2017) [56] and Biemans' (2015) [60] groups have reported 5 year outcomes.

Rasmussen had a significant loss to mid-term follow up with only 223 of the initial 580 legs available for 5-year review. GSV occlusion/absence was noted in 68.4% of UGFS and 93.2% of legs in RFA and EVLA on duplex, however, clinically apparent recurrence was noted in 18.7% RFA, 38.6% EVLA and 31.7% for UGFS. Biemans' team evaluated 193 of

224 initially randomised legs when Kaplan-Meier estimates demonstrated GSV obliteration in 77% of EVLA and 23% of UGFS legs; however, freedom from additional treatments over the 5-year period showed no difference between EVLA and UGFS. This perhaps illustrates the importance of technique (Biemans used approximately half the volume of foam compared with Rasmussen's study) to ensure improved long-term outcomes with UGFS when techniques are compared across case series [69].

Rasmussen did not study patient reported outcome measures at 5 years, however Bieman's group did perform this analysis. They found CIVIQ scores statistically worsened for UGFS (0.98 increase per year, 95 per cent CI 0.16 to 1.79) and improved for EVLA at 5 years (−0.44 decrease per year, 95 per cent CI −1.22 to 0.35), however, EQ-5D improved slightly (EVLA: 0.02, CI; 0.01, 0.03 and UGFS: 0.01 CI; 0.01, 0.02) and EQ-VAS worsened slightly in all groups. Multivariable analysis including age of CIVIQ, EQ-5D and EQ-VAS scores demonstrated no statistically significant differences between EVLA and UGFS.

2.1.6 Status Of Level - 1 Evidence and CG168

Clearly the sources of level-1, RCT evidence are limited by variation in technique, equipment details, definition of technical versus clinical success/failure, extent and duration of patient follow-up, relatively sparse use of patient reported outcomes and costs. Importantly, patient variation did not reflect daily UK practice since only primary GSV disease was studied in all RCTs. Reassuringly, all studies demonstrated good safety

[65,66] and efficacy was clinically measurable with statistically confirmed improvement in venous disease.

In terms of improvement in patients' wellbeing, ETA and UGFS seemed similar with similar PROMS and low complication rates; however, the CG168 hierarchy was supported by the consistently greater technical success with ETA relative to UGFS. UGFS was reproducibly less expensive than ETA.

2.2 OBESITY AND CHRONIC VENOUS INSUFFICIENCY DISEASE

There is increasing evidence linking obesity and chronic venous insufficiency independent of the risk of venous thromboembolism (VTE) as a cause as reviewed below. Obesity is clearly a complex disease process demanding several disease-related considerations for any treatment modalities in people suffering from this serious condition. NICE CG168 does not make any recommendations specific to venous disease in obesity except advising weight loss as part of lifestyle measures; the extant literature however demonstrates the link between obesity and venous disease and raises a number of questions pertinent to venous disease and its management in relation to CG168 in people with both conditions. As the evidence for the relationship between obesity and venous disease builds and the observed increase in incidence of obesity continues, perhaps updated guidelines will go further in making recommendations for the suitability of treatment methods for superficial venous disease in obese people. Incorporating this evidence into future guidelines will

inform clinicians and policy makers alike in commissioning interventions for obese patients.

2.2.1 Epidemiology of Obesity

The World Health Organisation (WHO) defines obesity as a Body Mass Index (BMI) >30kg/m^2 [70]. In the UK levels of obesity have steadily risen from 1993 to 2012, from 13.2% to 24.4% (men) and 16.4% to 25.1% (women) [71]. Worldwide, the WHO reports there are approximately 2.8 million deaths annually as a result of excess body weight and in 2008, 10% of men and 14% of women were classified as obese (approximately double the prevalence in 1980). Rates of obesity were highest in the Americas with a 26% prevalence of obesity with slightly lower prevalence of 23% in Europe [72].

The Health Survey England (HSE) 2012 [73] work found a strong relationship between age and obesity. Correspondingly, rates where 12% males and 14% females aged 16-24, rising to 33% of men and women aged 65-74 but the prevalence then decreases to 19% men and 18% women aged greater than 85.

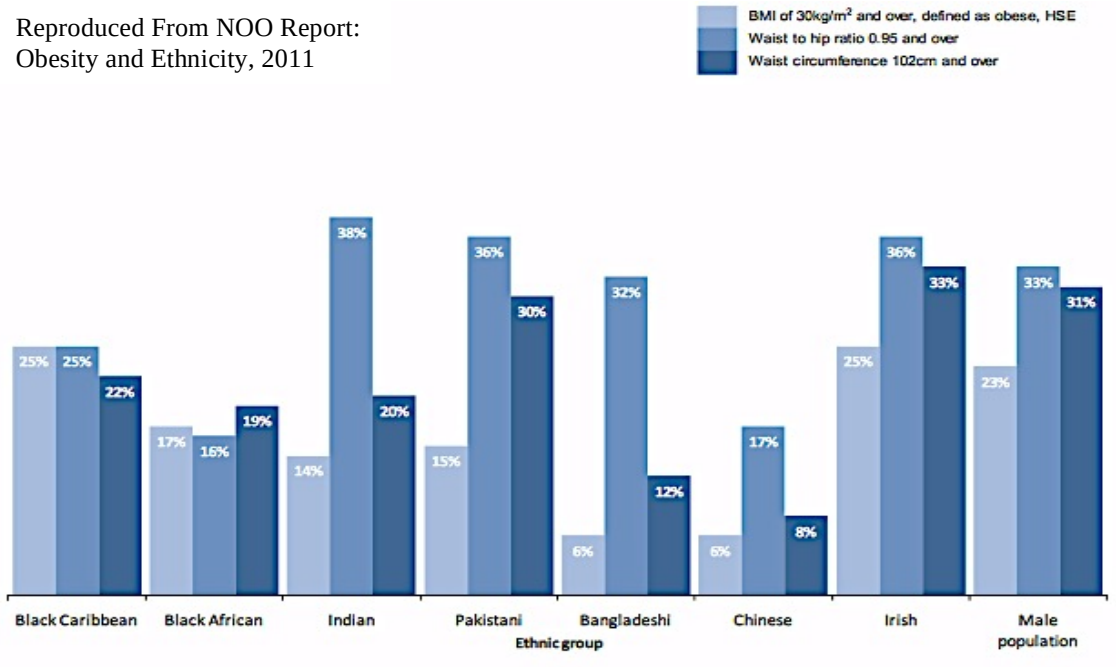
Income also appears to affect obesity; rates were lowest in higher (first quintile) income groups (21% men and 19% women) and highest in the fourth quintile (27% men and 33% women). This relationship appeared strongest in females.

Geographically, in the UK, age-standardised measurement of adult obesity did not vary significantly by region; however, by the inclusion of all those categorised as overweight (i.e. all those with BMI>25), in men, London was found to have the lowest rate (58%) and the West Midlands the highest (73%). In regard to women, London again displayed the lowest prevalence (51%) with the rest of the UK exhibiting similar levels of obesity five of the nine regions ranged from 60-61%.

Little data is available regarding the variation of obesity in differing ethnic groups. HSE produced a 'boosted sample' from minority ethnic groups in its 2004 survey, which was assimilated into the National Obesity Observatory (NOO) part of the Public Health England report of 2011 [74]. Figure 2.2.1 demonstrates that rates of obesity by ethnicity vary greatly depending upon the measure of obesity used (BMI>30, waist: hip ratio or waist circumference >102cm).

Figure 2.2.1: BMI, Waist: Hip Ratio And Waist Circumference, Men, England

Reproduced From NOO Report:
Obesity and Ethnicity, 2011



The current trend is predicted to continue with an on-going increase in population levels of obesity. Evidence is plentiful in support of decreased energy expenditure and increased calorie intake as a cause for the epidemic of obesity [75-77].

2.2.2 The Pathogenesis of Obesity

The aetiology of obesity is a complex interaction between environmental, hormonal and genetic influences. Environmental factors include the influence of increasing portion size, parallel with the increase in the obesity epidemic [78]. There is also a preponderance of increasing dietary fat content [79, 80] and high-energy foods that do relatively little to supress appetite whilst contributing towards greater daily calorie intake. The convenience of modern day living also encourages a sedentary lifestyle, thus decreasing energy expenditure [80-82]. Therefore, there is a trend towards increased energy consumption with decreased energy expenditure.

Multiple hormones have been implicated in obesity. These hormones can be centrally derived, gut-related or from adipose tissue itself. Hormones involved in obesity that are centrally derived include growth hormone and other components of the hypothalamo-pituitary-adrenal axis [83] as well as complex pathways for controlling energy homeostasis in the hypothalamus [84]. Ghrelin, a peripherally acting, stomach-derived hormone acts to increase appetite [85]. Other gut hormones act as anorectic agents, limiting food intake and allowing optimal digestion and absorption. These include cholecystokinin [86], peptide YY [87], pancreatic polypeptide [88], oxyntomodulin [89] and glucagon-like peptide 1 [90]. Appropriate

balance between appetite stimulating and suppressing influences obviously avoids the problems linked with overfeeding such as hyperinsulinaemia and insulin resistance.

Adipokines are a collection of hormones produced by adipocytes. These include tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), leptin and adiponectin. These hormones act both centrally, reducing appetite and regulating energy expenditure, as well as peripherally to affect insulin sensitivity, oxidative capacity and lipid uptake. It is the action of these hormones that is thought to be responsible for metabolic disturbances resulting in insulin resistance, type 2 diabetes and related cardiovascular disease [91, 92].

Genetic influences can be divided into syndrome associated obesity (e.g. Prader-Willi) and non-syndromic obesity. The heritability of non-syndromic obesity appears to be in the range of 40-70% [93]. Over the last few years the 'human obesity gene map' has described 11 single gene mutations, 50 loci related to Mendelian syndromes and 127 candidate genes related to obesity and numerous obesity-related genes have been described in animal models of obesity [94]. A full understanding of the genetic preponderance of obesity must await further research. Thus the pathophysiology of obesity is complex and multi-factorial. The effects of obesity are widespread and result in greater problems than just an increase in physical size.

2.2.3 Measures of Obesity

BMI (weight divided by height squared) is a commonly used method of indirectly assessing obesity. It can be calculated by measures easily made in most clinical settings. Height and weight, however, do not necessarily reflect body fat content exactly as body fat increases and muscle mass decreases with age (giving a falsely low BMI) and athletes with a large muscle mass (but low body fat) may have an elevated BMI. Other methods of estimating body fat include dual-energy x-ray absorption and impedance-based techniques. Whilst these are likely to be more accurate, their expense and impracticalities make them unsuitable for routine practice. Despite its inaccuracies, BMI is a strong predictor of risk [95] and therefore is the most commonly used measure of obesity in clinical practice.

2.2.4 Search Strategy

A Medline/PubMed (from 1946-2015) and Cochrane library literature search was conducted for articles related to obesity, overweight, thrombosis, varicose veins. These terms were linked with intra-abdominal pressure, inflammation, haemodynamics, CEAP (Clinical, aEtiology, Anatomy, Pathology classification of VVs), CVI, treatment, endovenous, endothermal, sclerotherapy, bariatric surgery, VTE, deep vein thrombosis (DVT). Further articles were located by following citations in previously identified papers.

2.2.5 Obesity and Superficial Venous Reflux Disease

A significant number of epidemiological studies have reported obesity to be a risk factor for the development of VV, chronic venous insufficiency and leg ulceration (Table 2.2.1).

2.2.6 The Effect of Obesity on Lower Limb Venous Haemodynamics

Obesity [96-98], and other factors which increase intra-abdominal pressure (IAP) (as measured and validated by Iburti et al [99, 100]) [101 102], are associated with increased femoral vein pressure and diameter [96, 97, 103] and decreased femoral vein flow leading to lower shear stress [102, 104] and possibly, increased predisposition to inflammation [15]. While in some young and otherwise fit people this increase in venous outflow resistance maybe compensated by improved calf muscle pump function [105], in the immobile and the elderly, these features are likely to favour the development and progression of lower limb venous disease (LLVD).

2.2.7 Obesity and The Symptoms and Signs of Lower Limb Venous Disease

Symptoms suggestive of LLVD are common in the overall adult population; however, there is an inconsistent relationship between these symptoms and presence of venous disease on objective clinical and duplex ultrasound examination [106]. This suggests that other factors, such as obesity, may be important in the aetiology of such "venous" symptoms [103, 107]. Correspondingly, obesity appears to be associated with a worse CEAP clinical grade in patient cohorts [103, 108-112] and epidemiological studies [113] whilst patients with skin changes [103] and active venous ulceration are more likely to be obese [114].

2.2.8 'Diabesity' and Lower Limb Venous Disease

No confirmed link exists between diabetes mellitus and varicose veins but there is a strong correlation between obesity and diabetes embodied in the term 'diabesity' [115]. In patients

who develop venous ulceration, diabetes is likely to impair wound healing and prolong ulcer duration [116]. There is no extant evidence that obesity is an independent risk factor for LLVD ulceration; however, given the ‘pro-inflammatory’ state in diabetes (along with obesity) and that obesity is a risk factor for LLVD, this link would appear likely.

Table 2.2.1: Cohort Studies: Relationship Of Obesity And Varicose Veins.

Author	Year	Journal	Number of Participants	Relationship with obesity
Mekky et al[8]	1969	Brit Med J	971 women	Increasing body weight correlated with prevalence of varicose veins (P<0.001)
Abramson et al[11]	1981	J Epidemiol Com Health	4888	Those with VV tended to be heavier – mean difference 3.8kg (P<0.00001)
Ducimetiere et al[117]	1981	Int J Epidemiol	7432 men	VV positively associated with increased BMI (P=0.001)
Seidell et al[118]	1986	Am J Pub Health	19126	In women raised BMI associated with VV (OR 3.06; 95% CI 2.03-4.62 in severely overweight)
Brand et al[7]	1988	Am J Prev Med	3822	Women with VV more likely to be obese (P<0.01)
van Noord et al[119]	1990	Int J Epidemiol	11825 women	Quintiles with BMI<27.93 less likely to have VV ($P \leq 0.05$)
Stvrtinova et al[120]	1991	Int Angiol	696 women	Patients with VV more likely to be obese ($P \leq 0.05$)
Sadick et al[121]	1992	J Dermatol Surg Oncol	500 women	Raised BMI is risk factor for VV
Sisto et al[122]	1995	Eur J Surg	8000	Raised BMI associated with VV
Scott et al[123]	1995	J Vasc Surg	335	Obesity increases risk of CVI (OR 1.06/kg/m^2; 95% CI 1.01-1.1; P=0.014)
Canonico et al[124]	1998	Angiol	1319	Raised BMI associated with increasing prevalence of VV (P<0.0001)
Kontosic et al[125]	2000	Acta Med Okayama	1324	Raised BMI associated with VV (OR = 1.04; 95% CI 1.01-1.07)
Iannuzzi et la[126]	2002	J Vasc Surg	104 women	BMI >30 associated with VV (OR = 5.8; 95% CI 1.2-28.2)
Maurins et al[127]	2008	J Vasc Surg	3072	BMI > 30 associated with more superficial reflux
Robertson et al[6]	2013	Eur J Vasc Endovasc Surg	880	Risk of developing reflux if overweight (OR = 2.1; 95% CI 1.0-4.4)
Vlajinac et al[112]	2013	Eur J Vasc Endovasc Surg	1116	Obesity related to 'C' category of CEAP (multivariate analysis, P<0.001)

VV – varicose veins, BMI – body mass index, CVI – chronic venous insufficiency

2.2.9 Treatment of Lower Limb Venous Disease in Obese People.

Obesity is associated with delayed healing of chronic venous ulceration and increased risk of ulcer recurrence [107] following treatment with compression compared with 'normal weight' patients [128]. The reasons for this probably include, in obese people, the increased technical difficulty in applying adequately sustained compression, immobility, poor compliance, and the adverse venous haemodynamics described above. Obese people are more prone to anaesthetic [129] and surgical morbidity, such as surgical site infection [114] and mortality [130, 131]; additionally, venous surgery may be technically challenging in the obese leg. The same may be true of endovenous techniques although, as obese patients are notably absent from many of the published trials, it is difficult to draw any firm conclusions [132-135]. Similarly, some [136-138], but not all studies [139], have found obesity to be associated with increased treatment failure/varicose vein re-canalisation.

2.2.10 Treatment of Obesity in Patients With Lower Limb Venous Disease

Bariatric surgery, comprising either Roux-en-Y gastric bypass (up to 80% of patients improve) [140] or vertical band gastroplasty (up to 100% patients improved) [141] has been shown to lead to an improvement in the symptoms and signs of LLVD. This may be due to an improvement in the adverse haemodynamics associated with obesity [104]. Although level 1 evidence is lacking, whenever possible, it would seem appropriate to try to manage obesity before embarking upon traditional surgical or endovenous treatment of LLVD.

2.2.11 A Reflective Approach to Venous Disease in People Suffering Obesity

Evidence of obesity as a risk factor for venous disease has been well documented by numerous epidemiological studies. Table 2.2.1 illustrates the many studies linking obesity and venous disease; the correlation appears mainly between BMI and VV in older manuscripts and between BMI and chronic venous insufficiency in more recent publications. Perhaps this is a reflection of the increased understanding of both obesity and LLVD as inflammatory conditions rather than simply a combination of excess adipose tissue and superficial venous reflux? The literature demonstrates that obesity worsens the symptoms of LLVD and is related to a worse CEAP score. These features may result from the venous haemodynamic changes found in several studies, but may also be compounded by a degree of 'functional' venous insufficiency as a result of obese patients' poor mobility and lack of activation of the calf muscle pump. Venous ulceration is likely to be more common and when present has been linked to reduced healing rates. The latter is particularly true of diabetic, obese patients. Obesity is a complex disease process, which is not yet fully understood. As such the aetiology of combined excess body fat and LLVD or 'phlebesity,' is further still from being understood. With more severe symptoms and greater risk of ulceration, perhaps obese patients present a greater degree of clinical urgency in their need for definitive VV treatment?

Treatment of LLVD in the obese is an area where definitive evidence is truly lacking. Whilst endovenous techniques are likely to be safer, they are also likely to be technically more difficult than in normal weight patients; post -treatment compression is more difficult to apply. The durability of treatment methods has not been examined raising questions of

whether re-canalisation is more likely because of higher femoral vein pressure or does there exist the potential for higher rates of VTE? Along with the former considerations there are many other unanswered questions. Perhaps it is more prudent for patients to first undergo weight-loss management programmes/surgery, which has been demonstrated to improve their LLVD symptoms before undergoing venous interventions, the latter could be used subsequently if still required?

VTE is more prevalent in the obese and even normal weight diabetic patients suffer a more complicated clinical course. No clinical scoring system for VTE has been separately validated in the obese, therefore diagnosis can be clinically challenging. Confirmatory imaging of flow and compressibility by DUS is technically demanding due to the depth of the deep veins. Diagnostic imaging may be improved with cross-sectional techniques, however this is more 'resource-heavy' and further research into the reliability of CT and MRI venous imaging in obese people seems required?

2.2.12 Obesity, Venous Disease and NICE Guidance CG168

LLVD and obesity have both increasingly common around the world. As such, surgeons or phlebologists will be treating ever-greater numbers of obese patients with LLVD. Furthermore, clinicians in many other specialties are going to be treating a wide range of obesity-related health problems in people who also have, or are at risk of developing LLVD, and complications including deep vein thrombosis (DVT). Unfortunately, obese people have been specifically excluded from many, if not most, of the pivotal studies. As such, many basic questions remain unanswered and there is an urgent need for further

research in this area and further development of NICE guidance using what evidence is currently available although some may argue that the currently available data are not strong enough to make any recommendations? Presently, clinicians are left with the task of advising venous treatments based primarily upon clinical judgement supplemented by adjuring people to use lifestyle modification with weight loss to improve symptoms as well as general health.

As discussed above, CCGs are using 'lifestyle' rationing (based on BMI or smoking status) to reduce costs. Significant proportions of CCGs are applying these measures to VV interventions[142]. With the absence of evidence at present to inform NICE guidance regarding obesity and venous disease, it is perhaps unsurprising that no guidance is offered over weight loss as a lifestyle measure in VV. This prevents vascular specialists from challenging this behaviour. With the accumulation of evidence and its incorporation, future guidance will inform both clinicians and commissioners alike.

Chapter 3

RESULTS

OVERVIEW AND HYPOTHESES TESTED

Sections 3.1-3.3 describe the impact of CG168 upon a local secondary care vascular unit by comparing 18-month periods before and after July 2013 when the guidelines were introduced. The data presented centres upon sections of the guidelines directly appropriate to vascular surgeons in Sections 3.1 and 3.2; Sections 3.3, 3.4 and 3.5 show evidence of the effects of CG 168 on the general practice/vascular surgical interface, 3.3 and 3.4/3.5 at local and national levels, respectively. Changes of varicose vein management in local secondary care are reported in section 3.1. Evidence for any improvement in the secondary care management of leg ulcer patients is related in Section 3.2. Local referral patterns from general practice generated the data for Section 3.3 to find if CG 168 had affected access to specialist care in relation to social deprivation.

Section 3.4 and 3.5 present the data from The Health Improvement Network (THIN) database to try to delineate the national impact of CG168 on general practice and its influence upon the practice of vascular surgery with Sections 3.4 and 3.5 focusing on simple venous disease (varicose veins) and venous leg ulceration, respectively.

***Hypotheses Tested By Section**:*

3.1 Introduction of NICE CG168 at HEFT has resulted in increased numbers of varicose vein interventions. These will be performed at an earlier CEAP stage and using an increasing number of endovenous modalities.

Null hypothesis – introduction of CG168 has not affected VV interventions.

3.2 Introduction of NICE CG168 at HEFT has increased the number of leg ulcer referrals. Leg ulcers will be referred earlier.

Null hypothesis – introduction of CG268 has resulted in no change in leg ulcer referrals.

3.3 Introduction of NICE CG168 has increased number of referring GP practices. There has been no change in access to specialist care relating to social deprivation.

Null hypothesis – NICE CFG168 has not increased the number of GP practices referring patients and has adversely affected access to specialist care related to social deprivation.

3.4 Introduction of NICE CG168 has improved the numbers of patients referred with varicose veins by primary care. There has been a reduction in prescription of compression hosiery and more varicose vein interventions are being performed.

Null hypothesis – NICE CG168 has not increased varicose vein referrals or affected compression hosiery prescription/varicose vein interventions.

3.5 Introduction of NICE CG168 has increased the number of leg ulcers referred by primary care nationally.

Null hypothesis – NICE CG168 has not affected referrals for patients diagnosed with leg ulcers in primary care

3.1 CHANGES IN VARICOSE VEIN TREATMENT ACTIVITY AFTER INTRODUCTION OF NICE CG168 IN EAST BIRMINGHAM

NICE CG168 declared that patients with symptomatic varicose veins should receive NHS treatment and that waiting for skin changes to develop was inappropriate. CG168 also introduced a treatment hierarchy for superficial venous disease. The clinical data presented below aimed to assess the impact of these components of CG168 on local (Heart of England NHS Foundation Trust) (HEFT) secondary care management of varicose veins.

3.1.1 Abstract

- **Objective:** Although varicose veins (VV) are a common cause of morbidity, the UK National Health Service (NHS) and private medical insurers (PMI) have previously sought to ration their treatment in order to limit health care expenditure

and reimbursement but this approach was lacking an evidence base. The July 2013 UK National Institute for Health and Care Excellence (NICE) Clinical Guidelines (CG168) embodied the promotion of evidence-based commissioning and management of VV. The aim of this study was to evaluate the impact of CG168 on the referral and management of VV at the Heart of England NHS Foundation Trust (HEFT), Birmingham, UK.

- **Methods:** Interrogation of the HEFT Performance Unit prospectively gathered database, yielded numbers of patients undergoing interventions for VV from 1 January 2012 to 31st December 2014. Patients treated before (group 1) and after (group 2) publication of CG168 were compared.

- **Results:** There were 253 patients, 286 legs (48% male, mean [range] age 54 and [20-91] years) treated in group 1 and 417 patients, 452 legs, (46% male, mean [range] age 54 and [14-90] years) treated in-group 2, an increase of 65%. CG168 was associated with a significant reduction in the use of conventional surgery (131 patients [52%] group 1 vs. 127 patients [30%] group 2, p=0.0003, χ^2), no change in endothermal ablation (30 patients [12%] group 1 vs. 45 patients [11%] group 2), a significant increase in ultrasound guided foam sclerotherapy (92 patients [36%] group 1 and 245 patients [59%] group 2, p=0.0001, χ^2), and an overall increase in treatment for CEAP class C2/3 disease (53% group 1 and 65.2% group 2, p=0.0022, χ^2).

- **Conclusions:** Publication of NICE CG168 has been associated with a significant increase (65%) in the number of patients treated, referral at an earlier (CEAP class C) stage and increased use of endovenous treatment. CG 168 has been effective in improving access to, and quality of care, for VV at HEFT.

3.1.2 Introduction

Varicose veins (VVs) are common in the adult population [6] causing considerable morbidity, disability and loss of productivity [25, 46, 143-145]. Previous local, regional and national guidelines, such as those published by the UK National Institute for Health and Care Excellence (NICE) in 2001, discouraged referral and interventional treatment for VV [146]. Instead, this earlier guidance advocated conservative management in primary care with advice on exercise, leg elevation and compression hosiery and indicated that referral to secondary care was only required for specialist assessment. Interventional treatment was reserved mainly for those patients who had bled from their VV, had active ulceration or skin changes, or who had suffered repeated bouts of thrombophlebitis. Patients suffering from 'severe' VV symptoms could be referred but treatment was only funded if their VVs were judged as causing a 'significant' impact on their quality of life. The overall low clinical priority placed on the treatment of VV by NICE and other bodies encouraged the UK National Health Service (NHS) and private medical insurers (PMI) to ration treatment in the absence of a clear evidence base thus limiting health care expenditure and re-imbursement. This situation became increasingly unsatisfactory to patients, as well as health care purchasers and providers; subsequently NICE experienced pressure to reconsider initial guidance in the light of a growing body of evidence demonstrating the

clinical and cost effectiveness of VV interventions, especially non-surgical endovenous techniques. Correspondingly, the revised evidence-based NICE Guidance (CG168) of July 2013 [147] advised that symptomatic CEAP class C2 patients be referred for specialist clinical and duplex ultrasound assessment with treatment allocated according to an interventional treatment hierarchy (endothermal ablation, foam sclerotherapy or surgery) in preference to conservative therapy with compression hosiery [18]. NICE CG168 and the accompanying Quality Standards (QS) for commissioning [148] have been widely welcomed by patients and endorsed by professional bodes such as the Vascular Society of Great Britain and Ireland (VSGBI) and the Royal College of Surgeons (RCS) [149]. Increasing pressure on NHS resources and PMIs means that the publication of national guidelines such as NICE CG168 does not always lead to changes in commissioning, referral practice and reimbursement. The aim of this study, therefore, was to evaluate the impact of CG168 on the referral and management of VV at the Heart of England NHS Foundation Trust (HEFT), which serves a population of about 1.2 million people in East Birmingham, UK.

3.1.3 Methods

A prospectively gathered database of all VV interventions (delivered by 6 consultant vascular surgeons who offered endovenous and surgical interventions (one consultant offered only surgical treatments referring people appropriate for endovenous interventions to the other consultants) performed at HEFT from 1 January 2012 (18 months before the publication of NICE CG168, group 1) to 31 December 2014 (18 months after publication, group 2) was supplied by the HEFT Performance Unit using Hospital Episode Statistics (HES) data. Electronic patient records were interrogated for Intervention type, CEAP

class/clinical grade at presentation and early (up to 6 weeks) complications. The characteristics of group 1 and group 2 were compared using the χ^2 test. Ethical committee approval was not sought for sections 3.1-3.3 as these sections formed part of service evaluation and utilised anonymised routinely collected healthcare data. Data on leg ulcer (sections 3.2 and 3.3) patients was also recorded as part of the screening logs for the EVRA trial.

3.1.4 Results

During the three-year study period 670 patients (738 legs) underwent either conventional surgery (CS), endothermal ablation (ETA) by radio-frequency ablation (RFA) or ultrasound-guided foam sclerotherapy (UGFS). A significantly greater number of people were treated earlier in the course of venous disease in CEAP class 2/3 (53% group 1 and 65.2% group 2, p=0.0022, χ^2) in the period after publication of CG 168 guidance (Table 3.1.1).

Publication of CG168 was also associated with a subsequent 65% (p=0.0001, χ^2), increase in the number of patients undergoing interventions for VV in group one, 253 patients (48% men, mean age 54, range 20-91, SD15) and group two, 417 patients (46% male, mean age 54, range 14-60, SD15). Figure 3.1.1 demonstrates a steepening of the curve after July 2013, implying an increasing number of patients were undergoing VV treatments. This is confirmed by Figure 3.1.2, showing a greater number of patients treated per month comparing the Jan 2012 to June 2013 periods with the subsequent 18 months. CG168 was

associated with a significant reduction in the use of surgery (131 patients [52%] group 1 vs. 127 patients [30%] group 2, p=0.0003, χ^2). There was no change in the use of endothermal ablation (30 patients [12%] group 1 vs. 45 patients [11%] group 2) but a significant increase in ultrasound guided foam sclerotherapy occurred (92 patients [36%] group 1 and 245 patients [59%] group 2, p=0.0001, χ^2). The numbers of patients in each treatment category are shown in Table 3.1.2.

Figure 3.1.1. ***Cumulative Number of Patients Treated by Date***

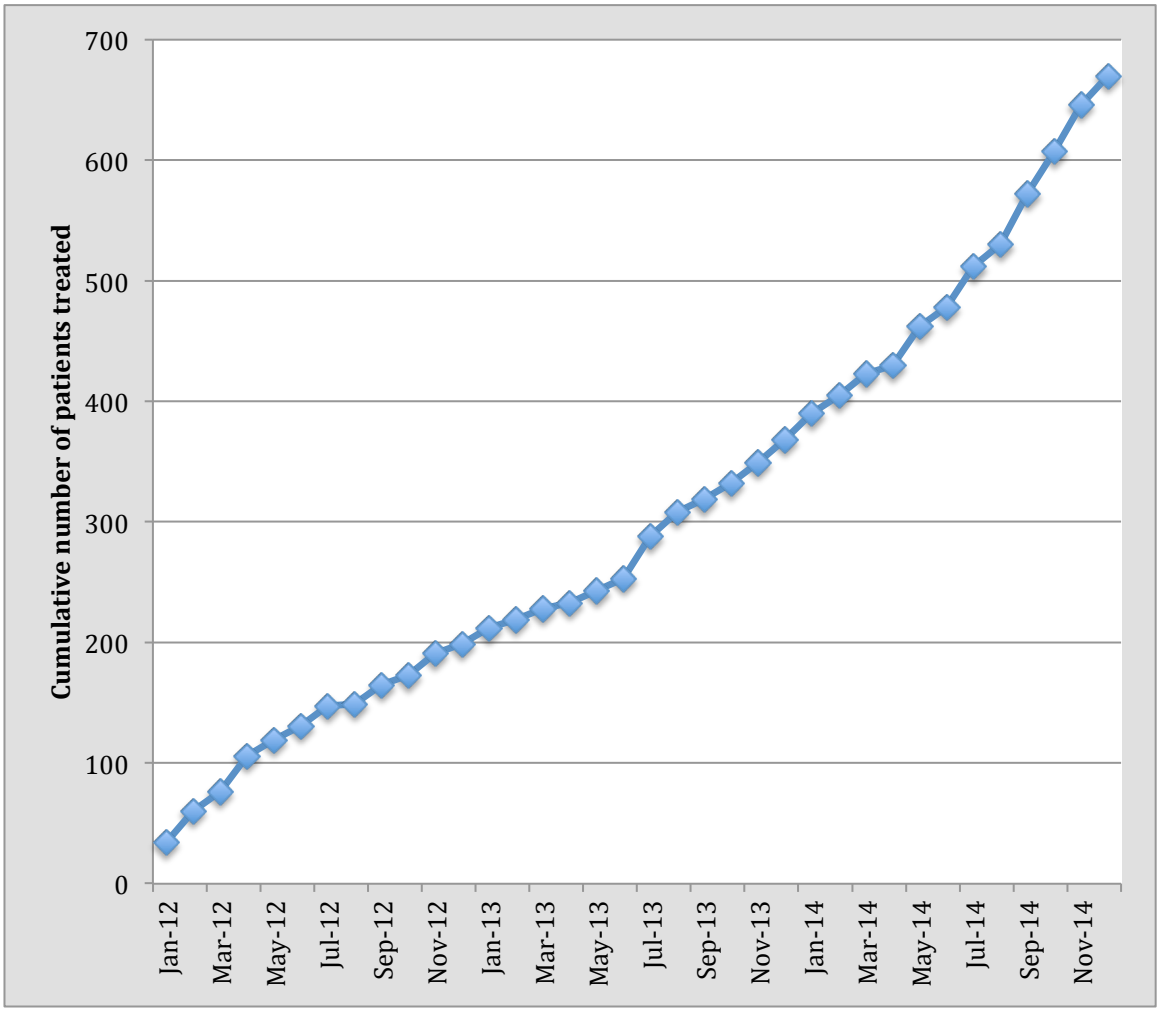


Figure 3.1.2. ***Number of Patients Treated per Month***

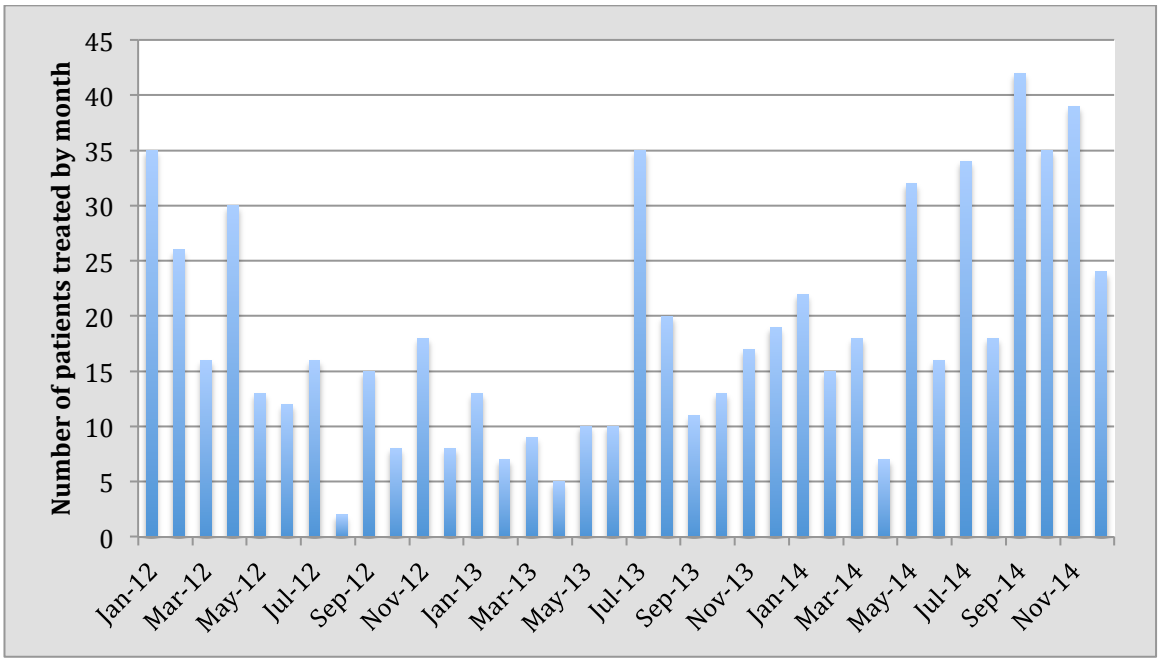


Table 3.1.1. ***CEAP Clinical Grade in Group 1 and 2 Before and After Publication of CG168***

Group 1			Group 2		
CEAP	Number	Percentage	CEAP	Number	Percentage
C2	94	37.2%	C2	231	55.4%
C3	40	15.8%	C3	41	9.8%
C4	80	31.6%	C4	99	23.7%
C5	18	7.1%	C5	19	4.5%
C6	21	8.3%	C6	27	6.5%

Up to and including, 6-week follow up, five complications were noted in the CS cohort, seven complications were noted in the conventional surgery cohort, in groups 1 and 2 respectively and none with ETA (Table 3.1.2). One complication occurred in the group 2 UGFS cohort (unplanned accident and emergency attendance with a small area of phlebitis requiring reassurance and simple analgesia). No endovenous complications were noted for group 1. Group 2 included 1 death (after conventional surgery) from pulmonary embolus (Table 3.1.2).

Table 3.1.2. ***6-Week Complications After VV Treatments***

Group 1			**Group 2**		
Surgery (n=131)	ETA (n=30)	UGFS (n=102)	Surgery (n=127)	ETA (n=45)	UGFS (n=245)
Wound infection 2	none	none	Wound infection 3	none	Phlebitis requiring unplanned hospital visit 1
Calf vein DVT 1			DVT 1		
Seroma 1			Seroma 1		
Post procedural ulcer 1			Hyperaesthesia 1		
			Thigh haematoma 1		
			Death 1 (PE)		

3.1.5 Discussion

The present study clearly indicates that publication of the NICE CG168 and the accompanying QS for commissioning, supported by guidance from the VSGBI, the RCS, and the Venous Forum of the Royal Society of Medicine [150], has led to a marked and precipitate increase in the numbers of patients referred, undergoing specialist assessment and intervention for VV at HEFT. An increase was detectable just before July 2013(Fig. 3.1.2), perhaps as a result of the increased awareness of varicose vein treatments from launching the new guidelines locally to community practitioners. The guidance was notified via letters to general practices, at community practice study days for doctors and community nurses and "informationals" in local press. Furthermore, in line with NICE recommendations, patients are being referred at an earlier stage (CEAP class 2 and 3, Table 3.1.1) and are more likely to undergo endovenous rather than surgical treatment as shown by the changes in numbers of patients treated in each treatment category (Table 3.1.2). As comprehensively reviewed in CG168, there is a large evidence base demonstrating that non-surgical, interventions for CEAP C2-C6 VV, especially, are highly clinically [151] and financially effective [152, 153]. Only 5-7% of VV patients present with thrombophlebitis, bleeding, skin changes or ulceration [154, 155] and so previous guidelines had excluded many people with symptomatic VV from highly effective treatment that is associated with a marked improvement in health related quality of life; such treatment is extremely safe and well tolerated as shown by the low complication rate in the HEFT series (Table 3.1.2). Endovenous treatment allows a rapid return to normal activities representing excellent 'value for money' for the NHS [156-158]. Furthermore, conservative management does not appear to prevent progression to worse CEAP class venous disease [159, 160] and a systematic review could not demonstrate that compression hosiery alone was

adequate to slow progression or prevent recurrence [161]. The use of compression stockings is well known to have poor compliance and despite their use, surgical treatment of VVs has been demonstrated to result in a greater improvement to quality of life and symptoms [151, 152] than stockings alone. A large increase was seen in UGFS treatments (Table 3.1.2) and the vascular surgery department at HEFT has published extensively on UGFS outcomes [69, 162-164] there being little difference in patient reported outcomes when comparing ETA to UGFS [165]. HEFT is able to offer UGFS at a fraction of the cost of ETA and this was a likely factor contributing to the increased use of this endovenous treatment modality.

Limitations

Data was collected through interrogation of prospectively gathered data. NICE CG168 was advertised locally to GPs by letters and at vascular themed community teaching days. During the study period the authors are not aware of any significant changes to the study population or to the number of referrers and the author can see no indication that the patient population served by HEFT would have changed significantly during the study period. This population however, is highly multi-culturally and socio-economically diverse[166] and may not be representative of the United Kingdom as a whole. The waiting lists across adjacent hospital trusts may have influenced patients to chose HEFT over other trusts through the 'choose and book system;' however, the author was unable to obtain accurate waiting list times for the study period from all surrounding NHS trusts to evaluate any bias this may have caused. HEFT vascular department is also known to have an interest in venous disease, which may have influenced referring practitioners.

3.1.6 Conclusion

Updated NICE guidelines and quality statements have greatly improved access to, and delivery of, evidence-based VV treatment in the HEFT catchment area. Continued advertisement of new guidelines and their recommendations to referrers will ensure that these improvements will be sustained in the longer term.

3.2 IMPACT OF UK NICE CLINICAL GUIDELINE 168 ON REFERRALS TO A SECONDARY CARE BASED LEG ULCER SERVICE

CG168 recommended that all those with varicose veins and a skin break below the knee present for two weeks or longer should be referred for specialist vascular opinion. Data presented in this section was collected in an attempt to assess the impact of this recommendation on referral numbers to a local (HEFT) secondary care vascular service.

3.2.1 Abstract

- **Background:** Leg ulcers are a common cause of morbidity and disability and result in significant health and social care expenditure. NICE Clinical Guideline (CG) 168 sought to improve care of patients with leg ulcers, recommending that patients with a break in the skin below the knee that had not healed within 2 weeks be referred to a specialist vascular service for diagnosis and management.

- **Aim:** To determine the impact of CG168 on referrals to a leg ulcer service.

- **Methods:** Numbers of patients referred with leg ulceration during the 18-month period prior to CG168 (January 2012-June 2013) and the 18-month period commencing 6 months after CG 168 publication (January 2014-June 2015) were compared.

- **Results:** There was a 2-fold increase in referrals (181 patients, 220 legs vs. 385 patients, 453 legs) but no change in mean age, gender or median-duration of ulcer at referral (16.6 vs. 16.2weeks). The mean time from referral to specialist appointment increased (4.8 vs. 6weeks, p=0.0001), as did the number of legs with superficial venous insufficiency (SVI) (36% vs. 44%, p=0.05). There was a trend towards more SVI endovenous interventions (32% vs. 39%, p=0.271) with an increase in endothermal procedures (2 vs. 32 legs, p=0.001) but no change in sclerotherapy treatments (24 vs. 51 legs). In both groups 62% legs had compression hosiery. There was a reduction in numbers of legs treated conservatively with simple dressings (26% vs. 15%, p=0.0006).

- **Conclusion:** Since CG168 there has been a considerable increase in leg ulcer referrals; however, patients are still not referred until ulceration has been present for many months. Although many ulcers are multi-factorial and the mainstay of treatment remains compression; there has been an increasing trend toward endovenous intervention in SVI. Further efforts are required to persuade community practitioners to refer patients earlier, to increase awareness in patients and to encourage further investment in chronically underfunded leg ulcer services.

3.2.2 Introduction

In the UK leg ulcers are estimated to affect 1% of the adult population with a greater preponderance (3-5%) in people aged over 65 [167]. Leg ulcers are associated with a significant reduction in quality of life for affected individuals [168, 169] and their families and carers [170] as well as considerable health and social care expenditure. Most leg ulcers are vascular in aetiology [171] and it is widely accepted that a prompt and full specialist assessment of the underlying venous and/or arterial disease is required in order to maximise chance of healing and to minimise recurrence rates [172]. In recognition of this, the NICE Clinical Guideline (CG) 168 recommended that all people with a break in the skin below the knee that has not healed within 2 weeks be referred to a specialist vascular service [173]. The aim of the study described in this section was to determine the impact of UK NICE CG 168 on referrals to the specialist leg ulcer service of the University of Birmingham academic department of vascular surgery at HEFT.

3.2.3 Methods

Patients referred to the University of Birmingham academic vascular unit specialist leg ulcer clinic based at Solihull Hospital, part of the Heart of England NHS Foundation Trust (HEFT), during an 18 month period prior to CG 168 (January 2012 to June 2013) were compared with those referred during an 18 month period commencing 6 months after publication of CG 168 (January 2014 to June 2015). HEFT covers a catchment population of approximately 1.2 million people comprising a mixture of inner city, socially deprived patients along with those from affluent suburbs. Referrals to the service were accepted from all sources, the vast majority came from general practitioners and community nurses.

All patients were assessed for vascular disease with presence of pulses and/or ankle brachial pressure index (ABPI) for arterial disease and for deep and superficial venous insufficiency with duplex ultrasonography. Data was gathered through retrospective interrogation of routinely collected NHS data and a prospective database of all patients referred with a leg ulcer. Venous disease was defined as the presence of superficial and/or deep venous incompetence (SVI/DVI) exceeding >0.5s on duplex ultrasonography. Significant arterial disease was defined by an ABPI of less than 0.8 at rest. The characteristics of the two groups of patients were compared using t-test and χ^2-test as appropriate using the analysis programme SPSS 22 (IBM, USA).

3.2.4 Results

After publication of CG 168 there was an approximately 2-fold increase in referrals (181 patients, 220 legs vs. 385 patients, 453 legs) but no change in age (mean, range, respectively: 75, 23-98 vs. 76, 33-104, years), gender (47% vs. 43% male) or median or inter-quartile range (IQR) duration of ulcer history at referral (respectively, 16.6, 7-30 vs. 16.2, 6-46, weeks) or at first clinic appointment (respectively 20, 12-36 vs. 23, 12-52 weeks) (Table 3.2.1). A mean of 9.5 patients/month were referred before the CG 168 guideline increasing to a mean of 17.5 patients/month with obviously, a corresponding increase in overall numbers of patient referrals after guideline introduction (Figure 3.2.1, Table 3.2.1). Mean time from referral to first clinic appointment increased (4.8 vs. 6 weeks, $p = 0.0001$) (Table 3.2.1), as did the proportion of legs with SVI (82 legs, 37% vs. 214 legs, 47%, $p = 0.05$) (Table 3.2.2). There was no change in the proportion of legs with DVI (8.2%, 1 obstruction and 17 reflux vs. 8.8%, 11 obstruction and 29 reflux), traumatic /

pressure ulceration (22 legs, 10% vs. 37 legs, 8.2%), functional venous insufficiency [174] (57 legs, 26% vs. 86 legs, 19%), or with pure arterial ulcers (21 legs, 9.5% vs. 53 legs, 11.7%, Table 3.2.2). It is axiomatic that the exact numbers of patients in the various categories of venous disease would be greater in view of the overall approximately 2-fold increase in number of people referred (Table 3.2.1). Significantly less legs with mixed arterio-venous ulcers (13 legs, 5.9% vs. 6 legs 1.3%, p = 0.0018) and proportionately less non-arterial, non-venous ulceration (106 legs, 48% vs. 154 legs, 34%, p=0.0012) were seen in the period after CG 168 publication (Table 3.2.2). There was no significant increase in the proportion of legs with SVI undergoing superficial venous intervention (32% vs. 39%)(Table 3.2.3). No patient had traditional venous surgery. There was a significant increase in endothermal ablation procedures (2 vs. 32 legs, p = 0.001) but no statistically significant change in ultrasound-guided foam sclerotherapy although overall numbers of legs were greater (24 vs. 51 legs) (Table 3.2.3). Both groups of patients received compression hosiery in equal proportions (136 legs, 62% vs. 281 legs, 62%) but there was a significant reduction in legs treated conservatively with simple dressings only (52 legs, 11.5% after publication of CG168, before CG168 corresponding figures were 26% vs. 58 legs, 26%, p = 0.0006) (Table 3.2.3); clearly this represented a 15% decrease in the use of simple dressings after introduction of CG168. Arterial ulceration was treated using an endovascular approach in 21 legs (6 legs in group 1 and 15 legs in group 2) and by means of surgery in 10 legs (1 leg in group 1 and 9 legs in group 2) (Table 3.2.3). Some patients in groups 1 and 2 were diagnosed with ‘non-vascular’ causes of leg ulceration and these are detailed in Table 3.2.4.

Figure 3.2.1. ***Leg Ulcer Referrals by Month***

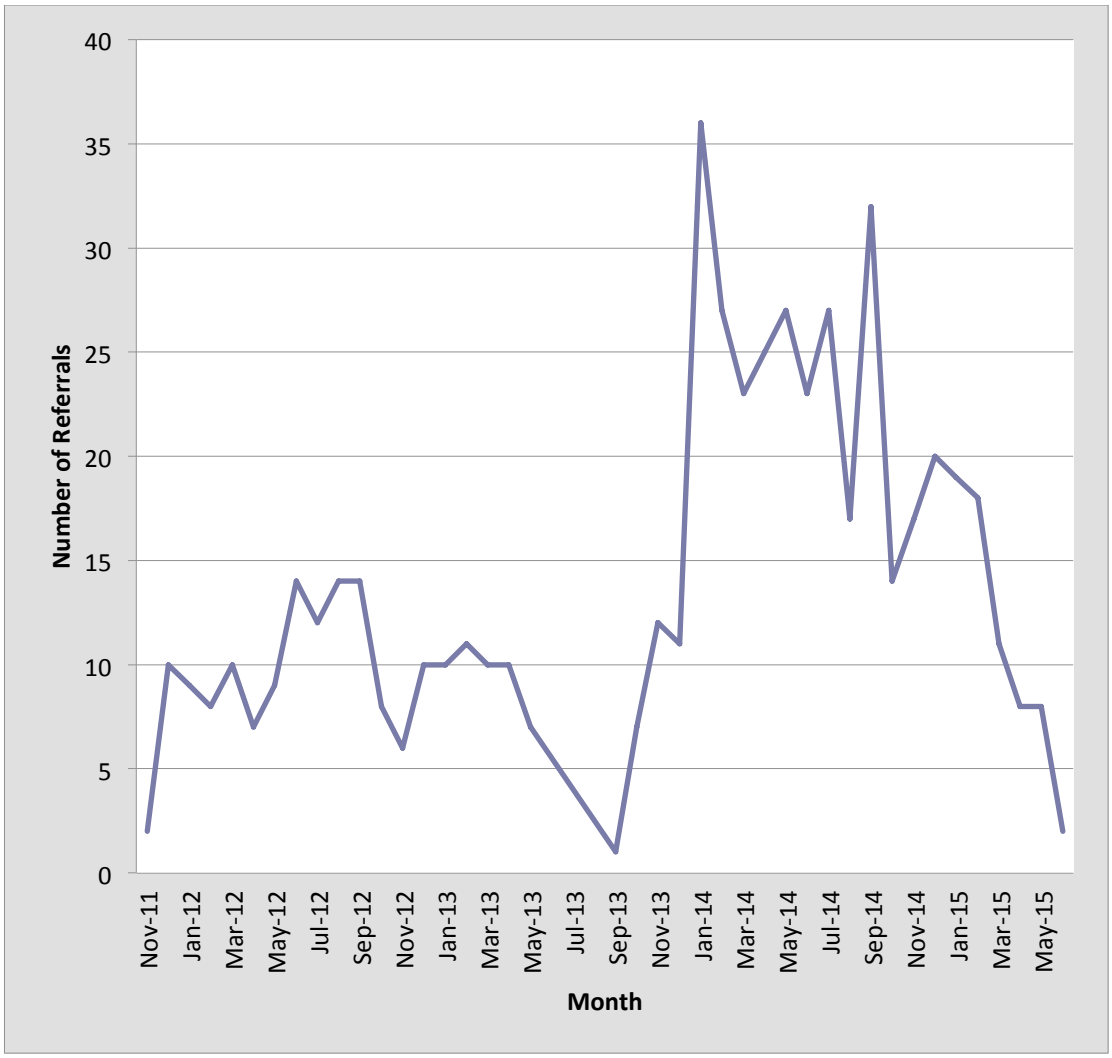


Table 3.2.1 ***Patient Characteristics, Leg Ulcer History And Service Involvement***

Feature	Before CG 168 (Group 1)	After CG 168 (Group 2)
Number referred	181	385
Number of legs ulcerated	220	453
Age Mean	75	76
S.D.	13.5	12.7
Range	23-98	33-104
Gender		
Male number (%)	85(47)	166(43)
Female number (%)	96(53)	219(57)
Ulcer duration (weeks) at referral - median	16.6	16.2
Interquartile range	7-30	6-46
Ulcer duration at first appointment – median	20	23
Interquartile range	12-36	12-52
Patients referred per month		
Mean	9.5	17.5
S.D.	3.0	9.5
Time to first appointment (weeks) –		
Mean	4.8	6*
S.D.	2.5	3.5

***p<0.0001, χ^2, all other features not statistically different though overall referral numbers clearly increased*

Table 3.2.2 ***Aetiological Processes in Ulceration in Referred Patients***

Feature	Before CG 168 Group 1	After CG 168 Group 2
SVI **Number (%)**	**82 (37)**	**214 (47)***
DVI (total) **Number (%)**	**18 (8.2)**	**40 (8.8)**
DVI with obstruction (number)	**1**	**11**
DVI with reflux (number)	**17**	**29**
Trauma/pressure ulceration: number (%)	**22 (10)**	**37(8.2)**
Functional Venous Insufficiency	**57 (26)**	**86 (19)**
Pure Arterial Ulcers numbers (%)	**21 (9.5)**	**53 (11.7)**
Mixed Arterio-venous Ulcers – Number (%)	**13.5 (5.9)**	**6 (1.3)****
Non-arterial, Non-venous Ulcers Number (%)	**106 (48)**	**154 (34)*****

*Numbers in features column denote number of legs seen in referred patients. * $p<0.05$, ** $p<0.0018$, *** $p<0.0012$ (all p values for χ^2 comparing group 1 with group 2 patients*

Table 3.2.3 ***Treatments for Ulceration in Referred Patients***

Method	Before CG 168 Group 1	After CG 168 Group 2
Simple dressings number (%)	58 (26.4)	52 (11.5)**
Compression hosiery number (%)	136 (62)	281 (62%)
Intervention for SVI number (%)	70 (32)	177 (39)
Endothermal ablation number (%)	2 (0.9)	32 (7.1)*
UGFS	24 (10.9)	51 (11.3)
Endovascular treatment for arterial ulcer number (%)	6 (2.7)	15 (3.3)

*Figures relate to number of legs with ulceration (total 220, 453 in groups 1 and 2 respectively). * p =0.001 or ** 0.0006,* χ^2 *comparing groups 1 and 2*

Table 3.2.4 ***Non-Vascular Causes Of Leg Ulceration in Referred Patients***

Ulceration Cause	Legs (group 1) (n=220)	Legs (group 2) (n=453)
Rheumatoid arthritis	4	1
Lymphoedema	6	7
Oedema with congestive cardiac failure	3	2
Diabetic foot ulcer (neuropathy)	2	7
Allergy to ointment	0	1
Elephantiasis verruca nostra	0	1
Infected orthopaedic prosthesis	0	1
Pyoderma gangrenosum	4	1
Warfarin skin necrosis	1	0

3.2.5 Discussion

Perhaps unsurprisingly, there is strong evidence that early diagnosis and treatment of leg ulcers improves healing and reduces recurrence rates resulting in less health and social care expenditure [172, 175, 176]. CG168 recommends that people with a below the knee break in the skin which has not healed within 2 weeks are referred for specialist vascular assessment. It is anachronistic therefore, that the NICE clinical knowledge summary [177] published in 2015 (which appears to be based on earlier advice from the Scottish Intercollegiate Guidelines Network (2010) [178] and Royal College of Nursing guidance (2006) [179]) recommend referral only when 12 weeks of community management has not resulted in improvement or healing? Perhaps this inconsistency helps, at least in part, to explain why, in spite of an approximate doubling of referrals to the HEFT specialist leg ulcer clinic, over half of referred patients had their ulcer for more than 16 weeks at the time of referral with no improvement in the history of ulcer duration ascertained at the times of referral or clinic first appointment before or after CG168 (Table 3.2.1)? Although no information is available on those people who were not referred, bearing in mind the catchment size of approximately 1.2 million, there seems no reason to suspect significant changes in the study population or referral sources over the period of interest. Features of the patient groups 1 and 2 ‘before and after NICE CG168’, respectively were similar in terms of demographics, ulcer history and the frequency of the use of simple dressings and compression hosiery (Tables 3.2.1 and 3.2.3); this suggests stability of patient characteristics from the ‘pre-CG 168’ through the ‘post- CG168’ study periods and similar practice in sources of referral. In further support of this contention, is the absence of substantial differences in the aetiological processes involved in the leg ulcers seen in patient groups 1 and 2, although there was a 10% increase in the numbers of legs with

superficial venous insufficiency, there were lesser numbers of mixed, arterio-venous and proportionately fewer non-arterial, non-venous ulcers in group 2 (Table 3.2.2). The mixture of inner city deprived areas and affluent suburbs forming the HEFT vascular service catchment makes it likely that there remains a significant, but unknown group of patients with leg ulcers who have never been referred for specialist assessment. Extrapolating Mekkes' prevalence of 1% [167], gives an estimated prevalence of 12 000 patients suffering ulceration in HEFT's catchment area. An increase in referrals after CG168 introduction was clearly shown (Table 3.2.1, Fig. 3.2.1); however, whilst the latter portion of the curve in Fig. 3.2.1 appears to show a 'tailing off 'of referrals, this may well result from the increased waiting time from referral to specialist review (Time to First Appointment in Table 3.2.1) plus the limited service personnel numbers?

Current data further emphasise the importance of engaging with colleagues in primary care, as well as affected individuals and their families/carers [180] so that all are aware of the strong evidence to show that prompt referral for specialist assessment improves healing and reduces recurrence rates and decreases overall expenditure on health and social services [181, 182]. Future work could concentrate on closer working between secondary care vascular services and community practitioners and encouraging general practices to audit their leg ulcer patient referrals to ensure all appropriate patients receive secondary care assessment on a timely basis. Despite no increase in clinic space or staffing the approximate doubling of referrals led to only a one week increase in time to first clinic appointment (Table 3.2.1) without increase in clinic space or staffing. The HEFT leg ulcer clinic personnel comprise mainly research doctors and nurses who are not funded by the

NHS. It is interesting to consider that if this were not the case, perhaps a significant increase in waiting time for specialist opinion would have developed, and NHS waiting - time targets would have been breached [183] so highlighting the need for additional resources particularly as awareness of guidelines and correspondingly early referral numbers has continued to grow.

As expected, although most ulcers were predominantly vascular in aetiology, many were multi-factorial in origin (Tables 3.2.2 and 3.2.4). There was a significant increase (37 to 47%) in the proportion of legs with SVI (Table 3.2.2) and in the proportion of legs with SVI that had been ulcerated for less than 6 months. This may relate to the local promotion of the NIHR HTA-funded "Early Endovenous Reflux Ablation (EVRA)" Trial increasing the local awareness of SVI as a cause for leg ulceration among community practitioners in addition to increased awareness of potentially treatable venous disease in leg ulceration after publication of CG168. Comparison of the figures in Table 3.2.2 with other ulcer series [171, 184, 185] suggests the proportion of ulcers caused by "pure" SVI may be falling; additionally a lower proportion of DVI ulceration in group 1 and 2 (Table 3.2.2) was encountered than described in other studies [186]. The previous literature may have overestimated the occurrence of DVI ulceration as venous ulcer experts attract more complex disease or population differences may have played a role? Specifically, significant numbers of patients were referred with functional venous insufficiency (FVI) (Table 3.2.2) defined as the presence of skin changes (lipodermatosclerosis, haemosiderin deposition, healed or active ulceration) but without demonstrable superficial and/or deep venous disease on duplex ultrasonography [174]. Factors contributing to the presumed

ambulatory venous hypertension and impaired calf muscle pump dysfunction include sedentary lifestyle, cardio/respiratory disease, working in a standing position, and especially, morbid obesity (Section 2.2, Obesity and Chronic Venous Insufficiency Disease).

Compression remains a mainstay of venous leg ulcer management [187] (either compression hosiery or bandaging are equally appropriate [188]); this treatment was used to a similar extent in both 'pre-CG 168' and 'post-CG 168' patient groups (Table 3.2.3) and is applicable not only to SVI ulcers (whether intervention is offered or not), but also to those with DVI and FVI [189, 190]. There is a general view in vascular surgical departments that there is a reluctance to apply adequate compression in primary care as a result of concern about potentially undiagnosed arterial disease and difficulty with patient compliance. There is always a consideration that a significant minority of ulcers are not 'vascular' and it is particularly important that a malignant aetiology is not missed [191].

NICE CG 168 recognises that the management of leg ulcers requires a multi-disciplinary approach co-ordinated by the vascular specialist. Patients with venous and/or arterial disease need careful assessment and investigation to plan appropriate interventions and where possible, for conservative management, close co-operation with multi-disciplinary colleagues, e.g., in areas of dermatology / anaesthetics / pharmacy / palliative / community care. The 'open-door' policy of the HEFT clinic was a catalytic factor in the markedly increased referral rate shown in Fig.3.2.1 and Table 3.2.1 and this situation ensured that the

people with leg ulcers of ‘non-vascular’ causation listed in Table 3.2.4, received prompt specialist diagnosis and referral to appropriate specialties/multi-disciplinary care.

Differing leg ulcer care models, e.g., via dermatologists, phlebologists or wound care centres, exist throughout Europe. The salient points remain similar for each model, the emphasis being upon early specialist assessment/diagnosis and working with the patient to plan an appropriate treatment strategy. Whichever model is utilised depending upon local healthcare resources and protocols, this must be the cornerstone of effective leg ulcer management to maximise healing rates [192]? An interesting sequel to the current thesis might be a study to evaluate any change in these treatment models in response to NICE Guidance CG 168?

Limitations

Data was collected through interrogation of prospectively gathered data. NICE CG168 was advertised locally to GPs by letters and at vascular themed community teaching days. The author is not aware of any significant changes to the study population or to the number of referrers (either general practitioners or community nurses) to the leg ulcer clinic during the study period. Through careful planning the waiting times were only marginally increased compared to pre-CG168. Patients and primary care practitioners may have referred more patients to HEFT through the ‘choose and book’ system preferentially. There may have been increased referrals if community practitioners were aware of the EVRA trial, which initiated recruitment in October 2013 and that HEFT vascular department has an interest in venous disease research. As described in section 3.1, the catchment area

served by HEFT is highly multi-culturally and ethnically diverse and may not be truly representative of the UK as a whole.

3.2.6 Conclusion

NICE Guidance CG 168 was associated with an approximately two-fold increase in referrals of people with leg ulcers to the HEFT academic vascular unit leg ulcer service. The dramatic increase in new patient numbers resulted in a lengthening of the waiting time for first clinic appointment of only just over one week in spite of the lack of extra clinic space and minimal personnel numbers. Unfortunately there was no decrease in the duration of leg ulcer history such that there remains a need to reinforce the message of CG 168 to make early referral for leg ulcers to obtain a specialist vascular opinion by working more closely with community practitioners and encouraging patients to seek early medical attention in the presence of leg ulceration. It may help to amalgamate different guideline resources such as the NICE guidelines and clinical knowledge summary to clarify the situation for community practitioner colleagues.

3.3 IMPACT OF NICE CLINICAL GUIDELINE 168 AND SOCIAL DEPRIVATION ON ACCESS TO INTERVENTIONAL TREATMENT FOR SYMPTOMATIC VARICOSE VEIN AND SPECIALIST REFERRAL FOR LEG ULCERATION AT A LOCAL, EAST BIRMINGHAM LEVEL

By increasing the access to a hierarchy of VV treatments it is important that CG168 does not disadvantage those from less privileged areas, this is particularly important for leg ulceration. Leg ulcers (LU) are associated with increased socio-economic disadvantage and therefore secondary care must ensure it makes services as accessible as possible. The research for this section attempted to examine any effect of CG 168 on access to secondary care management of VV and LU for people with social deprivation before and after CG168.

3.3.1 Abstract

- **Background:** NICE clinical guideline CG 168 aimed to improve the management of lower limb venous disease by innovatively recommending interventional treatment for all people affected by symptomatic varicose veins (VV) and specialist vascular referral for all people suffering from a leg ulcer (LU) that had been present for ≥2 weeks.
- **Methods:** The study aimed to utilise Index of Multiple Deprivation quintiles (IMD-Q) as a measure of social deprivation to assess the impact of CG168 on interventional treatment for symptomatic VV and LU referrals in the highly multi-cultural, socio-economically diverse, mixed urban/suburban population of

approximately 1.2 million people living in and around East Birmingham, UK. IMD-Q were used to compare levels of social deprivation of people undergoing interventions for symptomatic VV or referred with a LU during 18-month periods before and after publication of CG168. The referring general practitioner practices (GPP) were also recorded.

- **Results:** There was no change in overall IMD-Q distribution before and after CG168 in terms of VV interventions; however, there was a non-significant increase in the proportion of people classified in the IMD-Q5 quintile representative of the greatest level of social deprivation. After CG168, fewer IMD-Q5 people with LU were referred, with a shift in referrals towards those from less socially deprived areas. More GPP referred people with both VV and LU after CG168 and those that referred patients before and after CG168 tended to refer more after introduction of CG168.

- **Conclusions:** CG168 has increased VV interventions as well as the number referred with LU but this improvement in access to treatment and referral may have disproportionately favoured the more socio-economically privileged. Professional and public awareness is required to ensure the beneficial impact of the CG168 recommendations are maximised and that those with the greatest health needs have equal access to evidence-based management of their venous disease.

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3.3.2 Introduction

The NICE clinical guideline, CG 168 of July 2013, aimed to improve the management of lower limb venous disease innovatively recommending interventional treatment for all people affected by symptomatic varicose veins (VV) and specialist vascular referral for all people suffering from a leg ulcer (LU) that had been present for 2 or more weeks [173]. Although little is known about the effects of social deprivation on the epidemiology of uncomplicated VV, there is considerable evidence of an association between LU, often the most severe manifestation of lower limb venous disease and social deprivation [193].

The index of multiple deprivation (IMD) methodology, based on a UK government qualitative study of deprived areas within England [194], assigns each postal code an overall deprivation score based upon seven domains: income, employment, health deprivation and disability, education and skills and training, barriers to housing and services, crime and living environment. These scores are then divided into quintiles (Q) with Q1 indicating the least and Q5 the most deprived.

The aim of this study was to examine the impact of CG 168 and social deprivation on access to interventional treatment for symptomatic VV and specialist vascular referral for LU using the CEAP classification system [18] (Section 1.1.5 and Table 1.1.5.1) to estimate the grade of venous disease severity and Index of Multiple Deprivation quintiles in people referred before and after the introduction of CG 168. A particular focus was whether publication of CG 168 had increased access to care at The Heart of England NHS Foundation Trust hospitals for people from more socially deprived areas of East

Birmingham where a greater need for such services might be anticipated. The Heart of England NHS Foundation Trust (HEFT) comprises three hospitals and serves a highly multi-cultural, socio-economically diverse, mixed urban and suburban population of approximately 1.2 million people living in and around East Birmingham, UK.

3.3.3 Methods

Patients (n = 1236) undergoing surgical or endovenous intervention at the Heart of England NHS Foundation Trust (HEFT) for symptomatic VV, or referred because of LU, during 18 month periods before (1 January 2012 to 30 June 2013, group 1) and after (for VV, from 1 July 2013 to 31 December 2014; for LU, from 1 January 2014 to 30 June 2015) publication of CG 168 were compared in terms of clinical severity (CEAP clinical grade) [18], index of multiple deprivation quintile (IMD-Q) and the referring General Practitioner Practice (GPP).

3.3.4 Results

- **VV Interventions Before And After Publication Of CG 168**

  Publication of CG 168 was associated with a 65% increase in the number of people (253 to 417) undergoing intervention for symptomatic VV at HEFT. This increase was observed in all IMD-Q and there was no significant change in the IMD-Q distribution overall (Table 3.3.1) or, specifically, in those undergoing surgery, endothermal ablation, or ultrasound guided foam sclerotherapy. Inspection of the raw data in Table 3.3.1 shows greater numbers of people in IMD-Q 5 than in the

other quintiles were referred before and after CG 168, though this was not statistically significant. There was an overall increase in patients undergoing intervention for CEAP clinical grade (C) 2 and 3 disease but no significant association between this increase and the distribution of IMD-Q between the two groups. There was also no significant change in the IMD-Q of people undergoing intervention for CEAP C4 and C5 disease. A non-significant increase (from 29 to 52 % of total) in the number of IMD-Q5 (most deprived) people undergoing intervention for CEAP C6 disease was seen (Table 3.3.2).

Table 3.3.1 ***VV Interventions Before and After CG 168 by IMD-Q***

	Before CG 168		**After CG 168**		
IMD Quintile	Patients (n)	%	Patients (n)	%	p-value
1	49	19.4	75	18.0	0.731
2	54	21.3	76	18.2	0.374
3	48	19.0	69	16.5	0.486
4	25	9.9	56	13.4	0.214
5	77	30.4	141	33.8	0.412
Total	**253**	**100**	**417**	**100**	**0.529**

P values for χ^2 *Tests*

Table 3.3.2 ***VV Interventions Before and After CG 168 in Patients With Open LU (CEAP C6)***

	Before CG 168		After CG 168		
IMD Quintile	Patients (n)	%	Patients (n)	%	p-value
1	5	23.8	3	11.1	0.435
2	2	9.5	5	18.5	0.643
3	4	19.0	4	14.8	0.696
4	4	19.0	1	3.7	0.211
5	6	28.6	14	51.9	0.184
Total	**21**	**100**	**27**	**100**	**0.190**

LU referrals before and after publication of CG 168

Publication of CG 168 was associated with a 112% increase in the number of people (181 to 385) referred with LU. Although an increase was observed in all IMD-Q there was a significant (χ^2, p = 0.023) change in the IMD-Q distribution away from the most socially deprived quintiles with the proportion of IMD-Q5 referrals falling from 30% to 20% (χ^2, p = 0.011) after CG 168 (Table 3.3.3). With the exception of functional venous insufficiency, defined as typical venous skin changes and ulceration in the absence of superficial or deep venous reflux on duplex ultrasound and which was most commonly seen in IMD-Q5

patients in both cohorts, there was no significant relationship between LU aetiology and IMD-Q either before or after publication of CG 168.

Table 3.3.3 ***LU Referrals Before and After CG 168 by IMD-Q***

	Before CG 168		After CG 168		
IMD Quintile	Patients (n)	%	Patients (n)	%	p-value
1	37	13.2	94	24.4	0.348
2	43	23.8	84	21.8	0.684
3	20	11.0	74	19.2	0.021
4	26	14.4	55	14.3	0.961
5	55	30.4	78	20.3	0.011
Total	**181**	**100**	**385**	**100**	**0.023**

People undergoing VV intervention before and after publication of CG 168 had been referred from 102 and 122 GPP respectively (Table 3.3.4). After CG 168 patients came from 44 ‘new’ GPP that had not referred people prior to introduction of CG 168. In contrast 22 GPP that had referred people prior to CG 168 did not refer any people afterwards whilst of the 78 GPP represented in both cohorts, 45 referred more people in the post-CG 168 cohort, 19 made the same number and 14 sent fewer referrals.

Table 3.3.4 ***East Birmingham GP Practice Referrals For VV Intervention Before/After CG168***

Number	Before CG 168	After CG 168
Total Patients Referred	181	385
Total GPP referring	102	122
Additional GPP ('new') only referring after CG 168	-	44
GPP not referring after CG 168	-	22
GPP referring before and after CG 168	78	78
After CG168* GPP patient referrals number more	-	45
Unchanged	-	19
Less	-	14

GPP = General Practitioner Practices

Following publication of CG 168, the number of GPP referring people with LU increased from 64 to 102 with 54 'new' GPP referring people after CG 168, but, 16 GPP from which referrals had been made before CG 168 did not refer any people after CG 168 (Table 3.3.5). Of the 48 GPP referring LU's before and after CG 168, 48% referred more patients after CG168, 29% referred the same number of patients, and 23% referred fewer patients.

Table 3.3.5 ***East Birmingham GP Practice Referrals For Leg Ulcer Before and After CG 168***

Number	Before CG 168	After 168
Total	181	385
Total GPP referring	64	102
Additional 'New' GPP referring ONLY after CG 168	-	54
GPP not referring after CG 168	-	16
GPP referring before and after CG 168	48	48
After CG 168 GPP Patient referral number/percentage		
More		23 (48%)
Unchanged		14 (29%)
Less		11 (23%)
		TOTAL 48

3.3.5 Discussion

- **VV interventions**

In a literature search examining the relationship between social deprivation and the prevalence and management of uncomplicated VV, only the Edinburgh vein study was seen to have looked at deprivation (social class was determined by occupation) and found no relationship [2]. The study in this section demonstrated that although publication of CG 168 led to an increase in the overall number of VV interventions, it

was not found to have produced any significant difference in the IMD-Q distribution of the people being treated (Table 3.3.1). Thus, people from the most deprived quintile (IMD-Q5) accounted for approximately 30% of VV interventions before and after CG 168.

In relation to CEAP clinical grade, publication of CG 168 was not associated with any detectable change in the IMD-Q distribution except with regard to C6 disease where there was a decrease in IMD-Q1 and an increase in IMD-Q5 (Table 3.3.2) but this trend did not attain statistical significance. Perhaps overall low patient numbers were responsible for the absence of statistical significance since the percentage change was relatively substantial. It would have been hoped that that CG 168 might have improved access to superficial venous intervention in CEAP grade 6 disease (VV with open LU) for the most socially deprived. There was no relationship between IMD-Q and choice of superficial venous treatment with most patients being treated with endovenous, non-surgical techniques in both cohorts and across all IMD-Q groups (Tables 3.3.2 and 3.3.3).

- **LU Referrals**

Although publication of CG 168 was associated with a considerable increase in the overall numbers of people with LU being referred from all IMD-Q, the number of people from IMD-Q5 decreased proportionally and significantly from about 30% to about 20% of total referrals ($p=0.011$, χ^2, Table 3.3.3). This could suggest that people from socially deprived areas of East Birmingham may have been less likely to be

referred than those from more affluent areas; although, as noted above, once referred, they appear to be just as likely to receive intervention? The reasons for this apparent lack of access to LU referral among the most socially deprived people remain unclear. People from socially deprived areas are more likely to have significant co-morbidity such as diabetes [195], atherosclerosis [196], as well as higher levels of cigarette smoking [197] and obesity [195], all of which are recognised risk factors for LU development, poor ulcer healing and higher recurrence rates. It may be, however, that despite a greater LU burden [198], people from socially deprived backgrounds are less likely to present to medical services in a timely manner [199]. It is also possible that GPP in more socially deprived areas are relatively underfunded [200] and so less likely to make specialist referrals? By contrast, more affluent and perhaps better-educated patients may be more health aware and so more likely to seek medical advice earlier and then request specialist referral for their health problems. In Table 3.3.2, the raw data showed and increase of IMD-Q5 patients after CG168 who underwent VV interventions for open LU though this was not statistically significant at P=0.184 using χ^2 testing (Table 3.3.2). This trend might be interpreted as supporting the argument regarding late presentation of patients in IMD-Q5 with health problems in general and leg ulceration in particular. Non-parametric statistical tests such as $\chi^2$are generally regarded as less sensitive than parametric methods and so the test may have 'missed' significance; however it seems possible that the trend was due to chance and the numbers of patients were relatively small for the IMD-Q5 group in CEAP C6 grade being, respectively, 6 and 14 before and after CG168. The observation, although only a 'trend,' is at odds with the 'statistically significant' p value = 0.011 (χ^2) for a decrease in the overall numbers of people in IMD-Q5 referred for LU after CG168 (Table 3.3.3). The latter

finding although statistically significant, may not be clinically significant in the 'real world' since the numbers of people referred in IMD-Q5 increased from, respectively, 55 to 78 comparing 'before' and 'after' CG168? The explanation may simply be that more people in the other categories of IMD-Q were referred in greater numbers by chance?

- **General Practitioner Practice (GPP) Referral Patterns**

Encouragingly, publication of CG 168 was associated with an overall increase in the number of GPP referring people for intervention for symptomatic VV and for LU (Tables 3.3.4 and 3.3.5). Furthermore, the majority of practices that referred people before and after CG168 referred more people afterwards for both referral indications. A few GPP referred fewer or no VV and LU people after CG168; however, these tended to be smaller GPP that referred one or two patients before the guideline was published. Unfortunately, it is not possible to accurately calculate the IMD-Q distribution for patients from individual GPP as the catchment areas are often complex with imprecise boundaries; hence the decision to study patients by their individual post-code of residence and not by registered GPP. It was a general impression that the GPP that referred more patients with VV and LU after CG168 tended to be located in the more affluent regions of the HEFT catchment area. This, if it were possible to quantitate, would further strengthen the suggestion that publication of CG 168, whilst improving access to care for lower limb venous disease overall, may have tended to favour those who reside in the less socially deprived areas of East Birmingham?

NICE clinical guidelines are highly respected in the UK and overseas. Although the recommendations contained in guidance are advisory and have no legal authority in terms of the services that individual NHS clinical commissioning groups (CCGs) choose to purchase and prioritise, it would be unwise for CCG and individual GPP to ignore or contravene them. Thus in other areas, such as the management of the 'diabetic foot', a failure to follow NICE guidelines may be accepted as a breach of duty in cases of alleged clinical negligence [201]. There appears to be no reason why this should not be the case in respect of CG 168; however, colleagues in primary care often claim, justifiably, that they are overwhelmed by guidelines and that it is simply impossible to be aware of and follow them all, all of the time.

- ***Limitations***

Clearly patients must present to medical services to receive a diagnosis of VV/LU. The greater likelihood of less socially deprived people to seek medical attention may disproportionately increase the numbers with VV/LU giving a false impression of greater incidence/prevalence in these groups. A more likely explanation is the lesser tendency for socially deprived people to present to medical services with, correspondingly, an under-estimate of numbers of VV/LU. IMD-Q scores cannot distinguish between these alternative explanations of the data. Those from more socially privileged background are also more likely to seek private medical attention and this may further skew the proportions of people in different IMD-Q groups presenting with VV and LU. The area served by HEFT is highly multi-culturally and ethnically diverse[166] and may not be truly representative of the UK as a whole (as described in section 3.1) and the data are based on

postal code and not on the true socioeconomic standing of individuals, e.g., those who are deprived but live in affluent areas; both these features may be confounding factors in the interpretation of the results of this study. It was decided not to include analysis by ethnicity from local data as this was extremely poorly recorded (significant numbers had absence of recorded ethnicity and ethnicity recorded very broadly e.g. Asian, white, black). The catchment population is predominantly white European and south Asian (Indian, Pakistani, Bangladeshi etc.)[166].Within the significant proportion of south Asians in HEFT's catchment, there is considerable variation and heterogeneity. Although the heterogeneity of south Asian populations has not been investigated in VV/LU, there is evidence to suggest significant effect in other disease states[202, 203]

- **Future Directions**

At present little is known about the incidence of VV or indeed LU related to social deprivation in the general population, as patients are required to present to medical services to obtain a diagnosis, although LU has a higher proportion of socially deprived patients seeking medical attention [193] and is likely to be more common in these groups. It may be possible for large observational studies (such as the Edinburgh Vein Study) to estimate this from re-analysis of their data. This work would be important to ensure social demographics are considered in strategies to ensure equality of access to services.

3.3.6 Conclusion

It is very encouraging that, at least in the HEFT catchment area, CG 168 has clearly increased numbers of interventional treatments for VV as well as the number of people being referred with LU. There is a possibility depending upon result interpretation, that this improvement in the care of lower limb venous disease may have disproportionately favoured people from more privileged socio-economic backgrounds. Further professional and public awareness may help to ensure that the beneficial impact of the CG 168 recommendations is maximised and that those with the greatest health needs have equal access to evidence-based management of their lower limb venous disease.

3.4 ANALYSIS OF THE EFFECT OF NICE CLINICAL GUIDELINE 168 ON GENERAL PRACTICE MANAGEMENT AND REFERRAL OF VARICOSE VEINS AT NATIONAL LEVEL USING THE HEALTH IMPROVEMENT NETWORK DATABASE

General Practitioner (GP) colleagues have a major role to play in community management of superficial venous disease and in the referral of patients to specialist, secondary care vascular surgery services. This section aimed to study the effect of NICE CG 168 on management of VV by GP Practices at a national level as a sequel to the study of local GP management in East Birmingham as described in Section 3.3 above. In view of the recognition of aspects of social deprivation in venous disease, the latter feature was studied as for the East Birmingham cohorts in Section 3.3, but this time using the Townsend Quintile method [204] to represent social deprivation (as this is the method used to record

deprivation within the health improvement network database) instead of the Index of Multiple Deprivation Quintiles or IMD-Q which was the method chosen for local deprivation measurement.

Comparison of Townsend Quintiles Versus Index of Multiple Deprivation

Townsend quintiles were used in the analysis of sections 3.4 and 3.5, compared with IMD used in 3.3. Townsend quintiles consist of 4 domains (of equal weighting), compared to the 7 domains in IMD (with unequal weighting) (Table 3.4.1). Townsend data focuses on a narrow definition of material deprivation. This allows consistent calculation over time in comparison to IMD, which reviews and revises its indicators for each domain at each update and therefore does not allow direct comparison between different IMD datasets. Townsend data is based upon UK census data, which is infrequently (2001, 2011, 2021) updated in comparison to IMD, which is updated more frequently (2007, 2010, 2015, 2019) and may lead to bias. However there appears to be good correlation between Townsend and IMD in urban areas, certainly in terms of health[205]. The correlation is less marked in rural areas, perhaps a weakness of Townsend, where significant weight is placed on car ownership which, is more of a necessity in areas of poor public transport[206]. There is also greater heterogeneity in the rural population which may mask some areas of poverty[207]. Both however are excellent at recording deprivation and allowing the calculation of deprivation over small areas. Whilst the direct comparison of IMD data and Townsend data cannot be made, the comparison of general trends is possible[205].

3.4.1 Abstract

- **Background:** National Institute for Health and Care Excellence (NICE) Clinical Guideline (CG) 168 (July 2013) recommended all patients with symptomatic varicose veins (VV) be referred for consideration of intervention. Additional advice was to no longer prescribe compression hosiery with the contention that conservative management was no longer appropriate unless intervention was contraindicated. Primary care functions as 'gatekeeper' to vascular services in the NHS and the awareness of this new guidance was critical to ensure patients were managed in line with national, contemporary, evidence-based recommendations.

- **Aim:** To assess the impact of NICE CG168 on primary care management of VV at a national level.

- **Methods:** Interrogation of 18-month periods before and after NICE CG168 introduction using the Health Improvement Network (THIN) database was used to analyse VV diagnosis, referral patterns, to secondary care, compression hosiery prescriptions and interventions recorded in primary care.

- **Results:** 18-month cohorts (of approximately 2 million patients) before and after CG168 were well matched demographically and of these, 13 014 patients were diagnosed with VV before CG168 and 12 466 'post-CG168'. An increase in referrals from 3 173 to 3 457 was noted with a Cox model hazard ratio post-CG168

of 1.15 ($p<0.001$). A decrease in compression hosiery prescription (Cox hazard ratio 0.93, $p=0.008$) and an increase in VV interventions (Cox hazard ratio 1.16, $p=0.023$) were also apparent after CG168.

- **Conclusion:** There was a statistically significant change in the management of VV in primary care in line with recommendations of NICE CG168. This response to CG168 requires continued involvement of GP and other community practitioner colleagues to ensure its maintenance and to further the improvement in the management of superficial venous insufficiency.

3.4.2 Introduction

General practitioners (GPs) in the UK function as 'gatekeepers' in the process of referral of patients to hospital specialists. These community - based colleagues are required to have broad knowledge of patient care and management and to refer appropriately to ensure efficient and effective secondary care in the UK. To aid accurate and appropriate referrals to hospital specialists, as well as guide investigation and management in secondary care, the National Institute for Health and Care Excellence (NICE), produce clinical guidelines (CG). These at the time of writing, number one hundred and seventy-two, cover a broad spectrum of topics and are accompanied in addition by other advisory documents, e.g., clinical knowledge summaries. It is therefore difficult for GP colleagues to maintain awareness of all up to date guidance, whilst managing a continually increasing work load which leaves little time for other professional and non-clinical duties [208, 209].

Using The Health Improvement Network (THIN) database, the effects on referral to vascular specialists and primary care management of NICE CG168 were studied. The changes that CG168 recommended in primary care were that all people with symptomatic varicose veins (VVs) should be referred for specialist opinion; previously only those with skin changes, ulceration or bleeding could be referred for funded intervention; furthermore, compression hosiery was no longer seen as adequate treatment for simple superficial venous reflux unless intervention was inappropriate, e.g., during pregnancy [21]. With the prevalence of VVs between 20-50% [3, 14], it is likely that a large number of patients will present to GPs complaining of symptomatic VVs; therefore primary care awareness of CG168 is paramount in ensuring NICE guidelines are followed and patients have equality of access to superficial venous interventions.

The THIN database comprises approximately 450 GP practices with data for over 3.5 million 'current' patients; data is entered at a GP practice level and is wholly anonymous for use in healthcare research. The database is representative of the UK national population for demographics and major disease prevalence [210].

3.4.3 Methods

- Study Design And Setting

A retrospective open cohort study was undertaken using The Health Information Network database (THIN) into which UK general practices using the Vision patient record system, enter anonymous patient electronic medical records

(www.inps.co.uk/vision/health-improvement-network-thin). THIN includes patient records from approximately 3 million current and 12 million former patients (4.5% of UK population), and may be generalised to the UK population [210].

Data in THIN include patient demography, coded symptoms and diagnoses, clinical measurements, prescriptions and laboratory test results. Data collection for this was approved by the National Health Service (NHS), Southeast, Multicentre Research Ethics Committee in 2003, with prior approval for individual studies using anonymous data subject to review by an independent scientific review committee. (http://csdmruk.cegedim.com/our-data/ethics.shtml). This study, pertaining to sections 3.4 and 3.5, was approved by a THIN Scientific Review Committee (16THIN007) (Appendix 2). The Townsend Quintile system was used as a measure of social deprivation in the population studied [204].

- Study Periods

NICE CG168 was introduced in July 2013. The pre-CG168 period for the study was defined as 1/1/2012 – 30/6/2013 and the post-CG168 period was defined as 1/1/2014 – 30/6/2015. A six-month interval directly after the introduction of the guidelines was included before the 'post-CG168' to allow for them to be fully disseminated.

- Practices and Participants

Individual practices were included from the latest of: Vision installation date plus one year (to ensure that they were using the system to its full extent); practice acceptable

mortality recording date (to ensure accurate recording of patient deaths and de-registrations) [211]; and the start of the period of interest. Practices could continue to contribute patients to each cohort until the earlier of the following time intervals: end of the period of interest and last data collection from practice. Practices outside England and Wales and practices that did not contribute patients for the entire study period (1/1/2014 - 30/6/2015) were excluded.

Individual practice patients were eligible from inclusion from the latest of the following time intervals: practice start date; one year after registration with practice (to allow baseline data to be collected by the practice) and age 18 years. Patients exited from the cohort at the earliest of the following time intervals: practice end date; patient death and patient deregistration. Patients who were temporarily registered and patients with inconsistent registration dates were excluded.

- Case And Outcome Definitions

The index date for a new episode of varicose veins was defined as the date of a Read code (http://systems.digital.nhs.uk/data/uktc/readcodes, Appendix 3) for varicose veins in a patient record if there was no record of varicose veins in the previous year. A referral for an index varicose vein episode was defined as a referral flag in the patient record on the same day as the index episode, or a Read coded entry indicating an outward referral within one day of the index episode. Referrals during follow-up were identified using the same method if the patient had a subsequent GP consultation for varicose veins. Compression stocking use after the index episodes and within each

period was identified from prescribing data, and varicose vain surgery was identified using Read coded records for the procedures of interest. The most recent BMI recorded prior to each index episode was used in the analyses.

- Analysis

The baseline demographic and clinical characteristics of the source population and varicose vein cases for the two periods of interest were obtained. χ^2 tests were used to compare data and Wilcoxon rank-sum tests were used to compare non-normally distributed continuous data. Separate Cox proportional hazard models were used to compare the risk of referral and surgery adjusted for patient demographic and clinical characteristics. Multiple imputation (10 imputations) was used to allow individuals with missing BMI, Townsend quintile, and urban/rural residence data to be included in the analyses [212]. Model standard errors were adjusted for clustering by practice and non-linear effects for age and BMI on each outcome using fractional polynomials [213]. All analyses were carried out using Stata 14.2 (StataCorp 2015, Stata Statistical Software, College Station, Tx).

- **Validation of THIN Data Extraction**

No previous work using the THIN database and VV has been published, however there have been numerous validation studies performed in other areas, e.g., leg ulceration (allowing validation of section 3.5)[214], pharmaco-epidemiological research[215], non-melanoma skin cancer[216], death and sucide[217]. Unfortunately there was not time during the researching and writing of this thesis to perform a validation exercise and the lack

of linking to HES data at present prevented this from being used to validate VV data. The data extraction methods described above have been well described and to ensure accurate data retrieval from the THIN database, with such wide-ranging validation for disease states, the author makes the assumption that the THIN data for VV is of reasonable quality to allow its analysis and inclusion in this thesis but accepts that if patients present with two diagnoses (e.g. chest pain and varicose veins), there may be poorer recording of what might be considered more medically 'trivial' diagnoses.

3.4.4 Results

Two hundred and eighty five practices with approximately 2 million patients were eligible for inclusion within the study and both pre and post-CG168 groups of patients, diagnosed with new or recurrent VV, were well matched for number of patients, age, sex, Townsend quintile as a measure of social deprivation, urban/rural residence and ethnicity (Table 3.4.1). The two 'pre-CG168' and 'post-CG168' cohorts numbered 13014 and 12466 patients, respectively.

There was an increase in the number of patients referred to vascular surgery after CG 168 introduction: 3173 patients, pre-CG168) (24% of the pre-CG168 eligible population) to 3457 patients, post-CG168), (28% of the post-CG168 eligible population). Patients were 15% more likely to be referred post-CG168 (Hazard ratio, HR=1.15; 95% CI 1.09-1.20; $p<0.001$). Most of these patients were referred immediately after their initial consultation (Figure 3.4.1); median interval between VV consultation and referral was 1.5 days in both pre and post-CG168 groups. A reduction occurred in the number of patients prescribed

compression hosiery from 2558 (20%) pre-CG168, to 2292 (18%) post-CG168 and patients were 7% less likely to receive compression stocking prescription post CG-168 (HR=0.93; 95% CI 0.88-0.98; p=0.008). The majority of patients were prescribed stockings within the first few days of their initial consultation (Figure 3.4.2). There was also an increase in the number undergoing superficial venous intervention (possible techniques were, conventional surgery, endothermal ablation or ultrasound-guided foam sclerotherapy) from 469 (3.6%) patients pre-CG168 to 526 (4.2%) patients post-CG168 with the post-CG168 figure reflecting a 16% increased chance of undergoing VV intervention (HR=1.16; 95% CI 1.02-1.31; p=0.023) which was, specifically, statistically significant for endothermal ablation post-CG168 (Table 3.4.2). There was no difference between both cohorts in median time between GP consultation for VV and timing of VV intervention at 4.13 months pre-CG168 and 4.35 months post-CG168.

Cox models for VV referral were constructed (Table 3.4.3). Age, through a non-linear relationship (Figure 3.4.3) was a statistically significant factor, the chance of referral with varicose veins being highest between late 30s and 60 years of age. Males were 5% less likely to be referred (HR=0.95 relative to females; 95% CI 0.91-1.00; p=0.05). Those from Townsend quintiles 3, 4 and 5 were less likely to be referred than those from quintiles 1 and 2 (Table 3.4.3). BMI (although statistically significant, the hazard ratio was 0.99) or urban residence did not seem to have a significant impact on referral for VV to secondary care although the number of people referred seemed to fall off at higher BMI values (Fig. 3.4.5).

For VV intervention, Cox models were constructed (Table 3.4.4). The relationship with age and VV intervention was non-linear (Figure 3.4.4), demonstrating increased likelihood of intervention from late 30s to 60 years of age. BMI, as mentioned above, was also related (again non-linearly) those with a BMI of >30kg/m^2 (Figure 3.4.5) being less likely to receive VV intervention. Townsend quintiles 3, 4 and 5 were less likely to receive VV intervention compared to those in Quintile 1 (Table 3.4.4). Urban residence compared with rural location did not have an effect on the chance of intervention (Table 3.4.4) even though the raw data in Table 3.4.1 showed approximately four-fold greater numbers for urban relative to rural location.

3.4.5 Discussion

It is encouraging that after the introduction of NICE CG168 there was a statistically significant increase in VV referrals at a national level demonstrated by the numbers from the THIN Database (Table 3.4.3). This finding may be interpreted as a sign of increased awareness of these guidelines and their recommendations for primary care physicians. The hazard ratio for the increase in referrals of 1.15(CI 1.1-1.2, $p<0.001$, Table 3.4.3) is slightly below the predicted increase of 25% by the NICE CG168 costing report [47], the latter, however, also included the predicted increase in leg ulcer referrals. The lack of a striking difference in numbers of patients presenting with primary or recurrent VV before and after guidelines (Table 3.4.1) suggested that more work was needed to further engage public awareness to continue improved utilisation of health care resources. As expected most patients were referred immediately after their initial consultation in line with NICE CG168 recommendations that conservative management is not appropriate (Fig. 3.4.1).

The effects of CG168 were also noted in prescription of compression hosiery. After CG168, rates of prescription reduced, although not as much as anticipated; prescription of hosiery was made very rapidly, within the first few days for most patients (Fig.3.4.2) given how strongly guidelines recommend that treatment solely with compression hosiery was ineffective (unless intervention is contraindicated). Further encouragement of GP colleagues is needed in this area to reduce stocking prescription costs. Anachronistically, some attempts at patient education may limit attendance at GP practices for consultation for VV, despite the recommendations of CG168: the NHS choices website (last reviewed in September 2014) informs patients that they may be recommended 6 months of 'self-caring' including compression stockings [218]! This advice was reviewed in September 2016, but was sadly not amended in light of CG168 – it seems important that all sources of information from the NHS, particularly those based on national guidance should be harmonised to maximise impact and reduce confusion?

Comparison of Townsend quintiles of social deprivation showed that the distribution of VV by Townsend quintile was equivalent to the distribution among the general population. There was some reduction in chance of referral for higher (more deprived) Townsend quintiles; however, the hazard ratios demonstrated this reduction was small in spite of the statistically significant p values (Table 3.4.4). This hopefully, implied reasonable equality of access to secondary care referral for those suffering from symptomatic VVs, although more work is needed to ensure access for all social groups for specialist opinions regarding their VV. Work in coronary heart disease has demonstrated interaction between age and sex with social deprivation in terms of chest pain and coronary heart disease diagnoses[219].

This study included the analysis of nearly 200 000 patients. The potential for interaction between age, sex and deprivation with regards to varicose vein diagnoses and subsequent referral was not studied in this work due to considerably lower numbers and the time required to complete these analyses. Epidemiological studies have suggested that VV are more commonly reported in women (see section 1.1.2). However, thus far, the evidence that younger women from less socially deprived quintiles tend to be the most prevalent group seeking referral for their VV remains anecdotal.

Numbers of VV interventions increased after CG168, appropriately, as it is recommended that all those with CEAP [18] clinical grade 2 VV or worse should be treated (Table 3.4.3). This increase was similar to the increase in proportion of referrals and again a similar amount below the increase predicted by NICE [47]. Also it is encouraging that despite the increase in VV interventions, the time from referral to intervention did not increase (Fig. 3.4.1), perhaps due to careful planning by secondary care vascular units in light of the publication of NICE CG168? The total numbers of patients undergoing treatment, however, were considerably lower than anticipated. It is possible that these rates are falsely low, as GP practices may not accurately record hospital interventions within their databases. A crude comparison was performed using the THIN database and NHS England hospital episode statistics (HES), suggesting that VV intervention rates were recorded as approximately 2 per 10 000 patients in the THIN database and 8 per 10 000 patients using NHS England HES procedure codes! As with other THIN database work, where the outcome of interest is under-reported [220], it can be assumed that the recording patterns of this data are likely to be broadly similar between the two cohorts and that the statistical

increase post-CG168 is clinically significant, particularly as the increase was equivalent to the increase in VV referrals. Unfortunately, at the time of writing linked data between THIN and HES is not available. Lack of experience in coding HES data at a primary care level and likely poor understanding of differing VV intervention types by non-clinical administrative staff, may explain the lack of marked changes in VV interventions. CG168 recommended a treatment hierarchy of

1. Endothermal ablation,
2. Ultrasound-guided foam sclerotherapy
3. Conventional surgery.

In spite of the increase in endothermal ablation after CG168 (an increase of 47 procedures, p=0.025 for 'post' versus 'pre -CG 168', Table 3.4.2), the majority of VV interventions were recorded as conventional surgery. Coding errors are widely reported and can lead to significant loss of organisational income [221, 222], closer physician involvement can improve the accuracy of recording [223]. It was also disappointing to note a lower likelihood of receiving VV interventions with increasing degrees of social deprivation (Tables 3.4.1 and 3.4.3). This might, perhaps, be a product of patient unwillingness to undergo intervention once they have been reassured by specialist opinion that their problem is 'solely varicose veins' or alternatively, reluctance on the part of clinicians to treat what is likely to be a more co-morbid patient group who are possibly more likely to experience complications. The difference seems more likely to be co-morbidity based as suggested by the lower likelihood of treatment for those who are older and obese that was seen in the Cox model for VV interventions and indicated by Figures 3.4.4 and 3.4.5, respectively and Table 3.4.3.

Unfortunately, from THIN data the cause for the smaller number of treatments for more socially deprived patients cannot be determined.

Limitations

THIN database analysis may inflict bias in several ways. There may be selection bias recruiting more 'academically' minded GP practices or those that benefit from the small pecuniary incentive from participating in THIN; therefore, there may be under-representation from practices in deprived areas. Data was collected through interrogation of prospectively gathered data on general practice electronic patient records (Vision software). Whilst patients were only entered into the analysis if GPs had been registered with THIN for more than 1 year with acceptable mortality rates etc., it is possible that through user error VV diagnoses were under-coded, for example, the instance of patients presenting with symptoms suspicious of another, more urgent condition such as malignancy may result in VV coding being overlooked as GPs only record events they deem relevant to patients' care. As described above, THIN data was not linked with HES at the time of analysis and this may have led to errors in recording VV interventions. The use of multiple imputation to allow analysis of missing variables may have affected data evaluation as data is assumed to be missing at random.

3.4.6 Conclusion

The management and referral of VV patients has improved since the introduction of NICE CG168 in terms of increased referral and intervention and a reduction in prescription of compression hosiery. Further encouragement of GP colleagues and closer working

relationships between primary and secondary care is required to ensure the management of this extremely common health complaint continues to improve in line with NICE recommendations. Continuing efforts are needed to increase awareness of patients so empowering them to seek medical attention and referral for the management of their VV.

Table 3.4.1 Comparison of Domains of Townsends vs IMD

Townsend Domains	IMD Domains
Unemployment (25%)	Income (22.5%)
Overcrowding (25%)	Employment (22.5)%
Non-car ownership (25%)	Education, skills and training (13.5)
Non-home ownership (25%)	Health/disability (13.5%)
	Living environment (9.3%)
	Barriers to housing (9.3%)
	Crime (9.3)

Figures in brackets – percentage contribution to overall score

Table 3.4.2: ***Characteristics of Incident Varicose Vein Patients***

	Pre-CG168	Post-CG168	p-value
Number of Patients	13 014	12 466	
Male (%)	40.2	39.5	0.2840
Mean age (SD)	62.7 (17.5)	61.8 (17.5)	0.7966
Townsend Quintile (%)			0.108
(Least deprived) 1	3 768 (29)	3 697 (30)	
2	2 981 (23)	2 808 (23)	
3	2 686 (21)	2 479 (20)	
4	2 102 (16)	2 079 (17)	
(Most deprived) 5	1 283 (10)	1 179 (10)	
Missing	194 (2)	224 (2)	
Urban/rural residence (%)			0.706
Urban	10 358 (80)	9 865 (79)	
Rural	2 471 (19)	2 382 (19)	
Missing	185 (1)	219 (2)	
Ethnicity (%)			
Asian	260 (2.0)	264 (2.1)	
Black	83 (0.6)	89 (0.7)	
Chinese	21 (0.2)	20 (0.2)	
Mixed	29 (0.2)	31 (0.3)	
Other	66 (0.5)	65 (0.5)	
White	6 234 (47.9)	6 148 (49.3)	
Missing	6 321 (48.6)	5 849 (46.9)	
BMI: Mean (SD)	28 (6)	28 (6)	0.0520

SD=standard deviation. χ^2 *used for count data, t-test for normally distributed continuous data. Wilcoxon rank-sum test used for non-normally distributed data*

Table 3.4.3: ***Varicose Vein Interventions***

	Pre-CG168	Post-CG168	p-value
Number of interventions (%)	469 (3.6)	526 (4.2)	0.023
Intervention type			0.666
Endothermal ablation	107	154	0.025
Foam sclerotherapy	74	73	0.451
Conventional Surgery	288	299	0.163

Table 3.4.4: ***Cox Model for Varicose Vein Referral***

	Hazard Ratio	95% CI	p-value
Male	0.95	(0.91,1.00)	0.05
Townsend			
(Least deprived) 1	(Reference) 1.00	-	-
2	0.99	(0.91,1.05)	0.513
3	0.82	(0.76,0.89)	<0.001
4	0.90	(0.82,0.98)	0.016
(Most deprived) 5	0.90	(0.81,1.01)	0.084
BMI (per kg/m^2)	0.99	(0.99,0.99)	0.002
Urban residence	1.09	(0.98,1.22)	0.097
Post-NICE CG168	1.15	(1.10,1.20)	<0.001

CI = confidence interval. Multiple imputation used for missing values of Townsend, BMI and urban residence. Standard errors adjusted for clustering by practice.

Table 3.4.5: ***Cox Model for Varicose Vein Interventions***

	Hazard Ratio	95% CI	p-value
Male	0.87	(0.76,1.00)	0.058
Townsend			
(Least deprived) 1	(Reference) 1.00	-	-
2	0.79	(0.65,0.97)	0.025
3	0.70	(0.55,0.90)	0.005
4	0.63	(0.48,0.82)	0.001
(Most deprived) 5	0.49	(0.33,0.73)	<0.001
BMI_1	0.98	(0.98,0.99)	<0.001
Urban residence	0.99	(0.76,1.28)	0.923
Post-NICE CG168	1.15	(0.99,1.32)	0.065

CI = confidence interval. Multiple imputation used for missing values of Townsend, BMI and urban residence. Standard errors adjusted for clustering by practice.

Figure 3.4.1. ***Time to Varicose Vein Referral After Initial Consultation***

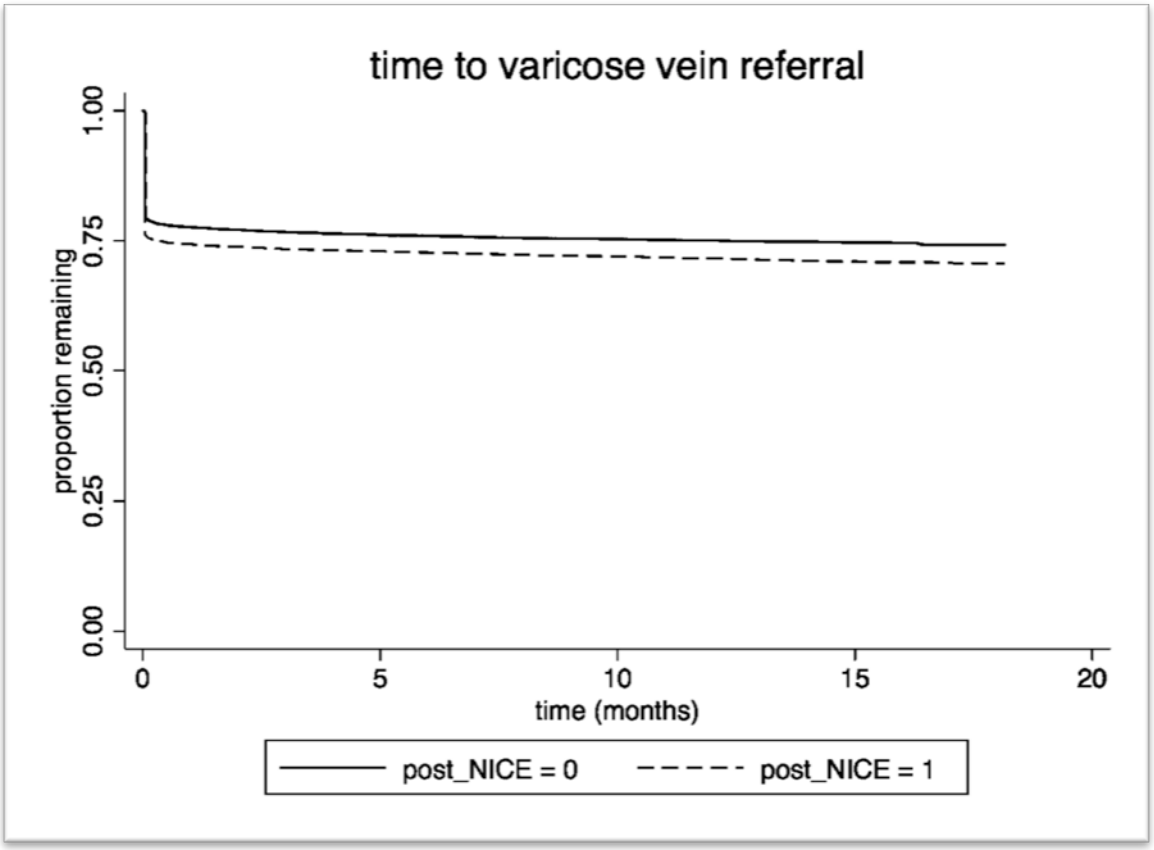


Figure 3.4.2. ***Time to Prescription of Compression Hosiery After Initial GP Consultation***

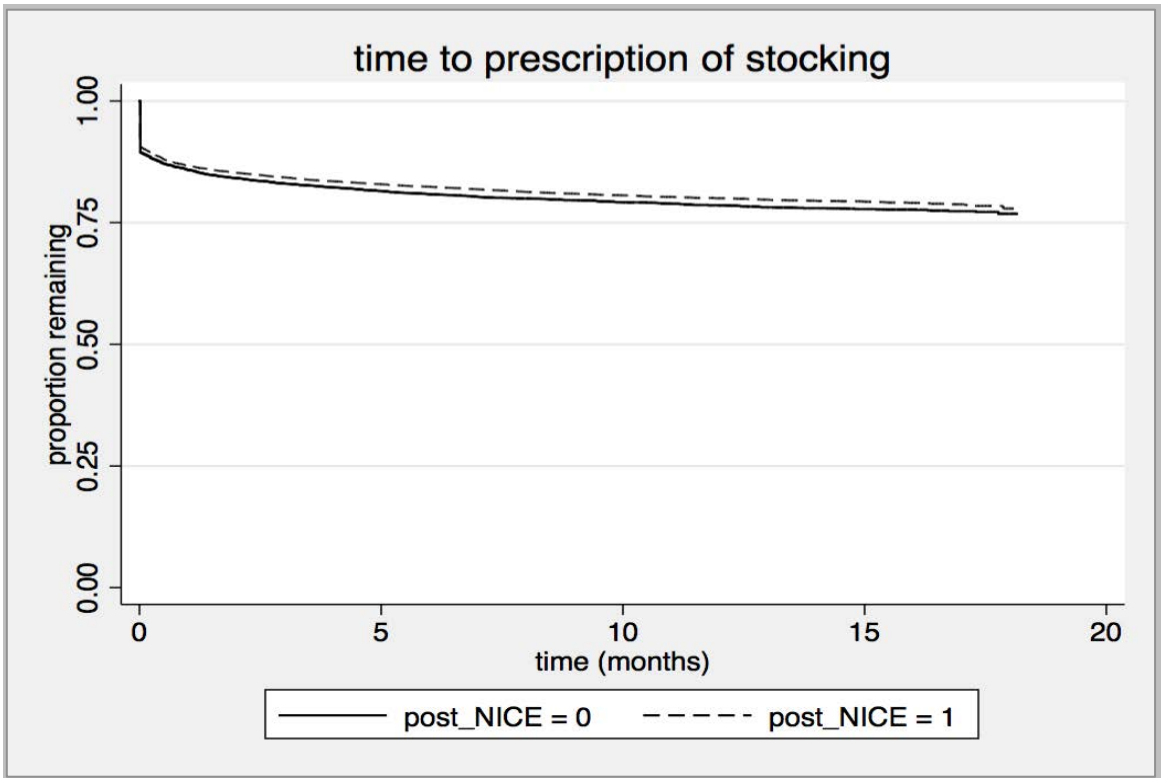


Figure 3.4.3. ***Effect of Age on Probability of Referral for Varicose Veins***

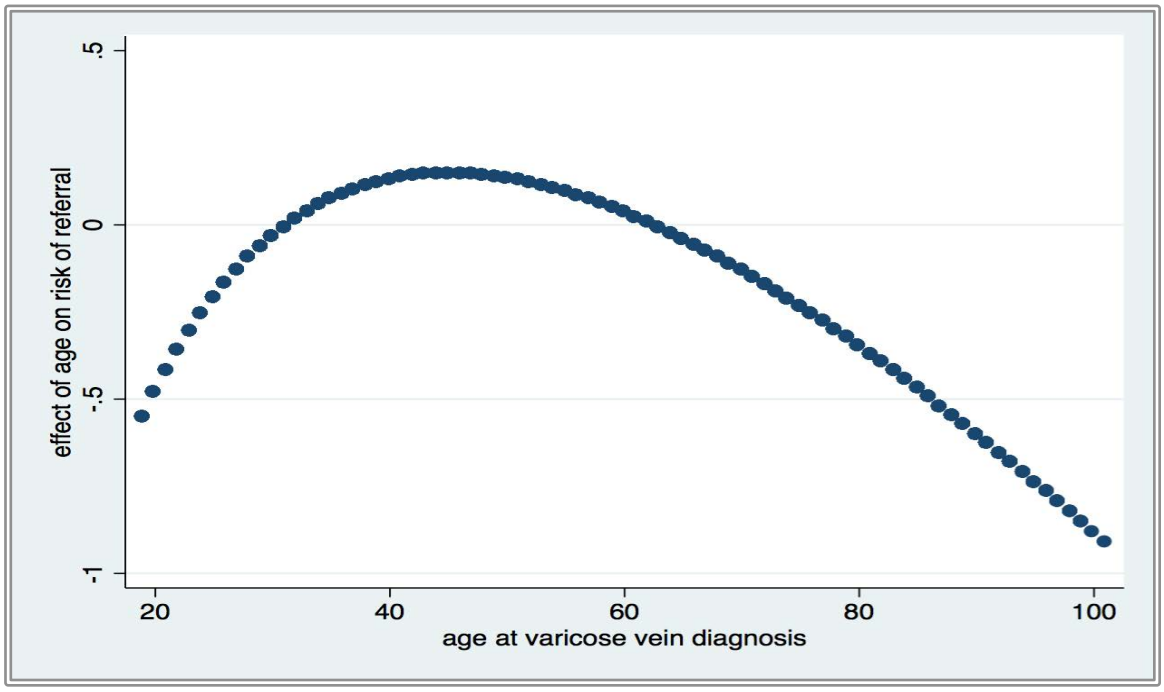


Figure 3.4.4: ***Effect of Age on Probability of Varicose Vein Intervention***

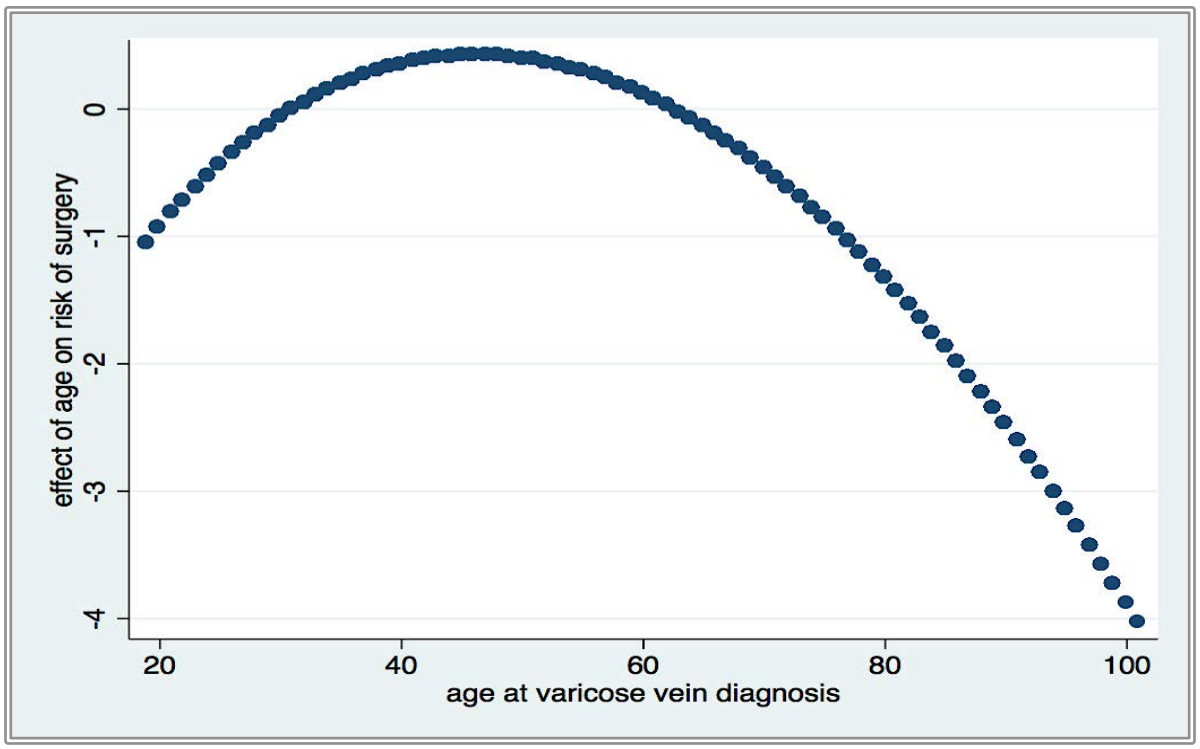
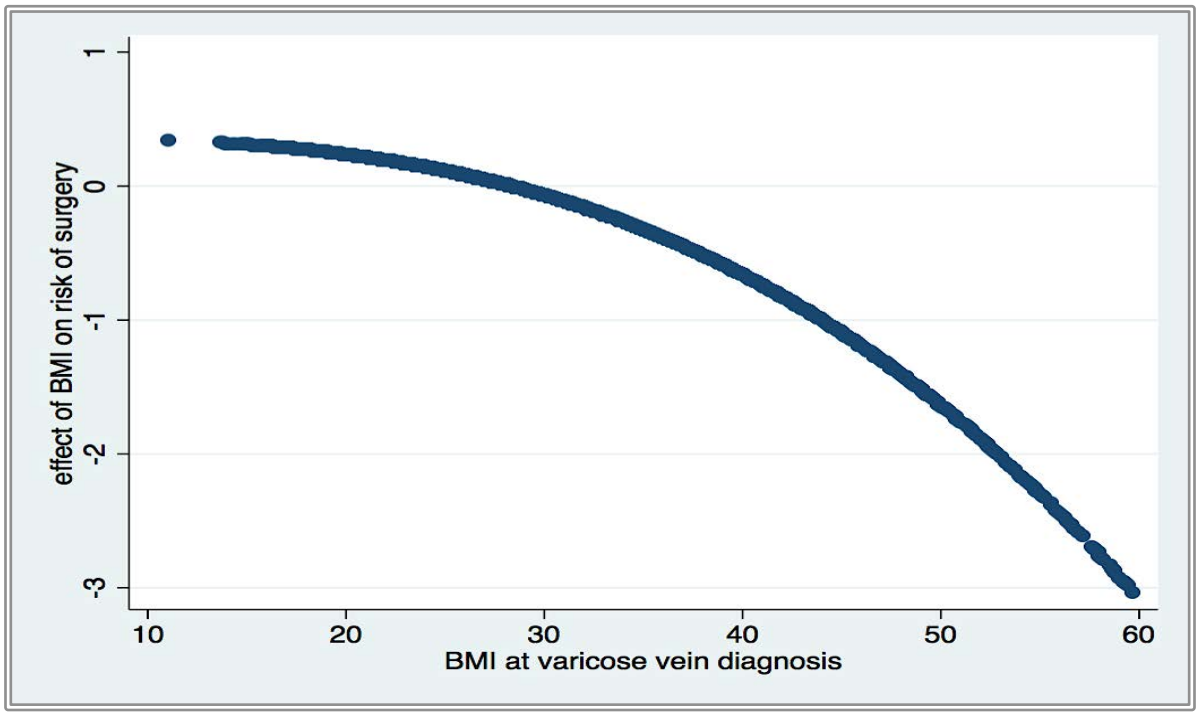


Figure 3.4.5. Effect of BMI on Probability of Varicose Vein Intervention



3.5 ANALYSIS OF THE HEALTH IMPROVEMENT NETWORK DATABASE ON THE PRIMARY CARE MANAGEMENT OF LEG ULCERS AT A NATIONAL LEVEL

NICE guidance CG 168 advocates referral to a vascular specialist of any leg ulcer lasting longer than two weeks; compliance with this recommendation should be taken as good clinical practice. Adherence to the advice to rapidly refer people with new diagnosis of leg ulceration was therefore explored at a national level as a sequel to the study of primary care leg ulcer management at a local level in East Birmingham as presented in Section 3.3. The methodology used for the current section was similar to that used in Chapter 3.4 above but has been described again, in detail, in the 'Methods' section 3.53 below for the sake of clarity.

3.5.1 Abstract

- **Background:** NICE Clinical Guideline (CG) 168, published in July 2013 predominates over other guidelines for management of leg ulcers (LU) in England and Wales; CG 168 recommends specialist referral for skin breaks below the knee that have been present for longer than 2 weeks.

- **Aim:** To delineate the changes in primary care management of LU using a retrospective cohort study of prospectively gathered data from The Health Improvement Network database.

- **Methods:** Eighteen month periods before and after introduction of CG168 were examined analysing an eligible population of approximately 2 million adult patients. Those patients with a new diagnosis of LU in each time period were studied demographically and any related primary care coded episodes of referral for specialist review and superficial venous interventions were recorded.

- **Results**: There were 7 532 new diagnoses of LU 'pre-CG168' and 7 462 'post-CG168'. A lower proportion of male patients with LU were found (46.6% pre-CG168, 46.9% post-CG168) in the eligible population. Patients with LU were older (median age both pre and post-CG168 cohorts of 77, pre-CG168 IQR 65-85, post-CG168 IQR 64-85)) than the eligible population; 2 259 (30.0%) patients were referred pre-CG168 and 2 329 (31.2%) were referred post-CG168 (slightly but not significantly more, p=0.053). A Cox model for leg ulcer referral computed a hazard ratio of 1.05 (95% CI 0.99, 1.11, p=0.096). There was an interval (median) of 0.05 months between LU consultation and referral in both pre-CG 168 and post-CG 168 cohorts with respective interquartile ranges of, pre-CG168, 0.05 to 0.20 and post-CG168, 0.05 to 0.05. Patients were just as likely to receive superficial venous intervention (either surgery, endothermal ablation or ultrasound-guided foam sclerotherapy) in the pre-CG 168 as in the post-CG 168 periods; with a Cox model hazard ratio of 0.94 (95% CI 0.69, 1.27, post-CG168) and p=0.681 for post-CG 168 relative to pre-CG 168.

- **Conclusion:** The apparent increase in the number of referrals for LU after CG 168 did not reach statistical significance. Patients that were referred were sent to specialists early. Consolidation of LU guidance in the UK is required to further improve access to specialist opinion and referral should be open to all community practitioners.

3.5.2 Introduction

In the United Kingdom (UK), the Scottish Intercollegiate Network (SIGN) [178], the Royal College of Nursing (RCN) [179] and National Institute for Health and Care Excellence (NICE), in form of their clinical knowledge summary (CKS) [177] and Clinical Guideline (CG) 168 [21], have all provided advice and recommendations for the management of leg ulcers (LU). Unfortunately, there are important inconsistencies revealed by comparison of these UK guidelines and by comparison with international guidelines [224] [225]. There is strong evidence to show that the longer a LU has been present, the larger it is likely to be, the longer it is likely to take to heal, the more likely it is to recur and the greater the resulting burden on health and social services. As such, there is widespread agreement among vascular specialists that early referral, leading to diagnosis and appropriate, evidence-based, treatment of LU results in more clinically successful and cost-effective care [172, 175] [176] [16] For this reason NICE CG168, which was published in 2013 and supersedes all other UK guidelines (outside Scotland) recommends that people with a 'skin break, below the knee, which has not healed within 2 weeks' be referred to a vascular specialist [21]. The aim of the present study was to use The Health Improvement Network (THIN) database to determine whether publication of CG 168 had led to an increase in

compliance with the recommendations of CG 168 for the primary care management of people affected by LU at a national level as a sequel to the local, East Birmingham study described in Section 3.2.

3.5.3 Methods

- Study Design and Setting

A retrospective open cohort study was undertaken using The Health Information Network database (THIN), a large database of anonymous routine electronic medical records from approximately 450 UK general practices including patient records from approximately 3 million current and 12 million former patients [210] as described in Sections 3.4.3 and 3.4.4, above. Townsend Quintiles were used as an index of social deprivation in the study population as for Section 3.4, above.

- Study Periods

NICE CG168 was introduced in July 2013. The pre-CG168 period was defined as 1/1/2012 – 30/6/2013 and the post-CG168 period was defined as 1/1/2014 – 30/6/2015. A six-month gap directly after the introduction of the guidelines was included to allow for them to be fully disseminated.

- Practice and Participants

Individual practices were included from the latest of: Vision installation date plus one year (to ensure that they were using the system to its full extent); practice

acceptable mortality recording date (to ensure accurate recording of patient deaths and de-registrations) [211]; and the start of the period of interest. Practices could continue to contribute patients to each cohort until the earlier of the following dates: end of the period of interest and last data collection from the practice. Practices outside England and Wales, and practices that did not contribute patients for the entire study period (1/1/2014 - 30/6/2015) were excluded.

Individual practice patients were eligible from inclusion from the latest of the following dates: practice start date; one year after registration with the practice (to allow baseline data to be collected by the practice); and age 18 years. Patients exited from the cohort at the earliest of the following dates: practice end date; patient death and patient de-registration. Patients who were temporarily registered and patients with inconsistent registration dates were excluded.

- Case and Outcome Definitions

The index date for a new episode of leg ulcer was defined as the date of a Read code (http://systems.digital.nhs.uk/data/uktc/readcodes, Appendix 3) for leg ulcer in a patient record, if there was no record of leg ulcer in the previous year. A referral for an index leg ulcer episode was defined as a referral flag in the patient record on the same day as the index episode, or a Read coded entry indicating an outward referral within one day of the index episode. Referrals during follow-up were identified in a similar manner if the patient had a subsequent GP consultation for leg ulcer. Leg ulcer surgery was identified using Read coded records for the

procedures of interest. The most recent BMI recorded prior to each index episode was used in the analyses.

- Analysis

The baseline demographic and clinical characteristics of the source population and leg ulcer cases for the two periods of interest were described. χ^2 tests were used to compare 'count' data, and Wilcoxon rank-sum tests were used to compare non-normally distributed continuous data. Separate Cox proportional hazard models were used to compare the 'risk' or chance of referral and surgery and were adjusted for patient demographic and clinical characteristics. Multiple imputation (10 imputations) was used to allow case histories with missing BMI, Townsend quintile, and urban/rural residence data to be included in the analyses [212]. Model standard errors were adjusted for clustering by practice. Non-linear effects for age and BMI on each outcome were estimated using fractional polynomials[186]. All analyses were carried out using Stata 14.2 (StataCorp 2015, Stata Statistical Software, College Station, Tx).

3.5.4 Results

The two cohorts were well matched for age, sex, urban/rural residence, Townsend quintile and ethnicity. There were 7 532 new diagnoses of LU before and 7 462 after publication of CG168. Affected people were well matched for the above characteristics (Table 3.5.1). Compared with the eligible group as a whole, there were less men in the LU groups before

and after CG 168 as follows: pre-CG 168, 46.6% vs. 49.0% in the eligible population; post-CG168; 46.9% vs. 48.9% in the eligible population. LU patients were older than the general eligible population with median and inter-quartile age ranges, pre-CG 168, 77 [65-86] vs. 48 [34-63] years and post-CG 168, 77 [64-85] vs. 48 [34-63] years for the total eligible population (Table 3.5.1). About 78% of LU patients in pre- and post-CG 168 groups were of urban residence (Table 3.5.1). The raw data suggested that the number of people diagnosed with new LU decreased with the increasing Townsend Quintiles of social deprivation but proportionately there seemed no difference between pre- and post CG 168 groups or between the LU groups and the total eligible population (Table 3.5.2).

Cox model construction for LU referral (Table 3.5.3) demonstrated increasing age was not a significant factor (HR=1.00; 95% CI 0.99-1.00; p=0.001), the 'statistically significant' p value did not reflect clinical significance with the hazard ratio of 1 and narrow 95% CI; however, male sex increased likelihood of referral. More patients were of urban residence in both study groups as mentioned above (Table 3.5.1) but the Cox proportional modelling for this feature did not demonstrate statistical significance (p=0.065, Table 3.5.3). Those from Townsend quintiles 3 and 4 were less likely to be referred than those from the least deprived Townsend quintile 1.

Patients were just as likely to receive SVI intervention (surgery, endothermal ablation or ultrasound-guided foam sclerotherapy) post CG168. 87 patients underwent superficial venous intervention pre-CG168 and 80 post-CG168 with HR=0.94 (95% CI 0.69-1.27;

p=0.681). A Cox model for leg ulcer intervention (for SVI) (Table 3.5.4) demonstrated a non-linear relationship with age, with increased hazard ratio of intervention for those aged from 50-70 years (Figure 3.5.2). There was also a 14% increase in intervention for males (HR=1.14; 95% CI 0.85-1.55; p=0.386), but this did not reach statistical significance. Townsend quintile did not appear to have an effect on the likelihood of undergoing SVI intervention. Those with BMI >30kg/m^2 were less likely to undergo intervention (Figure 3.5.3). There was no statistically significant difference in risk of intervention for SVI induced ulceration for rural versus urban residence. LU incidence (new diagnoses per 1000 patient years) was 28.64 (95% CI 26.44, 31.07) pre-CG168 and 27.85 (95% confidence interval (CI) 25.73, 30.20) and the adjusted incidence rate ratio pre-CG168 vs. post-CG168 was HR=0.97; 95% CI 0.94-1.00; p<0.001 (Table 3.5.5).

Before CG 168, 2 259 (30.0%) people with a new diagnosis of LU referred pre-CG168 compared with 2 329 (31.2%) after CG168 (p=0.053). Patients seemed 5% more likely to be referred after CG-168 (HR=1.05; 95% CI 0.99-1.11; p=0.096)(Table 3.5.5) but this was not statistically significant. There was a median (IQR) delay between consultation (diagnosis) and specialist referral of 0.05 (0.05-0.20) months before and 0.05 (0.05, 0.05) after CG 168 (Figure 3.5.1, Table 3.5.5); however, the interval between consultation and intervention increased from median 4.48 months (IQR 3.07, 7.47) pre-CG168 to 5.78 (IQR 3.87, 10.74) post-CG168 (Table 3.5.5).

3.5.5 Discussion

Disappointingly, this study suggests that publication of NICE CG 168 has led to no significant increase in primary care specialist referral rates for people newly diagnosed with LU; with around 70% of people with LU were not rapidly referred the small increase from 30% to 31.25% did not achieve statistical significance (p=0.053, Table 3.5.5). Certainly, the total number of referred patients did not differ significantly from pre- to post-CG 168 periods (Table 3.5.5) and the characteristics of the patient groups did not differ significantly on a clinical basis (Table 3.5.1, 3.5.3 and 3.5.5) or in terms of numbers eventually receiving interventional treatment for their superficial venous disease (Table 3.5.4). Referrals are likely to be 'under-coded' and hopefully the true figure is a smaller departure from that recommended? Further reasons for the 'static' level of compliance might include ignorance of CG 168 or a preference to follow other guidelines. In stark contrast to NICE CG 168, the RCN, SIGN, and NICE CKS guidelines recommend referral only after 12 weeks of failed community management. The overall discouraging situation is however, mitigated by the observation that those people with a new diagnosis of LU who were referred, were referred almost immediately perhaps suggesting that where GP colleagues are aware of CG 168 they are willing to comply with its recommendation?

A larger proportion of patients with greater degrees of social deprivation in Townsend quintiles 4 and 5 (and less in Townsend quintile 1) were diagnosed with LU compared with the eligible population (Tables 3.5.2, 3.5.3). This finding is similar to previous work which has shown an association of LU with increasing social deprivation [193]. Evidence that social class inequality in access to healthcare has been shown in several studies [226] and it is quite

possible that the proportion of LU patients in Townsend quintiles 4 and 5 are actually under-represented and the disparity is actually far greater. At least there was no significant difference in the numbers of people receiving intervention for their superficial venous disease (Table 3.4.4). As previously demonstrated, LU was commoner in women and in the elderly (Tables 3.5.1, 3.5.3, 3.5.4, Fig. 3.5.2) [171] though interventions decreased with increasingly 'older' age (Fig. 3.5.2). It is possible this may be a product of elderly male reluctance to seek healthcare and the stigma of 'seeking help' [227]. Seeking GP appointments later, led to poorer prognoses [228] and this reluctance may be the mechanism of the gender difference rather than a true reflection of higher incidence of LU in females? It is perhaps important for future LU guidance to specifically target elderly (in particular males) and the socially deprived to ensure adequate access to specialist review so improving healthcare seeking behaviour? This contention is supported by a reduced chance of referral for those from Townsend Quintiles 3 and 4 (but not from the most deprived quintile 5) (Table 3.5.3). Encouragingly however, as mentioned above, Townsend quintile did not seem to affect the likelihood of receiving an intervention for SVI induced ulceration (Table 3.5.4) perhaps reflecting the hoped-for equality of access to intervention in secondary care.

Although urban versus rural residence did not affect likelihood of referral (Table 3.5.3) it seemed that proportionately there might have been a preponderance of LU in people from rural areas? Evidence has demonstrated that rural patients have significant barriers to healthcare including limited healthcare resources and difficulties in accessing transport (particularly important in LU patients who are often elderly) [229, 230]. It is therefore

important to ensure rural patients continue to have access to specialist referral to ensure early review and that previously reported barriers do not prevent patient referral.

CG168 is not specific to leg ulceration and indeed mainly covers guidance on management of varicose veins of the legs, however, the referral recommendations for LU patients are clear. It is not the only NICE guidance to have little impact upon patient management and indeed a study of the impact of NICE guidelines on GP prescribing patterns showed little was achieved [231]. This may be a result of the sheer number of guidelines, most of which have recommendations with obvious implications for overworked general practitioners. NICE guidelines focused on specific specialties seem to have influenced practice more positively [232, 233], however this does not always seem to be the case [234, 235]. Whilst slavish adherence to guidelines will not protect against litigation, their standards are often used as a benchmark for courts to judge clinical conduct [236] and although NICE guideline use in medico-legal cases has been limited thus far, it is likely to increase [201]. It would seem therefore, that it is increasingly important that patients are cared for (whilst not necessarily appropriate for every patient) in close adherence to NICE recommendations.

There was no change in superficial venous interventions for LU (Table 3.5.4) though overall numbers appeared low (~1% LU patients underwent intervention). Whilst the absolute numbers may be less important (data in THIN database recorded from hospital based care episodes is currently not linked to Hospital Episode Statistics and is likely to be a considerable underestimate) the lack of increase may be a cause for concern? The effect of age on likelihood of SVI intervention interestingly, showed a reduced likelihood of

interventions for those <50 years, perhaps because non-SVI causes of ulceration are more likely in this age group and similarly, intervention 'dropped off' in those aged >70 years (Table 3.5.4, Fig. 3.5.2), perhaps as a result of a reluctance to intervene in a more frail and co-morbid group?

Those people with a BMI >30 were less likely to receive SVI intervention (Tables 3.5.1, 3.5.4, Fig.3.5.3). This may be a result of immobility and co-morbid status, along with the likelihood of a more technically difficult procedure and higher risk of complications. Those who are obese however, are more likely to suffer ulceration [114] and are an increasingly prevalent group [237]. Certainly conventional surgery for venous insufficiency has been shown to reduce recurrence of venous ulceration [238] and with CG168 recommending an endovenous first treatment strategy for varicose veins, this is supported by the early results of the Early Venous Reflux Ablation trial (www.nets.nihr.ac.uk/projects/hta/11129197). Hopefully longer-term follow-up will continue to add evidence to this field and may well result in an increase in beneficial interventions in the future?

Limitations

Methodology in 3.5 is similar to that of section 3.4 and therefore similar limitations apply to this section also. Perhaps, however, the diagnosis of a LU is seen as a more severe condition than 'just' VV and therefore is more likely to be recorded? Similarly, for section 3.2, the recruitment for the EVRA trial may have influenced referrals although EVRA only

recruited patients from 20 centres in the UK and no significant increase in referrals was noted in the THIN data making this seem unlikely.

3.5.6 Conclusion

Leg ulceration tends to affect the elderly, female gender and more socially deprived. This section has shown that publication of CG 168 has not led to improved compliance with its advice on leg ulcer management in primary care at a national level. Therefore, leg ulcer management guidance in the UK requires consolidation to ensure clarity and consistency of message for all healthcare practitioners. Further efforts are required to publicise the importance of CG168 guidance to community health professional colleagues who refer patients to secondary care and amongst the socially deprived and elderly themselves.

Table 3.5.1: ***Characteristics of Incident Leg Ulcer Patients***

	Pre-CG168	Post-CG168	p-value
No. Patients	7 532	7 462	
Male (%)	46.6	46.9	0.734
Median age (IQR)	77 (65-85)	77 (64-85)	
Urban/rural residence (%)			0.029*
Urban	5 784 (77)	5 825 (78)	
Rural	1 658 (22)	1 530 (21)	
Missing	90 (1)	107 (1)	
Ethnicity (%)			0.305
Asian	66 (1)	66 (1)	
Black	54 (1)	72 (1)	
Chinese	4 (0)	1 (0)	
Mixed	8 (0)	10 (0)	
Other	13 (0)	16 (0)	
White	3 350 (45)	3 395 (46)	
Missing	4 037 (54)	3 902 (52)	
BMI: Mean (SD)	29 (8)	29 (8)	0.0234*

SD=standard deviation. χ^2 *used for count data. *Wilcoxon rank-sum test used for non-normally distributed data. Probability values relate to comparison of pre- with post-CG 168 groups.*

Table 3.5.2. ***Comparison Of Townsend Quintiles In The Eligible Population With The Population Having A New Diagnosis Of Leg Ulcer***

Townsend Quintile (%)	Whole Cohort		People Diagnosed With New LU	
	Pre-CG168	Post-CG168	Pre-CG168	Post-CG168
(Least deprived) 1	523 920 (27)	533 088 (27)	1 835 (24)	1 839 (25)
2	419 856 (22)	427 415 (21)	1 639 (22)	1 638 (22)
3	410 908 (21)	419 473 (21)	1 571 (21)	1 545 (21)
4	345 372 (18)	362 651 (18)	1 449 (19)	1 454 (20)
(Most deprived) 5	203 528 (10)	208 494 (10)	945 (13)	877 (12)
Missing	39 842 (2)	49 002 (2)	93 (1)	109 (2)
Total	1 952 426	2 000 123	7 532	7 462

- *% Refers to proportion of Townsend Quintiles in the pre- and post-CG 168 total eligible populations on the left, right hand columns refer to corresponding proportions in the leg ulcer groups*

Table 3.5.3. ***Cox Model for Leg Ulcer Referral***

	Hazard Ratio	95% CI	P-value
Total number of referrals Post –CG 168	1.05	(0.99, 1.11)	0.096
Age	1.00	(0.99,1.00)	0.001
Male	1.07	(1.01,1.12)	0.025
Townsend Quintile			
(Least deprived) 1	(Reference) 1.00	-	-
2	0.93	(0.85,1.00)	0.055
3	0.83	(0.76,0.92)	<0.001
4	0.87	(0.79,0.95)	0.003
(Most deprived) 5	0.88	(0.78,1.00)	0.056
BMI (per kg/m^2)	1.00	(1.00,1.01)	0.075
Urban Residence	1.15	(0.99,1.34)	0.065

- *Multiple imputation used for missing values of Townsend Quintiles, BMI and urban residence. Hazard ratio p values for significance of comparing pre- and post-CG 168 groups.*

Table 3.5.4. ***Cox Model of Superficial Venous Intervention for Leg Ulceration***

		Hazard Ratio	95% CI	P-value
Number of patients receiving all interventions Post –CG168		0.94	(0.69, 1.27)	0.681
Male		1.14	(0.85,1.55)	0.386
Townsend				
	(Least deprived) 1	(Reference) 1.00	-	-
	2	0.84	(0.53,1.32)	0.446
	3	1.13	(0.71,1.80)	0.610
	4	0.74	(0.45,1.19)	0.216
	(Most deprived) 5	0.98	(0.53,1.78)	0.934
BMI_1		0.99	(0.98,0.99)	<0.001
Urban Residence		1.12	(0.66,1.89)	0.673

CI = confidence interval. Multiple imputations used for missing values of Townsend Quintiles, BMI and urban residence. Standard errors adjusted for clustering by practice. Hazard ratio p values are for the significance of comparing pre- with post-CG 168 groups.

Table 3.5.5 ***Occurrence And Referral Features For New Diagnosis Of Leg Ulcers***

	Pre -CG 168	Post- CG 168
Number with new LU diagnosis	7532	7462
Incidence of LU (new diagnosis per 1000 patient years) median and 95% CI	28.6 (26.4, 31.1)	27.9 (25.7, 30.2)
Adjusted LU incidence rate ratio, 95% CI	-	HR 0.97 (0.94, 1) p < 0.001
Number of referrals of new LU (% of total LU patients)	2259 (30%)	2329 (31.2%) p = 0.053
Likelihood of referral post – CG 168 (ratio and 95% CI)	-	HR 1.05 (0.99, 1.11) p = 0.096
Median (IQR) delay from new diagnosis to referral	0.05 (0.05-0.2)	0.05 (0.05-0.05)
Time/months to intervention*	4.48 (3.1-7.5)	5.78 (3.9-10.8)

**Time from new diagnosis to all interventions; all p values for comparison of pre- versus post-CG 168*

Figure 3.5.1. ***Time from LU Consultation to Referral to Specialist***

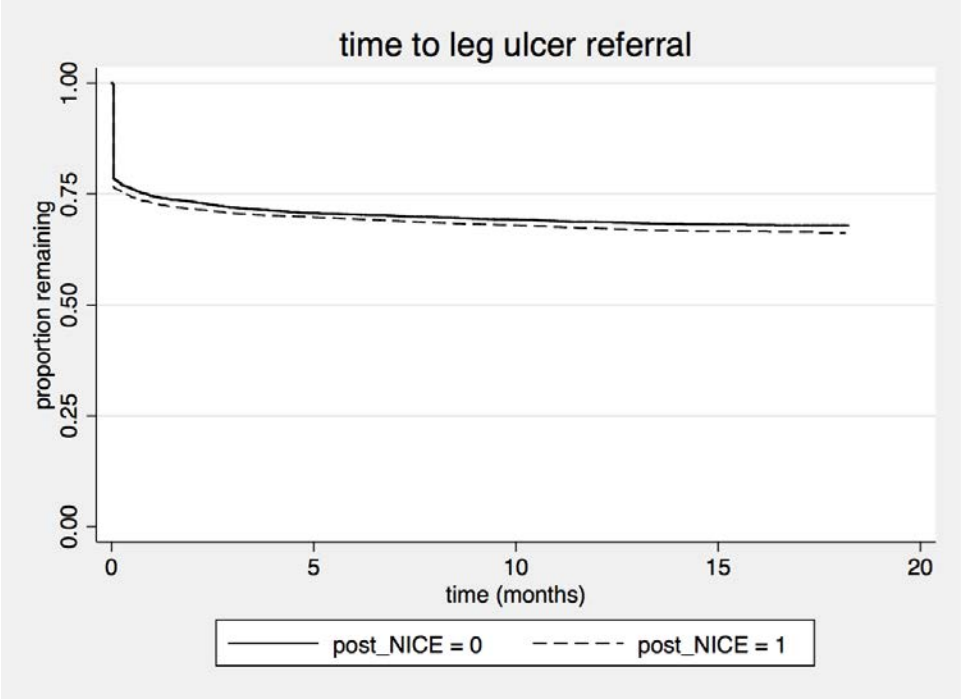


Figure 3.5.2. ***Effect of Age on Probability of Superficial Venous Intervention for Leg Ulcer***

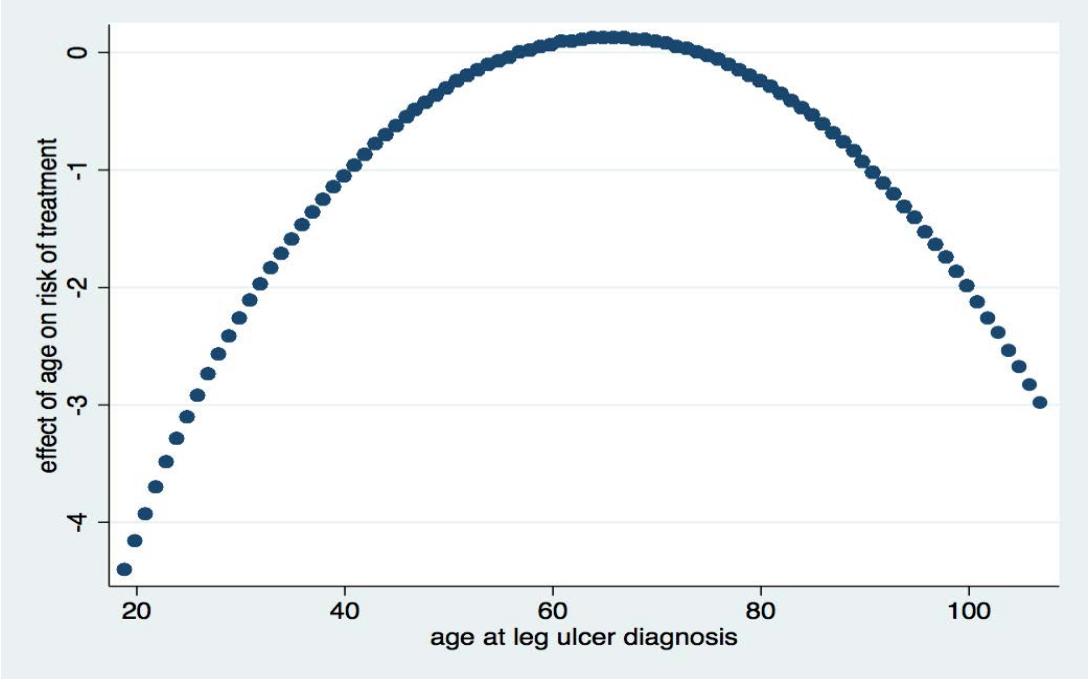
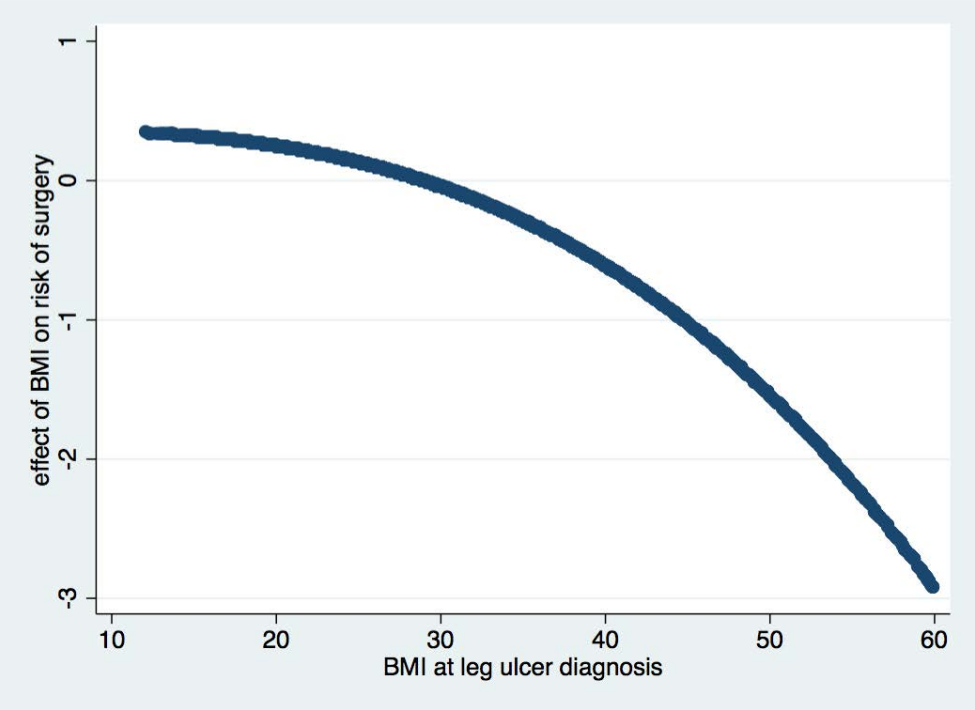


Figure 3.5.3. ***Effect of BMI on Probability of Superficial Venous Intervention for Leg Ulcer***



Chapter 4

DISCUSSION

4.1 LIMITATIONS OF THESIS METHODOLOGY

This thesis aimed to examine the impact of NICE CG168 on the referral and management of venous disease in both secondary care and primary care, at a local level in East Birmingham and at a national level via the Health Improvement Network database. Data for the studies were gathered in eighteen - month periods before and after the publication of guideline CG 168 in July 2013.

Secondary care data from HEFT was a mixture of prospectively collected data and retrospectively analysed data from prospectively gathered databases. Data from secondary care was limited to the local trust catchment population of East Birmingham numbering 1.2 million and comprising a mixture of inner city deprived and affluent suburbs and a wide-ranging ethnic diversity. The complexities and potential inaccuracies of data collected from hospital episode statistics (HES) generally prompted a decision to confine secondary care analysis to the carefully, prospectively collected information in the HEFT database. It was felt that inclusion of other units' data would then, be less accurate as relying solely upon HES figures with no possible quality control checks. It was hoped to mitigate this potential source of error in the local, HEFT secondary care data by cross-checking data entries against hospital operating logs and appointments using local

electronic clinical records to ensure the accuracy of the data and the inclusion of all index cases. All other data sources were compiled from prospectively kept data logs in the University of Birmingham Department of Vascular Surgery. These methods it was hoped, would reflect good clinical practice and provide reasonably accurate data so truly reflecting the effects of CG168.

It is possible that the impact of NICE CG168 was exaggerated locally. This may be due to several reasons, which include:

- The lead for our university department of vascular surgery was involved in the formulation of CG 168
- These guidelines were publicised locally by writing to GP colleagues to inform them of the importance of the new guidelines.
- Local, contemporaneous, promotion of the importance of leg ulcer referral from general practices to enhance recruitment into the Early Venous Reflux Ablation (EVRA) ulcer trial.
- The academic department of vascular surgery has a pre-existing interest in venous disease and its treatment with widely published previous research, which may have increased referrals.

Primary care data was obtained from the THIN database. This national network of GP practices provides all of their patient data in anonymous form for analysis. Practices that participate however, may be more likely to take part in research and perhaps be more

'forward thinking' and consequently aware of current research and clinical guidelines? Practices involved in contributing to the THIN database are not randomly selected throughout the UK and this feature may introduce a degree of selection bias in the patients that are included. There is also a small financial incentive for practices recording anonymous patient data into the THIN database and this might represent another source of bias. The UK, however has been quick to adopt electronic patient record data analysis and the results produced are of generally high quality, particularly those relating to chronic disease and prescribing [239]. The results are however, dependent upon individual clinicians coding diseases, diagnoses and treatments correctly and their individual assessment of whether the episode is relevant to the patients' care and thus worth coding. This is complicated somewhat by the ability to use several codes with similar meaning, this necessitates very careful interrogation of Read codes to identify all potential ways of coding the condition of interest as based on the International Classification of Diseases (ICD)-10 [240]. Indeed the ICD-10 includes over 14000 codes! Analysis of the incidence of CEAP scores in the primary care patients would have been interesting, but unfortunately, there is no extant method to ensure accurate coding for disease severity. This is disappointing and prevents an understanding of whether probability of referral to secondary care was dependent on severity of CEAP score.

Some data deemed to be less important (e.g. ethnicity or BMI) is often poorly recorded and requires multiple imputation in constructing the Cox proportional hazard models to allow analysis between groups. Another confounding feature, as highlighted in Results sections 3.4 and 3.5, is a result of interventions performed in secondary care being very poorly

recorded in the THIN database making comparison of interventions before and after CG168 rather difficult. The assumption was made that problems relating to coding in the pre-CG168 group were ostensibly, of similar prevalence in the post-CG168 group and consequently, although the numbers of recorded interventions were low, it was still possible to at least, broadly, compare trends in the data. Data for THIN is planned to be linked with HES data in the future which will improve the rate of recording of secondary care interventions but there will always remain a potential for error.

4.2 THE ROLE OF NICE CG168 IN LOCAL SECONDARY CARE MANAGEMENT OF VENOUS DISEASE

Careful planning was required by the HEFT vascular directorate before the introduction of NICE CG168 to allow for the predicted increase in VV and LU referrals. This involved consideration of the most efficient use of both outpatient clinic space and operating space for VV procedures in line with the predicted increase of 25% in activity [47]. HEFT saw an increase of 65% in venous treatment activity after CG168 as described in Chapter 3.1.4 and illustrated graphically in Figs.3.1.1 and 3.1.2. An increase in referrals and endovenous treatments was also noted nationally in the THIN database work (Chapter 3.4 and specifically for interventions in Tables 3.4.2 and 3.4.4). The data presented show that, in the author's opinion, NICE CG 168 acted as a catalyst to secondary care activity and that this increased workload had to be absorbed into static resources of space and departmental personnel.

Prior to NICE CG168, in HEFT, as in most vascular departments, there was already an endovenous treatment programme underway. The recommendation for an 'endovenous first' treatment strategy was significant not only to improve patient outcomes and recovery (evidence reviewed in Chapter 2.1, page 19), but allows VV treatments to take place in 'procedure rooms' rather than formal operating theatres. This is of great benefit to hospital theatre schedules as the projected increase in activity in venous treatments could be largely undertaken as day-cases in procedure room based procedures; this is far easier to resource in the cash-limited NHS environment than theatre space and in-patient hospital beds. The recommendation of 'conventional surgery last' again frees vascular operating room space for arterial cases and will have the benefit of improving waiting times for non-venous operations within hospitals vascular directorates.

Improvement in management of VV disease in HEFT was supported by local clinical commissioning groups (CCGs) with financing of VV interventions in accordance with the new guidelines. CG168 provided a strong evidence-based framework for the referral, assessment and treatment of VV. Some commissioning groups elsewhere have considered VV to be procedures of 'low-clinical value' [241] and as such limited the commissioning of related services; this has resulted in significant variation in access to treatment around the country [50] and is not in accord with NICE recommendations. Sadly, further work by Carradice in 2018 has demonstrated that this regional variation is continuing and some CCGs are continuing to ration treatments[48]. While CCGs have local freedom of action, they have a complex relationship of accountability; the most significant is likely to be their accountability to NHS England [242]. It is thus important that CCGs who are not compliant

with commissioning services in accordance with CG168 are highlighted to improve their compliance with national recommendations and thereby ensure equality of access to VV interventions across the NHS. It seems that lack of access to NICE recommended treatment may put CCGs at medico-legal risk, particularly if patients were able to demonstrate a deterioration from symptomatic C2 VV to skin damage and ulceration due to lack of appropriately timed referral and intervention or their intervention was denied by commissioners based on BMI in the presence of minimal evidence to exclude these patients from intervention (as reviewed in section 2.2).

Review of previous UK publications of varicose vein activity suggests that the number of interventions was decreasing. Harris compares local treatments from 2000 compared to 2002/3[52] and Lim reviewed treatment numbers using HES data between 2002-2006[49]. Both describe significant reductions. HES data along with a freedom of information request for treatments commissioned by primary care trusts (the predecessors to CCGs) also revealed a national reduction in VV interventions year on year from 2008-2011[33]. This tends to suggest that UK treatment numbers were reducing pre-CG168, but it cannot be ruled out that in the approach to the release of CG168 that treatment numbers had not started to increase from 2012-2013. The HEFT data presented does suggest that even if this was the case, CG168 has still significantly increased treatment numbers locally regardless of that possibility.

Whilst the NHS costing report does predict an increase in expenditure for the NHS associated with the implementation of CG168, the increase is modest - £1200 per 100 000 patients though this is perhaps an under-estimate of potential financial burden. This calculation includes only direct costs and savings from assessment and treatment of patients and does not include added costs such as litigation. VV litigation is certainly the most common cause for medico-legal cases in vascular surgery [243, 244]. Although endovenous ablation methods have lower complication rates and certainly less risk of inadvertent major arterial or venous injury than conventional surgery, it is possible that the financial burden of medico legal claims to the NHS will not improve as a result of an increasing tendency toward litigation and higher patient expectations from these minimally invasive techniques [245]?

LU referrals increased significantly in number in East Birmingham as described in Chapter 3.2 and e.g., in Table 3.2.1, pages 52 and 57, respectively); in preparation for this a specialist leg ulcer clinic was created. As a result there was no clinically significant increase in waiting times for specialist vascular review, the average increase was only just over 1 week (Chapter 3.2.4 and Table 3.2.1, respectively, pages 55 and 57; discussed in Chapter 3.2.5, page 61).). In terms of cost implication this service was supported by a research team who were not directly funded to staff this clinic, the author suspects that elsewhere it may be difficult to deliver this service without impacting other services or departmental budgets. This considerable increase in referral of leg ulcer patients likely improved ulcer management for significant numbers in the HEFT catchment area with a statistically significant increase in endothermal ablation (Chapter 3.2.4 and Table 3.2.3,

pages 55 and 59, respectively). There are however, likely to be significant numbers of patients suffering ulceration in the community who are still being managed symptomatically with dressings, rather than having underlying ulcer aetiology diagnosed and treated as necessary by secondary care specialists. In East Birmingham, CG168 was followed by a significant decrease in the use of simple dressings, from 26% to 11.5%, p=0.0006, (Table 3.2.3) showing that within HEFT's catchment area, CG 168 can be linked with improved community management of venous disease.

Whilst the IMD data from local, East Birmingham secondary care for VV appears to show no disparity in access to treatment before and after NICE CG168 in terms of social deprivation using the Index of Multiple Deprivation Quintiles (IMD-Q) (Table 3.3.1). It appears there may be some limitation of access to LU patients in the most deprived social groups at a national level. The THIN database analysis, using Townsend Quintiles as indicators of social deprivation, suggested that smaller numbers of people with social deprivation received VV interventions with statistically significantly lower Cox Model hazard ratios for intervention than the 'least-deprived' reference group in Townsend Quintile 1 (Table 3.4.4). There is considerable need to confirm and if so, address this disparity.

4.3 THE ROLE OF NICE CG168 IN PRIMARY CARE MANAGEMENT AND REFERRAL OF VENOUS DISEASE

CG168 guidelines recommendations appropriate for primary care are mainly based around referral (at CEAP C2) and the recognition that compression hosiery is no longer a suitable, general, treatment for VV. The analysis using the THIN database demonstrated a marked improvement in referral numbers to secondary care along with a modest reduction in compression hosiery from 20% of patients to 18% after CG 168 when patients were 7% less likely to receive a prescription for pressure hosiery (hazard ratio 0.93, 95% CI 0.88-0.89, p=0.008, section 3.4.4). Compression hosiery prescriptions still remained relatively high and prescriptions were commonly started just after initial consultation, within the first few days (Fig. 3.4.2) and certainly before they attended secondary care review, demonstrating that GP colleagues were still, perhaps, not fully aware of all of the recommendations.

This increase in referrals will hopefully have improved the identification and treatment of a considerable number of VV patients since the introduction of CG168, as the chances of referral to a vascular specialist have seemingly increased, this, however, may be disproportionately biased towards those from less deprived areas with IMD-Q1/2 and Townsend Quintile 1 patients favoured? This work is based on GP coded referrals; it does not specify whether patients were referred for private practice or NHS vascular review. If private practice is considered (most patients undergoing private VV intervention are likely to be from more affluent areas, therefore IMD – Q1/2), this may bias the dataset, indeed

examining the data from HEFT secondary care (solely NHS patients), as described above (section 3.3) did not show a bias towards any one IMD quintile.

In contrast to improvements noted locally (Chapter 3.2) in LU care, the data obtained from the THIN database did not show any significantly improved compliance with CG 168 in the primary care management of these patients including referral to vascular specialists. Whilst there was an increase in absolute numbers of referrals to vascular care, statistically this was not significant (Table 3.5.5). This is unfortunate as the early referral after two weeks of ulceration is a key part of improving chronic venous insufficiency care in CG168. LU patients are often poorly served, for multiple reasons. Anecdotally, LU is less 'clinically exciting' for surgeons, patients may be self-neglectful and from more socially deprived backgrounds and likely to present at more advanced disease states and be less compliant with treatment regimens. It is a shame that CG168 does not appear to have made an improvement here, where it has, perhaps, the highest potential to improve quality of life for patients and their families/carers? It is possible that CG168 does not place guidance for LU referral prominently enough within its structure. The multiplicity of other sources of leg ulcer guidance (RCN and SIGN) that are more likely to be read by district and practice nurses who are the ones most likely to see and manage LU patients in the community may add to the problem. GP colleagues often do not see LU patients who can be managed conservatively in the community for it may take many months before review by a doctor and eventual consideration of referral to a vascular specialist.

4.4 POTENTIAL FUTURE DIRECTIONS OF NICE VENOUS GUIDELINES

An overarching conclusion to emerge from the work programmes in this thesis is the importance of GP and patient/public awareness. It is difficult for GPs to remain abreast of all current NICE guidelines due to their sheer size and number and the heavy workload in primary care. It may be pertinent to consider publishing primary care summaries containing only the information relevant to general practice to enhance the ability of practitioners to consider current guidance. For example, could CG168 be simply summarised as:

- Provide simple advice on varicose veins and lifestyle advice
- Refer the following for specialist opinion:
  - Symptomatic varicose veins
  - Those with skin changes (eczema/pigmentation) or bleeding
  - Superficial thrombophlebitis
  - Those with skin break below the knee present for longer than 2 weeks
- Compression hosiery is not a recommended treatment for varicose veins unless the patient is not suitable for intervention (e.g. during pregnancy).

This simple summary can then reference guidelines where interested practitioners can find greater detail if necessary. Whilst this might not be possible with all NICE guidelines it would certainly help reduce the burden upon primary care, leaving the in depth knowledge to specialists who may have considerably fewer guidelines relevant to their practice.

It is also important to ensure patients are health aware and can seek help from their GPs. This is particularly important in the more socially deprived areas. NICE CG168 has a concurrent patient information resource, which is thorough and describes the basics of venous disease and treatments along with providing links to other patient resources. In the current financial climate advertising changes to treatment availabilities on television/internet is probably unattainable; however, local advertising in community centres/GP practices with clear posters is possible. This is particularly important with CG168. A large number of patients who were previously deemed to have a medical problem of low clinical significance (symptomatic varicose veins) are now eligible for treatment recommended by evidence -based guidance that, if followed, could appreciably improve their quality of life. It is also important for patients with leg ulceration to understand their entitlement to referral for specialist opinion, rather than waiting for weeks to months having their ulcer 'treated' with regular dressings.

The conclusion from Chapters 3.1 to 3.5 must be that whilst things have improved locally for LU patients the national situation seems less agreeable and much needs to be done to improve matters. In terms of guidelines, CG168 makes strong recommendations to refer patients with leg ulcers after two weeks; however, there remains confusion with the SIGN and RCN guidelines recommending referral after twelve weeks. A unified set of guidelines could encourage the awareness of community health practitioner colleagues of the importance of timely aetiological diagnosis and treatment of LU. Both SIGN and RCN are in need of urgent review hopefully to embody the evidence-based recommendations of CG 168.

One year data from the EVRA trial [246] demonstrates the improved healing times from a median of 82 to 56 days and increased 'ulcer free' time over the first 12 months of follow up with early (within 2 weeks of specialist review) endovenous intervention. There was also an improvement in the quality of life of patients and the findings were highly cost effective. This randomised controlled trial will surely significantly influence the review of CG168 and strengthen the recommendations for LU patients, building upon the ESCHAR trial data from almost 15 years ago!

Perhaps further exploration of treatment hierarchy is required in the next revision of NICE guideline CG168; with increasing financial pressures it is difficult to accept a more expensive treatment strategy (endothermal) as a first line over UGFS (discussed in depth in Chapter 2.1) when in terms of patient reported outcomes, symptomatic improvement is similar? This is particularly pertinent given the recognition of patient reported outcomes becoming more widely recognised for their importance rather than anatomical closure/absence of treated superficial veins as a marker of treatment success. As with the acceptance of endothermal and UGFS treatments, new guidelines will need to address the results of still newer non-thermal, non-tumescent treatment modalities (cyanoacrylate glue and mechano-chemical ablation) [247]. Consideration of what recommendations are appropriate for these techniques is needed; it seems likely that the status of these treatments will be deferred whilst evidence for their use (or at least their non-inferiority) is accumulated and the equipment costs decrease.

There has been a considerable shift in approach to venous disease over the past few years. The importance of recognition of deep venous disease and the prevention of its sequelae (post-thrombotic syndrome and LU) along with novel endovenous treatment strategies for both acute and chronic deep venous disease are steadily acquiring an evidence base. The corresponding treatments are expensive and evidence in terms of randomised controlled trials and registry data is limited at present. Is it therefore likely that in the future there will evolve a separate clinical guideline for deep venous disease and associated interventions?

CG168 only mentions excess weight and venous disease in terms of advising patients of weight loss as part of lifestyle measures and referring clinicians to NICE CG43 [248] (the clinical guideline for obesity management). As described in Chapter 2.2, 'phlebesity' is increasing in prevalence. Current evidence suggests obesity as a potential contributing factor to venous disease and also demonstrates these patients have more severe symptoms and are more likely to have a higher CEAP clinical grade than their normal-weight counterparts. This perhaps makes obese patients more in need of treatment for venous disease, yet these patients are technically more difficult to treat as well as being at greater risk of complications post- procedure. As the evidence grows in this area guidance will be required to aid clinicians' decision-making and support decisions to intervene or manage conservatively as appropriate.

4.5 FUTURE DIRECTION OF RESEARCH ASSOCIATED WITH NICE GUIDELINES

The presented thesis attempts to examine the impact of CG168 upon the management of superficial venous disease by studying primary care and secondary care responses. A national overview for England, of the effect of CG168 has been gleaned from the THIN database in terms of the primary care perspective, further research is required to examine whether CG168 has had any impact at a national level in secondary care. The absence of an accurate, nation wide database makes the latter task extremely difficult to perform. It is suspected that there would be considerable variation around the UK in the uptake and adherence to the guidelines. This variation will be a combination of local clinical commissioning groups disregarding the guidance and not commissioning enough endovenous procedures from secondary care providers and local secondary care variance in procedures and pathways. The expense of producing NICE guidelines means that ensuring their utilisation is imperative; otherwise with limited NHS budgets this money may be better spent elsewhere. Exploration of this area could be based upon a search of hospital episode statistics and perhaps providing an additional ‘clinician’ component to the current VV PROMs data collection that is already underway? This data would not only yield information on adherence to NICE guidelines but could also provide data on equality of access to interventions around the UK, perhaps improving the ‘postcode lottery’ leading to some variance in access to healthcare.

Increased data on nationwide management of venous disease would allow better cost modelling for predicting NHS budget requirements. It would also allow consideration of the role of independent sector treatment centres (ISTCs) for the assessment and treatment of superficial venous disease. ISTCs contracts require further investigation into their cost-effectiveness as the present system of guaranteed payments may result in under-delivery of treatments and thus result in a financial loss to the NHS. There is also a reduction in 'profitable' services for 'low-risk' patients with low levels of co-morbidity undergoing out-patient based venous interventions for NHS hospitals and a reduction in training opportunities by ISTCs taking straightforward cases away from teaching hospitals.

There is also a need for further investigation into the effects of social deprivation upon leg ulcer patients. At present these patients lack optimal service and change is required to improve their predicament. It may be that community based leg ulcer clinics would encourage and empower these patients to present at an earlier stage to specialists, correspondingly appropriate management could be initiated in the community. This would require relatively little resources; the majority of patients require a history/examination/venous ultrasound (from a portable scanner) to identify any reversible causes and treatment with compression bandages could be initiated before referring on those with superficial venous reflux for consideration of intervention and those whose ankle-brachial pressure index suggests arterial insufficiency or whose underlying pathology was non-vascular in nature.

4.5.1 Suggestions For Future Studies

- Study of adherence/non-adherence to NICE guidelines and reasons behind CCG non-adherence. This could be performed by freedom of information requests to individual CCGs with corroboration via questionnaires sent to Vascular Society of Great Britain and Ireland members to detect geographical variation and access to treatments as per CCG commissioning.
    - Hypothesis – CCGs are rationing treatments due to financial constraints.

- Investigation into nationwide numbers of varicose vein interventions post-CG168. This could be performed by analysis of HES data thus monitoring numbers of interventions performed to gauge changes in commissioning VV interventions against NICE guidance.
    - Hypothesis – VV interventions would have increased post-CG168 and be maintained at steady state.

- Investigation into social deprivation and the incidence of VV and LU diagnoses. This may be achieved by further analysis of patient data from existing epidemiological databases (e.g. the Edinburgh or Bonn vein studies) provided it is possible to identify deprivation by, e.g., postcode; however the limitations of these methods of social deprivation assessment have been discussed earlier in this thesis. Additionally the Bonn and Edinburgh studies were not contemporaneous or sufficiently recent. The data could reflect frequency/availability of VV

interventions within different social groups to identify any prejudicial effects of social deprivation.

  - Hypothesis – VV and LU are associated with social deprivation.

- Further study of possible linkage of social deprivation, age and sex on referral for VV and LU within the limitations of interrogation of the THIN or other primary care databases.
  - Hypothesis – young females from less socially deprived areas are more likely to present seeking VV interventions. Elderly females from less socially deprived areas are more likely to seek LU referral.

- Considerable work on obesity and venous disease is required.
  - Does obesity affect success/longevity of endovenous interventions?
  - Does obesity increase complications after endovenous interventions?
  - Do obese patients have similar improvement or lesser/greater improvements in quality of life after superficial venous interventions?

Answers to the above questions will help shape recommendations in future NICE clinical guidelines for venous disease.

Chapter 5

CONCLUSION

NICE CG168 has recommended substantial changes and improvements for the management of superficial venous disease in the UK. This thesis has demonstrated that after introduction of CG168 there has been a significant increase in referral of VVs to secondary care and that at least locally, there as been an increase in treatments for VVs. This has been particularly in those with symptomatic CEAP C2 VVs who previously were not treated with intervention. There has also been a marked shift towards endovenous first treatment strategy as recommended by CG168.

The impact on leg ulcer patients sadly, has been less marked. There has been no real difference in the referral of people with leg ulcers from primary care as evinced by evidence from the THIN database. More promisingly, locally, in East Birmingham, there has been a considerable increase in the number of patients referred; however, these patients are not being referred any earlier than 'before CG168'. There also appears to be a possible disadvantage to the socially deprived that requires further investigation.

Overall, whilst there has been improvement, further work is required to ensure greater awareness amongst community practitioners of CG168, to enhance referral from primary care for specialist vascular assessment, to encourage understanding by commissioners to adequately fund services and to promote greater awareness in the general public to seek

advice for their lower limb venous disease. Future superficial venous guidelines will need to consider addressing these areas of need.

APPENDIX 3 – Read Codes To Identify THIN Database Patients

Read Codes To Identify Varicose Vein Patients

Read code	Description
2482.00	O/E - varicose veins
G83..00	Varicose veins of the legs
G830.00	Varicose veins of the leg with ulcer
G831.00	Varicose veins of the leg with eczema
G831.11	Varicose eczema
G832.00	Varicose veins of the leg with ulcer and eczema
G833.00	Varicose veins of the leg with rupture
G834.00	Varicose veins of leg without mention of complications
G834000	Varicose veins of leg with long saphenous vein distribution
G834100	Varicose veins of leg with short saphenous vein distribution
G835.00	Infected varicose ulcer
G836.00	Varicose vein of leg with phlebitis
G837.00	Venous ulcer of leg
G83z.00	Varicose veins of the leg NOS
G85..00	Other varicose veins
G85y.00	Other specified varicose veins
G85z.00	Other varicose veins NOS
Gyu8600	[X]Varicose veins of other specified sites
L41..11	Varicose veins - obstetric
L410.00	Varicose veins of legs in pregnancy and the puerperium
L410000	Varicose veins of legs in pregnancy/puerperium unspecified
L410100	Varicose veins of legs in pregnancy/puerperium - delivered
L410200	Varicose veins of legs in pregnancy/puerperium -del+p/n comp
L410300	Varicose veins of legs in pregnancy/puerperium + a/n comp
L410400	Varicose veins of legs in pregnancy/puerperium + p/n comp
L410500	Varicose veins of legs in pregnancy
L410600	Varicose veins of legs in the puerperium
L410z00	Varicose veins of legs in pregnancy and puerperium NOS

Read Codes To Identify Leg Ulcer Patients

Read code	Description
2G48.00	O/E - ankle ulcer
2G54.00	O/E - Right foot ulcer
2G55.00	O/E - Left foot ulcer
2G5H.00	O/E - Right diabetic foot - ulcerated
2G5L.00	O/E - Left diabetic foot - ulcerated
2G5V.00	O/E - right chronic diabetic foot ulcer
2G5W.00	O/E - left chronic diabetic foot ulcer
8CMT.00	Leg ulcer care pathway
8CS3.00	Agreeing on leg ulcer treatment plan
8CT1.00	Leg ulcer compression therapy finished
8CV2.00	Leg ulcer compression therapy started
9NM5.00	Attending leg ulcer clinic
C108500	Insulin dependent diabetes mellitus with ulcer
C108511	Type I diabetes mellitus with ulcer
C108512	Type 1 diabetes mellitus with ulcer
C109400	Non-insulin dependent diabetes mellitus with ulcer
C109411	Type II diabetes mellitus with ulcer
C109412	Type 2 diabetes mellitus with ulcer
C10E500	Type 1 diabetes mellitus with ulcer
C10E511	Type I diabetes mellitus with ulcer
C10E512	Insulin dependent diabetes mellitus with ulcer
C10F400	Type 2 diabetes mellitus with ulcer
C10F411	Type II diabetes mellitus with ulcer
G830.00	Varicose veins of the leg with ulcer
G832.00	Varicose veins of the leg with ulcer and eczema
G835.00	Infected varicose ulcer
G837.00	Venous ulcer of leg
M271.00	Non-pressure ulcer lower limb
M271.11	Foot ulcer
M271.12	Ischaemic leg ulcer
M271.13	Leg ulcer NOS
M271.14	Neurogenic leg ulcer
M271.15	Trophic leg ulcer
M271000	Ischaemic ulcer diabetic foot
M271100	Neuropathic diabetic ulcer - foot
M271200	Mixed diabetic ulcer - foot
M271300	Arterial leg ulcer
M271400	Mixed venous and arterial leg ulcer
M271500	Venous ulcer of leg
M271600	Traumatic leg ulcer
M271700	Neuropathic foot ulcer
M273.00	Non-healing leg ulcer
M274.00	Recurrent leg ulcer

Read Codes To Identify Varicose Vein Intervention

Read code	Description
7A66100	Subfascial ligation of perforating vein of leg
7A66111	Cockett subfascial ligation of perforating varicose vein
7A66112	Subfascial ligation of varicose veins
7A66y00	Other specified other operation for venous insufficiency
7A66z00	Other operation for venous insufficiency NOS
7A67.00	Ligation of varicose vein of leg
7A67000	Ligation of long saphenous vein
7A67011	Trendelenburg ligation of long saphenous vein
7A67100	Ligation of short saphenous vein
7A67200	Ligation of recurrent varicose vein of leg
7A67300	Ligation of perforating varicose vein of leg
7A67311	Linton ligation of perforating varicose vein of leg
7A67400	High ligation of long saphenous vein
7A67411	High tie ligation
7A67y00	Other specified ligation of varicose vein of leg
7A67z00	Ligation of varicose vein of leg NOS
7A68.00	Injection into varicose vein of leg
7A68000	Injection of sclerosing substance into varicose vein of leg
7A68100	Microsclerotherapy to spider veins of leg
7A68200	Ultrasound guided foam sclerotherapy for varicose vein leg
7A68300	Transilluminated powered phlebectomy of varicose vein of leg
7A68400	Injection of sclerosing substance into varicose vein leg NEC
7A68y00	Other specified injection into varicose vein of leg
7A68z00	Injection into varicose vein of leg NOS
7A69.00	Other operations on varicose vein of leg
7A69000	Stripping of long saphenous vein
7A69100	Stripping of short saphenous vein
7A69200	Stripping of varicose vein of leg NEC
7A69211	Mayo stripping of varicose vein
7A69300	Avulsion of varicose vein of leg
7A69311	Babcock subcutaneous enucleation of varicose veins
7A69400	Local excision of varicose vein of leg
7A69500	Incision of varicose vein of leg
7A69600	Endovascular radiofrequency ablation of varicose vein of leg
7A69700	Endovascular laser ablation of varicose vein of leg
7A69y00	Other specified other operation on varicose vein of leg
7A69z00	Other operation on varicose vein of leg NOS
7A6L.00	Combined operations on varicose vein of leg
7A6L000	Combined operations on primary long saphenous vein
7A6L100	Combined operations on primary short saphenous vein
7A6L200	Combined operations on primary long and short saphenous vein

7A6L300	Combined operations on recurrent long saphenous vein
7A6L400	Combined operations on recurrent short saphenous vein
7A6L500	Combined operations recurrent long and short saphenous vein
7A6Ly00	Other specified combined operations on varicose vein of leg
7A6Lz00	Combined operations on varicose vein of leg NOS
7A6M.00	Transluminal operations on varicose vein of leg
7A6M000	Percutaneous transluminal laser ablation long saphenous vein
7A6M100	Radiofrequency ablation of varicose vein of leg
7A6M200	Percutaneous transluminal laser ablation of vein NEC
7A6M300	Perc transluminal laser ablation of varicose vein of leg NEC
7A6My00	Other specified transluminal operations on varicose vein leg
7A6Mz00	Transluminal operations on varicose vein of leg NOS

APPENDIX 4 – Papers Arising

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