Truncal varicose vein diameter and patients reported outcome measures

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Abstract:

Background

Varicose veins and chronic venous disease are common, and some funding bodies ration treatment based on a minimum diameter of the incompetent truncal vein. This study assesses the effect of maximal vein diameter on clinical status and patient symptomatology.

Methods

A prospective observational cohort study was conducted of patients presenting with symptomatic varicose veins to a tertiary referral public hospital vascular clinic between January 2011 and July 2012 (18 month period). Patients underwent standardised assessment with venous duplex ultrasound and completed questionnaires assessing quality of life and symptomatology (Aberdeen Varicose Vein Questionnaire - AVVQ, EurolQol 5 Domain Quality of life assessment - EQ-5D QOL and EuroQol Visual Analogue Scale - EQ-VAS). Clinical scores (Venous Clinical Severity Score - VCSS and Clinical Etiological Anatomical and Pathological stage - CEAP) were also calculated. Regression

analysis was used to investigate the relationship between quality of life, symptomatology and vein diameter.

Results

Some 330 patients were assessed pre-operatively (overall median maximum vein diameter 7.0mm (IQR 5.3-9.2mm), GSV was 7.9mm (IQR 6.0-9.8mm) and SSV was 6mm (IQR 5.2-8.9mm)). Following linear regression vein diameter was shown to have a significant association with VCSS (p=0.041). CEAP 4 class had a 2.7 fold incidence risk compared to CEAP 2 with 1mm increase in vein diameter. No other quality of life or symptom measures were related to vein diameter.

Conclusion

This study provides evidence that vein diameter is not associated with many clinical or patient reported outcomes. Its use as a rationing tool would appear to be inappropriate.

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Introduction

Varicose veins are a common but often underestimated condition, with significant symptoms and societal costs [1,2], [3,4]. Epidemiological estimates suggest a prevalence of 25-50% [5] and there is extensive evidence that intervention provides significant cost-effective improvements in quality of life [6-8], [9].

Due to financial constraints and the ageing population, rationing of treatment has been proposed as a necessary evil [10], and is best assessed on cost effectiveness of the treatment itself [11] and clinical need [12]. Varicose veins have long been classed as a condition with low priority [13], partly due to its prevalence, partly due to the wide spectrum of symptoms [14] and partly the poor understanding of the disease in the primary care setting [15]. Recent extensive meta-analysis and statistical modelling work by the National Institute for Health and Care Excellence (NICE) has shown that conservative treatment of varicose veins with compression stockings is inferior to venous intervention (endovenous thermal ablation, surgery or foam sclerotherapy) in terms of cost-effectiveness [16].

There has been a recent movement towards using vein diameter of the great saphenous vein (GSV) or small saphenous vein (SSV) to stratify patients suitable for treatment and indeed reimbursements in some countries depend on vein diameter criteria being met,

including the UK and the referral guidance local to our unit [17] (see supplemental material). The assumption is that larger incompetent veins equate to more symptomatic varicose veins. This is despite clear referral recommendations against such rationing [18,19], which have been re-affirmed with the 2013 guidelines from NICE in the UK [20].

The evidence that bigger veins are more painful is sparse, and often made on the presumption of traditional surgical operations [21], and despite the natural variability of varicose vein diameter [22]. There is some evidence to show that chronic venous insufficiency (CVI – Clinical Etiological Anatomical and Pathological classification – CEAP C4-C6) is associated with lower disease specific quality of life scores (Aberdeen Varicose Vein Questionnaire – AVVQ) and a larger vein diameter, when compared to chronic venous disease (C1-C3) [23-26], [3]. However Shepherd et al. showed no association between anatomical reflux (venous segmental disease score) or haemodynamic assessments (venous refill time) and outcomes [27].

The aim of this study was to assess the association between clinical grading, clinical severity score, disease specific quality of life score, generic quality of life and maximal vein diameter. The hypothesis was that increased incompetent vein diameter would lead to worsened clinical status and quality of life.

Methods

The study was designed as a prospective observational cross-sectional study to assess the relationship between anatomical data and clinical status. Regional ethical sub-

committee approval was sought and obtained for this study which was classified as service evaluation (see supplemental material) [28].

Consecutive patients were recruited from those attending a tertiary referral vascular clinic for assessment and treatment of varicose veins between January 2011 and July 2012 (18 months). Methodology followed the STROBE checklist [29].

During recruitment, the local referral criteria allowed for referral for symptomatic varicose veins >3mm in size, bleeding, skin changes, thrombophlebitis, ulceration or mixed arterio-venous disease (see supplemental material for changing local referral guidance).

Patients were clinically assessed by a vascular surgeon and scored according to the CEAP staging system and the VCSS clinical scoring system [30,31]. Patients who were thought to be suffering from symptomatic venous disease underwent standardised Duplex ultrasound scans of the venous tree in the standing position by qualified vascular scientists. Venous reflux time of >0.5s was considered significant and a full vein map of the lower leg was completed. Patients were included in analysis if they showed truncal incompetence and the maximal vein diameter of the GSV or SSV at a point 5-10cm from the saphenofemoral junction or saphenopopliteal junction as appropriate (excluding venous aneurysms – defined as localised extreme dilatation <5cm in length) was recorded. Basic demographics were recorded. Patients were also invited to complete quality of life questionnaires; assessing disease specific quality of life (AVVQ [32]) and generic quality of life (EuroQol 5-Domain Quality of Life score - EQ5D-5L and the EuroQol Visual Analogue Scale – EQVAS [33]). Finally patients completed a validated depression score - CES-D [34,35]. All questionnaires were completed in clinic. Patients

who declined to or were not able to fully complete the quality of life questionnaires were not included in this analysis.
In the case of bilateral disease, the leg with the worse disease was analysed. AVVQ was not amended due to its mixed nature of joint and separate questions.

Data were collated on a dedicated database (Access 2010, Microsoft, Richmond, USA) and underwent statistical analysis using SPSS version 23 (IBM, Armonk, USA), STATA 14.2 SE (Statcorp, College Station, USA) and Wizard Pro v1.8.28 (Evan Miller, Chicago, USA). Data were visually inspected to assess distribution and log transformed if distribution was not normal.

Regression analysis was used to investigate the relation between quality of life and symptoms score (VCSS, AVVQ, EQ5D QOL and CEAP) and vein diameter adjusting for age, gender, BMI and GSV/SSV incompetence. Positive co-efficients indicate an increase in independent variable will lead to an increase in dependent variable, and negative to a decrease.

Then subgroups were analysed for quality of life differences with a further analysis - as two groups stratified by CEAP stages 1-3 and 4-6. Binary logistic regression analysis was used to investigate the relationship between CEAP 1-3 and CEAP 4-6 groups and vein diameter, adjusting for age, gender, BMI and GSV/SSV incompetence. Group differences in VCSS, vein diameter, AVVQ, EQ5D QOL, EQ5D VAS and CES-D were analysed using Mann-Whitney tests.

Results

Some 330 patients were recruited (Table 1). 10 patients in this cohort (3%) had mixed truncal disease. 6 patients (2%) had a maximal vein diameter < 3mm.

Men and women were of similar age (49 years versus 53 years, p=0.107), and had an equivalent maximal venous diameter (7.5mm versus 7mm, p=0.443) but men had a significantly higher median CEAP clinical stage (4 vs 3, p=0.002). Despite these factors male patients also had a significantly better baseline QOL - both disease specific and generic - AVVQ (15.17 vs 23.51, p<0.001), EQ5D QOL (0.773 vs 0.721, p<0.001) and EQ5D VAS (75 vs 80, p=0.008). There was no significant difference between genders in VCSS scores (7 versus 7, p=0.820) and CES-D (9 versus 10, p=0.328).

Obese patients (BMI > 30) were 75% female (p=0.001), but were not significantly younger (Obese - 46 years versus Not Obese - 52 years, p=0.062), and had similar levels of C4-C6 disease (Obese - 57.5% versus Not Obese - 48.5%, p=0.239). Obese patients had a significantly greater maximal vein diameter (8.1mm versus 7.0mm, p=0.005) compared to non-obese patients. VCSS, AVVQ and CES-D scores were equivalent among obese patients. EQ-5D QOL and VAS were significantly worse in the obese group (0.69 versus 0.76, p<0.001 and 65 versus 80, p<0.001 respectively) compared to the non-obese group.

Median GSV and SSV maximal vein diameters were similar – GSV 7.9mm (6.0-9.8mm) versus SSV 6.0mm (5.2-8.9mm), p=0.052. No significant differences were seen between GSV and SSV incompetence for AVVQ (p=0.323), VCSS (0.287), CEAP (p=0.587), CES-D (p=0.765), EQ-5D QOL (0.281) and EQ-5D VAS (p=0.347).

Linear Regression

The results of regression analysis are outlined in *Table 2* (VCSS), *Table 3* (AVVQ), *Table 4* (EQ5D QOL) and *Table 5* (CEAP).

Following logarithmic transformation of VCSS, a multiple linear regression was used to predict the association between VCSS and vein diameter adjusting for age, sex, GSV or SSV and BMI. Vein diameter and age both showed significant positive associations ($p=0.041$ and $p<0.001$ respectively) (*Table 2).*

Following logarithmic transformation of AVVQ, multiple linear regression was used to predict the association between AVVQ and vein diameter adjusting for age, sex, GSV or SSV and BMI. Vein diameter did not show a significant association. Sex was significant ($p<0.001$) with a negative association – this indicates increased (worsened) AVVQ with female sex (*Table 3).*

Following logarithmic transformation of EQ5D QOL, multiple linear regression was used to predict the association between EQ5D QOL and vein diameter adjusting for age, sex, GSV or SSV and BMI. Vein diameter did not show a significant association. BMI however, was significant ($p=0.006$) and negatively associated, indicating reduced (worsened) EQ5D QOL with BMI > 30 (*Table 4).*

Multi-nomial logistic regression was used to predict the association between CEAP categories and vein diameter adjusting for age, sex, GSV or SSV and BMI. The base case scenario was CEAP 2 (as CEAP 1 had insufficient results – n=6). No variables were significant for CEAP 3 or CEAP 6. For CEAP 4 Vein Diameter ($p=0.025$) and Age ($p<0.001$) were significant and positively associated. The relative risk ratio for CEAP 4 was 2.747, indicated that for every 1 unit (mm) increase in vein diameter, there is a 2.747 fold increase in risk of being in CEAP 4

compared to CEAP 2. For CEAP 5 Age (p=0.001) and Sex (p=0.019) were significant and positively associated *(Table 5)*.

Stratification by Uncomplicated or Complicated Venous Disease (Clinical CEAP Grade 1-3 or 4-6) (Table 6 a and b)

The results were divided into two groups depending on clinical grading - CEAP score (*Table 6)*. Group one represented mild venous disease - C1-C3 (telangectasia to leg swelling); and group two represented more severe venous disease - C4-C6 (skin changes to active ulceration). 51% of patients were graded as having mild disease (167 of 330) and 49% as severe. The severe group had a significantly higher mean age (55 years vs 46.5 years, p<0.001) and a higher proportion of men in the group (56% vs 38%, p<0.001).

Binary logistic regression was used to predict the association between CEAP categories (1-3 and 4-6) and vein diameter adjusting for age, sex, GSV or SSV and BMI. The base case scenario was CEAP 1-3. Vein diameter showed no significant association. Age and sex were significantly and positively associated (p<0.001 and p=0.001 respectively) with group (*Table 6a)*.

The severe group were found to have similar median maximal vein diameter (7.8 mm (IQR 6.0-9.5mm) vs 6.8mm (5.0-9.1mm), p=0.055), but higher median AVVQ scores (24.96 (14.91-35.12) vs 16.18 (11.92-25.20), p<0.001) and higher median VCSS (9 (7-11) vs 5 (4-7), p<0.0001) (*Table 6b*).

Discussion

This study demonstrated that for patients with symptomatic varicose vein disease there is no significant association between maximal vein diameter and clinical stage (CEAP), symptomatology (AVVQ) or generic quality of life (EQ-5D QOL). There was an association with clinical score (VCSS), but the effect size was extremely small (0.018). This is not a clinically significant association and is probably not clinically relevant. Compared to the base case of CEAP 2, patients with CEAP 4 had a significant positive association with vein diameter with a 2.7 times increased risk of chronic venous disease with each 1mm increase in vein diameter. However this association was not seen on comparison of CEAP 1-3 and CEAP 4-6, or at other levels of the multinomial regression for CEAP.

In summary, maximal vein diameter assessment did not provide accurate prediction of clinical scores or patient symptoms.

The natural history and progression of varicose vein disease is poorly understood and screening based on vein diameter may miss late onset cases and lead to treatment of asymptomatic disease with the burden of procedural complications. Assessment with clinical review, symptomatology and targeted treatment from venous duplex ultrasound as is current practice is supported by the results of this study, which does not find a find a role for rationing based on vein diameter. Symptomatology and haemodynamics of venous disease is extremely complex with multiple facets requiring separate assessment.

Multiple previous studies have shown that the treatment of varicose veins is cost-effective [6,7,16,36], and modern care pathways offer all types of treatment as day cases. Due to the size of the population afflicted with symptomatic varicose veins, many healthcare systems are attempting to limit treatment to those who need it most. This rationing has been achieved with the use of maximal vein diameter as a hurdle. In the UK many National Health Service regions have utilised 3 mm, as have insurers in the UK [37] and US [38] and some have thresholds at a greater diameter than this (e.g. 4.5mm) [39]. Whilst this may be rational from a technical viewpoint (as there may be difficulty cannulating and treating smaller veins), it has no basis in the literature or clinical guidelines [20]. The availability of micropuncture sets at 4 and 5 French sizes (1.3mm or 1.7mm diameter) coupled with 600-900 μm diameter laser fibres allow technical success in small veins. Additionally, foam sclerotherapy is routinely performed with 22 gauge needles (0.7mm diameter) or smaller. Indeed, many patients have symptomatic varicose veins without truncal reflux and this has led to the development of techniques such as ambulatory selective varices ablation under local anaesthesia (ASVAL) and conservative hemodynamic treatment for chronic venous insufficiency (CHIVA) [40,41]. Finally, there is a significant practical limitation to using vein diameter as a rationing tool, as it requires the use of venous Duplex ultrasound in primary care to ascertain whether the vein is large enough for referral.

From this study it is clear that maximal vein diameter measurement is not appropriate as a rationing tool. Additionally, the true nature of progression of venous disease and maximal vein diameter changes are not yet known [42-44] - treating a small but

symptomatic vein now may prevent more costly treatment and extensive morbidity in the future [45]. Extensive work by Carradice has demonstrated that increasing clinical severity is associated with increasing symptoms loads but more crucially, that withholding treatment until the onset of chronic venous changes leads to greater recurrence and a level of irreversible morbidity that could be avoided with treatment on symptomatic basis [3,46].

From a patient perspective, the usual reason for seeking medical treatment is not due to the size of the truncal vein but due to symptoms. There is no evidence linking varicosed surface tributary diameter with truncal vein diameter. Indeed there is evidence of isolated varicosity reflux with a normal saphenous system [47]. This prevents clinicians from making accurate diagnosis on examination alone. Therefore, clinical history and validated questionnaires are crucial methods of assessing outcomes of this extremely common but relatively benign disease, in addition to ultrasound vein mapping. The recent NICE guidance on varicose vein referral and intervention covers both primary and secondary care with extensive patient data modelling. This guidance recommends referral based on symptoms, not on clinical staging (CEAP) or clinical severity (VCSS) [20].

Interestingly, the data from this study agrees with the general trend for men to present with more clinically advanced disease than women [48,49]. Men are over-represented in the severe disease group (C4-6) compared to the total group (56% vs 38%, p=0.001). However, the male group have better disease specific and generic quality of life scores despite this. This could explain the higher rate of more complicated disease, due to a

lower symptom burden, however this requires further investigation. It may be that a sex-specific quality of life scores are required to assess venous disease more precisely.

The main strength of this study is the large numbers involved with data collected in a prospective manner, with both clinical and quality of life scoring systems utilised. However, limitations exist due to lack of follow-up post-procedure data. A large number of patients in this cohort displayed CEAP class C4 disease and therefore this cohort was weighted towards more severe disease. This may be related to referral practice at the time of the cohort both locally and nationally, as our unit has a significant tertiary practice with patients refused local treatment due to rationing seeking review. However, this does allow robust conclusion between uncomplicated and complicated disease, but it must be appreciated that there may be a sampling bias present. Additionally, as there were only 6 patients with a maximal vein diameter of < 3mm this may limit transferability. However these patients had similar symptoms scores as the larger vein group, and no correlation with vein diameter was seen in this study. A further limitation is lack of detailed symptomatology information. It may be that certain symptoms correlate better with vein diameter than others. This was not recorded in this study and would like be a fruitful avenue of further investigation.

Most crucially this study does not answer the question of whether large maximal vein diameter is associated with the development of venous skin changes and ulceration. The Bonn and Edinburgh Vein Studies [50,51] are epidemiological studies that have started to publish long-term outcome data which indicates a significant rate of progression from "simple" venous disease (C2 class) to chronic venous insufficiency (C3+) at 4.3% per

annum [52,53]. A long-term large cohort study of patients pre and post endovenous intervention would enable assessment of recurrence and/or progression of the disease in the context of modern minimally invasive treatment.

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Disclosures

The authors declare no conflicts of interest.

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Table Legends

Table 1: Vein Diameter Cohort Demographics

Table 2: Linear Regression Analysis for VCSS.

Table 3: Linear Regression Analysis for AVVQ.

Table 4: Linear Regression Analysis for EQ-5D QOL.

Table 5: Multinomial logistic regression for CEAP

Table 6: a) Regression analysis - Study population stratified by CEAP Classification into groups C1-C3 (mild venous disease) and C4-C6 (severe venous disease). b) Study population stratified by CEAP Classification into groups C1-C3 (mild venous disease) and C4-C6 (severe venous disease).

Table 1: Vein Diameter Cohort Demographics

N	330	
Age Median (IQR)	52 (38-64)	
Male : Female	47 : 53	
Proportion with BMI > 30	10%	
GSV : SSV	86 : 14	
Maximum Vein Diameter Median (IQR)	7.0 mm (5.3-7.0)	
VCSS Median (IQR)	7 (5-9)	
AVVQ Median (IQR)	21.065 (12.73-29.83)	
EQ-5D QOL Median (IQR)	0.740 (0.647-0.837)	
EQ VAS Median (IQR)	80 (65-90)	
CEAP Median (IQR)	3 (2-4)	
CEAP 1 (N and proportion)	6	1.8%
CEAP 2 (N and proportion)	86	26.1%
CEAP 3 (N and proportion)	78	23.6%
CEAP 4 (N and proportion)	135	40.9%
CEAP 5 (N and proportion)	16	4.8%
CEAP 6 (N and proportion)	12	3.6%

VCSS Analysis VARIABLES	Co-Efficient	95% Confidence Interval	Effect Size (partial eta^2)	p
Vein Diameter	0.132**	0.006 - 0.259	0.018	0.041
	(0.0643)			
Age	0.00846***	0.005 - 0.012	0.099	0.000
	(0.00170)			
Sex	0.0286	-0.077 - 0.135	0.001	0.595
	(0.0538)			
BMI > 30	0.0369	-0.131 - 0.204	0.001	0.664
	(0.0850)			
GSV / SSV	-0.0850	-0.242 - 0.072	0.005	0.288
	(0.0798)			
Constant	1.184***	0.866 - 1.503		0.000
	(0.161)			
Observations	233			
R-squared	0.117			
F Test	6.03			0.000

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

AVVQ Analysis VARIABLES	Co-Efficient	95% Confidence Interval	Effect Size (partial eta^2)	p
Vein Diameter	0.0747	-0.113 - 0.263	0.003	0.436
	(0.0956)			
Age	0.00436*	-0.001 - 0.001	0.013	0.084
	(0.00251)			
Sex	-0.300***	-0.457 - 0.142	0.059	0.000
	(0.0798)			
BMI > 30	0.0340	-0.214 - 0.282	0.000	0.788
	(0.126)			
GSV / SSV	0.106	-0.124 - 0.337	0.004	0.365
	(0.117)			
Constant	2.739***	2.267 - 3.212		0.000
	(0.240)			
Observations	232			
R-squared	0.080			
F Test	4.00			0.0017

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

EQ-5D QOL VARIABLES	Co-Efficient	95% Confidence Interval	Effect Size (partial eta^2)	p
Vein Diameter	-0.0538	-0.195 - 0.087	0.003	0.452
	(0.0714)			
Age	-0.00121	-0.005 - 0.002	0.002	0.519
	(0.00187)			
Sex	0.0999*	-0.018 - 0.218	0.013	0.095
	(0.0597)			
BMI > 30	-0.263***	-0.450 - 0.077	0.034	0.006
	(0.0948)			
GSV / SSV	0.102	-0.069 - 0.273	0.006	0.240
	(0.0868)			
Constant	-0.267	-0.620 - 0.085		0.136
	(0.179)			
Observations	226			
R-squared	0.069			
F Test	3.28			0.007

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

EQ-5D QOL VARIABLES	Co-Efficient	95% Confidence Interval	Effect Size (partial eta^2)	p
Vein Diameter	-0.0538	-0.195 - 0.087	0.003	0.452
	(0.0714)			
Age	-0.00121	-0.005 - 0.002	0.002	0.519
	(0.00187)			
Sex	0.0999*	-0.018 - 0.218	0.013	0.095
	(0.0597)			
BMI > 30	-0.263***	-0.450 - 0.077	0.034	0.006
	(0.0948)			
GSV / SSV	0.102	-0.069 - 0.273	0.006	0.240
	(0.0868)			
Constant	-0.267	-0.620 - 0.085		0.136
	(0.179)			
Observations	226			
R-squared	0.069			
F Test	3.28			0.007

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

CEAP Analysis VARIABLES		CEAP 1	CEAP 2 Base	CEAP 3	CEAP 4	CEAP 5	CEAP 6
Vein Diameter	Co-Efficient	0.721		0.534	1.010 **	0.587	0.268
	Standard Error	(1.981)		(0.466)	(0.449)	(0.918)	(0.933)
	95% Confidence Interval	-3.161 – 4.604		-0.379 - 1.448	0.130 - 1.891	-1.213 – 2.386	-1.561 – 2.097
	Relative Risk Ratio	2.057		1.706	2.747	1.798	1.307
	p	0.716		0.251	0.025	0.523	0.774
Age	Co-Efficient	0.799		0.015	0.047 ***	0.083 ***	0.0267
	Standard Error	(0.54)		(0.13)	(0.013)	(0.024)	(0.025)
	95% Confidence Interval	-0.025 – 0.184		-0.011 - 0.041	0.022 - 0.072	0.036 – 0.130	-0.023 - 0.077
	Relative Risk Ratio	1.083		1.015	1.048	1.087	1.027
	p	0.135		0.271	0.000	0.001	0.294
Sex	Co-Efficient	0.095		-0.535	0.577	2.609 ***	0.192
	Standard Error	(1.507)		(0.404)	(0.374)	(1.109)	(0.776)
	95% Confidence Interval	-2.858 – 3.048		-1.326 - 0.256	-0.156 - 1.310	0.436 – 4.782	-1.330 - 1.713
	Relative Risk Ratio	1.010		0.585	1.781	13.582	1.211
	p	0.950		0.185	0.123	0.019	0.805
BMI > 30	Co-Efficient	-13.271		0.971	1.169 *	-12.707	-14.079
	Standard Error	(3075.598)		(0.712)	(0.686)	(1185.81)	(1686.744)
	95% Confidence Interval	-6041.333 – 6014.792		-0.424 – 2.367	-0.176 - 2.515	-2336.851 – 2311.437	-3320.036 - 3291.878
	Relative Risk Ratio	$1.72e^{-6}$		2.641	3.220	$3.03e^{-6}$	$7.68e^{-7}$
	p	0.997		0.173	0.088	0.991	0.993
GSV / SSV	Co-Efficient	2.285		0.773	0.324	0.982	0.249
	Standard Error	(1.548)		(0.602)	(0.607)	(0.908)	(1.179)
	95% Confidence Interval	-0.750 – 5.320		-0.407 - 1.953	-0.865 - 1.514	-0.798 – 2.762	-2.062 - 2.559
	Relative Risk Ratio	9.826		2.167	1.383	2.671	1.282
	p	0.140		0.199	0.593	0.279	0.833
Constant	Co-Efficient	-9.487 *		-1.502	-4.074 ***	-9.070 ***	-3.691
	Standard Error	(5.488)		(1.157)	(1.171)	(2.613)	(2.344)
	95% Confidence Interval	-20.243 – 1.269		-3.770 - 0.765	-6.369 - -1.781	-14.191 - -3.948	-8.287 - 0.905
	Relative Risk Ratio	0.000		0.223	0.170	0.000	0.025
	p	0.084		0.194	0.000	0.001	0.115
Observations		234	234	234		234	234

Log Likelihood = -285.57559, LR Chi^2 = 59.30, p = 0.0001, Pseudo R^2 = 0.0941

Standard errors in parentheses

*** p<0.01, ** p<0.05, * p<0.1

Complicated Venous Disease Analysis VARIABLES		CEAP 1-3 Base	CEAP 4-6
Vein Diameter	Co-Efficient		0.619*
	Standard Error		(0.348)
	95% Confidence Interval		-0.063 - 1.301
	Relative Risk Ratio		1.858
	p		0.075
Age	Co-Efficient		0.0385***
	Standard Error		(0.00951)
	95% Confidence Interval		0.020 - 0.057
	Relative Risk Ratio		1.039
	p		0.000
Sex	Co-Efficient		0.945***
	Standard Error		(0.288)
	95% Confidence Interval		0.380 - 1.510
	Relative Risk Ratio		2.573
	p		0.001
BMI > 30	Co-Efficient		0.410
	Standard Error		(0.446)
	95% Confidence Interval		-0.464 - 1.285
	Relative Risk Ratio		1.507
	p		0.358
GSV / SSV	Co-Efficient		-0.127
	Standard Error		(0.424)
	95% Confidence Interval		-0.959 - 0.705
	Relative Risk Ratio		0.880
	p		0.764
Constant	Co-Efficient		-3.629***
	Standard Error		(0.924)
	95% Confidence Interval		-5.441 - -1.817
	Relative Risk Ratio		0.027
	p		0.000
Observations		234	234

Log Likelihood = -147.22623, LR Chi^2 = 29.87, $p < 0.0001$, Pseudo R^2 = 0.0921

Standard errors in parentheses

*** p<0.01, ** p<0.05, * p<0.1

Table 6a: Regression analysis - Study population stratified by CEAP Classification into groups C1-C3 (mild venous disease) and C4-C6 (severe venous disease).

Complicated Venous Disease Analysis VARIABLES		CEAP 1-3	CEAP 4-6	p
Vein Diameter	Mm – Median (IQR)	6.8 (5.0-9.1)	7.8 (6.0-9.5)	0.055 *
VCSS	Median (IQR)	5 (4-7)	9 (7-11)	<0.001 ***
AVVQ	Median (IQR)	16.18 (11.92-25.20)	24.96 (14.91-35.12)	<0.001 ***
EQ-5D QOL	Median (IQR)	0.767 (0.696-0.837)	0.727 (0.620-0.837)	0.004 ***
EQ-5D VAS	Median (IQR)	80 (70-90)	75 (65-89)	0.189
CES-D	Median (IQR)	9 (3-14)	10.5 (5-18)	0.087 *

Table 6b: Study population stratified by CEAP Classification into groups C1-C3 (mild venous disease) and C4-C6 (severe venous disease).