ILIAC VEIN STENTING IN THE MANAGEMENT OF CHRONIC VENOUS OUTFLOW OBSTRUCTION

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IMPERIAL

Declaration of originality

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Matthew Machin

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ABSTRACT

Background

Chronic venous outflow obstruction (CVOO), encompassing post-thrombotic syndrome (PTS) and non-thrombotic iliac vein lesions (NIVL), is treated with iliac vein stenting or medical therapy. High-quality evidence on treatment success, resource use, and cost-effectiveness are limited, and randomised evidence for clinical efficacy is scarce. This thesis addresses these shortfalls.

Methods

Five work packages (WP) were undertaken: A) meta-analysis of iliac vein stenting using reconstructed individual-patient data with meta-regression; B) trend analysis of deep venous procedures across England (1998–2024); C) retrospective cohort studying factors associated with successful stenting; D) multi-level Markov state-transition model to evaluate cost-effectiveness; and E) an international assessor-blinded multicentre randomised controlled trial (RCT).

Results

At 60 months, pooled primary patency (PP) was 61.6% for PTS (n=3,628; 95% CI 55.3–64.8) and 80.5% for NIVL (n=2,557; 95% CI 76.0–85.2). Mean reductions in venous clinical severity score were 4.53 for PTS (n=266; 95% CI 4.00–5.05) and 4.69 for NIVL (n=723; 95% CI 4.12–5.26). In the single-centre regression, underlying pathology was significantly associated with patency, with PTS exerting the largest negative effect. Chronic venous obstruction classification grade was associated with baseline pathology and long-term patency. The incremental cost-effectiveness ratio (ICER) for stenting was £15,150.37 for PTS and £9,449.07 for NIVL. Deterministic sensitivity analysis identified health-utility gain as the dominant driver; stenting was not cost-saving. The BEST trial activated 6 sites, accrued 15.5 active-centre months, and recruited 10 participants in a 6-month internal pilot. After loss of funding, the trial was redesigned but failed to recruit further due to limited equipoise and patient preference.

Conclusion

Non-randomised evidence suggests early safety and clinical efficacy of stenting in CVOO, but PTS has poor long-term patency with frequent reintervention. While ICERs appear below the NICE threshold, uncertainty around utility gains is substantial. A RCT remains necessary to determine benefit over medical therapy.

CONTENTS

CHAPTER 1: INTRODUCTION 22

1.1 Chronic venous disease 22

1.1.1 Definition of chronic venous disease 22
1.1.2 Clinical manifestation of chronic venous disease 22
1.1.3 Classification of chronic venous disease 26
1.1.4 Pathophysiology of chronic venous disease 29

1.2 Chronic venous outflow obstruction 33

1.2.1 Definition of chronic venous outflow obstruction 33
1.2.2 Diagnosis of chronic venous outflow obstruction 33
1.2.3 Role of chronic venous outflow obstruction in venous hypertension 35
1.2.4 Post thrombotic syndrome 40
1.2.5 Non-thrombotic iliac vein lesions 43
1.2.6 Interplay between non-thrombotic iliac vein lesions, acute deep vein thrombosis, and subsequent post thrombotic syndrome 49

1.3 Management of chronic venous outflow obstruction 51

1.3.1 Medical management 51
1.3.2 Operative management 54

1.4 Endovenous reconstruction of the iliac vein segment with venous stenting 56

1.4.1 History of iliac vein reconstruction 56
1.4.2 Development of dedicated iliac vein stents 58
1.4.3 Evidence to support venous stenting 70

1.5 Thesis aims 72

CHAPTER 2: WORK PACKAGE A 74

2.1 Introduction 74

2.1.1 The continued need for a comprehensive review of the literature 74
2.1.2 Shortfalls with current meta-analyses in the literature 74
2.1.3 Utilising reconstructed individual-patient data 75
2.1.4 Aims 77

2.2 Methods 78

2.2.1 Search strategy 78
2.2.2 Eligibility criteria 79
2.2.3 Study screening & article selection 79
2.2.4 Data extraction & quality assessment 80
2.2.5 Generation of reconstructed individual-patient data from survival probabilities 80
2.2.6 Meta-analysis of survival probabilities 85
2.2.7 Calculation of restricted mean survival time 85
2.2.8 Meta-analysis of continuous outcomes 86
2.2.9 Meta-analysis of dichotomous outcomes 86
2.2.10 Meta-analysis of continuous outcomes before and after an intervention 86

2.3 Results 87

2.3.1 Included articles 87
2.3.2 Study characteristics 88
2.3.3 Aggregate baseline characteristics for the included articles 89
2.3.4 Industry-funded prospective cohort trials 97
2.3.5 Primary patency – post thrombotic syndrome 98
2.3.6 Primary patency – non-thrombotic iliac vein lesion 101

2.3.7 Primary-assisted patency – post thrombotic syndrome 104
2.3.8 Primary-assisted patency – non-thrombotic iliac vein lesion 106
2.3.9 Post thrombotic syndrome vs. non-thrombotic iliac vein lesion – primary patency 108
2.3.10 Severity of disease at baseline – post thrombotic syndrome 109
2.3.11 Severity of disease at baseline – non-thrombotic iliac vein lesion 112
2.3.12 Severity of disease treatment response – post thrombotic syndrome 113
2.3.13 Severity of disease treatment response – non-thrombotic iliac vein lesion 114
2.3.14 Severity of disease treatment response – sensitivity analysis for pathology 115
2.3.15 Venous ulceration at baseline – post thrombotic syndrome 116
2.3.16 Venous ulceration at baseline – non-thrombotic iliac vein lesion 116
2.3.17 Venous ulceration treatment response – post thrombotic syndrome 116
2.3.18 Venous ulceration treatment response – non-thrombotic iliac vein lesion 116
2.3.19 Venous ulceration treatment response – sensitivity analysis for pathology 118
2.3.20 Venous claudication at baseline – post thrombotic syndrome 119
2.3.21 Venous claudication at baseline – non-thrombotic iliac vein lesion 119
2.3.22 Venous claudication treatment response – post thrombotic syndrome 119
2.3.23 Venous claudication treatment response – non-thrombotic iliac vein lesion 119
2.3.24 Venous claudication treatment response – sensitivity analysis for pathology 121
2.3.25 Quality of life treatment response – post thrombotic syndrome 122
2.3.26 Quality of life treatment response – non-thrombotic iliac vein lesion 124
2.3.27 Quality of life treatment response – across both pathologies 125
2.3.28 Reintervention rate – post thrombotic syndrome 125
2.3.29 Reintervention rate – non-thrombotic iliac vein lesion 125
2.3.30 Reintervention rate – sensitivity analysis for pathology 125
2.3.31 Major bleeding – post thrombotic syndrome 127
2.3.32 Major bleeding – non-thrombotic iliac vein lesion 127
2.3.33 Major bleeding – sensitivity analysis for pathology 127
2.3.34 Stent fracture – post thrombotic syndrome 130
2.3.35 Stent fracture – non-thrombotic iliac vein lesions 130
2.3.36 Stent fracture – sensitivity analysis for pathology 130
2.3.37 Stent migration – overall rate 130
2.3.38 Censoring proportion – overall rate 131
2.3.39 Factors significantly associated with primary patency – overall cohort 132
2.3.40 Factors significantly associated with primary patency – post thrombotic syndrome 133
2.3.41 Factors significantly associated with primary patency – non-thrombotic iliac vein lesion 134
2.3.42 Validation with restricted mean survival time 134
2.3.43 Comparative evidence of iliac vein stenting in comparison to medical therapy 134
2.3.44 Conflict of interest 135
2.3.45 Risk of bias 136
2.4 Discussion 138
2.4.1 Post thrombotic syndrome and non-thrombotic iliac vein lesions are different pathologies with different fates 138
2.4.2 Treatment response with respect to disease improvement was similar 139
2.4.3 Disease-specific markers readily improve, but generic markers are less consistent 139
2.4.4 Pathology was significantly associated with patency 140
2.4.5 Large proportions of the data are censored 140
2.4.6 Limitations 141
2.5 Conclusion 143
CHAPTER 3: WORK PACKAGE B 145

3.1 Introduction 145
3.1.1 A changing deep venous landscape 145
3.1.2 The rates of venous stenting across the United Kingdom 145
3.1.3 Establishing the current landscape of iliac vein stenting across England 146
3.1.4 Aims 147
3.2 Methods 148
3.2.1 Data retrieval from the Hospital Episodes Statistics database 148
3.2.2 Rationale for target diagnoses and procedures 148
3.2.3 Data retrieval – codes extracted 150
3.2.4 Statistical analysis 152
3.2.5 Ethical approval 153
3.3 Results 154
3.3.1 Rate of care episodes with primary diagnosis of post thrombotic syndrome 154
3.3.2 Rate of care episodes with primary diagnosis of chronic venous insufficiency 155
3.3.3 Rate of care episodes with primary diagnosis of deep vein thrombosis 156
3.3.4 Rate of care episodes with primary procedure of percutaneous deep venous interventions for chronic indications 157
3.3.5 Rate of hospital episodes with primary procedure of early thrombus removal procedures 160
3.4 Discussion 162
3.4.1 The rate of chronic interventions has plateaued 162
3.4.2 Increasing trend of early thrombus removal procedures 163
3.4.3 The trends visualised in the primary diagnoses for post thrombotic syndrome likely reflect code utilisation patterns 164
3.4.4 Acute deep vein thrombosis has increased since the coronavirus pandemic 164
3.4.5 Limitations 165
3.5 Conclusion 167
CHAPTER 4: WORK PACKAGE C 169
4.1 Introduction 169
4.1.1 Shortfalls with existing cohort studies 169
4.1.2 The need to establish if the underlying pathology or technical factors are associated with long-term treatment success 169
4.1.3 The need for resource use data 170
4.1.4 The use of acute deep vein thrombosis as a comparator group for technical covariates 170
4.1.5 Aims 170
4.2 Methods 171
4.2.1 Study design 171
4.2.2 Inclusion criteria & cohort identification 171
4.2.3 Data collection 171
4.2.4 Radiological imaging analysis 171
4.2.5 Chronic venous obstruction classification 172
4.2.6 Diagnostic work-up & procedure details 173
4.2.7 Standard clinical follow-up 173
4.2.8 Quality improvement 174
4.2.9 Statistical analysis 174
4.2.10 Ethical approval and information governance 174
4.3 Results 175
4.3.1 Patient (baseline) characteristics 175

4.3.2 Operative details 175
4.3.3 Technical success and pre-discharge stent patency 178
4.3.4 Chronic venous obstruction classification 178
4.3.5 Post-discharge anticoagulation strategy 178
4.3.6 Primary patency 180
4.3.7 Primary-assisted patency 182
4.3.8 Secondary patency rate 184
4.3.9 Venous ulcer healing 184
4.3.10 Reinterventions 184
4.3.11 Perioperative complications 185
4.3.12 Complications during follow-up 186
4.3.13 Stent-related adverse events 186
4.3.14 Resource use 186
4.3.15 Censoring rates over time 187
4.3.16 Validation of the chronic venous obstruction classification 189
4.3.17 Factors associated with stent patency 189
4.4 Discussion 191
4.4.1 Long-term patency for post thrombotic syndrome is poor 191
4.4.2 Long-term patency decline follows differing failure patterns across pathologies 191
4.4.3 Conventional technical factors associated with stent patency are confounders for pathology and venous inflow 192
4.4.4 Chronic venous obstruction classification is a predictor of stent patency 192
4.4.5 Aggressive anticoagulation strategies increase the risk of bleeding without improving stent patency 193
4.4.6 Iliac vein stenting is associated with substantial resource use and poses a burden to patients 193
4.4.7 Limitations 195
4.5 Conclusion 196
CHAPTER 5: WORK PACKAGE D 198
5.1 Introduction 198
5.1.1 There is a lack of cost-effectiveness evidence in the literature 198
5.1.2 The need for cost-effective analysis 198
5.1.3 Aims 199
5.2 Methods 200
5.2.1 Model structure 200
5.2.2 Probabilistic sensitivity analysis 202
5.2.3 Deterministic sensitivity analysis 202
5.2.4 Data from the stent versus conservative treatment in patients with deep venous obstruction randomised controlled trial 202
5.2.5 Statistical analysis - establishing the relationship between EuroQol EQ5D-5L and venous clinical severity score 203
5.2.6 Source data for the model 203
5.2.7 Statistical analysis – establishing a time-varying function for stent patency 204
5.2.8 Statistical analysis – establishing a function for reintervention 205
5.2.9 Assigning cost values to resource use 206
5.2.10 Ethical approval and information governance 206
5.3 Results 207
5.3.1 EuroQol EQ5D-5L as a function of venous clinical severity score 207
5.3.2 Mapping EuroQol EQ5D-5L to change in venous clinical severity score after iliac vein stenting 208

5.3.3 Time-varying function for stent patency – post thrombotic syndrome 208
5.3.4 Time-varying function for stent patency – non-thrombotic iliac vein lesion 208
5.3.5 Reintervention function – post thrombotic syndrome 209
5.3.6 Reintervention function – non-thrombotic iliac vein lesion 209
5.3.7 Venous ulceration – post thrombotic syndrome 209
5.3.8 Venous ulceration – non-thrombotic iliac vein lesion 209
5.3.9 Costs associated with index iliac vein stenting procedure for post thrombotic syndrome 210
5.3.10 Costs associated with index iliac vein stenting procedure for non-thrombotic iliac vein lesions 211
5.3.11 Costs associated with stent surveillance across both post thrombotic syndrome and non-thrombotic iliac vein lesion groups 212
5.3.12 Costs associated with reintervention across both post thrombotic syndrome and non-thrombotic iliac vein lesion groups 212
5.3.13 Costs associated with medical care for post thrombotic syndrome not undergoing iliac vein stenting 213
5.3.14 Costs associated with medical care for non-thrombotic syndrome not undergoing iliac vein stenting 213
5.3.15 Cost-effectiveness analysis for iliac vein stenting in post thrombotic syndrome in comparison to standard medical therapy 214
5.3.16 Deterministic sensitivity analysis for iliac vein stenting in post thrombotic syndrome in comparison to standard medical therapy 215
5.3.17 Cost-effectiveness analysis for iliac vein stenting in non-thrombotic iliac vein lesions in comparison to standard medical therapy 217
5.3.18 Deterministic sensitivity analysis for iliac vein stenting in post thrombotic syndrome in comparison to standard medical therapy 218
5.4 Discussion 220
5.4.1 Venous clinical severity score and EuroQol EQ5D are correlated 220
5.4.2 Cost-effectiveness of iliac vein stenting hinges on improvement in quality of life rather than any cost-saving effect 221
5.4.3 Treating post thrombotic syndrome is more expensive 222
5.4.4 Iliac vein stenting appears to be cost-effective in respect to current willingness-to-pay thresholds in the United Kingdom 222
5.4.5 Limitations 223
5.5 Conclusion 224
CHAPTER 6: WORK PACKAGE E 226
6.1 Background 226
6.2 Patient public involvement 227
6.2.1 Patient public involvement in the funding application 227
6.2.2 Patient public involvement in the trial management 228
6.3 Methods 229
6.3.1 Trial design 229
6.3.2 Intervention and comparator: 229
6.3.3 Eligibility criteria 229
6.3.4 Description of the interventions 230
6.3.5 Primary outcome 231
6.3.6 Study duration 233
6.3.7 Study sites, in alphabetical order: 233
6.3.8 Recruitment and randomisation 234
6.3.9 Blinding 234

6.3.10 Follow-up 234
6.3.11 Sample size calculation 235
6.3.12 Data collection and confidentiality 236
6.3.13 Statistical analysis 236
6.3.14 Internal pilot of feasibility 237
6.3.15 Cost-effectiveness analysis 238
6.3.16 Data monitoring, safety and quality control 238
6.3.17 Ethical approval 239
6.4 Results 240
6.4.1 Internal pilot of feasibility – study set-up 240
6.4.2 Internal pilot – recruitment 241
6.4.3 Adaption strategies to improve deliverability 243
6.4.4 Revised sample size 244
6.4.5 Result of the internal pilot and proposed trial adaptions 245
6.4.6 Trial redesign and relaunch 245
6.4.7 Re-launch of the BEST trial 249
6.4.8 Closure of the BEST trial 249
6.4.9 Results of the included participants 249
6.5 Discussion 251
6.5.1 There was a marked delay in achieving local approvals from study sites 251
6.5.2 Participant preference for intervention hampered recruitment 252
6.5.3 Delay in radiological investigations for potential participants were as a result of the lesser prioritisation of venous disease 254
6.5.4 Commercial trials provide higher value per participant reimbursement 254
6.5.5 Throughput of eligible participants was lower than anticipated 255
6.5.6 Lack of clinical equipoise amongst clinicians was a key contributing factor to the failure of the trial 256
6.6 Conclusion of the BEST trial 258
CHAPTER 7: DISCUSSION & FUTURE WORK 260
7.1.1 Post thrombotic syndrome and non-thrombotic iliac vein lesions are different diseases 260
7.1.2 The long-term patency of iliac vein stents placed for post thrombotic syndrome is poor 261
7.1.3 Iliac vein stenting has reasonable probability of being cost-effective 262
7.1.4 A randomised controlled trial is still required 262
7.1.5 Timing of an RCT, the ‘Goldilocks’ phenomena 264
7.1.6 The use of novel trial designs in place of a traditional randomised trial 265
7.1.7 More non-commercial research is required 269
REFERENCES 270
APPENDICES 295
PUBLICATIONS 338
RESEARCH GRANT FUNDING 340
COPYRIGHT PERMISSIONS 341

TABLES

Table 1: Revised Clinical-Eitology-Anatomical-Pathology classification system 2020 28
Table 2: Spur classification system observed in May Thurner Syndrome 44
Table 3: Common venoactive medications and their demonstrated effect on the signs and symptoms of chronic venous disease 51
Table 4: Summary of dedicated venous stents 68
Table 5: Search strategy undertaken for the systematic review 78
Table 6: Overview of included articles 90
Table 7: Summary statistics for baseline characteristics of the included study arms 95
Table 8: Investigational device exemption trials with US-based sponsors 97
Table 9: Pooled estimate of primary patency, and associated 95% confidence interval, of iliac vein stents placed for post thrombotic syndrome, utilising reconstructed individual-patient data 99
Table 10: Pooled estimate of primary patency, and associated 95% confidence interval, of iliac vein stents placed for non-thrombotic iliac vein lesions, utilising reconstructed individual-patient data 102
Table 11: Pooled estimate of primary-assisted patency, and associated 95% confidence interval, of iliac vein stents placed for post thrombotic syndrome, utilising reconstructed individual-patient data 105
Table 12: Pooled estimate of primary-assisted patency, and associated 95% confidence interval, of iliac vein stents placed for post thrombotic syndrome, utilising reconstructed individual-patient data 107
Table 13: Pooled primary patency for post thrombotic syndrome and non-thrombotic iliac vein lesions 108
Table 14: Pooled restricted mean survival time, primary patency, for post thrombotic syndrome and non-thrombotic iliac vein lesions 108
Table 15: Median and interquartile range of baseline Villalta score for post thrombotic syndrome 111
Table 16: VEINES QOL/Sym scores at baseline and last follow-up for post thrombotic syndrome 122
Table 17: CIVIQ-20 scores at baseline and last follow-up for post thrombotic syndrome 123
Table 18: Factors associated with primary patency at 12 months in a univariate meta-regression 132
Table 19: Factors associated with primary patency at 12-months in a univariate meta-regression for post thrombotic syndrome 133
Table 20: International Classification of Diseases (ICD-10) used to retrieve primary diagnoses from the Hospital Episode Statistics database 150
Table 21: Office of Population Censuses and Surveys Classification of Interventions and Procedures, version 4 (OPCS-4) used to retrieve primary diagnoses from the Hospital Episode Statistics database 151
Table 22: Baseline characteristics for included cohort 176
Table 23: Key operative variables for the included cohort 177

Table 24: Chronic venous obstruction classification and presence of cross-pelvic collaterals across the three subgroups 179
Table 25: Anticoagulation strategies on discharge for the three subgroups 179
Table 26: Kaplan-Meier survival probability for primary patency across the three pathology groups 181
Table 27: Kaplan-Meier survival probability for primary-assisted patency across the three pathology groups 183
Table 28: Number of participants censored for loss to follow-up at each timepoint across the three pathology groups 188
Table 29: Logistic regression estimates for chronic venous obstruction classification and stent patency, including data from all three pathology groups 189
Table 30: Costs included in the Markov model for the index stenting procedure in post thrombotic syndrome 210
Table 31: Costs included in the Markov model for the index stenting procedure in non-thrombotic iliac vein lesions 211
Table 32: Costs included in the Markov model in respect to stent surveillance for those with a patent stent 212
Table 33: Costs included in the Markov model in respect to reintervention to maintain stent patency for those with a clinically relevant in-stent stenosis 212
Table 34: Costs included in the Markov model in respect to medical care for those with post thrombotic syndrome not undergoing iliac vein stenting 213
Table 35: Costs included in the Markov model in respect to medical care for those with non-thrombotic iliac vein lesions not undergoing iliac vein stenting 213
Table 36: Date of activation for included study sites 240
Table 37: Reasons for screening failures for potentially eligible participants 242
Table 38: Baseline characteristics for participants recruited into the BEST trial 250
Table 39: Baseline and 12-month venous clinical severity for participants recruited into the BEST trial 250

FIGURES

Figure 1: Stone tablet depiction of varicose veins dated 400 BC 23
Figure 2: Clinical manifestations of chronic venous disease 25
Figure 3: Photomicrograph illustrating a mast cell, fibroblast and macrophage extravasated around a central capillary, at a magnification of 4,300..... 32
Figure 4: Poiseuille's law..... 35
Figure 5: Bernoulli's equation..... 35
Figure 6: Deriving resistance from Poiseuille's law..... 36
Figure 7: Pre-stenotic pressure plotted against degree of stenosis in an iliac vein model, figure reused from original article with permission 38
Figure 8: Inferior vena cava and iliac vein computational flow model, demonstrating the pressure increase prior to the stenosis with increasing iliac vein stenosis 39
Figure 9: Left-sided retrograde ascending venography demonstrating post thrombotic lesions of the common iliac, external iliac and proximal common femoral vein 42
Figure 10: Types of spurs observed in May Thurner Syndrome..... 45
Figure 11: Bilateral retrograde ascending venogram demonstrating a left-sided non-thrombotic iliac vein lesion, with the lucency and pancake signs present..... 47
Figure 12: Left-sided retrograde venography lateral view demonstrating a non-thrombotic iliac vein lesions 48
Figure 13: Illustration of the Palma saphenous vein crossover graft..... 55
Figure 14: Diagrammatic illustration showing the difference between a) arrangement of fibres in a honeycomb that is subject to the Poisson effect, and b) an auxetic material that increases in volume when stretched 60
Figure 15: Lateral radiograph illustrating kinking of an iliac vein stent in the pelvis.. 61
Figure 16: Representative 3-dimensional computed tomography showing the stented vessel with the hip in a neutral 0' position (green) and hip flexion at 90' (brown)..... 62
Figure 17: Illustration of the hysteresis loop of stress plotted against strain for nitinol stents..... 64
Figure 18: Venogram demonstrating the Poisson effect after stenting with diameter of the external iliac vein decreasing from a) 7.8mm to b) 3.4mm 65
Figure 19: Image illustrating a) braided nitinol stent on the left; and b) laser cut nitinol stent on the right..... 66
Figure 20: Image illustrating some of the commonly used dedicated venous stents. Reproduced with permission..... 69
Figure 21: Equation for calculating survival probability at a given time (t) 81
Figure 22: Estimating the number of censored participants across an interval i 83
Figure 23: Algorithm used in reconstructing individual-patient data 84
Figure 24: PRISMA flowchart illustrating the study selection process..... 87
Figure 25: Pooled survival curve for primary patency of iliac vein stents placed for post thrombotic syndrome, utilising reconstructed individual-patient data 98
Figure 26: Forest plot for the restricted mean survival time, primary patency, of iliac vein stents placed for post thrombotic syndrome, utilising reconstructed individual-patient data, at 12 months..... 100
Figure 27: Pooled survival curve for primary patency of iliac vein stents placed for non-thrombotic iliac vein lesions, utilising reconstructed individual-patient data 101

Figure 28: Forest plot for the restricted mean survival time, primary patency, of iliac vein stents placed for non-thrombotic iliac vein lesions, utilising reconstructed individual-patient data, at 12 months 103
Figure 29: Pooled survival curve for primary-assisted patency of iliac vein stents placed for post thrombotic syndrome, utilising reconstructed individual-patient data 104
Figure 30: Pooled survival curve for primary-assisted patency of iliac vein stents placed for non-thrombotic iliac vein lesions, utilising reconstructed individual-patient data 106
Figure 31: Forest plot for baseline venous clinical severity score for post thrombotic syndrome 109
Figure 32: Forest plot for baseline Villalta score for post thrombotic syndrome 110
Figure 33: Forest plot for baseline venous clinical severity score for non-thrombotic iliac vein lesions 112
Figure 34: Forest plot illustrating the change in venous clinical severity score at last follow-up for post thrombotic syndrome after iliac vein stenting 113
Figure 35: Forest plot illustrating the change in venous clinical severity score at last follow-up for non-thrombotic iliac vein lesions after iliac vein stenting 114
Figure 36: Forest plot illustrating the change in venous clinical severity score at last follow-up for both underlying pathologies 115
Figure 37: Forest plot illustrating the proportion of venous ulcer healing at last follow-up after iliac vein stenting for post thrombotic syndrome 117
Figure 38: Forest plot illustrating the proportion of venous ulcer healing at last follow-up after iliac vein stenting for non-thrombotic iliac vein lesions 117
Figure 39: Forest plot illustrating the proportion of venous ulcer healing at last follow-up after iliac vein stenting for both underlying pathologies 118
Figure 40: Meta-analysis of proportion of venous claudication post iliac vein stenting for post thrombotic syndrome 120
Figure 41: Meta-analysis of proportion of venous claudication post iliac vein stenting non-thrombotic iliac vein lesions 120
Figure 42: Meta-analysis of proportion of venous claudication post iliac vein stenting for both underlying pathologies 121
Figure 43: Meta-analysis of proportions for reintervention at last follow-up for post thrombotic syndrome 126
Figure 44: Meta-analysis of proportions for reintervention at last follow-up for non-thrombotic iliac vein lesions 126
Figure 45: Meta-analysis of proportions for major bleeding for post thrombotic syndrome 128
Figure 46: Meta-analysis of proportions for major bleeding for non-thrombotic iliac vein lesions 128
Figure 47: Meta-analysis of proportions for major bleeding for both underlying pathologies 129
Figure 48: Equation used to calculate the variance and the associated Z-statistic in the Mann-Kendall test(328) 152
Figure 49: Tricube equation used to calculate weight in the LOcally WEighted Scatterplot Smoothing model 153

Figure 50: Number of episodes with primary diagnosis of post thrombotic syndrome between 1998 and 2024 154
Figure 51: Number of episodes with primary diagnosis of chronic venous insufficiency between 1998 and 2024 155
Figure 52: Number of episodes with primary diagnosis of deep vein thrombosis between 1998 and 2024 156
Figure 53: Number of episodes with primary procedure code representing interventions for chronic indications between 2005 and 2024 158
Figure 54: LOcally WEighted Scatterplot Smoothing graph of the number of primary procedures pertaining for chronic indications (all cases) between 2005 and 2024 158
Figure 55: Locally Weighted Scatterplot Smoothing graph of the number of primary procedures for non-caval stents (all cases) between 2005 and 2024 159
Figure 56: Linear regression for the number of primary procedures for non-caval stents (all cases) between 2005 and 2024 159
Figure 57: Number of episodes with primary procedure codes for acute and chronic interventions between 2005 and 2024 160
Figure 58: Locally Weighted Scatterplot Smoothing graph of the number of primary acute thrombectomy / thrombolysis procedures (all cases) between 2005 and 2024. 161
Figure 59: Classification system of venous inflow based on anatomy of the iliofemoral tract 172
Figure 60: Kaplan-Meier curve for primary patency across the three pathology groups 180
Figure 61: Kaplan-Meier curve for primary-assisted patency across the three pathology groups 182
Figure 62: State transitions within the Markov model 201
Figure 63: Equation used to calculate Weibull survival function 204
Figure 64: Equation used to calculate instantaneous hazard from Weibull survival function 205
Figure 65: Relationship defining reintervention using the survival probabilities of primary patency and primary-assisted patency 205
Figure 66: Scatterplot of EQ5D index utility value and venous clinical severity score with linear mixed model output 207
Figure 67: Weibull survival function for stent patency in Post Thrombotic Syndrome 208
Figure 68: Weibull survival function for stent patency in Non-thrombotic Iliac Vein Lesion 209
Figure 69: Markov trace showing the number of simulated patients in each health state across Markov cycles for the post thrombotic syndrome model 214
Figure 70: Cost-effectiveness acceptability curve for iliac vein stenting in comparison to standard medical therapy for post thrombotic syndrome 215
Figure 71: Markov trace showing the number of simulated patients in each health state across Markov cycles for the non-thrombotic iliac vein lesion model 217
Figure 72: Cost-effectiveness acceptability curve for iliac vein stenting in comparison to standard medical therapy for non-thrombotic iliac vein lesions 218
Figure 73: Flowchart illustrating the intended overview of the BEST trial 232

Figure 74: Internal pilot of feasibility at 6-months recruitment, equating to month 12 of the study 237
Figure 75: Actual vs. Predicted centre-months accrued and participant recruitment for the BEST trial after 6 months of recruitment (equating to 12 months post funding commencement) 242
Figure 76: Flowchart illustrating the intended overview of the re-designed BEST trial 248
Figure 77: Instrument variable relationship for the treatment variable and outcome variable providing the required assumptions hold 267

APPENDICES

Appendix 1: Revised venous clinical severity score 295
Appendix 2: Code performing Guyot's algorithm for the reconstruction of individual patient data, adapted from Guyot et al. (188) 296
Appendix 3: Electronic photograph illustrating digitisation of a Kaplan Meier curve, the point selected shows the survival probability at 6 months to five decimal places. 301
Appendix 4: Code used to perform meta-analysis of single-arm survival studies with random effects 302
Appendix 5: Code used to calculate restricted mean survival time, i.e. integration of the survival function, for each survival curve 303
Appendix 6: Code used to perform meta-analysis of continuous and dichotomous outcomes 304
Appendix 7: Code used to perform meta-analysis for change in continuous outcome measure before and after an intervention 305
Appendix 8: Meta-analysis of the restricted mean survival time, primary patency, of iliac vein stents placed for post thrombotic syndrome, utilising reconstructed individual-patient data, at 36 months 306
Appendix 9: Funnel plot of with standard error plotted against restricted mean survival time, primary patency, at 36 months for post thrombotic syndrome 307
Appendix 10: Meta-analysis of the restricted mean survival time, primary patency, of iliac vein stents placed for non-thrombotic iliac vein lesions, utilising reconstructed individual-patient data, at 36 months 308
Appendix 11: Funnel plot with standard error plotted against restricted mean survival time, primary patency, at 36 months for non-thrombotic iliac vein lesions 309
Appendix 12: Meta-analysis of baseline venous clinical severity score for post thrombotic syndrome, including Moini 2024 et al. which was subsequently excluded from the analysis 310
Appendix 13: Meta-analysis of baseline venous clinical severity score for non-thrombotic iliac vein lesions, including Moini 2024 et al. which was subsequently excluded from the analysis 311
Appendix 14: Bubble plot illustrating the meta-regression of underlying pathology as a moderator for the meta-analysis of change in venous clinical severity score at last follow-up 312
Appendix 15: Forest plot for the proportion of baseline venous ulceration in post thrombotic syndrome 313
Appendix 16: Forest plot for the proportion of baseline venous ulceration in non-thrombotic iliac vein lesions 314
Appendix 17: Forest plot for the proportion of baseline venous claudication in post thrombotic syndrome 315
Appendix 18: Forest plot for the proportion of baseline venous claudication in non-thrombotic iliac vein lesions 316
Appendix 19: Meta-analysis of reintervention post iliac vein stenting at last follow-up for post thrombotic syndrome, including cohorts undertaking hybrid procedures which were subsequently excluded from the analysis 317

Appendix 20: Meta-analysis of major bleeding post iliac vein stenting at last follow-up for post thrombotic syndrome, including cohorts undertaking hybrid procedures which were subsequently excluded from the analysis 318
Appendix 21: Meta-analysis of stent fracture post iliac vein stenting for post thrombotic syndrome 319
Appendix 22: Meta-analysis of stent fracture post iliac vein stenting for non-thrombotic iliac vein lesions 320
Appendix 23: Meta-analysis of proportions for the censoring rate occurring in all included studies with data available 321
Appendix 24: ROBINS-I risk of bias assessment for the pooled outcome measures 322
Appendix 25: Code used to perform Mann-Kendall trend testing and LOcally WEighted Scatterplot Smoothing in R using the package 'Kendall' 323
Appendix 26: Q-Q plot for the residuals of the linear regression model for non-caval stents with time as the moderating variable 324
Appendix 27: Code used to calculate Kaplan-Meier probability for primary and primary-assisted patency 325
Appendix 28: Code used to perform logistic regression for a dichotomous outcome 327
Appendix 29: Code used to perform Markov state-transition model in bespoke package 'Heemod' in R 328
Appendix 30: Code used to perform linear mixed models to assess the association between two continuous variables 332
Appendix 31: Weibull survival function for primary-assisted patency of stents placed for Post Thrombotic Syndrome utilising pooled survival probabilities from reconstructed individual patient data 333
Appendix 32: Weibull survival function for primary-assisted patency of stents placed for Non-Thrombotic Iliac Vein Lesions utilising pooled survival probabilities from reconstructed individual patient data 334
Appendix 33: Number of simulated participants in the different states over Markov cycle observed in the Markov state transition model, standard medical therapy arm 335
Appendix 34: Monthly recruitment rate per active site during the internal pilot of feasibility for the BEST trial 336
Appendix 35: Consort diagram of the BEST trial 337

ABBREVIATIONS

AVP	Ambulatory venous pressure
BEST	Best Endovenous Treatment, Including Stenting, versus Best Non-endovenous Treatment in Chronic Proximal Deep Venous Disease—The BEST Multicentre Randomised Controlled Trial
CE	Conformité Européenne
CEAP	Clinical-Eitology-Anatomy-Pathophysiology
COF	Chronic outward force
CR	Crush resistance
CTV	Computed tomography venography
CVD	Chronic venous disease
CVOO	Chronic venous outflow obstruction
ESVS	European Society for Vascular Surgery
GCS	Graduated compression stockings
HRA	Health Research Authority
iDMC	Independent data monitoring committee
IL	Interleukin
IPC	Intermittent pneumatic compression
IPD	Individual patient data
IVC	Inferior vena cava
IVUS	Intravascular ultrasound
LOWESS	LOcally WEighted Scatterplot Smoothing
MAUDE	Manufacturer and User Facility Device Experience
MMP	Matrix metalloproteinases
MMP	Matrix metalloproteinases
MPFF	Micronised purified flavonoid fraction
MRV	Magnetic resonance venography
MTS	May Thurner syndrome
NIVL	Non-thrombotic iliac vein lesion
NMES	Neuromuscular electrical stimulation
PAP	Primary-assisted patency
PP	Primary patency
PSGL-1	P-selectin glycoprotein ligand-1
PTS	Post thrombotic syndrome
RCT	Randomised controlled trial
REC	Research Ethics Committee
RMST	Restricted mean survival time
RRF	Radial resistive force
rVCSS	Revised venous clinical severity score
SD	Standard deviation
SVC	Superior vena cava
TGF- β1	Transforming growth factor beta 1
TIMP	Tissue Inhibitors of Metalloproteinases
TNF-α	Tumour Necrosis Factor alpha
TSC	Trial steering committee
US FDA	United States Food and Drug Administration
VCSS	Venous clinical severity score
VDS	Venous disability score

1 - INTRODUCTION

CHAPTER 1: INTRODUCTION

1.1 Chronic venous disease

1.1.1 Definition of chronic venous disease

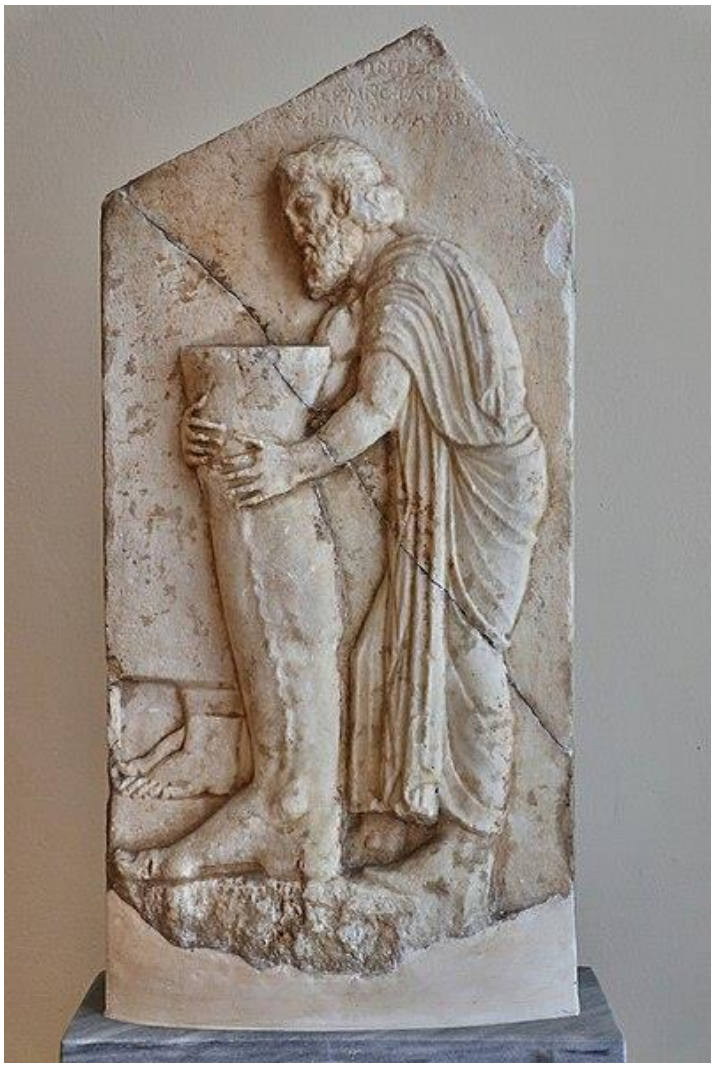
Chronic Venous Disease (CVD) is a term used to encompass the clinical manifestations of venous insufficiency, including superficial and deep venous disease. CVD is defined as any morphological and/or functional abnormality of the venous system, of long duration, manifesting as symptoms and/or clinical signs indicating the need for investigation and/or treatment(1).

1.1.2 Clinical manifestation of chronic venous disease

CVD comprises a spectrum of disease entities including lower limb pain and swelling, skin changes including, but not limited to, eczema, haemosiderin deposition and fibrosis, and ultimately venous ulceration. Its manifestations have been recognised for millennia – with the earliest known recording in the Egyptian medical papyrus (Ebers) dated 1550 BC(2, 3). The association between dilating veins on the surface of the lower extremities and lower limb ulceration was made as early as 400 BC by Hippocrates, this was documented within a series of aphorisms and carved into a votive relief stone tablet which is on display at the national archaeological museum of Athens (see Figure 1)(4).

The most common manifestation of CVD are varicose veins, which are defined as permanently dilated subcutaneous veins equal to, or more than, 3 mm in diameter in the upright position(3). Clinically, they are described as dilated, or bulging, tortuous, or twisting, veins running close to the surface of the skin. Patients often present complaining of an aching cramping pain and itchiness centred around the calves and, or, the cosmetic appearance of the dilated superficial varicosities(5, 6). Rarely, a patient can present with a hot and painful superficial vein which is due to thrombosis of the varicose veins known as superficial venous thrombosis. Varicose veins, which constitute superficial venous disease, will not feature often in this thesis but, in addition to telangiectasias and reticular veins, are one of the most common presentations of CVD(7).

Figure 1: Stone tablet depiction of varicose veins dated 400 BC



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Swelling is another common presenting complaint and is a sensitive marker for a functional abnormality in the venous system(6). The lower limb swelling associated with CVD is dependent oedema, it is best in the morning after prolonged elevation and worse after standing. This is a key distinguishing feature in differentiating CVD from lipoedema, another cause of primary lower limb oedema.

Skin changes are a key defining marker in advanced disease, there are a number of cutaneous manifestations including haemosiderin deposition, hyperpigmentation, atrophie blanche, eczematous dermatitis, and lipodermatosclerosis – see Figure 2B. These skin changes occur on the lower limbs and have a predilection around the ankles and in the gaiter region.

Less frequently, a first presentation of CVD can be with a non-healing wound of the lower limb which is subsequently diagnosed as a venous ulcer. There is irreversible cutaneous damage with fibrotic scarring in those with healed and recurrent venous ulceration. These more advance features of CVD are particularly prevalent when investigating deep venous causes of CVD. The Leg Ulcer Pathway Acceleration (LUPA) study, which investigated the efficacy of an accelerated ulcer pathway, reported that clinically relevant proximal obstructive disease was present in as many as 30% of ulcer patients(8).

Venous claudication is generally described as the deep bursting pain experienced in the thigh and calf when walking which causes the individual to stop and rest(9-11). Venous claudication is particularly disabling as the pain takes longer to resolve than typically experienced in arterial claudication, with the time period of 15 minutes often quoted. It is nearly exclusively associated with proximal obstructing disease, affecting between 10 – 74% of cases, and rarely seen in the refluxing pathologies alone(9).

Figure 2: Clinical manifestations of chronic venous disease



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A: Extensive varicose veins involving the thigh and leg.

B: Hyperpigmentation and severe lipodermatosclerosis with oedema.

C: Medial malleolar venous ulcers, concomitant eczema and lipodermatosclerotic skin.

1.1.3 Classification of chronic venous disease

Since 1995, CVD has been classified by a widely recognised and established system – the Clinical, Eitology, Anatomic, Pathophysiology (CEAP) classification, see Table 1(6, 13).

The ‘C‘ clinical domain describes the findings on clinical examination and is generally the most utilised part of the CEAP classification in communicating the severity of venous disease. ‘C’ is graded from C0 to C6, which encompasses the many clinical manifestations covered in 1.1.2, with the most severe feature present being the qualifying grade i.e., if a venous ulceration is present then it is C6 disease irrespective of the presence or absence of other clinical features. In the 2020 update of the CEAP classification, C4 was subcategorised into three differing skin and subcutaneous manifestations, with the escalation of corona phlebectatica from C1 to C4 disease due to its association with ankle ulceration(13, 14).

The eitology ‘E’ domain has three classifications: congenital, primary, and secondary. The updated CEAP classification has a further subcategorisation of the secondary eitology including intravenous and extravenous secondary causes, in addition to a separate category for ‘no cause identified’(13). Primary disease is largely the cause in refluxing conditions whereas secondary causes are more often encountered in obstructing conditions. This subcategorisation of secondary etiologies is particularly pertinent the classification of obstructing disease in respect to proximal iliac vein lesions.

The anatomic ‘A’ domain has three broad levels: superficial, deep, or perforating veins. There is a more detailed anatomic segment classification which was previously numerically coded from 1 – 18 and was subsequently updated to named anatomic descriptors. However, this is infrequently used in either research or clinical practice for communicating CVD disease states. The focus of this work will be to assess the obstructing pathologies affecting the deep veins. Superficial disease is already a well-researched topic with high-level evidence to support treatments(15-18).

The pathophysiology ‘P’ domain consists of the three chief pathological mechanisms: reflux, obstruction, or a combination of both, and lastly no pathophysiology identified. The updated recommendations suggest listing the anatomical segments outlined in

the ‘A’ classification under each ‘P’ domain to reflect the multiple differing active pathological mechanisms at play – however, again, this is infrequently used in clinical practice(13).

An important note is that the change in the ‘C’, or clinical, domain is often reported in research as a measure of effect and treated as a continuous data variable. While prevalent in the literature, this thesis will refrain from reporting such results as the classification system is ordinal in nature and illogical when treated as a continuous scale (with C5 disease being a fixed point). Corroborating this, the commission of authors reporting the latest update to CEAP also recommending against viewing CEAP as a severity scale(13).

Disease severity can be classified by validated clinical scoring systems such as the venous clinical severity score (VCSS). The VCSS does not look to classify the cause of the disease or provide a framework for communicating the disease state. Instead, it aims to provide a single descriptor of the sum total of the severity of disease experience by a patient at a given timepoint(19). Robert Rutherford described a preliminary version in his presidential address “Vascular Surgery – Comparing Outcomes” at the 43rd Scientific Meeting of the International Society for Cardiovascular Surgery in 1995(20). The VCSS was published in 2000, prior to being revised in 2010 to improve the descriptors used(21, 22). Therefore, it is often referred to as the revised VCSS or rVCSS. The original and revised VCSS both consist of 10 domains, each scored from zero to three, conferring a maximum of 30.

The VCSS is also an ordinal dataset, however, given its construction it behaves more parametrically with a graduated scale from 0 to 30. The parametric nature of VCSS will be validated within this thesis. A summary of the VCSS scoring system is included in the appendix, see Appendix 1. Together, the CEAP and VCSS systems provide a useful way to communicate and grade CVD.

Table 1: Revised Clinical-Eitology-Anatomical-Pathology classification system 2020

C classification	**Clinical description**
C0	No visible or palpable signs of venous disease
C1	Telangiectasias or reticular veins
C2	Varicose veins
C2r	Recurrent varicose veins
C3	Oedema
C4	Changes in skin and subcutaneous tissue secondary to CVD
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis or atrophie blanche
C4c	Corona phlebectatica
C5	Healed venous ulcer
C6	Active venous ulceration
C6r	Recurrent active venous ulceration
E classification	**Eitology description**
E_p	Primary
E_s	Secondary
E_{si}	Secondary – intravenous
E_{se}	Secondary – extravenous
E_c	Congenital
E_n	No cause identified
A classification†	**Anatomical description**
A_s	Superficial
A_d	Deep
A_p	Perforator
A_n	No venous anatomic location identified
P classification	**Pathophysiology description**
P_r	Reflux
P_o	Obstruction
$P_{r,o}$	Reflux and obstruction
P_n	No pathophysiology identified

†: Abbreviation classification system not including the anatomical descriptors.
Original production adapted from published recommendations(13).

1.1.4 Pathophysiology of chronic venous disease

The underlying uniting aetiology of CVD, irrespective of pathological cause, is an increase in pressure within the venous system referred to as venous hypertension(12). This increase in pressure is due to an increase in the volume of blood and ineffective emptying of the venous system. This occurs predominantly in the lower limbs but also occurs, less frequently, in other body cavities such as the pelvis, abdominal cavity, and upper limbs. The functional pathophysiological causes include superficial refluxing, deep refluxing, and deep obstructing disease processes. The various pathophysiological elements lead to impaired venous performance in returning the circulating volume from the peripheries to the inferior vena cava (IVC) leading to sustained chronic venous hypertension.

The venous system is divided into superficial and deep veins, in a healthy individual 90% of the blood volume transits through the deep veins(23). The normal central venous pressure is between 8 – 12mmHg when supine, with this increasing on standing up to 90mmHg at the ankle due to the hydrostatic pressure of the blood column(24).

In refluxing pathologies, the venous pressure is largely normal in the supine position but increases with standing(25). Severity of reflux is associated with erect venous pressure (but not with supine)(25). With exercise, the calf muscle pump ejects blood from the lower limb, the pressure decreases exponentially with each muscle pump ejection down to the minimum venous pressure sustained during exercise - the ambulatory venous pressure (AVP) which is also often abbreviated to AMVP(25). For those with reflux, the erect stationary and AVP is higher in comparison to healthy controls. Whereas, for obstructing lesions there is supine venous hypertension at rest but only a limited increase, outside of the normal range, in AVP on standing(25). There is a lack of evidence to support a mechanistic hypothesis as to why this is, although it has been hypothesised that the calf muscle pump activated on exercise can sufficiently increase the pressure to overcome the flow-limiting stenosis encountered at rest(26).

In a study of 251 limbs which directly measured AVP and categorised venous hypertension using dichotomous cut-off values, no ulceration occurred in limbs with a pressure <30 mmHg, with this increasing to an incidence of 100% with pressures >90 mmHg(27). This is further corroborated in a study of 8,456 limbs, which demonstrated a significant correlation between increasing calf volume (and reflux), surrogate markers of venous hypertension, and worsening CEAP classification(28).

The cellular pathophysiological changes will now be set out in brief. Sustained venous hypertension leads to an increase in capillary permeability. This appears clinically obvious on examination of a patient with lower limb oedema secondary to CVD. However, it has been demonstrated in animal models using isotopically labelled albumin, fibrinogen and sodium, that sustained venous hypertension leads to an increase in large molecule extravasation, namely fibrinogen(29). This study provides a pivotal observation, that the macroscopic application of increased pressure through the venous system leads to microscopic changes in the endothelium resulting in molecular extravasation. There is insufficient drainage from the lymphatics to compensate for the extravasation of fluid.

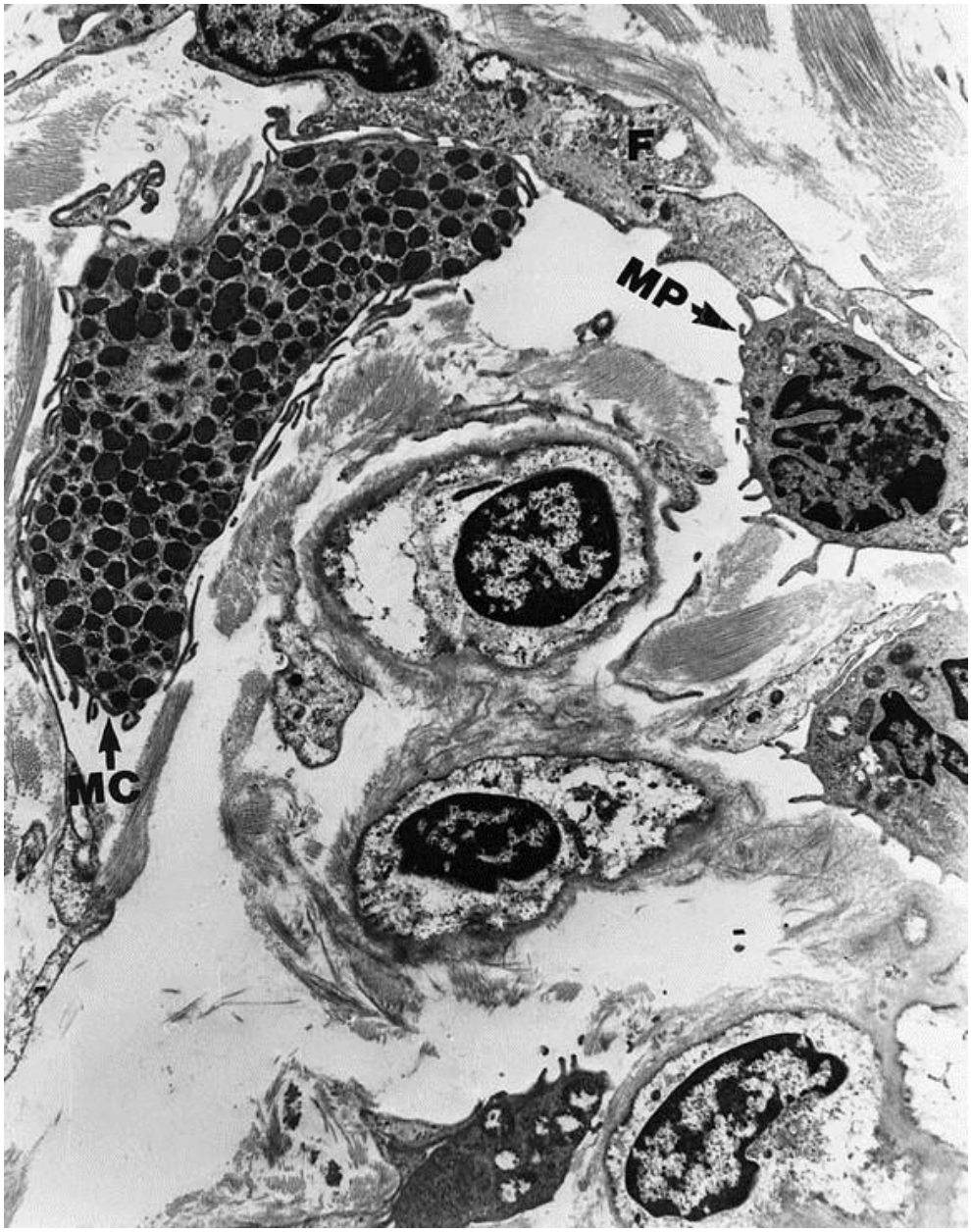
In 1998, the white cell trapping theory was proposed in which inflammatory cells trapped after extravasation produce a pro-inflammatory environment(30). It is postulated that the extravasation of large molecules and endothelial dysfunction stimulates chemotaxis and inflammatory cell infiltration(31).

A greater understanding was provided from histological studies of participants with CVD, namely venous skin changes or refluxing greater saphenous veins, where it was demonstrated that there is an increase in T lymphocytes, mast cells, macrophages and fibroblast infiltration peri-vascularly around the capillaries and also in the dermis(32, 33). Macrophages phagocytose red cells and the iron released from them, with genetic studies suggesting there is a genetic predisposition to the maladaptation of iron phagocytosis(34). Pro-inflammatory M1 macrophages, in response to the continued release of iron, reactive oxygen species, and local inflammatory environment, exacerbate the inflammatory response by producing pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-23(35). Histopathological examination of non-healing venous ulcer beds has demonstrated a persistence of the M1 macrophages with a failure to resolution and reversion to M2(35).

It is suggested that macrophages also produce TGF-β1 which stimulates fibroblasts to phenotypically change into contractile myofibroblasts(31) i.e., they go from an extra-cellular matrix producing cell to a cell-type fundamental in the formation of scar tissue. Additionally, there is an increase in matrix metalloproteinases (MMP-1, -2 and -13) and a reduction in the tissue inhibitors of metalloproteinases (TIMP-1 and -2)(36), resulting in the local extracellular matrix destruction occurring in subcutaneous tissues of those with CVD.

In summary, there is a macroscopic stressor in the form of venous hypertension that leads to a local sustained inflammatory process through extravasation, inflammatory cell chemotaxis and activation, with the result being degradation of the subcutaneous tissues and a non-healing environment.

Figure 3: Photomicrograph illustrating a mast cell, fibroblast and macrophage extravasated around a central capillary, at a magnification of 4,300



Reproduced with permission from Pappas et al.(33), see copyright permissions.
F: Fibroblast
MP: Macrophage
MC: Mast cell

1.2 Chronic venous outflow obstruction

1.2.1 Definition of chronic venous outflow obstruction

Chronic venous outflow obstruction (CVOO) describes proximal lesions affecting the common iliac, external iliac, and/or common femoral veins resulting in a impedance of the outflow of blood from the lower extremity(37). These lesions can be stenosing or occlusive. CVOO is essentially an anatomical description for two separate pathologies, these being:

1. Post thrombotic syndrome (PTS), as a consequence of deep vein thrombosis (DVT); and
2. Non-thrombotic iliac vein lesions (NIVL), which is a collection of non-thrombotic conditions.

CVOO can be unilateral or bilateral, with the latter being seen largely in PTS. There are also conditions in which the IVC is absent, with the iliac veins remaining patent, such as the congenital absence of the IVC or vena cava atresia. Vena cava atresia is rare and sits outside of the remit of this thesis. For the purpose of this manuscript, CVOO will refer to those conditions in which the iliac vein is involved, in the absence of, or in addition to, IVC lesions.

1.2.2 Diagnosis of chronic venous outflow obstruction

In line with the 2022 European Society for Vascular Surgery (ESVS) clinical practice guidelines on the management of CVD, the first line investigation for CVD is a full lower limb duplex ultrasound (class I, level B)(38). The ESVS guidelines also recommend additional cross-sectional imaging with either magnetic resonance venography (MRV) or computed tomography venography (CTV) if contemplating intervention (class I, level C).

Generally, all those with clinical manifestations of CVD will undergo lower limb duplex ultrasound. For those centres that scan the iliac veins, if there is a potential culprit lesion, or a high index of suspicion, then cross-sectional imaging will be performed. For those centres that do not scan the iliac veins, the phasicity of the femoral vein will be assessed with consideration of cross-sectional imaging if it is absent. Once a lesion

has been demonstrated, a diagnostic procedure with the potential to proceed to treatment at this index procedure could be considered. The ESVS guidelines recommend that where cross-sectional imaging is inadequate, venography and intravascular ultrasound (IVUS) may be considered for diagnostic purposes(38). IVUS is generally regarded as the gold-standard investigation for interrogation of a potential lesion, demonstrating a higher sensitivity in comparison to venography alone(39).

Irrespective of underlying pathology, a morphological obstruction of greater than 50% has been adopted as a common criteria for what constitutes a 'significant lesion'(37, 40). This is traditionally assessed through retrograde venography or, increasingly commonly, using IVUS. There is little evidence to support this morphological criteria, with many operators adding additional investigational features to guide their assessment.

Intra-procedural pressure measurements proximally and distally across the lesion are only useful when positive, this approach differs to that of arterial angiography. The venous system is considered as a low-pressure drainage system, where the artery is the high-pressure tap. Conceptually, a partially-blocked drain has similar dynamic pressures either side of it rendering pressure measurements somewhat redundant(37). Presence of cross-pelvic and paravertebral collateral veins are commonly viewed as a positive diagnostic finding that the obstructing lesion is a significant source of venous hypertension. However, again there is little evidence above logical deduction to support this observation with collaterals also apparent in healthy volunteers(41). Additionally, the rate at which the contrast clears through the vein once injected, colloquially referred to as the degree of 'hold up', is commonly used but rarely reported. This subjective feature of the rate of venous emptying can be used to add to the general picture of the aforementioned objective factors and often appears in radiological reports.

For NIVL it can be particularly challenging to ascertain if a diameter reduction seen on IVUS, or venography, is the culprit for the patient's symptoms. For these cases, a partially inflated non-compliant balloon can be 'trawled' from proximally down through the lesion to check if the balloon wastes and resistance is encountered. If the test is positive, it would suggest that the NIVL lesion is fixed and scarred rather than compliant. Ensuring that manoeuvres are performed in Valsalva is also key in helping

to establish if the lesion is a true culprit, with some diameter reductions disappearing in Valsalva(42). The prosection images in Figure 10 provide a useful insight into what a fixed NIVL is anatomically. These diagnostic findings, in the context of the clinical picture, helps to guide clinicians in deciding as to whether the lesion is significant.

1.2.3 Role of chronic venous outflow obstruction in venous hypertension

When outlining the haemodynamic impact of vessel stenosis, Poiseuille's law and Bernoulli's principle are frequently cited but insufficiently explained. Poiseuille's law, describes the flowrate of an incompressible fluid, while in laminar flow through a cylinder, in relation to fluid viscosity, length, and the pressure difference, see Figure 4. Bernoulli's principle describes the relationship between pressure, density, speed and height of an incompressible fluid, see Figure 5, which in turn is derived from the principle of conservation of energy within a system. Quoted alone, they do not explain the consequences of a critical stenosis within a vessel. The underlying mechanism will be briefly explored for illustrative purposes.

Figure 4: Poiseuille's law

$$\Delta P = \frac{8\eta LQ}{\pi r^4}$$

ΔP*: pressure difference*
L*: length*
η*: viscosity*
Q*: flowrate*
r*: radius*

Figure 5: Bernoulli's equation

$$\frac{v^2}{2} + gz + \frac{P}{\rho} = constant$$

v*: velocity*
g*: gravity*
z*: elevation*
P*: pressure*
ρ*: density*

Firstly, Poiseuille's law can be a rearranged to find the resistance (R) as a function of the diameter of a vessel, see Figure 6. Fluid resistance can be defined from first principles as a function of change in pressure (ΔP) and flowrate (Q).

Figure 6: Deriving resistance from Poiseuille's law

$$Q = \frac{\pi r^4 \Delta P}{8\eta L}, \qquad R = \frac{\Delta P}{Q},$$ *Substitute in Q from Poiseuille's law*

$$R = \frac{\Delta P}{\frac{\pi r^4 \Delta P}{8\eta L}},$$ *Simplify for R*

$$R\frac{\pi r^4 \Delta P}{8\eta L} = \Delta P\ ,$$

$$R\pi r^4 \Delta P = \Delta P 8\eta L\ ,$$

$$R\pi r^4 = 8\eta L\ ,$$

$$R = \frac{8\eta L}{\pi r^4}$$

ΔP: *pressure difference*
L: *length*
η: *viscosity*
Q: *flowrate*
r: *radius*
R: *resistance*

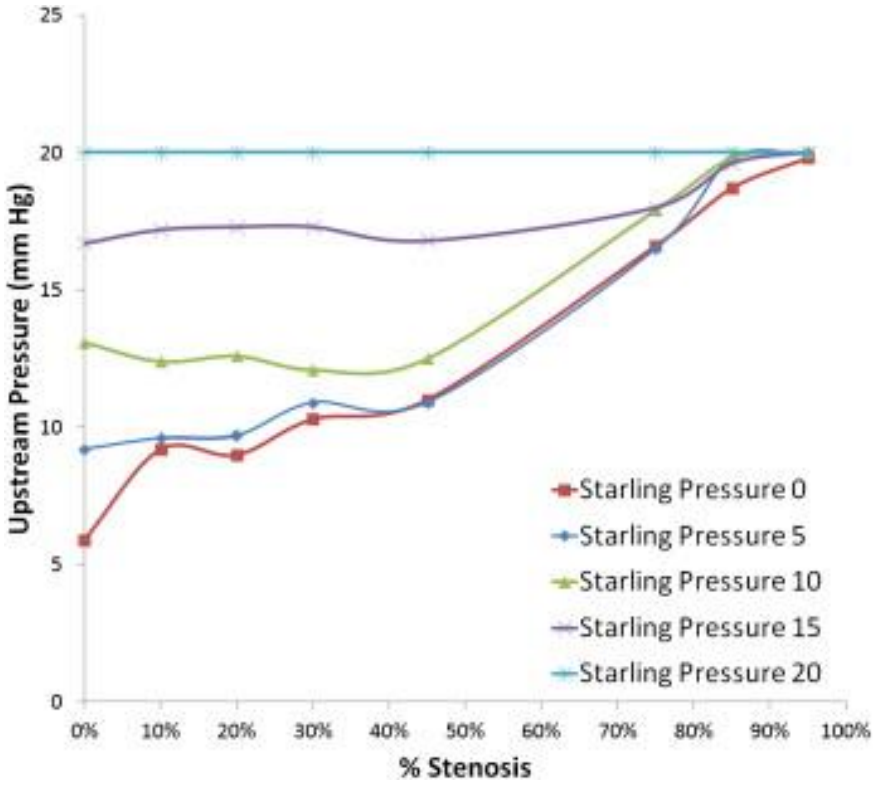
Figure 6 illustrates that the resistance associated with a stenosis in which the diameter of a vessel halves corresponds to a reduction in blood flow 16-fold i.e., a quartic relationship. Poiseuille's law in its original form details the same relationship in terms of pressure difference. From Bernoulli's principle, and the conservation of energy, we can see that the product of velocity (v) and pressure (ΔP) is equal to a constant. Therefore, the velocity (v) will increase through a stenosis as the resistance (R) is encountered, converting potential energy in the form of static pressure into kinetic energy.

As the radius (r) of a vessel reduces and the resistance (R) quarticly increases, the pressure difference (ΔP) required to drive the fluid through the stenosis will tend towards the pressure gradient in the vessel – the point at which critical stenosis is encountered(43, 44). Blood flow in large blood vessels has been shown to be largely laminar. However, there will inevitably be a point through a stenosis in which laminar flow ceases and becomes turbulent, adding further frictional losses due to eddy currents(45). In the arterial system, there are extensive compensatory mechanisms to push this critical point further – with most experimental research suggesting that a 80 – 90% diameter reduction is required(43, 44). In the venous system, this is not the case. Veins are histologically comprised of both longitudinal and circumferential smooth muscle fibres and elastin deposition, however, these are in much lower quantities in comparison to the arterial system(46). Veins contain a higher density of adrenergic receptors and hence are incredibly responsive to the sympathetic outflow(47), resulting in the venous system being one of capacitance(48, 49) that can contract to reduce its volume but not dynamically alter its flowrate.

Ex vivo models of iliac vein stenosis have demonstrated the proportional relationship between the increase in pre-stenotic vessel pressure with decreasing vessel diameter which begins at even minor vessel narrowing(50), see Figure 7. This has also been demonstrated in computational flow models of iliac vein stenosis, see Figure 8.

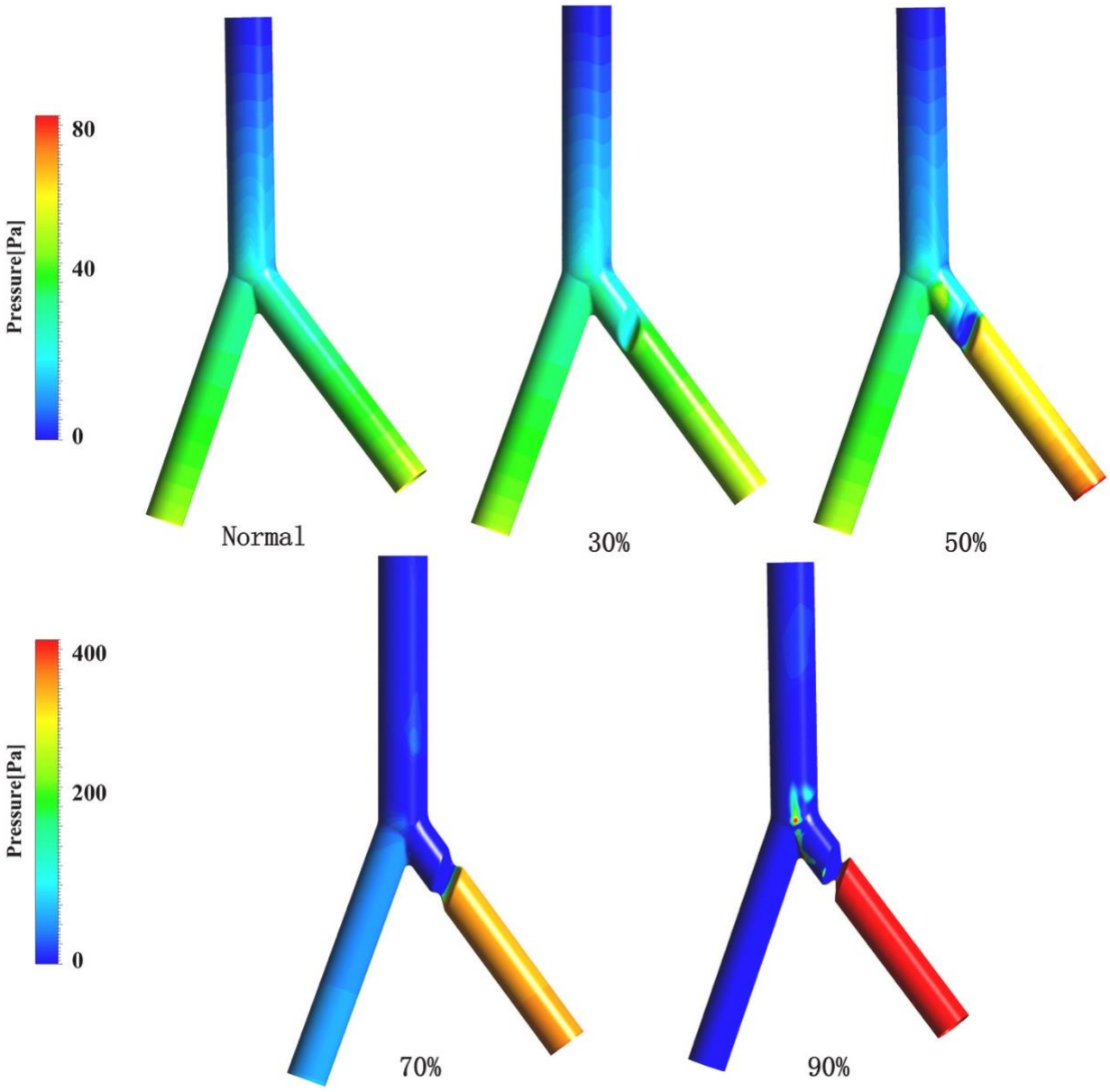
As blood volume accumulates, the venous capacitance will initially hold extra volume until their limit is reached when intravascular pressure will increase, with the clinical consequence being venous hypertension(24).

Figure 7: Pre-stenotic pressure plotted against degree of stenosis in an iliac vein model, figure reused from original article with permission



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Upstream pressure: pressure in vessel prior to stenosis.
%Stenosis: diameter reduction in model.
Starling pressure: added pressure to exterior of the graft to simulate abdominal pressure, expressed in mmHg (millimetres of mercury).

Figure 8: Inferior vena cava and iliac vein computational flow model, demonstrating the pressure increase prior to the stenosis with increasing iliac vein stenosis



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Number below each illustration represents degree of iliac vein stenosis (% diameter stenosis).

1.2.4 Post thrombotic syndrome

PTS is a term used to describe CVD that develops as a result of suffering from a DVT. It has previously been defined by Vascular Surgeons at the VEIN-TERM transatlantic interdisciplinary consensus meeting as “chronic venous symptoms and/or signs secondary to deep vein thrombosis and its sequelae”(1). This definition was adapted by the subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis, whom added in the Villalta scoring system as a qualifier to provide a minimum severity of disease “PTS is present if the Villalta score is ≥5, or a venous ulcer is present, in a leg with previous DVT”(52).

PTS is generally poorly recognised in primary care; therefore, its prevalence is largely unknown. DVT has an annual incidence of 148 per 100,000 person years in Europe(53). The exact proportion of which are iliofemoral DVTs is unclear, however, reports from single centre cohorts of unselected DVT cases suggest it could be as high as 20 – 30%(54). A significant proportion of those with acute iliofemoral DVT go on to develop subsequent PTS, the evidence on this is limited but two cohorts following the natural history of DVT estimate it is as high as 40 – 50%(54, 55). The subsequent rate of venous ulceration is high with up to 29% of those with PTS suffering from active or healed venous ulcers(56). Therefore, on a population level, PTS likely represents a significant source of disease burden.

Diagnosis of PTS is a logical deduction rather than an objective measure, the presence of the signs and symptoms of CVD in a lower limb previously affected by DVT is generally sufficient to make a diagnosis of PTS(57). There is consensus that a minimum time interval of 3 – 6 months is required between suffering from acute DVT and diagnosis of PTS as many of the signs and symptoms of DVT, such as pain and swelling, are similar to that of PTS(52, 57). The Villalta score is a disease severity measure in which a defined cut-off of 5 or more is used to diagnose the presence of PTS in those with an ipsilateral history of DVT. The Villalta score is comprised of 11 domains, graded from 0 to 3, to give a maximum score of 33 points. It has been used to diagnose PTS in an appreciable number of large clinical studies(58-61) but has faced criticism for the lack of definitions for each descriptor and the lack of inclusion of venous claudication as a domain(62), resulting in variability across assessors.

Some of these shortfalls have been overcome with recent updates to a patient-reported Villalta score published in 2016, however, the original score is still largely reported(63).

Both the initiation and resolution of thrombus is an inflammatory process with an innate immune response(64). There are key platelet-leukocyte interactions, known as immunothrombosis, such as the expression of P-selectin on platelet cells surface post activation which can interact with the leukocyte-expressed PSGL-1 receptor, which stimulates an innate immune response during thrombosis(65). After thrombus has established in the vein, there is a resolution process in which the thrombus ceases to propagate and subsequent remodelling occurs, this is mediated by pro-inflammatory cytokines, chemokines, and MMPs(66, 67). The end result is conversion of fibrin to collagen i.e., scarring in the vein wall(68). Complete recanalisation of the vein can occur during thrombus resolution with a patent lumen and peri-vascular scarring seen on IVUS.

However, in around one-third of patients, the process of thrombus resolution renders the vein narrowed creating an obstructing lesion which reduces the venous outflow from the lower limb(52, 69, 70). The open vein hypothesis(71) suggests that early thrombus removal may prevent this pathophysiological process from occurring, however, the evidence supporting this practice is conflicting and most patients are managed conservatively in the acute phase(72).

On venography and IVUS, the spectrum of maladaptation in PTS can be directly visualised. Figure 9 demonstrates post thrombotic complete occlusion of the left common and external iliac vein. Lesions tend to be lengthy, typically extending down to below the inguinal ligament. These lesions are densely scarred and often immediately recoil after ballooning, requiring purpose-designed angioplasty balloons that are short-shouldered and dilate up to high pressures e.g., 18 atmospheres.

Figure 9: Left-sided retrograde ascending venography demonstrating post thrombotic lesions of the common iliac, external iliac and proximal common femoral vein



1.2.5 Non-thrombotic iliac vein lesions

NIVL is an umbrella term that captures a collection of non-thrombotic pathologies, defined by “extrinsic compression of the iliac vein, most typically occurring between arterial structures and the vertebral body of the spine”. There are additional intraluminal findings including vein wall fibrosis and intraluminal webs/spurs(73, 74).

May Thurner Syndrome (MTS) is described within the definition of NIVL as the typical cause, it is a term used to collectively describe anatomical features that lead to compression of the left common iliac vein, it has been referred to by other eponymous names such as Cockett’s and Thomas’ syndrome. The main anatomical principle of MTS comprises compression of the left common iliac vein from the overlying right common iliac artery against the lumbar spine vertebral bodies with associated intraluminal venous spurs / trabeculations.

MTS was first described in 1908, in which 35 of 107 cadavers had lesions of the iliac vein(75). May & Thurner formed the foundation for MTS in 1957 after publishing their prosection findings from 430 cadavers, reporting spurs in the mouth of IVC and iliac vein in 15 – 22% of cases(76). An important distinction to draw is the difference between a May Thurner lesion and MTS, with MTS occupying the clinical manifestations of CVD. Less frequent NIVL etiologies include retroperitoneal fibrosis and uterine fibroids.

The overall prevalence of symptomatic NIVLs, or MTS, is unknown. The prevalence of NIVL lesions in unselected populations is as high as 20 – 30%(75-78). Although not all of these lesions will display the characteristic scarring and stenotic qualities of a ‘true’ symptomatic NIVL. With respect to advanced CVD, NIVL accounts for a significant proportion of the disease burden - a single centre study undertaking venographic and IVUS interrogation of 938 severely symptomatic limbs reported that NIVL were present in 53% of cases(79).

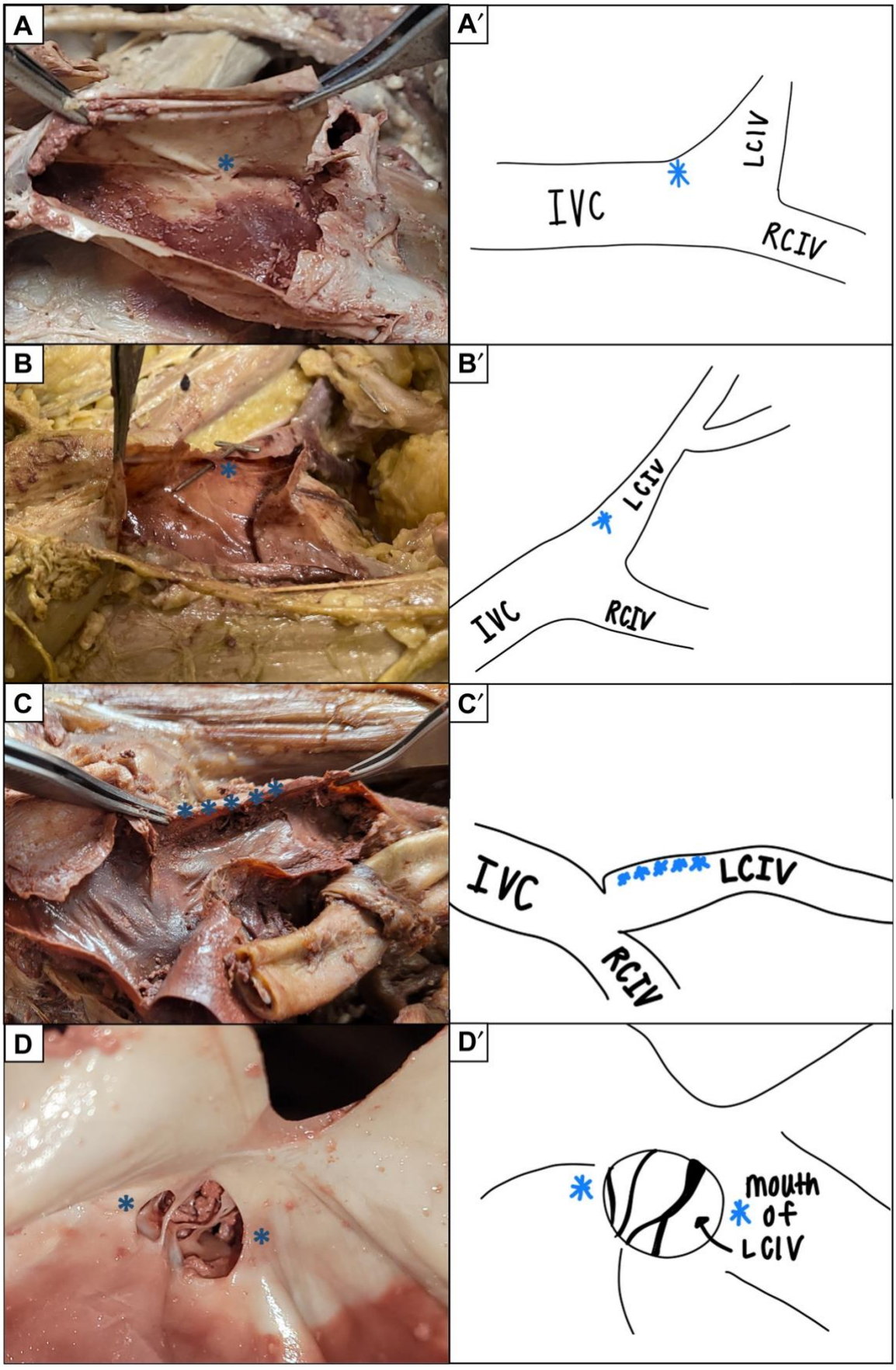
Several cadaveric studies have developed a classification system to describe the differing spur patterns visible on prosection. This was originally developed by McMurrich et al. but it has been corroborated and updated since(75-78), see Table 2.

Table 2: Spur classification system observed in May Thurner Syndrome

Spur type	Description	Classification origin
Columnar	**Bisects** the vein for a short period; often creates a **medial lumen** that is greater in calibre than the **lateral lumen**	McMurrich(75)
Marginal and triangular	**Triangular** spur at the lateral aspect of the vein, with apex pointing toward the centre of the lumen	McMurrich(75)
Marginal and linear	Occurs **longitudinally** along the **lateral** border of the vein, produces minor diminution of venous calibre	McMurrich(75)
Medial	Occurs along **medial** border of vein, protruding upward and outward to create a **90° angle** with the left common iliac vein	McMurrich(75)
Perforated	Vein is **doubled** for a short period	McMurrich(75)
Partial obliteration	Majority of lumen is **obstructed** ("quilted" appearance) with remaining opening divided by "slender bridges"	May & Thurner (76)

Amended from the published manuscript Murtha et al.(78).

Figure 10: Types of spurs observed in May Thurner Syndrome



Reproduced with permission from Murtha et al.(78), see copyright permissions.
Spur is denoted by a blue asterisk(s).
(A) Marginal and triangular spur, seen at the lateral junction of the left common iliac vein and inferior vena cava.
(B) Columnar spur; the pin is traveling through the secondary lumen created by the spur.
(C) Marginal and linear spur stretches several centimetres along the lateral wall of the left common iliac vein.
(D) Partially obstructed spur with abnormal tissue bands at both the lateral and medial aspects of the left common iliac vein with multiple synechiae stretching across the mouth of the left common iliac vein. The picture is oriented such that the mouth of the left common iliac vein is visualised from the inferior vena cava.

Regarding the pathophysiology of NIVL, there has been little mechanistic work published in the literature. Limited histological examination of lesions suggests that all spurs contain alpha-smooth muscle actin but are composed of heterogenous structures(77). For example, some spurs contained vascular structures, others did not. Some spurs were constituted from the inner elastic lamina with elastic plate-like structures. Those that lacked the elastic plate-like structures had a continuation of the tunica media of the opposite vein wall. It is uncertain how the compression of the vein could lead to these histological findings. It could be hypothesised that at the site of chronic compression, with ongoing inflammation, there is remodelling of the vein wall. These features coalesce to produce spurs(22), with the result of this chronic compression and inflammation being a stenotic and tightly narrowed vein segment. However, this is conjecture.

The venographic and IVUS findings are not as stark as those in PTS. There are several signs indicative of NIVL on venography including an area of lucency where the contrast is being displaced, pancaking / flattening of the vein in the anterior-posterior projection, and cross-pelvic and para-vertebral collateral vessels. See Figure 11 for the lucency and pancaking sign. The narrowing in NIVL can sometimes be best visualised in the lateral view, see Figure 12. A compliant stenosis is not regarded as a culprit, these are seen in up to 30% of the general population. Most operators require evidence of scarring as a pre-requisite for placement of a stent which is best identified on IVUS and using the balloon trawl/compliance techniques.

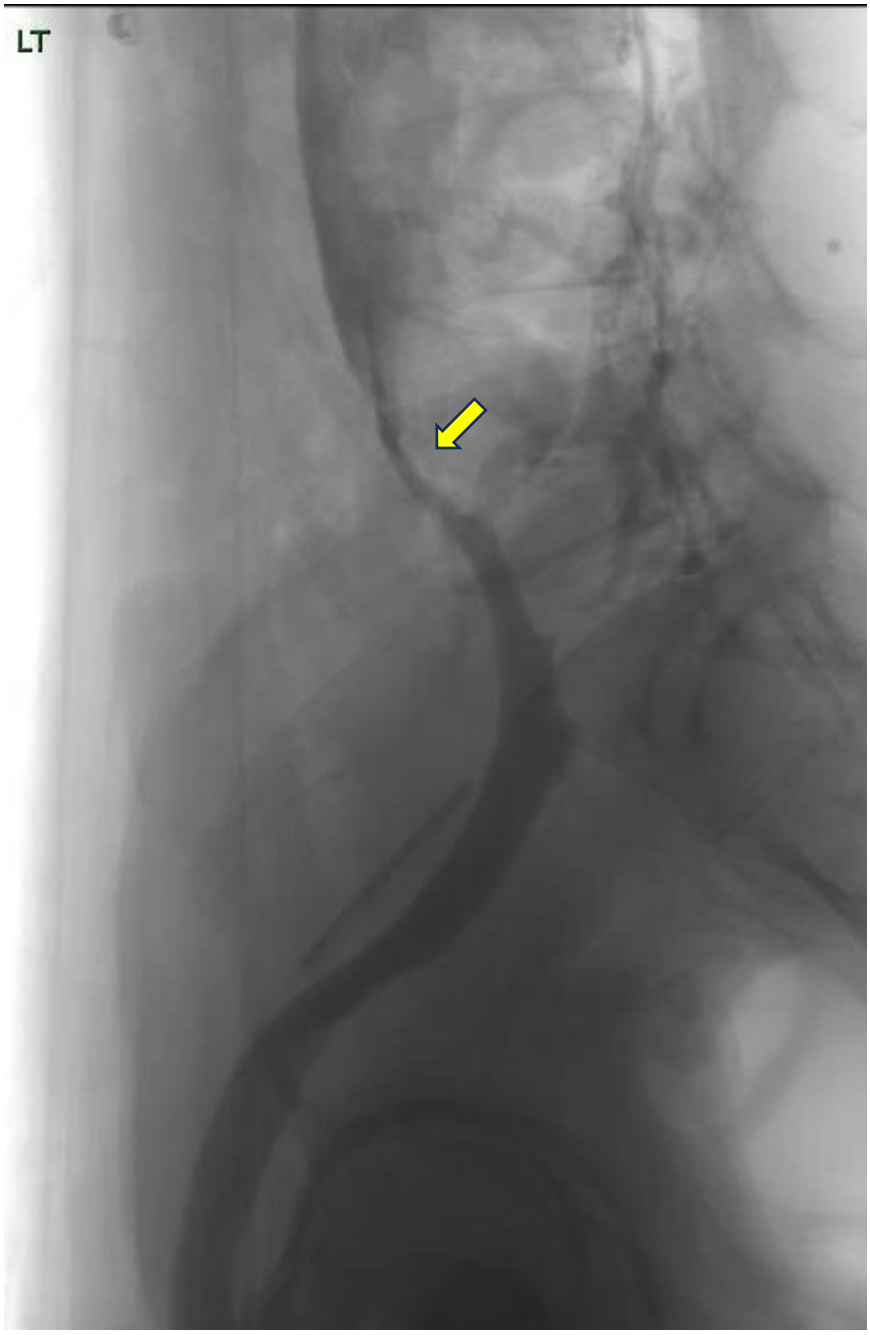
Generally, it is easier to restore luminal patency for NIVL in comparison to PTS. A single application of balloon angioplasty can break the spurs to re-establish full patency, with some operators not performing pre-stent venoplasty. They also tend not to recoil as PTS lesions do. The problem with NIVL is quite the opposite, successful

destruction of the spurs mean that the stents are not ‘pinned’ by the recoil. This can predispose the stent to migration, there have been numerous reports of stent migration proximally into the IVC up into the right atrium necessitating open cardiothoracic surgery(80).

Figure 11: Bilateral retrograde ascending venogram demonstrating a left-sided non-thrombotic iliac vein lesion, with the lucency and pancake signs present



Figure 12: Left-sided retrograde venography lateral view demonstrating a non-thrombotic iliac vein lesions



1.2.6 Interplay between non-thrombotic iliac vein lesions, acute deep vein thrombosis, and subsequent post thrombotic syndrome

There is an inherent interplay between NIVL, acute DVT, and PTS. Clinically, each pathological state can feature as part of the same natural history of disease. Venous stenting can be indicated in all three of these clinical presentations meaning they are often grouped together in clinical studies. However, it is important to distinguish them, as the pathophysiological process at each point is discrete and markedly different.

Proximal iliofemoral DVT can be initiated by a pre-existing NIVL, i.e., a May Thurner compression on the common iliac vein where stasis occurs, and thrombus originates – referred to as descending DVTs. Descending DVTs account for ~30% of all iliofemoral DVTs(54). In this case, the thrombus will propagate from proximal to distal. At the time of the index DVT, if the patient presents within two weeks of symptoms onset, it may be possible to undertake an early thrombus removal procedure through catheter-directed thrombolysis, pharmacomechanical thrombectomy or catheter-based mechanical thrombectomy. Once thrombus resolution has been achieved, this is likely to reveal an underlying lesion in the iliac vein, the previous NIVL, which now has a superadded thrombotic pathology. In unselected cases of iliofemoral DVT thrombolysis, 60-80% have an underlying lesion requiring iliac vein stenting to treat an underlying lesion(54, 81, 82).

Proximal iliofemoral DVT can also, more commonly, be caused by a DVT which initiates in the calf or popliteal veins – referred to as ascending DVTs. Ascending DVTs account for ~70% of all iliofemoral DVTs(54). The calf DVT propagates from distal to proximal, in these cases it is likely that a long course of venous anatomy is affected, and they are less likely to receive interventional treatment(54). In those that do have interventional therapy, it is less likely that an associated NIVL requiring treatment will be identified.

In those that have a proximal iliofemoral DVT but do not undergo early thrombus removal, as outlined earlier, as many as 50% will go on to develop PTS(54, 55). Approximately 30% will fail to recanalise with anticoagulation alone(69, 70). The result of which is a proportion of those suffering from an acute DVT will develop PTS with sufficiently severe disease to recommend interventional treatment of the chronic lesion with recanalisation and iliac vein stenting.

Therefore, there are clinical opportunities to perform iliac vein stenting for a NIVL prior to DVT, during the index admission for acute DVT, and later after the chronic maladaptation to DVT presents as PTS. However, each of these stages in the natural history of disease is a distinct pathological environment that will interact with the intervention differently. An important note is that the prophylactic treatment of NIVL in those without CVD is not recommended due to the low numbers that would go on to develop descending DVT(38).

1.3 Management of chronic venous outflow obstruction

1.3.1 Medical management

Mainstay of medical management for CVOO is venoactive medications, compression therapy, through compression stockings and compression devices, exercise, and weight loss(83). Venoactive medications are a heterogenous group of agents classified together by their clinical indication to treat CVD(84). They are broadly split into naturally occurring extracts and synthetic compounds. Common mechanisms of action include improved venous tone, decreased capillary permeability, and reduced inflammation. Interpretation of the evidence base is hampered by this unified grouping given that they differ in terms of their pharmacological action and intended effects. A Cochrane review, updated 2020, reviewed the results from 69 randomised controlled trials (RCTs) for eight different venoactive medications(85). It provided a moderate certainty recommendation that venoactive medications reduce lower limb oedema (relative risk 0.70, 13 studies; n=1,245). While the ESVS 2022 clinical practice guidelines classify venoactive medications in a similar unified way, providing a recommendation for their use in the reduction of venous symptoms (level IIa, grade A), they also provide an individual breakdown of the evidence for each agent. Table 3 provides an overview for the positive results observed in RCTs for each agent reported in the ESVS guidelines. These reported effects have a low certainty given the risk of bias. An important limitation is that these trials did not use a validated disease severity score, such as VCSS, and instead report on individual symptoms. This makes establishing their cost-effectiveness and overall net-benefit challenging.

Table 3: Common venoactive medications and their demonstrated effect on the signs and symptoms of chronic venous disease

Symptom / Sign	Ruscus extract	MPFF	Calcium dobesilate	Horse chestnut	Hydroxyethyl-rutosides	Red vine leaf extract	Sulodexide
Pain	Improved	Improved	Improved	Improved	Improved	Improved	Improved
Heaviness	Improved	Improved	Improved		Improved		Improved
Fatigue	Improved	Improved	Improved				Improved
Cramping	Improved	Improved	Improved		Improved		Improved
Paraesthesia	Improved	Improved	Improved				
Pruritus	Improved	Improved	Improved	Improved			
Oedema	Improved	Improved	Improved	Improved		Improved	

MPFF: Micronised purified flavonoid fraction

Compression therapy is intended to act as an adjunct to the calf muscle pump to empty osteofascial compartments(86). Graduated compression describes the process of applying the greatest pressure at the ankle and the lowest pressure at the knee, this superimposing a pressure gradient across the lower limb(87). There is pre-clinical evidence demonstrating that graduated compression improves venous haemodynamic parameters at rest and during ambulation(88). Graduated compression stockings (GCS) are widely recommended in the management of CVOO in clinical practice despite a lack of evidence to support their use, with just one comparative trial in the literature which failed to show an improvement in PTS(89, 90). A single study demonstrated that GCS improved venous haemodynamics, namely venous filling time and venous volume, as measured by air plethysmography(91) This is reflected in the ESVS 2022 clinical practice guidelines, providing a IIa, level B, recommendation for the use of class II (20 – 40mmHg) compression therapy to reduce PTS severity. There have been no significant trials investigating the role of GCS in NIVL patients. Intermittent pneumatic compression (IPC) in the reduction of PTS severity has been investigated in two studies, one of which was a randomised trial (n=27)(92, 93). The comparative study reported a reduction in Villalta score in comparison to the control group (12.2 vs.15.0, $p<0.05$). However, the sample size is inadequate. ESVS 2022 clinical practice guidelines have provided a class IIb, level B, recommendation for IPC to reduce PTS severity(38).

Exercise has been shown to improve calf muscle function and improve the calf pump ejection fraction(94) and is now recommended by the ESVS for symptomatic management in CVD (class IIa, grade B)(38). A recent systematic review on the use of supervised exercise in PTS identified a single RCT(95), reporting that the evidence was sparse and inconclusive. The RCT, comprising of 43 participants, reported a significant improvement in venous-related quality of life and a non-significant improvement in severity of disease as graded by the Villalta score for the exercise group in comparison to the control group(96). A Cochrane review assessing the use of exercise therapy for CVD(97) identified two further RCTs investigating its effect on the severity of disease, both of small sample size, and only one reporting the difference between the intervention and control arms(98, 99). The single trial which provided a meaningful comparison reported no difference in the severity of disease(99) with the

Cochrane review concluding that there is insufficient evidence to support the use of exercise in the treatment of CVD.

Obesity is an established risk factor for varicose veins and CVD(100-104), with higher rates of obesity associated with more severe CVD(100). Furthermore, in a large prospective cohort of 65,329 patients undergoing superficial venous interventions, increasing BMI (>35kg/m^2) was negatively correlated with post-treatment improvement in severity of disease(105). Obesity increases intra-abdominal pressure (>10mmHg), which is translated onto the iliac veins and IVC impeding the venous return from the lower limbs exacerbating any underlying venous pathology(23, 106). It is therefore logical that weight loss would be a remedy for CVD, however, the evidence to support this is sparse. Weight loss has been recommended in the 2022 ESVS clinical practice guidelines (class IIa, grade B). There is no evidence to support the role of weight loss in PTS specifically. In a non-randomised trial of morbidly obese patients with CVD, bariatric surgery led to significant improvements in disease severity, as ascertained by the VCSS and Venous Disability Score (VDS), and venous flow parameters(107). Weight loss is recommended for a variety of health benefits meaning that the limited evidence is not a barrier for recommendation in clinical practice.

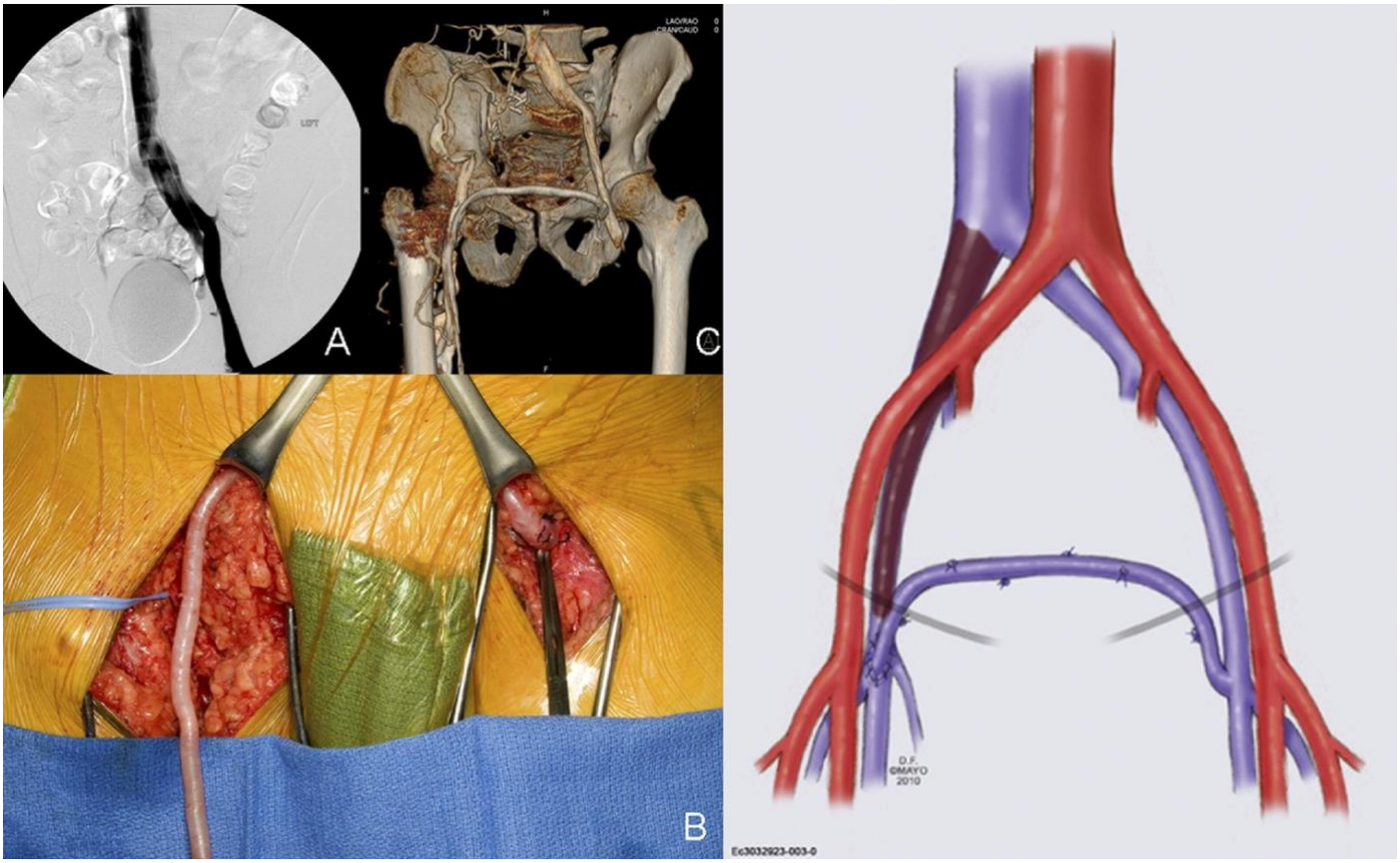
More experimental treatments include neuromuscular electrical stimulation (NMES) devices. NMES provides electrical stimulation to the nerves and muscles causing muscle contraction. The REVITIVE™ device, which is composed of a small platform with two endplates, was investigated in the treatment of CVD in a small sham-control randomised trial (n=20)(108). NMES lead to improved venous flow parameters and disease-specific quality of life in comparison to a placebo device. NMES is also available in other wearable forms such as the geko™ device which provides stimulation along the common peroneal nerve activating the calf pump(109). Again, there is currently no high-quality evidence to support their use in CVD.

In summary, the evidence to support medical and conservative interventions in the treatment of CVOO is weak. There are no medical therapies reported in the literature that offer a reliable and robust treatment effect.

1.3.2 Operative management

Historically, due to the retroperitoneal location of the iliac veins, surgical treatment of proximal obstructing lesions has previously been restricted to extra-anatomical venous bypass, which conferred a high morbidity and poor long-term outcomes(110). This was most commonly in the form of a long saphenous vein crossover graft, known as the Palma procedure, as it avoids the retroperitoneal exposure of the common iliac vein, see Figure 13. An arteriovenous fistula is normally performed at the same time to maintain patency in the early-to-medium post-operative period(111), during this time there is a profound increase in flow and pressure within the venous system. The fistula is later closed after post-operative recovery and ensuring that the anastomoses and graft are satisfactory. Rarely, ipsilateral iliofemoral venous bypass or panelled spiral venous interposition grafts are performed. The evidence to support open surgery for CVOO is poor, with low numbers of participants in case series and no comparative trials comparing it against medical therapy(112). This is mirrored by the level IIb grade C recommendation for open surgical treatments in CVD in the ESVS guidelines(38).

Figure 13: Illustration of the Palma saphenous vein crossover graft



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A: Contrast venogram shows chronic right iliofemoral obstruction.
B: Right-to-left femoral vein bypass with left great saphenous vein
C: Computed tomographic venogram

1.4 Endovenous reconstruction of the iliac vein segment with venous stenting

1.4.1 History of iliac vein reconstruction

The journey to achieving percutaneous iliac vein reconstruction is one of the history of interventional vascular radiology itself. On the 19th of September 1924, Dr Barney Brooks, an American Surgeon, performed arteriography of the femoral artery, which was the first time an artery had been visualised in a living person(113). A significant limitation to angiography was that there was no rolling fluoroscopy, images had to be taken one at a time – this meant it was cumbersome to undertake, and its use was limited. By 1950, the image intensifier and cineangiograms on roll film had been developed permitting more rapid acquisition of x-ray images(114).

Dr Charles Dotter, who would later perform the first ever angioplasty, was an American Radiologist utilising everyday materials such as guitar strings and speedometer cables alongside homemade Teflon catheters for angiographic navigation(115). Dr Dotter met Bill (Willian) Cook, a surgical technician, at the Radiological Society of North America meeting in 1963 where they forged an accidental alliance. Bill Cook would go on to be the founder of Cook Medical™. Together, they produced the 'Dotter dilator' set that permitted the first (accidental) arterial angioplasty in 1963 in which Dr Dotter inadvertently recanalised an occluded iliac artery while attempting to perform a retrograde aortogram(114, 115). On the 16th of January 1964, he performed the first intentional angioplasty of the superficial femoral artery.

Dr. Andreas Gruentzig, a Cardiologist from Zurich, built on this work developing an expandable balloon catheter(116). He built the rigid balloon out of polyvinylchloride, or PVC, on his kitchen table and performed the first ever balloon angioplasty on the superficial femoral artery for intermittent claudication on the 12th of February 1974. He continued to push the clinical reach of balloon angioplasty, performing the first ever coronary angioplasty on the 14th of September 1977, on a 38-year-old man who went on to outlive him(117, 118).

Dr Julio Palmaz, a Radiologist from Argentina, aimed to overcome the problematic recoil encountered after balloon angioplasty by designing a deployable rigid metallic stent(119). Dr Palmaz designed a balloon-expandable braided stent made from stainless steel prior to securing venture capital funding amounting to $250,000. It is

famously reported this was from Philip Romano, an unlikely partnership considering he was the owner of the Fuddruckers hamburger chain and The Macaroni Grill(120). The first ever balloon-expandable stent was placed in the iliac artery in May 1987 at the University of Freiburg. Less frequently cited is that the first ever stent (which was self-expanding) was placed by Jacques Puel in France on the 28th of March 1986(121, 122).

The first reported case of a stent being placed in the venous system was in the same year, Charnsanagavej et al. reported placement of a self-expanding stent in the superior vena cava (SVC) of a 42-year-old woman suffering from a carcinoma of the trachea that extended into the mediastinum(123). Venous stenting remained largely confined to the SVC and IVC for some time, it is not entirely clear when the first stent was placed in the iliac vein. However in 1991, there was a published report of stent extension down from the IVC into the iliac vein from a small case series undertaken in the Clarkson Hospital, Omaha(124). The first case series of iliac stent placement after early thrombus removal also occurred in 1991 at the University of Minnesota Hospital where Molina et al. performed the novel technique of placing Gianturco Z-stent™ and Wallstent™ stents in fibrotic iliac veins after balloon venoplasty(125). Berger et al. who published a case report in 1995(126) is sometimes incorrectly cited as the first iliac vein stent for a NIVL lesion after early thrombus removal(127).

In 1996, Nazarian et al., also based in the University of Minnesota Hospital, first published a case series of iliac vein stenting after failed balloon angioplasty for chronic indications. Their series was comprised of stents placed in the SVS and IVC alongside subclavian, innominate, iliac, femoral, and portal veins(128). Stents were placed in the iliac vein in 29 patients and in the common femoral vein in 5 patients. One-year primary-assisted patency (PAP) was 66% and 37% for iliac vein and femoral vein stents respectively. In the history of iliac vein stenting, this first series is infrequently mentioned, likely as the stent was seen as a bail-out technique.

The later reports from Stanford University Medical Center(129) and River Oaks Hospital are often regarded as the pivotal landmark publications that established iliac vein stenting as a potential therapy(130). Three years later, in 1999, O'Sullivan et al. from Stanford published the first case series of planned iliac vein recanalisation and stenting for chronic indications in 20 patients from a mixed cohort of acute and chronic

patients(129). Overall technical success was 87% with a 1-year patency rate of 79%. A year later, it was the combined efforts of a transplant surgeon, Dr Seshadri Raju, and vascular surgeon, Dr Peter Neglen, based in Mississippi who, on the back of these results, solidified the early evidence base. The pair began stenting chronic iliac vein lesions in 1997, publishing their famous case series of 94 patients in April 2000(131). Wallstent™ stents were placed in both of these cohorts. The teams from Stanford and Mississippi demonstrated promising early results and paved the way for iliac vein stenting as a potential mainstream therapy for CVOO.

1.4.2 Development of dedicated iliac vein stents

The most commonly placed iliac vein stent is the Wallstent™. The Wallstent™, is a general-purpose braided closed-cell stent, originally intended for arterial placement gaining United States Food and Drug Administration (US FDA) approval in 1996, later gaining approvals for enteric and venous indications(132). It is composed of Elgiloy®, which is a tradename for a 'super alloy' comprised of, in descending proportions, cobalt, chromium, nickel, iron, molybdenum, manganese and carbon(133). In early manuscripts, it is referred to as the Schneider's Wallstent™ prior to being acquired by Boston Scientific®. Its adoption was due to its availability in large diameters (≥12mm), sufficient length (90mm), flexibility, high radial force, and ability to resist compression(134, 135). At the time, in 1996, the only other (largely) available stents of similar diameter were the Gianturco Z-stent™ and the PALMAZ™ stent – the latter of which was balloon expandable and very rigid.

The Gianturco Z-stent™ was designed for tracheobronchial placement with a self-expanding scaffold rigid structure. It is not licenced for intravascular placement but has been used 'off-label' in SVC and IVC obstructions(136) and later used in combination with the Wallstent™ in a 'Wallstent-Z' configuration for iliac veins(137). The Wallstent-Z configuration describes the placement of a Wallstent™ in the iliac vein, placed up to, but not inside of, the iliocaval confluence, with extension into the IVC using the Gianturco Z-stent™, overlapping significantly with the Wallstent™(135). The purpose of this was to reduce the risk of contralateral DVT by avoiding extending the Wallstent™ across the confluence, with extension instead of the Gianturco Z-stent™

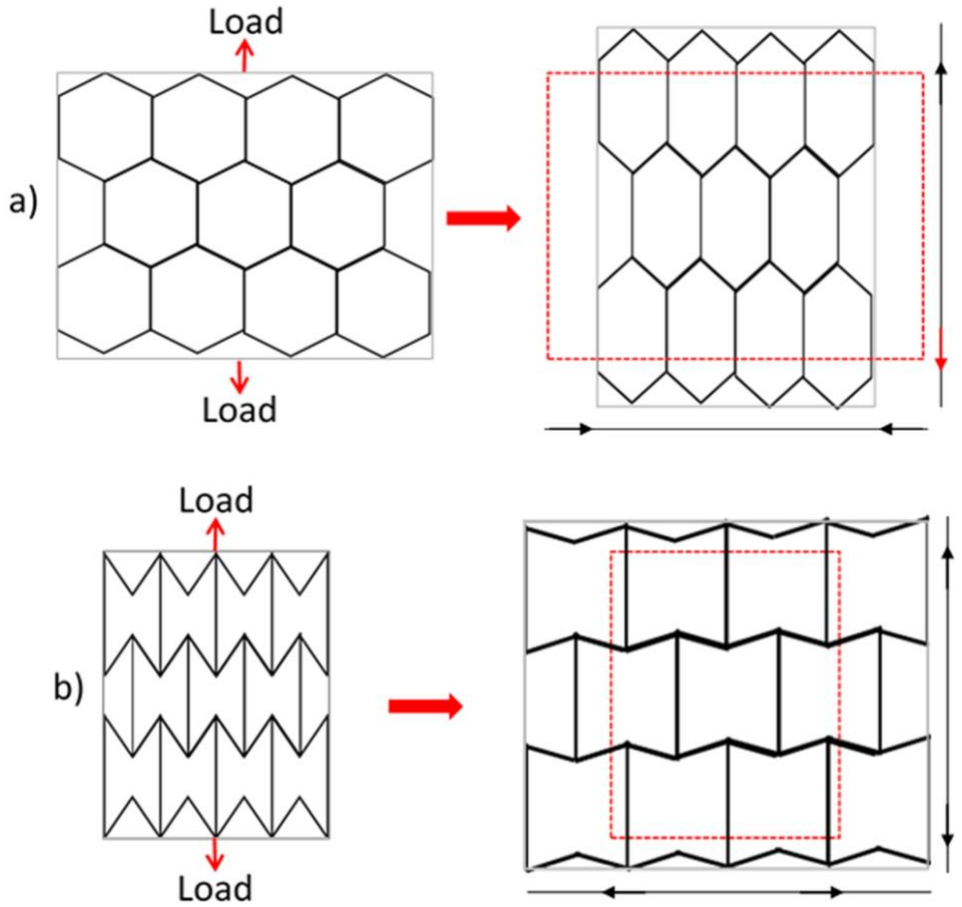
which is caged and less likely to limit flow, while being sufficiently rigid to prevent the collapse at the end of the Wallstent™.

Although, the Wallstent™, and the Wallstent-Z pairing, demonstrated good technical success rates and promising long-term patency, with a good safety profile, its design does have deficiencies when considering the ideal properties of an iliac vein stent. The need for a purpose-designed stent is best illustrated by the consistently reported shortfalls in the literature, with industry responding to overcome these with the development of dedicated venous stents(135, 138-140).

When considering what constitutes an ideal venous stent, it is important to consider the mechanical properties exhibited by the stent in response to the underlying pathology. All licenced venous stents, including the later licenced Wallstent™, are self-expanding stents – balloon-expandable stents are more commonly encountered in the arterial system. Given this, the properties unique to balloon-expandable stents will not be explored.

Foreshortening describes the shortening of stents as the radius of the stent is increased i.e., the shortening that occurs after deployment and further venoplasty(141). It occurs as a result of the Poisson effect, in which a material deforms in directions perpendicular to the direction of loading. If you apply pressure to an inflated balloon, it deforms in a direction perpendicular to that pressure. This can be overcome by incorporating auxetic patterns into the stent design. Auxetic materials are those that expand in all directions when stretched and have a negative Poisson's ratio, see Figure 14(142, 143). Foreshortening has been shown to occur to a greater degree with braided diamond-patterned stents such as the Wallstent™ in comparison to chevron and z-designs(144).

Figure 14: Diagrammatic illustration showing the difference between a) arrangement of fibres in a honeycomb that is subject to the Poisson effect, and b) an auxetic material that increases in volume when stretched



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Axial flexibility refers to the ability of the stent to be axially compliant, or how it achieves deformation and apposition to the natural curve of a blood vessel. Flexibility is inversely related to radial stiffness. Figure 15 illustrates how kinking can occur when stents that lack the required axial flexibility are placed in the curvature of the common iliac vein(145). Furthermore, stents can fracture from fatigue due to the repeated deformation and compression with the dynamic position of the external iliac and femoral veins during hip movements, see Figure 16. In a 50-year fatigue test, it was demonstrated that off-label (i.e., non-dedicated) stents fractured significantly more frequently than purpose-designed stents(146), although this has not been supported in clinical reports(147). Axial flexibility is achieved by arranging ring units that are radially stiff with links connecting them that can deform(141).

Figure 15: Lateral radiograph illustrating kinking of an iliac vein stent in the pelvis



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Figure 16: Representative 3-dimensional computed tomography showing the stented vessel with the hip in a neutral 0' position (green) and hip flexion at 90' (brown)



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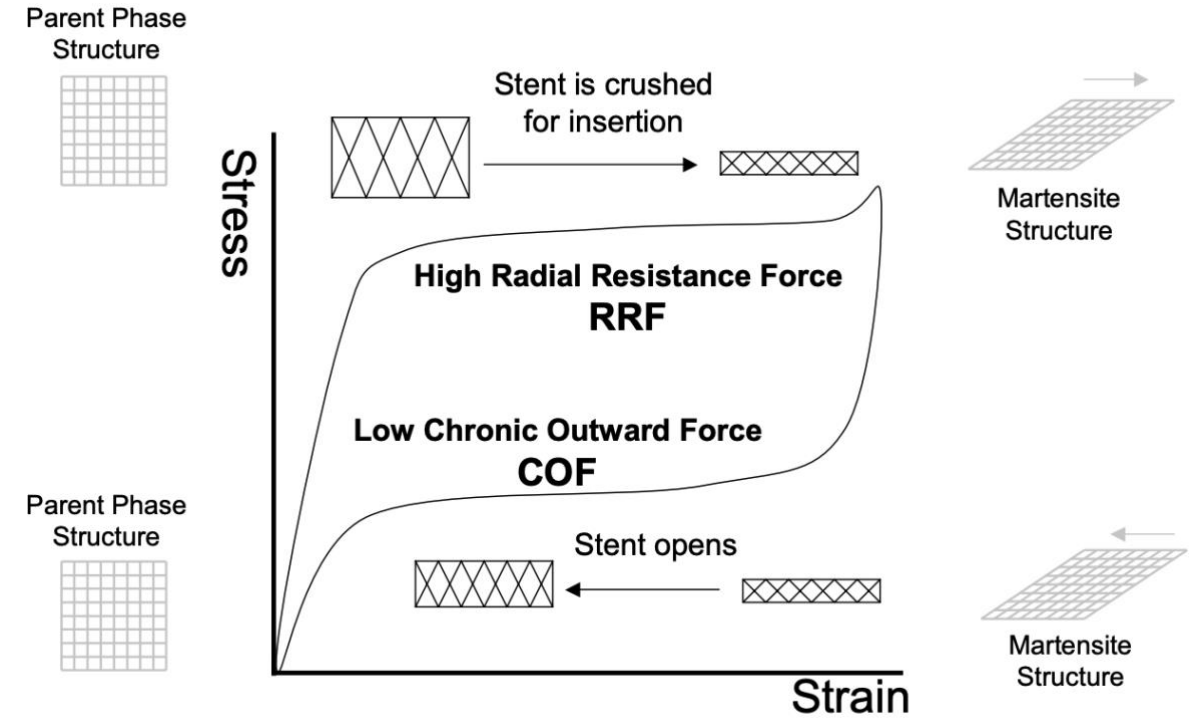
Chronic outward force (COF), also referred to as the spring constant, describes the radial force exerted by a self-expanding stent on the vessel wall(148). This force varies between stents, depending on the material composition and physical arrangement of stent struts, and varies within stents as the stent expands and the diameter increases. This is the force that opens the stent once released from the delivery system and may continue to push against the vessel wall (depending on the relative diameter of the stent and vessel in addition to the degree of oversizing). COF has been shown to be significantly higher in dedicated venous stents in comparison to the Wallstent™(149), this property has been postulated as protective against stent migration.

Radial resistive force (RRF) is the force exerted in resisting circumferential compression(148). This is the force that keeps the stent open against external compression, for example in a circumferential post thrombotic occlusion that has undergone balloon venoplasty but is subject to elastic recoil. This differs to the crush resistance (CR) which is the ability of a stent to withstand a force applied in one radial direction perpendicular to the stent. Stents with a high RRF tend to have a high CR, but it is not a direct relationship due to the deformation pattern. CR displays a linear force-diameter reduction, whereas RRF follows a non-linear force-diameter reduction(150). RRF has been shown to be generally high among dedicated venous stents, with variable CR(148). Demonstrating this lack of congruence between RRF and CR, the Wallstent™ has a mid-range RRF, whereas it had the highest CR in comparison to all other six venous stents tested(149). It has been suggested that this property is key in the treatment of NIVLs where there is an single direction non-circumferential compressive effect(151).

In summary, the COF and RRF differ in that COF is the force that the stent exerts on the vessel wall as it tries to expand to its final diameter and the RRF is the force the stent exerts as it resists being circumferentially squeezed by the vessel wall. These forces are not equal for a given diameter given the asymmetric loading and unloading stress-strain relationship of a superelastic material such as nitinol(152, 153), see Figure 17.

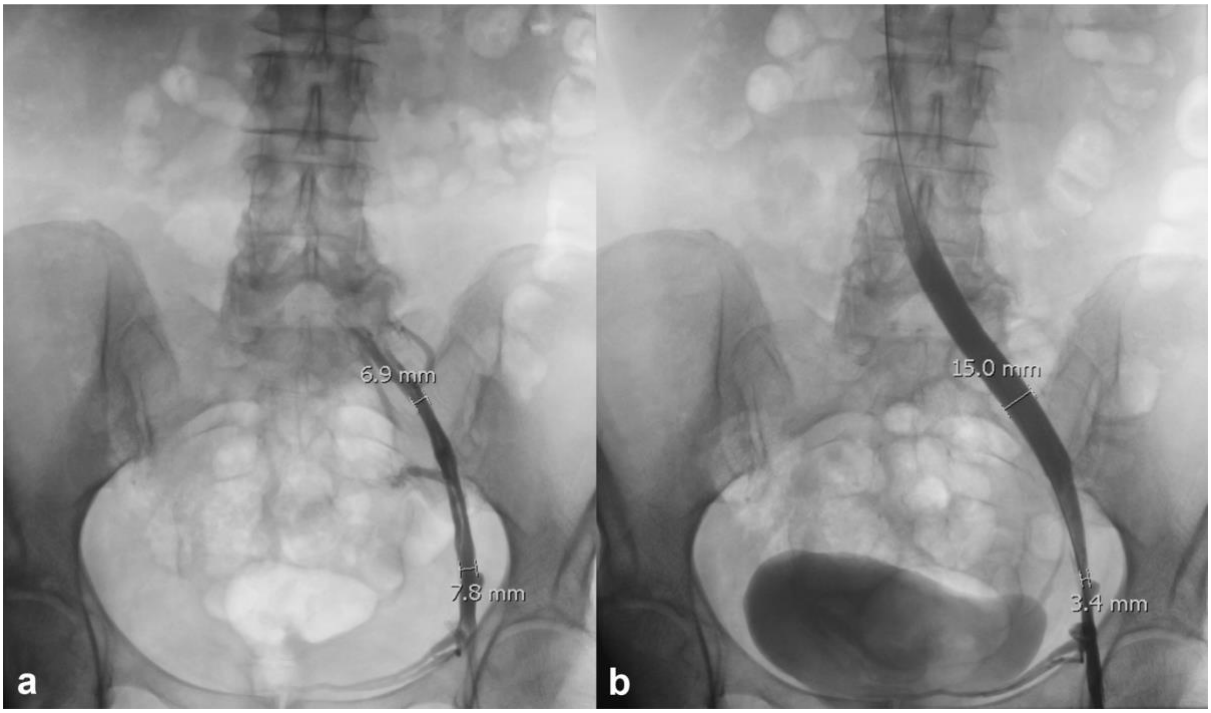
In comparison to the arterial system, veins are more susceptible to the Poisson effect, with redistribution of radially applied force to the longitudinal direction, this meaning that the adjacent unstented vein segments have a pronounced diameter reduction in response to the diameter gains in the stent section(154). Therefore, if a stent exerts sufficient COF to cause adjacent vein narrowing it may even compromise the inflow(155). The COF therefore needs to be sufficient but not excessive.

Figure 17: Illustration of the hysteresis loop of stress plotted against strain for nitinol stents



Reproduced with permission from Morgan et al.(153), see copyright permissions.
Stress: the internal force per unit area due to an externally applied force
Strain: the deformation of a material from stress
Martensite structure: state occupied at a lower temperature, which is more flexible and easily deformed crystalline structure
Parent phase structure, also referred to as the austenite state: state occupied at a higher temperature, which is a less flexible and hard to deform cubic structure

Figure 18: Venogram demonstrating the Poisson effect after stenting with diameter of the external iliac vein decreasing from a) 7.8mm to b) 3.4mm



Reproduced with permission from Ramsey et al.(155), see copyright permissions.

Stents are largely manufactured in one of two ways, either from a braided wire material or from an extruded laser-cut tube. These manufacturing processes have a significant over-arching impact on the mechanical properties of the stent. Braided stents are formed by braiding the wire around a mandrel along an axis of rotation, they can then be welded at pre-defined points(156). Braided stents generally have a reduced RRF, are prone to kinking, but are resistant to crushing and stent fracture.

Laser cut stents are produced by first manufacturing a uniform cylindrical structure and then melting pre-defined areas to produce the pattern and structure of the stent(156). Generally, laser cut stents have a high RRF and are resistant to kinking but are subject to heat effects which can anneal the material increasing its brittleness. Figure 19 shows the difference in appearance between a braided and laser cut nitinol stent.

Figure 19: Image illustrating a) braided nitinol stent on the left; and b) laser cut nitinol stent on the right



Reproduced with permission from Moeri et al.(157), see copyright permissions.

There is a lack of published, evidence-based, consensus on what properties the ideal venous stent would possess(151). However, to summarise, the ideal venous stent would:-

1. Be of sufficient diameter to restore the geometry of the iliac vein, enabling satisfactory flowrates, and permitting sufficient oversizing to provide the required COF;
2. Demonstrate sufficient RRF against the vessel recoil to maintain stent geometry and therefore stent patency; and
3. Demonstrate sufficient CR against unidirectional compressive stress to maintain stent geometry and therefore stent patency;
4. Demonstrate sufficient flexibility in order to conform to the natural path of the iliac and femoral vein avoiding vessel trauma and kinking and/or fracture of the stent;
5. Be made of a material that is durable, resistant to corrosion, and is not thrombogenic.

The first-ever dedicated venous stent was the Zilver Vena® stent manufactured by Cook® Medical. It received its Conformité Européene (CE) approval in October 2010 prior to receiving US FDA approval in 2020(125).

Table 4 lists the available dedicated venous stents, their approval date, and overall characteristics. Figure 20 shows the appearance of some of the common dedicated venous stents.

Two dedicated venous stents were subsequently withdrawn from the market due to safety concerns(158-161). The Vici venous stent™ was voluntarily recalled by Boston Scientific© on the 12th of April 2021 due to concerns regarding stent migration after receiving notification of 17 reported cases(159).

A systematic review investigating venous stent migration identified 54 cases in the literature and reported that 82.6% of the migrated stents were less than, or equal to, 60mm in length with no cases of migration in stents greater than 100mm in length(80). There are a greater number of reported cases of migration on the Manufacturer and User Facility Device Experience (MAUDE) database(162) suggesting its incidence is under reported in the literature.

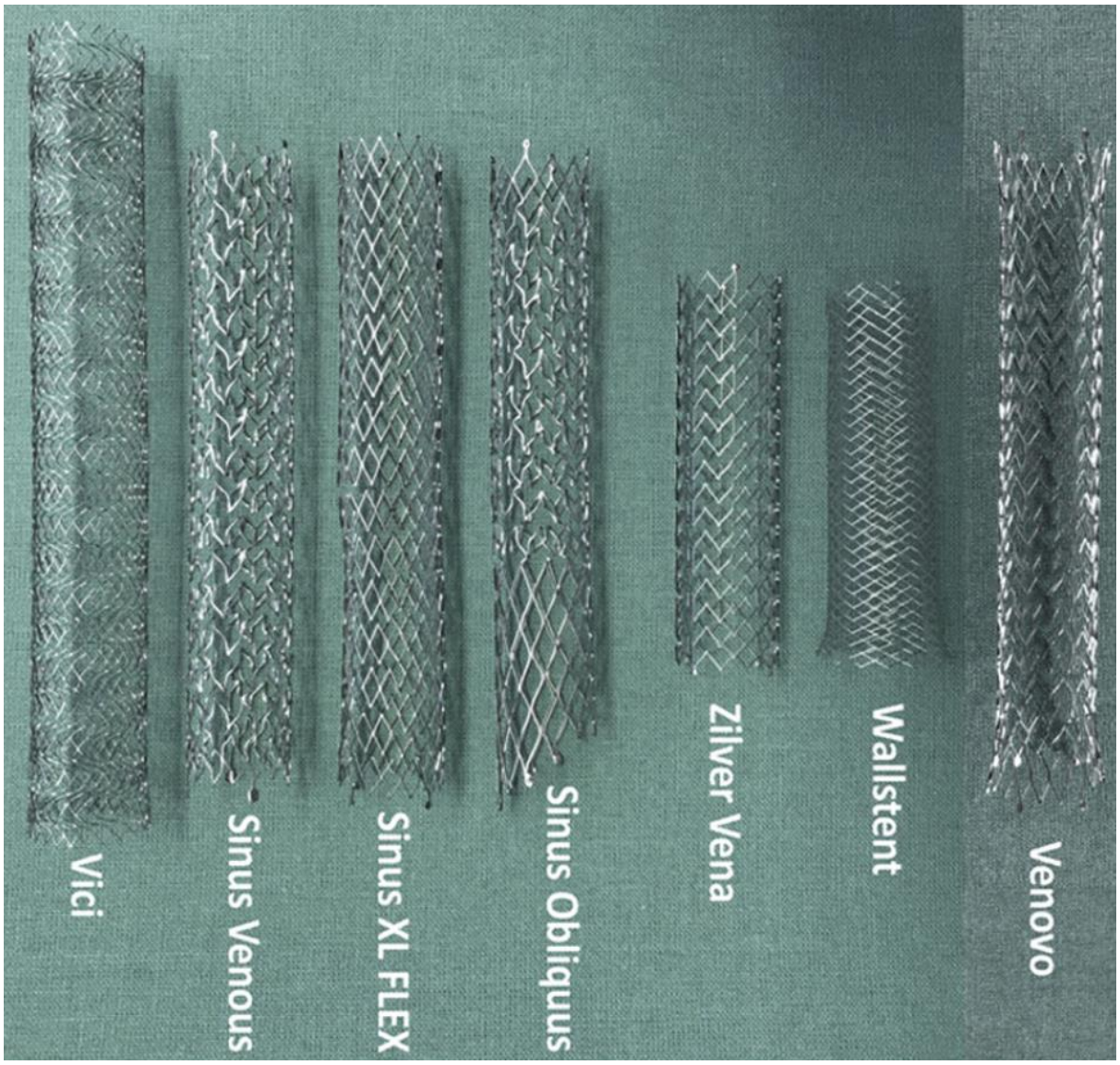
The Venovo stent was subject to a partial recall by BD© on the 14th of December 2020 due to reports of the proximal end of the stent not completely deploying and remaining attached to the stent delivery system(158). This was initially thought to just concern the 14mm diameter stent of all lengths, but on the 12th of May 2021 BD© expanded the scope of the recall to include all stent sizes after receiving further complaints. By May 2022, the Venovo stent had subsequently returned to the market and is currently available for use(160).

Table 4: Summary of dedicated venous stents

Stent	Manufacturer	CE/FDA approval†	Composition	Design	COF N/cm	CR N/cm
Wallstent	Boston Scientific	2015	Braided Elgiloy	Closed cell	0.45	1.30
Zilver Vena	Cook Medical	2010	Laser-cut nitinol	Open cell	2.02	0.54
Vici	Veniti (acquired by Boston Scientific)	2013	Laser-cut nitinol	Closed cell	1.39	0.89
Venovo	CR Bard, (acquired by BD)	2015	Laser-cut nitinol	Open cell	4.83	0.76
Sinus-Obliquus	Optimed	2015	Laser-cut nitinol	Hybrid	4.35	1.41
Sinus-Venous	Optimed	2015	Laser-cut nitinol	Open cell	4.26	0.95
Abre	Medtronic	2017	Laser-cut nitinol	Open cell	MD	MD
Blueflow	Plus Medica	2018	Braided nitinol	Closed cell	MD	MD
BeYond	Bentley	2020	Laser-cut nitinol	Open cell	MD	MD
Duo	Vesper Medical (Phillips)	2023	Laser-cut nitinol	Open cell	MD	MD

COF and CR values for a 14mm stent, COF values at 90% diameter, CR values at 50% diameter from a single independent study(149), industry reported values were not used.
N/cm: Newton centimetres
***†:** Year provided is for whichever of the two occurred first*
MD: missing data

Figure 20: Image illustrating some of the commonly used dedicated venous stents. Reproduced with permission.



Reproduced with permission from Dabir et al.(149), see copyright permissions.

1.4.3 Evidence to support venous stenting

There have been a number of systematic reviews assessing the use of venous stenting in CVOO(163-173), five of which pooled results in a meta-analysis(163, 167-169, 172). However, many of these reviews pre-date the key studies providing multicentre prospective data(168-170, 172). Furthermore, despite these reports being systematic, the studies identified, and restrictions imposed on them for analysis, varies substantially. An example of such is the two most contemporary reports(163, 167), both published in 2022. One of the articles reports available patency data from 11 studies (including both PTS and NIVL pathologies), and the second reports patency data from 28 studies in PTS alone. Because of this, it is challenging to evaluate the true effect of iliac vein stenting. There is general consensus that early technical success is high, and tends towards 100%, and that the intervention is safe with overall procedure-related mortality close to 0%. An important limitation to these meta-analyses is that the methodologies employed are insufficient to provide estimates of patency for timepoints that are not unified, hence they are all limited to 12 months. The pooled patency rate at 12 months were generally promising for NIVL, with more variation for PTS.

When reviewing the evidence on an individual study level, alongside the many single centre retrospective and prospective cohort studies reported in the literature, there are a number of key prospective cohort trials. There have been five completed Investigational Device Exemption (IDE) trials hosted in the US(174-178), alongside several prospective cohort trials undertaken across Europe(179-182) and China(183, 184). These prospective cohort trials demonstrated acceptable patency and safety results across a range of dedicated venous stent platforms. The IDE trials are often referred to as authoritative reports within the deep venous sphere as they are designed and undertaken as single-armed ‘trials’ akin to an RCT without a comparator group with a high degree of monitoring and relatively expansive outcome assessment.

There is just one (completed) RCT assessing the use of venous stents in chronic venous pathologies (encompassing both PTS and NIVL) reported in the literature(185). It reported symptomatic and quality of life improvement when comparing iliac venous stenting with non-interventional management. This single centre study had as few as 51 participants across both arms, with only six having PTS, severely limiting its validity. The evidence from this RCT cannot be used to inform clinical guidelines on the use of iliac vein stenting in PTS or NIVL.

The STEVECO trial was an industry-funded Europe-based RCT which aimed to produce randomised comparative evidence for the use of iliac vein stenting in both PTS and NIVL groups but unfortunately closed early due to incomplete recruitment(185). The C-TRACT trial is a publicly-funded ongoing US-based RCT assessing the use of iliac vein stenting in PTS(186), it too has faced difficulties with recruitment with its timeline being significantly extended.

The ESVS 2022 CVD clinical practice guideline now provides a level IIa, grade B, recommendation for consideration of venous stenting in the management of CVOO based on the multiple prospective cohort trials undertaken.

The total venous stent market is currently valued at $1.1 billion, and is forecasted to grow to $2.4 billion by 2030(187). Yet, there is no high-quality comparative evidence to support the use of iliac vein stenting in CVOO.

1.5 Thesis aims

Despite the innovations in the treatment of CVOO, there is currently a lack of granular research assessing factors associated with long-term technical success of iliac vein stenting, resource use, and cost-effectiveness alongside a paucity of high-quality randomised evidence supporting its clinical efficacy. This thesis aims to address these shortfalls in the evidence base. The aims of this thesis are as follows:-

1. Summarise the existing evidence supporting the use of iliac vein stenting in the management of CVOO;
2. Understand the current landscape of iliac vein stenting in the treatment of CVOO across England;
3. Evaluate the technical-, disease-, and patient-related variables associated with the long-term treatment success of iliac vein stenting;
4. Evaluate the cost-effectiveness of iliac vein stenting in comparison to current medical therapy in the treatment of CVOO; and
5. Through collaboration with key stakeholders and patient public involvement, design and deliver a RCT to assess the use of iliac vein stenting in comparison to current medical therapy for CVOO.

To fulfil these aims, the following five work packages (WP), A – E, will be undertaken:-

- WP A: Meta-analysis of iliac vein stenting in the management of CVOO utilising reconstructed individual-patient data with an accompanying meta-regression of covariates;
- WP B: Trend analysis of deep venous procedures performed across England from 1998 – 2024 utilising the Hospital Episode Statistics database;
- WP C: Single-centre retrospective cohort study investigating factors associated with successful iliac vein stenting in the management of CVOO;
- WP D: Development of a multi-level Markov-state transition model to evaluate the cost-effectiveness of iliac vein stenting in the treatment of CVOO; and
- WP E: An international assessor-blinded multicentre randomised controlled trial (RCT) investigating the use of iliac vein stenting in comparison to best medical therapy for the treatment of CVOO.

2 – WORK PACKAGE A:

Meta-analysis of iliac vein stenting in the management of CVOO utilising reconstructed individual-patient data with an accompanying meta-regression of covariates

CHAPTER 2: WORK PACKAGE A

Meta-analysis of iliac vein stenting in the management of CVOO utilising reconstructed individual-patient data with an accompanying meta-regression of covariates

2.1 Introduction

2.1.1 The continued need for a comprehensive review of the literature

The introductory chapter to this thesis has highlighted the complexity of iliac vein stenting as an intervention. The underlying pathologies comprising CVOO are appreciably different and likely confer different outcomes in respects to iliac vein stenting. There are also many patient- and procedural-related covariates that are likely to influence how successful iliac vein stenting is. Although there have been several reviews published in the literature, there is still a lack of clarity in respects to the long-term patency and treatment effects after iliac vein stenting. Therefore, there is a sustained need for careful interrogation of literature, considering the many influencing factors when reporting the effect of iliac vein stenting.

2.1.2 Shortfalls with current meta-analyses in the literature

Five reports were identified in the literature which performed pooled analyses of patency as their primary aim(163, 167-169, 172). A common, improper, method for combining patency data in the vascular literature is by manipulating survival probabilities into an event rate. This is achieved by multiplying the survival probability at a set timepoint (e.g. 12 months) by the total sample size, then finding the difference between the calculated value and the total sample size, generating a false event number. These false event rates are then pooled using a meta-analysis. This is statistically incorrect for several reasons. Firstly, the survival probability is a function over time dependent on a) the survival probability prior to that timepoint; b) the number of participants censored over that period; and c) the number of participants succumbing to the event. By multiplying the survival probability by the sample size, it ignores all of the censoring that has occurred and its associated uncertainty. Additionally, the meta-analysis calculates variance based on proportions assuming a

binomial distribution, applying this to survival probabilities underestimates uncertainty and incorrectly weights the studies.

A single meta-analysis employed digitisation of the survival curves and generation of reconstructed individual-patient data (IPD) from the included articles(163). However, the reconstructed IPD was then pooled into one indiscriminatory dataset prior to undertaking a single Kaplan-Meier survival analysis. This is incorrect as it assumes that all of the data originated from a single sample, not multiple studies, and therefore does not account for the variance introduced by each study – illustrated by the falsely narrow confidence intervals reported. The less misleading approach would be to pool the reconstructed IPD through meta-analysis of survival probabilities from each study incorporating the variance introduced by each sample. Furthermore, as illustrated earlier, there is a variation in the number of studies included in each meta-analysis even when considering the sub-grouping imposed on the article inclusion i.e., inclusion of dedicated venous stents only. When reviewing the literature, it becomes apparent that studies including relevant populations are missing. The more robust approach would be to include any study arm investigating venous stenting and ensure that the overall characteristics are accurately recorded, facilitating a powerful analysis and subsequent appropriate sub-group analysis and adjustment.

2.1.3 Utilising reconstructed individual-patient data

Reconstructed IPD describes the calculated individual data from aggregate data plots such as Kaplan Meier curves(188). This is possible as Kaplan Meier curves are pictorial representations of all the underlying data. The data that is used in plotting the survival probabilities can be reconstructed by working backwards. Guyot's algorithm was published in 2012 and describes the iterative numerical methods to solve the inverted Kaplan Meier equations, i.e., reconstructing through calculation of the original data that went into the construction the Kaplan Meier plot(188). A detailed outline of this process will be provided in the *Methods* section. This process has been peer-reviewed by world-leading statisticians(188) and externally validated in multiple studies, now being cited over 2000 times. In validation exercises comparing reconstructed calculated data to original datasets, the accuracy was deemed to be excellent(189). For example, in the validation of restricted mean survival times the

overall effect size from the reconstructed data was within 0.01 - 0.037 of the original. Inter-rater reliability for the reconstructed data in comparison to the original data had an interclass-correlation coefficient of 0.99 (CI: 0.99 – 1.0)(189).

Since 2014, Oncological studies have utilised Guyot's algorithm in reconstructing IPD for meta-analyses(190). This is now relatively commonplace in the oncological literature, however, remains underutilised in Vascular Surgery. Its application is well-suited to Vascular Surgery as the majority of outcomes, particularly patency rates, are based on survival analyses.

Furthermore, when constructing cost-effectiveness models, it is useful to be able to extrapolate from survival curves to an extended time horizon. This would not be possible from the data printed in a manuscript, the reconstructed IPD is needed to create a function over time for a given outcome in order to be able to model this.

As outlined above, a single study utilising Guyot's algorithm in the venous field exists in the literature but with its use statistically erroneous(163). This same error was repeated in a study investigating endovascular versus medical therapy for type B aortic dissection published recently(191). It is important that the reconstructed IPD is not simply pooled together to form one big dataset, they must remain individual studies. Other studies in Vascular Surgery have utilised coordinate mapping software such as PlotDigitizer™ in defining a result at a given time from a figure but did not undertake Guyot's algorithm to reconstruct IPD(163, 192).

2.1.4 Aims

The aims of WP A are as follows:-

1) To provide a narrative summary of the evidence base;

2) To generate reconstructed IPD for all study arms and provide survival probabilities over time for primary patency (PP) and primary-assisted patency (PAP) of iliac vein stents;

3) Identify significant covariates for patency by undertaking meta-regression of aggregate covariates against the reconstructed-IPD survival probabilities; and

4) To provide summary estimates of effect size through meta-analysis for the change in disease severity and venous ulceration which will serve as inputs in a cost-effectiveness analysis (WP D).

2.2 Methods

This systematic review and meta-analysis was undertaken following a publicly-available protocol (PROSPERO CRD42023447194) in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines(193).

2.2.1 Search strategy

Searches of online databases MEDLINE and EMBASE, alongside searches of clinical trial registries including ClinicalTrials.gov, were undertaken on the 20th of July 2022 and subsequently updated on the 14th of February 2025.

Searches of MEDLINE and EMBASE (1946–2025) were performed from inception using the online platform Ovid® based on 'Title' and 'Abstract'. The search strategy comprised of 28 search terms using keyword and adjacency search functions combined with Boolean operators, see Table 5. Adjacency searches were utilised in place of 'exploded' search terms to increase specificity. Search piloting and refinement was performed against a set-list of target articles to ensure the search was performing adequately. The search was amended and widened where necessary. No limits in respect to date or language were imposed on the search.

Table 5: Search strategy undertaken for the systematic review

Search #	Search Terms
1	(venous adj5 stent*) or (vein adj5 stent*) or (venous adj5 recanalization) or (vein adj5 recanalization) or (venous adj5 recanalisation) or (vein adj5 recanalisation) or Zilver vena or Sinus venous or Sinus obliquus or Vici venous or Venovo venous or Abre venous or Bentley beyond)
	AND
2	(post thrombotic syndrome or PTS post thrombotic or post-thrombotic or post thrombotic or outflow obstruction or COO or May-Thurner* or May Thurner* or Cockett* or Non-thrombotic iliac vein or Non thrombotic iliac vein or NIVL)
	AND
3	(iliac* or iliofemoral))

2.2.2 Eligibility criteria

The participants of the included study arms had the following properties:

- Adult participants with CVOO caused by either PTS secondary to previous DVT of the iliofemoral segment or NIVL;
- Confirmed using imaging such as intravascular venography or IVUS; and
- Treated with iliac vein stenting.

Pre-clinical studies or studies reporting animal data were not included. All study arms were included, meaning that the target population could form a constituent part of a wider clinical study.

The exclusion criteria were as follows:-

- Articles failing to report any outcome data after intervention;
- Articles reporting on iliac vein stenting for malignant compression;
- Articles reporting on a niche subset of participants where the results are not generalisable, for example iliac vein stenting in octogenarians;
- Articles reporting open revascularisation procedures only;
- Article reporting on secondary research only i.e., systematic review or meta-analysis;
- Articles reporting data on less than 30 participants; or
- Data published as conference abstract alone that has not undergone peer-review publication.

2.2.3 Study screening & article selection

Retrieved articles were uploaded onto the online platform Covidence©. Two reviewers (M Machin & M Salih) independently screened all of the abstracts on the platform in a blinded fashion against the eligibility criteria. Any vote of inclusion at the abstract stage resulted in a given abstract progressing to full-text review. References of full-text articles were imported into EndNote X9® and reviewed.

2.2.4 Data extraction & quality assessment

A single reviewer extracted data from all included articles (M Machin) with duplicate extraction undertaken by a second reviewer (M Salih) in 20% of articles for quality control purposes. The data extracted in duplicate was cross-referenced, with any significant discrepancy prompting complete duplicate extraction. Data extraction was undertaken using Microsoft Excel©. Studies were sorted into unique and replicated datasets, with the most comprehensive version of the dataset included. Replicated datasets were identified by tracking the recruitment centre and recruitment dates across manuscripts. Prospective cohort trials were defined as prospective studies that publicly register a trial protocol and collect data beyond which would normally be collected in clinical practice.

The ROBINS-I tool for assessing risk of bias in non-randomised studies of interventions was used to grade the risk of bias in each study providing quantitative results in the meta-analysis(194). The Cochrane guidance in determining the risk of bias in uncontrolled 'before-and-after' studies was used when completing the ROBINS-I assessment(195).

2.2.5 Generation of reconstructed individual-patient data from survival probabilities

The process in which reconstructed IPD is generated has several steps, these can be summarised as follows:-

1. Digitisation of Kaplan Meier curve and generating x-y coordinates for all Kaplan Meier curve attributes;
2. Formulate a 'number-at-risk table' for each timepoint describing the number at-risk corresponding to a set of relevant coordinates from the Kaplan Meier curve;
3. Import this data into an analytical environment constructed in R and deploy Guyot's algorithm to reconstruct events at each time point for each simulated participant; and
4. Formulate dataset including IPD segregated by study origin.

The underlying principle for reconstructing IPD is that it is possible to calculate numerical solutions to the inverted Kaplan Meier equations(188). The equation for calculating survival probability for a given timepoint in a study is illustrated in Figure 21.

Figure 21: Equation for calculating survival probability at a given time (t)

$$S(t) = S(t_{i-1}) \times \left(1 - \frac{d_i}{n_i}\right)$$

$S(t) =$ *survival past time* (t)
$t(i) =$ *time in question*
$di =$ *events*
$ni =$ *number at risk*

Guyot et al. describes the algorithm for reconstructing IPD in full in their original publication(188). However, I will outline some of the key steps for illustrative purposes. When digitising the Kaplan Meier curve, coordinates are accurately assigned to each point on the survival curve. The x-axis coordinates equal the time (T) at each point on the curve (T_k) and the y-axis coordinates equal the survival probability (S) at each point on the curve (S_k), where k equal 1, 2, 3, 4, 5… as the coordinates progress. The first coordinates are (0,1) where T_1equals 0 and S_1 equals 1 - equivalent to 100% survival at baseline.

This data is extracted using a platform such as PlotDigitzer© and arranged in a descending list. Quality control checks are undertaken at this point, ensuring that the survival probabilities extracted match the limited reported survival probabilities at set timepoints in the manuscript (e.g. survival at 1 year). Appendix 3 shows the digitisation of plots and how the coordinates are mapped to a high degree of accuracy with numerical data to five decimal places.

The second input in the algorithm pertains to the number at risk at each time interval presented in the Kaplan Meier curve. The curve is split into time intervals (i) (e.g. 6 months, 12 months, 18 months).

For each time interval there is a number at risk at the start of the interval ($nrisk_i$) and the timepoint at which that number at risk is reported ($trisk_i$). This numerical data is extracted from the original publication and entered into a table, the 'at risk table'.

The list of coordinates is then reviewed in light of this 'at risk table'. The coordinates are arranged by time, the first row of the coordinates for that given time interval is assigned $lower_i$ and the last row of coordinates relevant to that time interval is assigned $upper_i$. This numerical data comes from the digitised coordinates, not from the manuscript. Therefore, $lower_i$ is the first coordinate within an interval and $upper_i$ is the last coordinate within an interval. The 'at risk table' has now been effectively mapped to the coordinates for each interval. The total number of events is then gathered from the manuscript and defined ($totevents$).

The number of censored individuals is largely unreported in the literature, so this must be calculated. The number at risk ($nrisk_i$) is used to approximate the number censored for each time interval i. It is assumed that censoring occurs at a uniform rate within an interval which would occur if the censoring is non-informative (i.e., that censoring is unrelated to treatment failure).

The algorithm iteratively works through the coordinates and number at risk data, a full overview can be seen in Figure 23, however, the key steps will be outlined here. The code used to execute the algorithm can be reviewed in Appendix 2.

We need to first provide an initial estimate of the number censored that can then be iterated. If we use an assumption that there was no censoring during an interval i, then the number at risk ($nrisk_i$) at the start of the next time interval ($nrisk_{i+1}$) would be equal to the number at risk at the start of the current interval i ($nrisk_i$) multiplied by the probability of experiencing the event. The probability of experiencing the event, when assuming no censoring, can be calculated by dividing the survival probability at the start of the next interval ($S_{lower\ i+1}$) by the survival probability at the start of the current interval ($S_{lower\ i}$). The initial estimate for the number of censored participants across an interval i is sourced by finding the difference between the calculated number at risk at the start of the next interval under the assumption of no censoring ($no\ censoring\ nrisk_{i+1}$) and the number at risk at the next interval actually observed ($nrisk_{i+1}$). This is outlined in Figure 22.

Figure 22: Estimating the number of censored participants across an interval i

$$(no\ censoring)nrisk_{i+1} = nrisk_i \times \frac{S_{lower\ i+1}}{S_{lower\ i}}$$

$$n\ censored_i = (no\ censoring)nrisk_{i+1} - nrisk_{i+1}$$

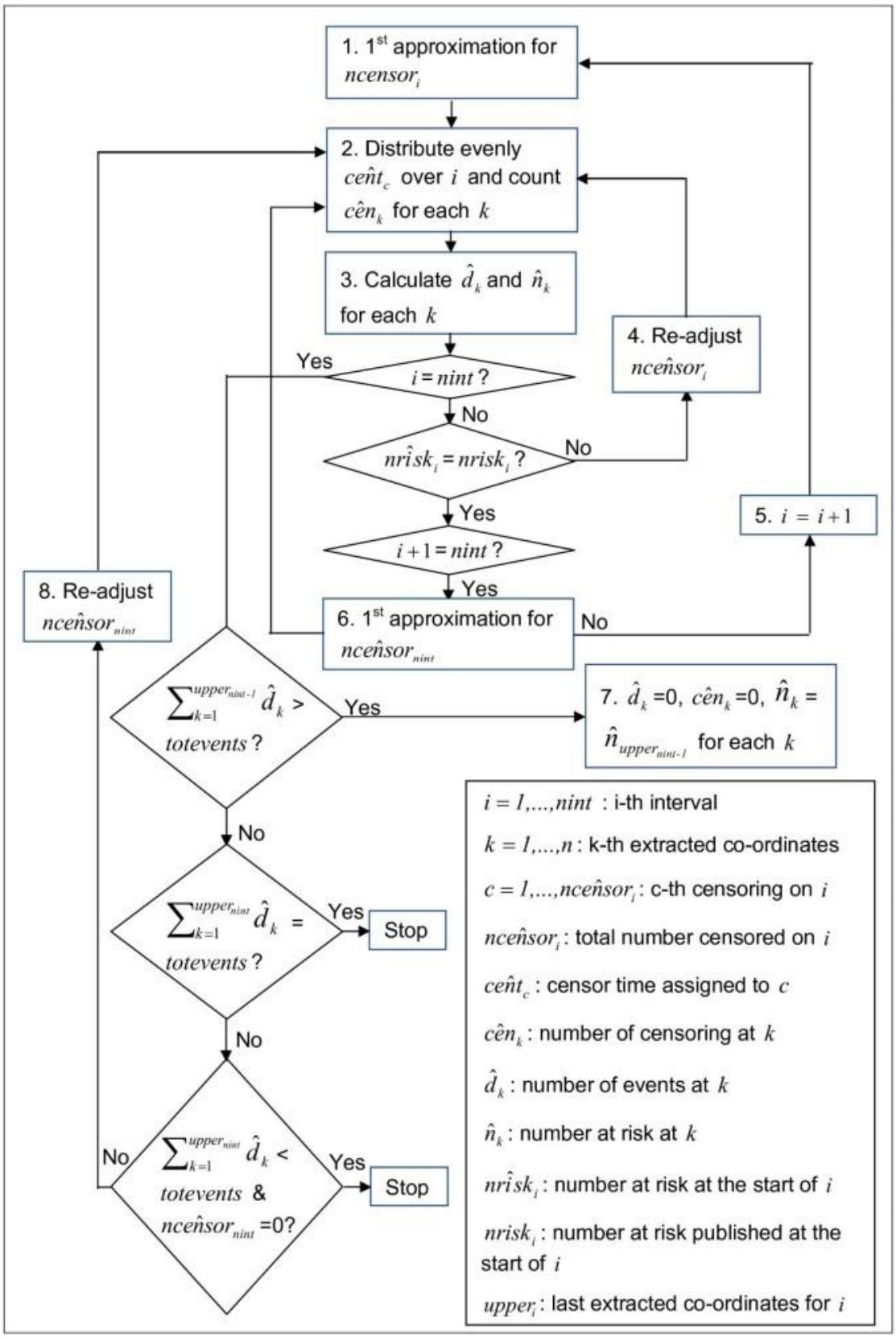
This estimated number of censored participants is then evenly distributed across the interval i.

The number of censored participants between extracted coordinates is calculated by counting the number of estimated censored times occurring between the two coordinates. The events between each coordinate are then calculated using the assumed censoring number just inputted, and the known extracted survival probability.

The number at risk for each coordinate is then recalculated based on the inputted censoring rate and calculated event rate. If the calculated number at risk at the start of the next interval is not equal to the observed number at risk at the start of the next interval ($nrisk_{i+1}$), then the distribution and number of censored data inputted across i is adjusted.

The cycle then repeats itself indefinitely until the calculated number at risk between coordinates across an interval is equal to the observed number at risk at the start of the next interval.

Figure 23: Algorithm used in reconstructing individual-patient data



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2.2.6 Meta-analysis of survival probabilities

For two-armed studies, pooling of survival data can be achieved by meta-analysis of hazard ratios. However, given the single-armed nature of the studies included, this is not possible. Pooling of survival data in single-armed studies is commonly achieved by treating them as standalone probabilities at a given unified timepoint and performing a meta-analysis of probabilities. The problem with this approach is that it excludes any study not reporting the survival probability at that given unified time, excluding relevant data from the analysis and decreasing the certainty in the estimate.

Meta-analysis utilising multivariate extension of DerSimonian and Laird methodology(196) described by Combescure et al. will be performed to pool reconstructed IPD across multiple studies to produce a summary survival curve for PP and PAP(196). This will permit the pooling of all survival data at any timepoint, which has yet to be undertaken in the vascular field. This method permits production of a distribution-free summary survival curve that accounts for between-study variance and is not restricted to a given timepoint. Other multivariate approaches require assumption of normality(196), which is unlikely given the stepwise nature of survival data. This approach makes no assumption about the underlying distribution of the data. Meta-analysis was performed using the ‘metaSurv’ package, which incorporates the multivariate methodology described above, in R(197). The code used to execute this can be found in Appendix 4.

2.2.7 Calculation of restricted mean survival time

The restricted mean survival time (RMST) is the area under the survival curve, it represents an average time for the event occurring over a defined time horizon(198). This is calculated by integrating the survival function. Unlike proportional hazards, it does not assume that the rate of the hazard is constant. The hazard can be variable which is accounted for by the total area under the curve. The RMST was calculated for each survival curve utilising the ‘survRM2’ package in R, the code used to execute this can be found in Appendix 5. The RMST was used as an individual study measure in regression analyses and also combined through meta-analysis to validate the meta-analysis of survival probabilities.

2.2.8 Meta-analysis of continuous outcomes

Meta-analysis of continuous outcomes summarised as means and standard deviations (SD), such as baseline VCSS, were performed as single means by using inverse variance weighting i.e., each variable is weighted inversely to its variance. Arcsine transformation was undertaken when the proportions were close to 0. Random and fixed effects models were performed. The analysis was undertaken utilising the 'meta' package in R using the function 'metamean', the code used to execute this can be found in Appendix 6.

2.2.9 Meta-analysis of dichotomous outcomes

Overall proportions were calculated through meta-analysis from pooling individual proportions using the inverse variance method. The analysis was undertaken utilising the 'meta' package in R using the function 'metaprop', the code used to execute this can also be found in Appendix 6.

2.2.10 Meta-analysis of continuous outcomes before and after an intervention

Meta-analysis of continuous outcomes before and after an intervention from single-armed studies, such as change in VCSS after stenting, were performed by pooling the calculated treatment effect (TE) and standard error (SE) of the TE using inverse variance weighting. The analysis was undertaken utilising the 'meta' package in R using the function 'metagen'. The code used to calculate the TE, calculate the SE of the TE, and to execute this function can be found in Appendix 7.

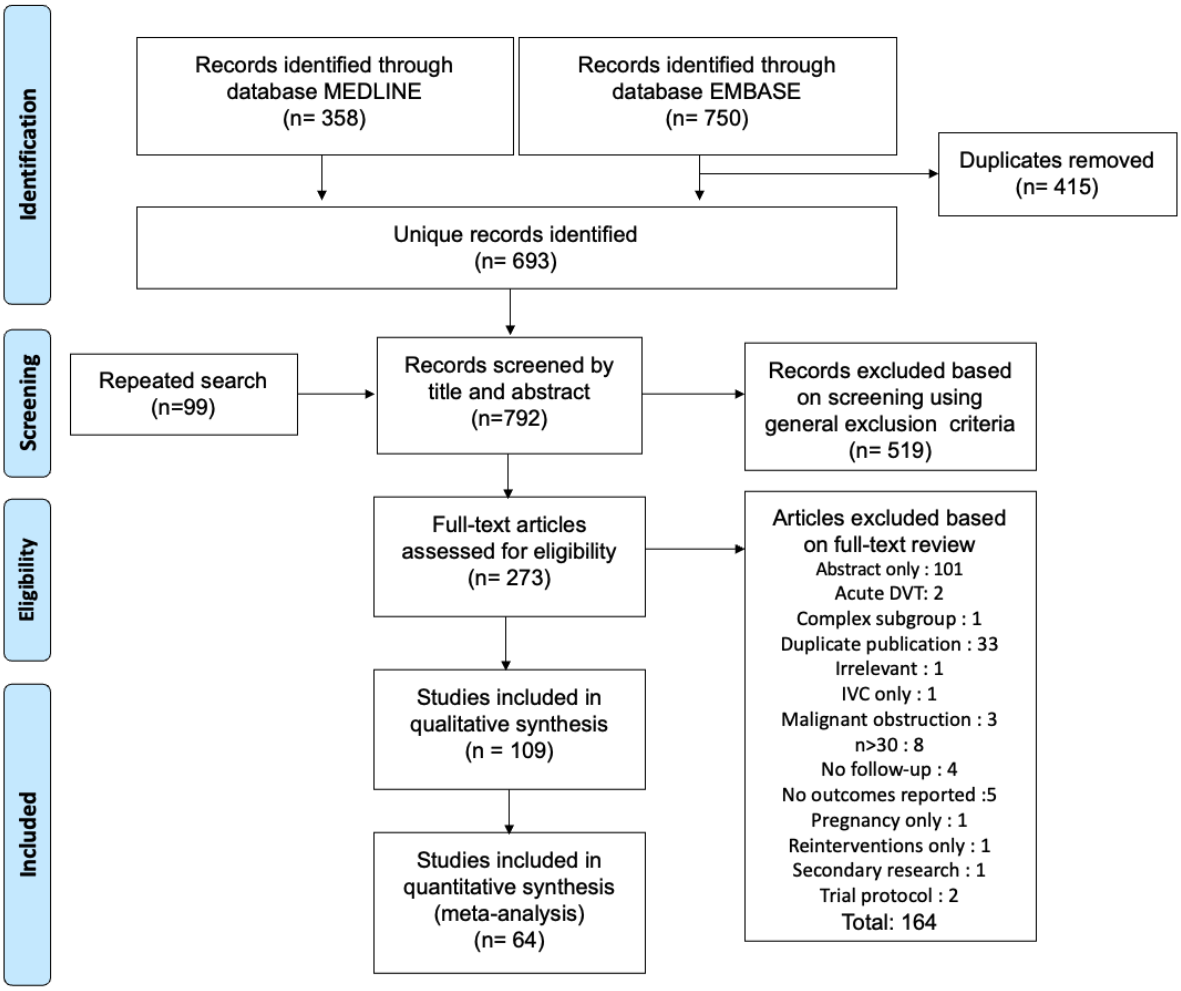
2.3 Results

2.3.1 Included articles

Searches of online databases retrieved 1,108 articles, 415 of which were duplicates. When including the updated search, a total of 790 unique articles were reviewed with subsequent inclusion of 108 articles meeting the inclusion criteria. The overall study selection process is illustrated in the PRISMA flowchart, see Figure 24.

The 109 articles reporting data on 27,579 participants were reviewed qualitatively(137, 177, 181, 184, 185, 199-301). From this, there were 64 articles, containing unique data on 12,224 participants, which were unreplicated and were subsequently included in the quantitative analysis(137, 177, 181, 184, 185, 200-203, 205, 206, 208, 209, 211, 212, 214-219, 221-226, 229-231, 238, 240, 242, 243, 246, 248-251, 254, 255, 259, 261-264, 275-278, 282-284, 286, 287, 292-294, 297-301).

Figure 24: PRISMA flowchart illustrating the study selection process



2.3.2 Study characteristics

An overview of the 109 included articles can be found in Table 6.

Included articles had the following study designs:

- retrospective cohort studies (n=48)(199-201, 203-205, 207, 209, 212, 213, 215, 218, 219, 221-225, 227, 231, 232, 236, 237, 239, 242, 244, 245, 247, 248, 250-252, 259, 262, 263, 276, 277, 279, 283, 288-293, 296-298, 300);
- prospective cohort studies (n=39)(137, 202, 206, 210, 217, 220, 226, 230, 233-235, 238, 241, 243, 249, 254-258, 260, 264-272, 278, 280-282, 284, 294, 295, 301, 302);
- prospective cohort trials (n=17)(177, 181, 184, 208, 211, 214, 216, 228, 240, 246, 253, 261, 273-275, 285, 299);
- case-control study (n=1)(287); and
- RCT (n=3)(185, 229, 286).

Two of the three RCTs randomised participants to either iliac vein stenting or medical therapy providing comparative evidence(185, 286), and the third randomised participants to one of two iliac vein stent devices(229). The majority were single centre studies (n=87), with 20 studies having more than one centre(181, 184, 208, 211, 214, 219, 228, 244, 246, 249, 253, 261, 273-275, 285, 286, 291, 292, 299). Studies were published from the year 2000 up to and including the year 2025.

Regarding study locations, studies were based in: Brazil (n=1)(185), China (n=10)(184, 229, 231, 246, 262, 297-301), France (n=5)(202, 219, 220, 223, 226), Germany (n=5)(240-243, 249), India (n=1)(224), Iran (n=1)(250), Ireland (n=1)(205), Italy (n=1)(203), Netherlands (n=9)(206, 215-217, 221, 260, 286, 294, 295), Norway (n=2)(225, 277), Russia (n=1)(263), Singapore (n=4)(230, 244, 291, 292), Spain (n=1)(209), Sweden (n=1)(238), Switzerland (n=3)(232, 284, 289), Turkey (n=2)(218, 282), UK (n=5)(207, 227, 251, 252, 279), US (n=46)(137, 199-201, 204, 210-213, 222, 228, 233-237, 239, 245, 247, 248, 254-259, 264-272, 276, 278, 280, 281, 283, 287, 288, 290, 293, 296, 302), Europe, multi-country (n=3) (181, 261, 285), and international, multi-continent (n=7)(177, 208, 214, 253, 273-275).

Both NIVL and PTS were investigated in 78 studies(137, 177, 184, 185, 199, 202, 204, 208, 210-214, 216, 219-224, 228, 230-232, 234-236, 238-246, 248, 250-258, 260, 261, 263-276, 278, 280, 281, 283, 284, 286-289, 291, 292, 294-296, 299, 302), NIVL alone in 10 studies(200, 201, 205, 229, 233, 237, 247, 259, 262, 293), and PTS alone in 21 studies(181, 203, 206, 207, 209, 215, 217, 218, 223, 225-227, 249, 277, 279, 282, 285, 297, 298, 300, 301).

Within the 64 articles reporting unique data, 36 studies reported disaggregated data for PTS(137, 181, 184, 203, 206, 208, 209, 211, 214-219, 222, 223, 225, 226, 240, 242, 243, 246, 249, 250, 255, 275, 277, 282, 284, 294, 295, 297-301) and 24 studies report disaggregated data for NIVL(184, 201, 208, 211, 214, 216, 219, 222, 229, 233, 235, 241-243, 246, 250, 255, 259, 262, 275, 285, 293, 294, 299). This disaggregated data was utilised to reconstruct IPD.

2.3.3 Aggregate baseline characteristics for the included articles

Summary statistics, in the form of unweighted means and medians, for the most commonly reported aggregated baseline characteristics are illustrated in Table 7. The baseline characteristics are organised by pathology, with the number of studies missing that variable included below the summary statistics.

Table 6: Overview of included articles

Study ID	Location	Start year	Design	n	CVOO Pathology
Aboubakr 2019(199)	US	2013	Retrospective cohort	490	NIVL & PTS
Ahmed 2016(200)	US	2007	Retrospective cohort	34	NIVL
Alerany 2014(209)	Spain	2009	Retrospective cohort	36	PTS
Alimi 2010(202)	France	1996	Prospective cohort	96	NIVL & PTS
Ardita 2024(203)	Italy	2018	Retrospective cohort	63	PTS
Bai 2023(204)	US	2011	Retrospective cohort	433	NIVL & PTS
Bajwa 2019(205)	Ireland	2007	Retrospective cohort	31	MTS
Barbati 2020(206)	Netherlands	2013	Prospective cohort	48	PTS
Black 2018(207)	UK	2014	Retrospective cohort	88	PTS
Black 2024(208)	International	2017	Prospective cohort trial	200	NIVL & PTS
Butts 2024(210)	US	2012	Prospective cohort	236	NIVL & PTS
Chait 2020(290)	US	2013	Retrospective cohort	682	NIVL & PTS
Comerota 2024(211)	US	2013	Prospective cohort trial	243	NIVL & PTS
Cooke 2022(212)	US	2011	Retrospective cohort	872	NIVL & PTS
Cooke 2022(213)	US	2011	Retrospective cohort	737	NIVL & PTS
Dake 2021(214)	International	2016	Prospective cohort trial	170	NIVL & PTS
de Graaf 2015(215)	Netherlands	2009	Retrospective cohort	40	PTS
de Wolf 2013(221)	Netherlands	2009	Retrospective cohort	63	NIVL & PTS
de Wolf 2015(216)	Netherlands	2012	Prospective cohort trial	75	NIVL & PTS
de Wolf 2017(217)	Netherlands	2010	Prospective cohort	70	PTS
Dumantepe 2020(218)	Turkey	2014	Retrospective cohort	157	PTS
Espitia 2023(219)	France	2014	Retrospective cohort	377	NIVL & PTS
Falcoz 2016(220)	France	2012	Prospective cohort	21	NIVL & PTS
Gagne 2019(222)	US	2007	Retrospective cohort	67	NIVL & PTS

Gautier 2022(223)	France	2014	Retrospective cohort	90	PTS
George 2014(224)	India	2011	Retrospective cohort	38	NIVL & PTS
Grøtta 2018(225)	Norway	2009	Retrospective cohort	39	PTS
Guillen 2020(226)	France	2012	Prospective cohort	42	PTS
Gwozdz 2020(227)	UK	2012	Retrospective cohort	136	PTS
Hofmann 2023(228)	US	2013	Prospective cohort trial	243	NIVL & PTS
Hong 2022(229)	China	2018	Randomised controlled trial	245	NIVL
Huang 2020(230)	Singapore	2016	Prospective cohort	71	NIVL & PTS
Huang 2024(231)	China	2022	Retrospective cohort	40	NIVL & PTS
Hügel 2019(232)	Switzerland	2008	Retrospective cohort	108	NIVL & PTS
Jayaraj 2019(233)	US	2005	Prospective cohort	202	MTS
Jayaraj 2021(235)	US	2014	Prospective cohort	480	NIVL & PTS
Jayaraj 2021(137)	US	2014	Prospective cohort	535	NIVL & PTS
Jayaraj 2022(234)	US	2014	Prospective cohort	578	NIVL & PTS
Kang 2024(236)	US	2011	Retrospective cohort	708	NIVL & PTS
Kibrik 2017(237)	US	2012	Retrospective cohort	192	NIVL
Kölbel 2009(238)	Sweden	1994	Prospective cohort	62	NIVL & PTS
Korff 2023(239)	US	2019	Retrospective cohort	22	NIVL & PTS
Lichtenberg 2018(241)	Germany	2014	Prospective cohort trial	75	NIVL & PTS
Lichtenberg 2019(240)	Germany	2016	Prospective cohort	79	NIVL & PTS
Lichtenberg 2020(241)	Germany	2016	Prospective cohort trial	80	NIVL & PTS
Lichtenberg 2022(242)	Germany	2018	Retrospective cohort	67	NIVL & PTS
Lim 2020(244)	Singapore	2014	Retrospective cohort	87	NIVL & PTS
Lurie 2020(245)	US	2013	Retrospective cohort	462	NIVL & PTS
Ma 2024(246)	China	2019	Prospective cohort trial	110	NIVL & PTS
Mandel 2018(247)	US	2012	Retrospective cohort	203	NIVL

Marston 2021(248)	US	2010	Retrospective cohort	106	NIVL & PTS
Moeri 2021(249)	Germany	2008	Prospective cohort	150	PTS
Moini 2020(250)	Iran	2015	Retrospective cohort	164	NIVL & PTS
Morris 2022(251)	UK	2015	Retrospective cohort	207	NIVL & PTS
Morris 2022(252)	UK	2014	Retrospective cohort	123	NIVL & PTS
Murphy 2022(253)	International	2017	Prospective cohort trial	200	NIVL & PTS
Murphy 2017(254)	US	2007	Prospective cohort	1737	NIVL & PTS
Neglen 2000(257)	US	1997	Prospective cohort	94	NIVL & PTS
Neglen 2003(258)	US	1996	Prospective cohort	429	NIVL & PTS
Neglen 2006(256)	US	1996	Prospective cohort	99	NIVL & PTS
Neglen 2007(255)	US	1997	Prospective cohort	870	NIVL & PTS
Neglen 2008(302)	US	1997	Prospective cohort	177	NIVL & PTS
Nguyen 2024(259)	US	2019	Retrospective cohort	409	NIVL
Notten 2020(260)	Netherlands	2012	Prospective cohort	79	NIVL & PTS
O'Sullivan 2021(261)	Europe	2012	Prospective cohort trial	35	NIVL & PTS
Peng 2023(262)	China	2016	Retrospective cohort	109	NIVL
Pokrovsky 2018(263)	Russia	2009	Retrospective cohort	71	NIVL & PTS
Powell 2023(264)	US	2019	Prospective cohort	167	NIVL & PTS
Raju 2009(265)	US	1997	Prospective cohort	101	NIVL & PTS
Raju 2010(266)	US	1997	Prospective cohort	1640	NIVL & PTS
Raju 2013(267)	US	2000	Prospective cohort	192	NIVL & PTS
Raju 2001(268)	US	1997	Prospective cohort	276	NIVL & PTS
Raju 2002(269)	US	1997	Prospective cohort	292	NIVL & PTS
Raju 2008(270)	US	1996	Prospective cohort	1009	NIVL & PTS
Raju 2009(271)	US	1997	Prospective cohort	1085	NIVL & PTS
Raju 2015(272)	US	1997	Prospective cohort	95	NIVL & PTS

Razavi 2018(273)	International	2014	Prospective cohort trial	30	NIVL & PTS
Razavi 2019(274)	International	2015	Prospective cohort trial	170	NIVL & PTS
Razavi 2022(275)	International	2014	Prospective cohort trial	200	NIVL & PTS
Razavi 2025(177)	International	2021	Prospective cohort trial	162	NIVL & PTS
Rizvi 2018(201)	US	2013	Retrospective cohort	210	NIVL
Robertson 2023(276)	US	2016	Retrospective cohort	161	NIVL & PTS
Rosales 2010(277)	Norway	2000	Retrospective cohort	34	PTS
Rossi 2018(185)	Brazil	2013	Randomised controlled trial	50	NIVL & PTS
Ruiz 2022(278)	US	2009	Prospective cohort	82	NIVL & PTS
Saha 2015(279)	UK	2012	Retrospective cohort	140	PTS
Saleem 2023(280)	US	1997	Prospective cohort	1379	NIVL & PTS
Saleem 2022(281)	US	2010	Prospective cohort	42	NIVL & PTS
Sarici 2013(282)	Turkey	2011	Prospective cohort	52	PTS
Satwah 2022(283)	US	2015	Retrospective cohort	1104	NIVL & PTS
Sebastian 2020(285)	Germany, Austria, Switzerland	2016	Prospective cohort trial	60	PTS
Sebastian 2020(284)	Switzerland	2015	Prospective cohort	219	NIVL & PTS
Sebastian 2024(181)	Germany, Austria, Switzerland	2016	Prospective cohort trial	60	PTS
Shekarchian 2023(286)	Netherlands	2017	Randomised controlled trial	63	NIVL & PTS
Sheng 2024(184)	China	2020	Prospective cohort trial	171	NIVL & PTS
Shiferson 2019(287)	US	2006	Case-control	109	NIVL & PTS
Sogomonian 2021(288)	US	2017	Retrospective cohort	180	NIVL & PTS
Stuck 2018(289)	Switzerland	2008	Retrospective cohort	93	NIVL & PTS
Tang 2021(291)	Singapore	2018	Retrospective cohort	60	NIVL & PTS
Tang 2022(292)	Singapore	2018	Retrospective cohort	60	NIVL & PTS
Tran 2020(293)	US	2015	Retrospective cohort	389	NIVL

van Vuuren 2017(294)	Netherlands	2009	Prospective cohort	369	NIVL & PTS
van Vuuren 2018(295)	Netherlands	2012	Prospective cohort	200	NIVL & PTS
Vasan 2022(296)	US	2011	Retrospective cohort	553	NIVL & PTS
Ye 2018(297)	China	2012	Retrospective cohort	45	PTS
Yin 2015(298)	China	2007	Retrospective cohort	122	PTS
Yu 2024(299)	China	2019	Prospective cohort trial	193	NIVL & PTS
Zhang 2021(300)	China	2016	Retrospective cohort	154	PTS
Zhou 2021(301)	China	2012	Prospective cohort	127	PTS

CVOO: Chronic venous outflow obstruction
UK: United Kingdom
US: United States

Table 7: Summary statistics for baseline characteristics of the included study arms

Baseline characteristic (pooled)	PTS study arms	NIVL study arms
n study arms	36	25
Age		
Mean:	47.7	52.3
Median:	46.0	53.3
n missing data:	7	7
Female sex (%)		
Mean:	58.3	63.9
Median:	60.0	67.6
n missing data:	7	7
Body mass index		
Mean:	26.4	26.9
Median:	26.3	25.4
n missing data:	23	18
C0 – C2 (%)		
Mean:	11.5	9.90
Median:	3.27	2.87
n missing data:	19	15
C3 (%)		
Mean:	39.9	37.8
Median:	36.5	37.0
n missing data:	19	16
C4 (%)		
Mean:	23.9	34.6
Median:	22.1	30.0
n missing data:	18	16
C5 (%)		
Mean:	10.6	6.87
Median:	5.55	6.94
n missing data:	18	16
C6 (%)		
Mean:	17.1	11.4
Median:	12.0	8.95
n missing data:	13	13

Table 7: continued…

Baseline characteristic (pooled)	PTS study arms	NIVL study arms
Venous claudication (%)		
Mean:	71.0	55.4
Median:	79.4	42.0
n missing data:	23	21
Previous DVT (%)		
Mean:	92.0	11.7
Median:	100.0	6.60
n missing data:	15	13
Previous PE (%)		
Mean:	15.0	3.02
Median:	13.0	3.45
n missing data:	22	18
Thrombophilia (%)		
Mean:	29.8	4.83
Median:	24.2	4.20
n missing data:	18	16
Hypertension (%)		
Mean:	25.4	34.9
Median:	24.4	44.8
n missing data:	26	16
Diabetes (%)		
Mean:	8.05	11.6
Median:	7.30	11.7
n missing data:	26	17
Total occlusion (%)		
Mean:	63.7	13.4
Median:	61.3	4.10
n missing data:	24	18
Below inguinal ligament (%)		
Mean:	62.5	13.2
Median:	65.3	6.97
n missing data:	11	12

C: C classification, Clinical-Eitology-Anatomical-Pathophysiology classification system
DVT: Deep vein thrombosis
Mean: mean of aggregate summary (unweighted)
NIVL: Non-thrombotic iliac vein lesion
PTS: Post thrombotic syndrome
PE: Pulmonary embolism

2.3.4 Industry-funded prospective cohort trials

Six IDE trials investigating dedicated venous stents, with study sponsors based in the US, exist in the literature. The five completed prospective IDE trials reported data on a total of 945 participants, see Table 8. The VIAFORT study of the GORE VIAFORT© stent is still ongoing, which commenced recruitment in 2023.

Table 8: Investigational device exemption trials with US-based sponsors

IDE study name	Year published	Stent	Manufacturer	Study sites	Sample size	Location
VIRTUS(178)	2019	Vici	Veniti®	23	170	US, France, Germany, Ireland, Netherlands, Spain, UK
VERNACULAR† (174)	2021	Venovo	Bard®	22	170	US, Australia, Germany, Ireland, Netherlands, Spain, UK
Abre(176)	2022	Abre	Medtronic©	24	200	US, France, Germany, Ireland, Italy, UK
VIVO†† (175)	2022	Zilver Vena	Cook© Medical	30	243	US, Taiwan
VIVID(177)	2025	Duo	Phillips©	30	162	US, Poland
VIAFORT	Ongoing	VIAFORT	GORE®	20	165	US

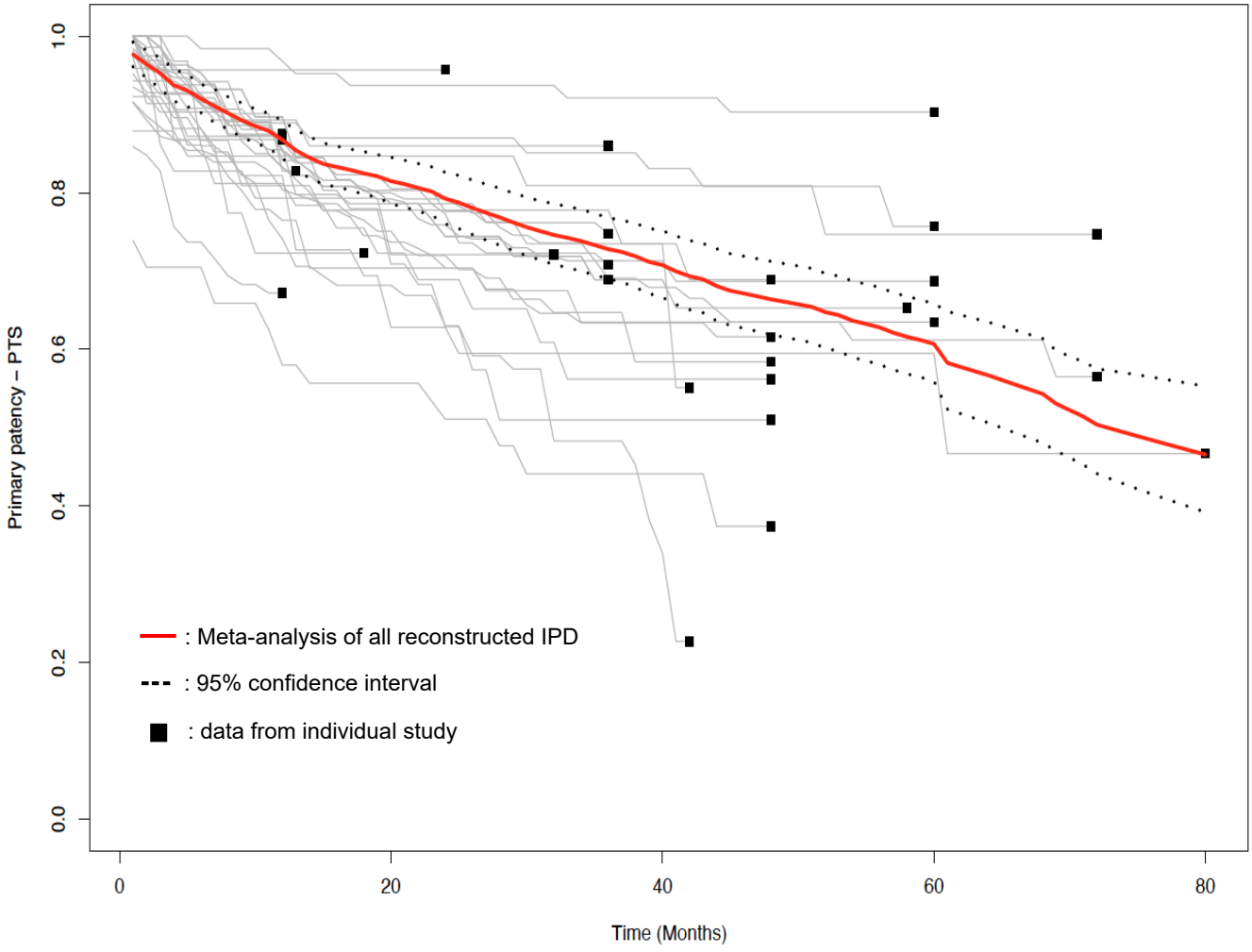
†VERNACULAR trial initial 12-month results only reported as an abstract, later reported as a full-text with three-year follow-up(303)
††VIVO trial finished recruitment in 2016
IDE: Investigational Device Exemption
UK: United Kingdom
US: United States

2.3.5 Primary patency – post thrombotic syndrome

PP for PTS (n=3,628) at 12 months, 36 months, and 60 months was 86.9% (95% CI: 83.7 – 89.0), 73.1% (95% CI: 68.13 – 76.30) and 61.6% (95% CI: 55.3 – 64.8) respectively (I^2 =51.98%).

Figure *25* illustrates the overall PP for iliac vein stents placed for PTS, the data was pooled from all studies reporting disaggregated data for PTS. This demonstrates a consistent reduction in PP over time. The median survival time for PP was 74.3 months. Table 9 shows the pooled PP for PTS over time at 6-monthly intervals (n=3,628; I^2=51.98%).

Figure 25: Pooled survival curve for primary patency of iliac vein stents placed for post thrombotic syndrome, utilising reconstructed individual-patient data



IPD: Individual-patient data
PTS: Post thrombotic syndrome

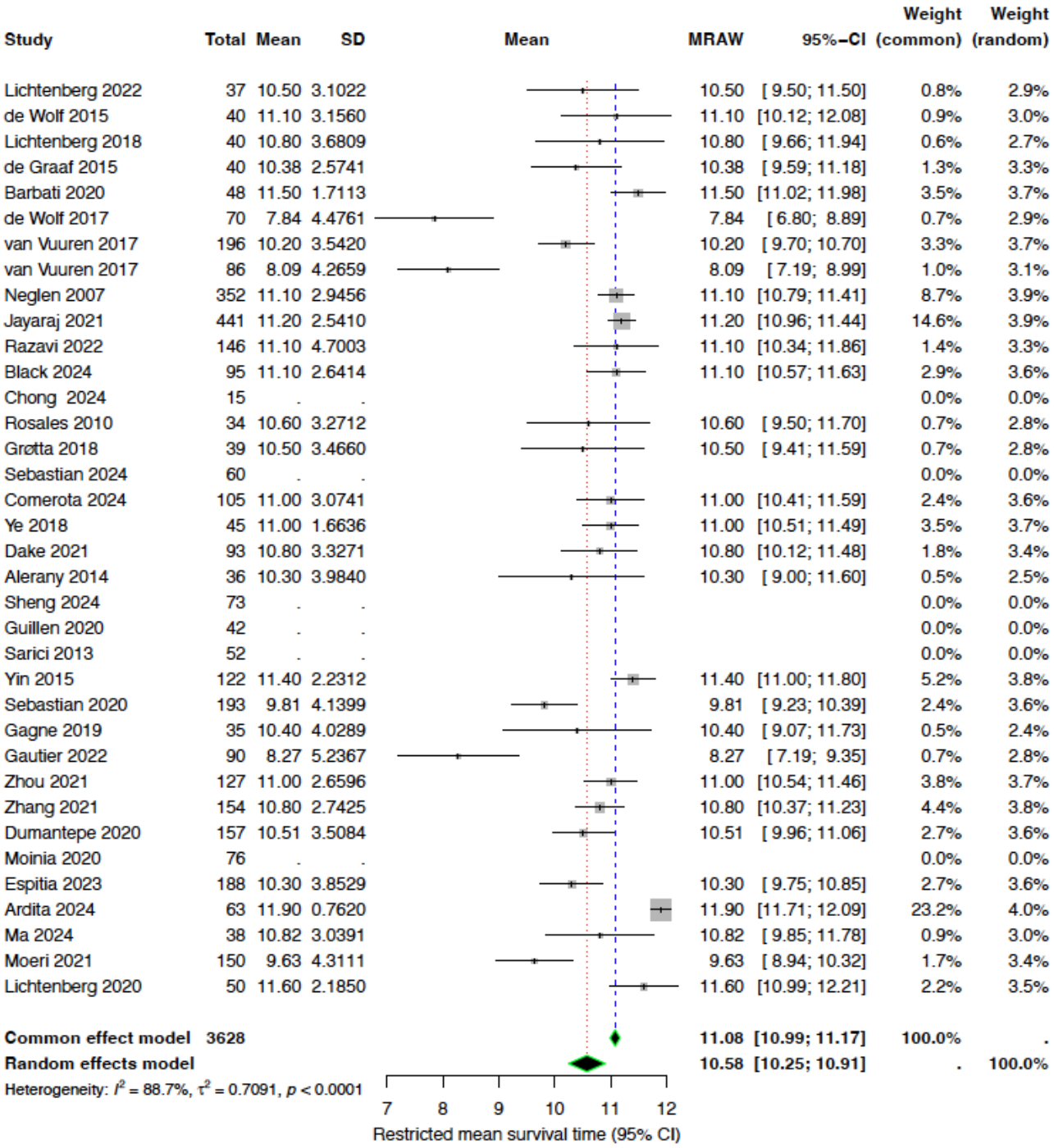
Table 9: Pooled estimate of primary patency, and associated 95% confidence interval, of iliac vein stents placed for post thrombotic syndrome, utilising reconstructed individual-patient data

Month	Pooled estimate PP (%)	Lower bound 95% CI (%)	Upper bound 95% CI (%)
12	86.90	83.74	89.02
18	82.57	78.97	84.92
24	79.36	75.16	82.13
30	75.78	71.00	78.97
36	73.09	68.13	76.30
42	70.41	65.29	73.64
48	67.37	61.71	70.87
54	64.62	58.60	68.10
60	61.62	55.31	64.82

CI: Confidence interval
PP: Primary patency

Restricted mean survival time, defined earlier as RMST, for PTS at 12 months and 36 months was 10.58 (95% CI: 10.25 – 10.91, I^2=88.7%) and 28.61 (95% CI: 27.30 – 29.91, I^2=84.3%) respectively. See Figure 26 for the forest plot for RMST at 12 months for PTS. Appendix 8 illustrates the forest plot for RMST at 36 months. The funnel plot of standard error against the RMST was symmetrical and demonstrated no signs of publication bias, see Appendix 9.

Figure 26: Forest plot for the restricted mean survival time, primary patency, of iliac vein stents placed for post thrombotic syndrome, utilising reconstructed individual-patient data, at 12 months



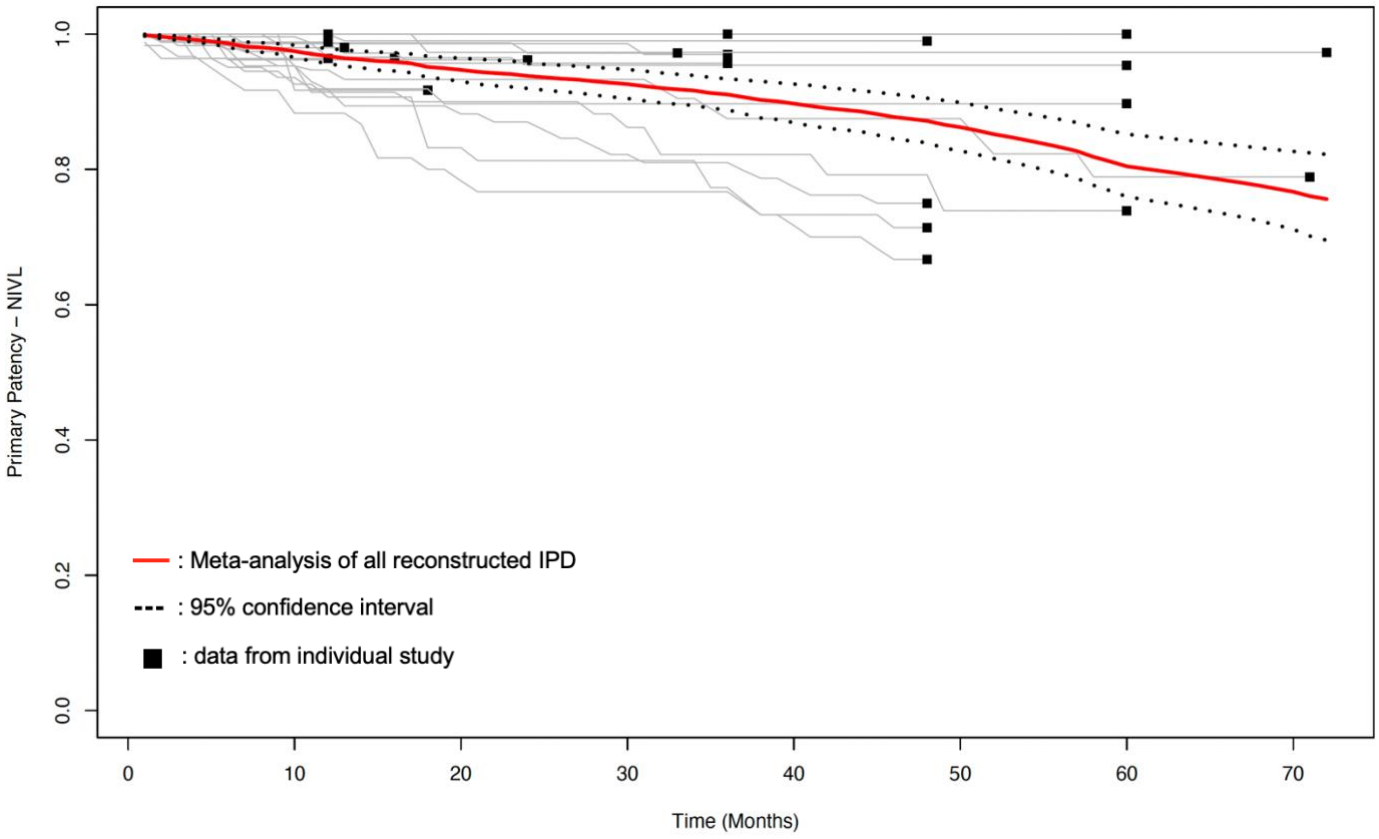
CI: Confidence interval
MRAW: Summary measure of untransformed means
SD: Standard deviation
Total: represents number of participants within each study

2.3.6 Primary patency – non-thrombotic iliac vein lesion

PP for NIVL (n=2,557) at 12 months, 36 months, and 60 months was 96.8% (95% CI: 95.66 – 97.88), 91.1% (95% CI: 88.82 – 93.39), and 80.5% (95% CI: 75.97 – 85.20) respectively (I^2=39.63%).

Figure 27 shows the overall PP for iliac vein stents placed for NIVL, the data was pooled from all studies reporting disaggregated data for NIVL. The median survival time for PP could not be calculated as this was beyond the scope of the data. Table 10 shows the pooled PP for NIVL over time at 6-monthly intervals (n=2,557; I^2=39.63%).

Figure 27: Pooled survival curve for primary patency of iliac vein stents placed for non-thrombotic iliac vein lesions, utilising reconstructed individual-patient data



IPD: Individual-patient data
NIVL: Non-thrombotic Iliac Vein Lesion

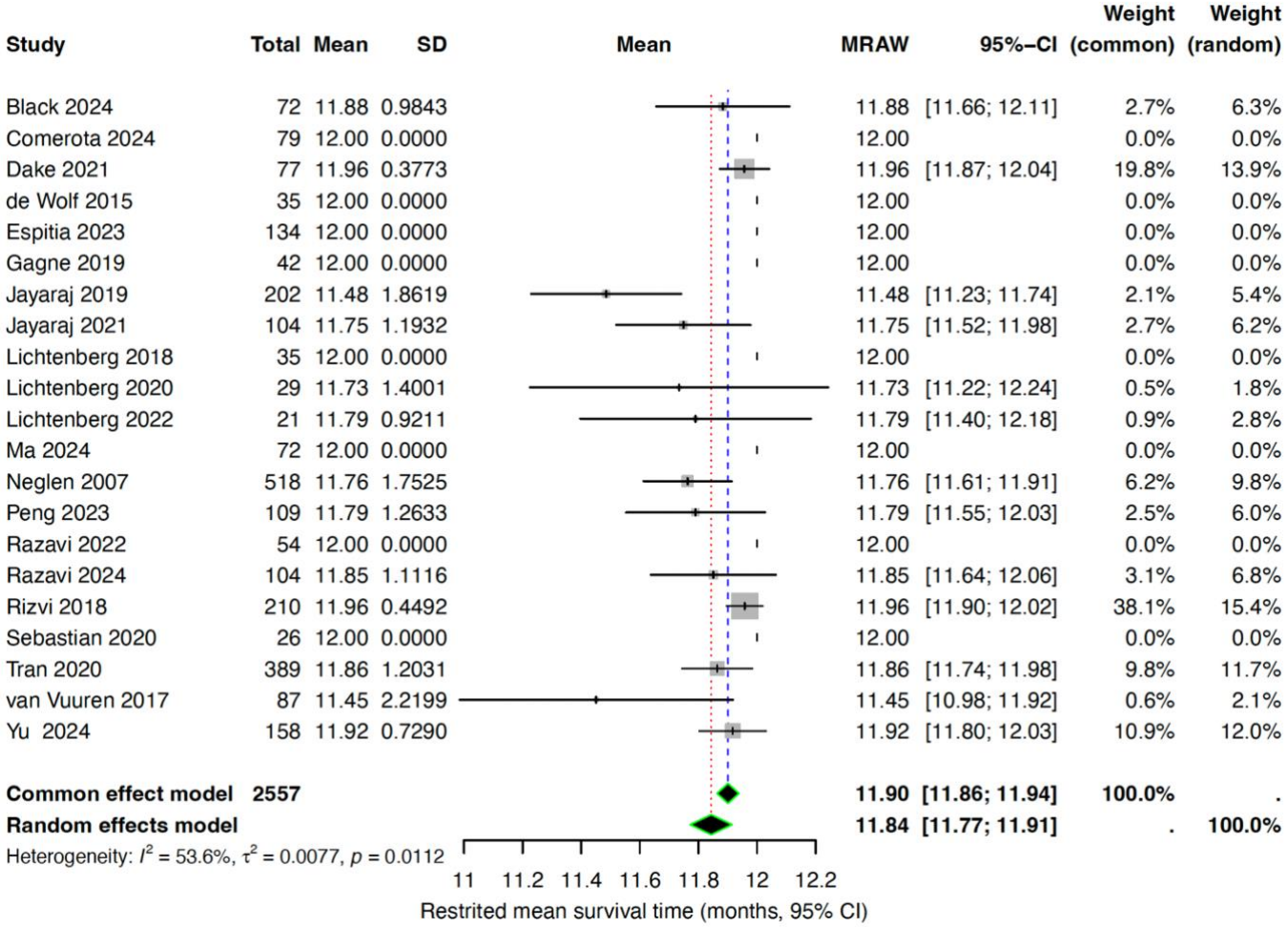
Table 10: Pooled estimate of primary patency, and associated 95% confidence interval, of iliac vein stents placed for non-thrombotic iliac vein lesions, utilising reconstructed individual-patient data

Month	Pooled estimate PP (%)	Lower bound 95% CI (%)	Upper bound 95% CI (%)
12	96.76	95.66	97.88
18	95.15	93.58	96.75
24	93.81	91.97	95.68
30	92.60	90.49	94.77
36	91.08	88.82	93.39
42	89.04	86.08	92.11
48	87.17	83.95	90.52
54	84.30	80.56	88.21
60	80.45	75.97	85.20

CI: Confidence interval
PP: Primary patency

RMST for NIVL was 11.84 (95% CI: 11.77 – 11.91, I^2=53.6%) and 34.24 (95% CI: 33.40 – 35.29, I^2=84.7%) at 12 months and 36 months respectively. See Figure 28 for the forest plot of pooled RMST at 12 months for NIVL. The forest plot for RMST at 36 months is included in Appendix 10. The funnel plot of standard error against the RMST was symmetrical for NIVL with no signs of publication bias, see Appendix 11.

Figure 28: Forest plot for the restricted mean survival time, primary patency, of iliac vein stents placed for non-thrombotic iliac vein lesions, utilising reconstructed individual-patient data, at 12 months

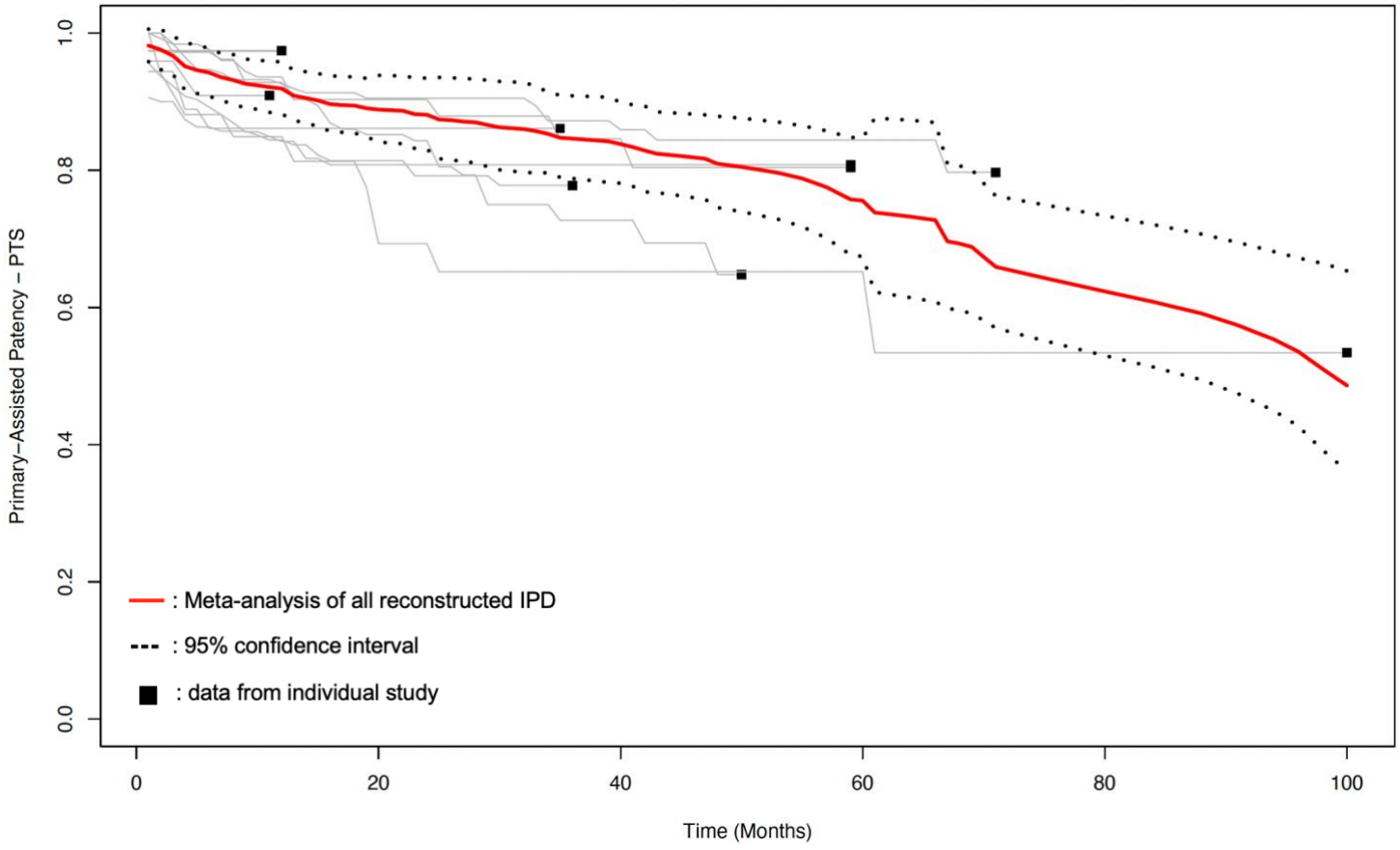


CI: Confidence interval
MRAW: Summary measure of untransformed means
SD: Standard deviation
Total: represents number of participants within each study

2.3.7 Primary-assisted patency – post thrombotic syndrome

PAP for PTS (n=1,264) at 12 months, 36 months, and 60 months was 91.9% (95% CI: 88.21 – 95.76), 84.6% (95% CI: 78.81 – 90.86), and 75.6% (95% CI: 67.43 – 84.71) respectively (I^2=64.02%). The median survival time for PAP was 98.9 months. Table 11 shows the pooled PAP for PTS over time at 6-monthly intervals (n=1,264; I^2=64.02%).

Figure 29: Pooled survival curve for primary-assisted patency of iliac vein stents placed for post thrombotic syndrome, utilising reconstructed individual-patient data



IPD: Individual-patient data
PTS: Post Thrombotic Syndrome

Table 11: Pooled estimate of primary-assisted patency, and associated 95% confidence interval, of iliac vein stents placed for post thrombotic syndrome, utilising reconstructed individual-patient data

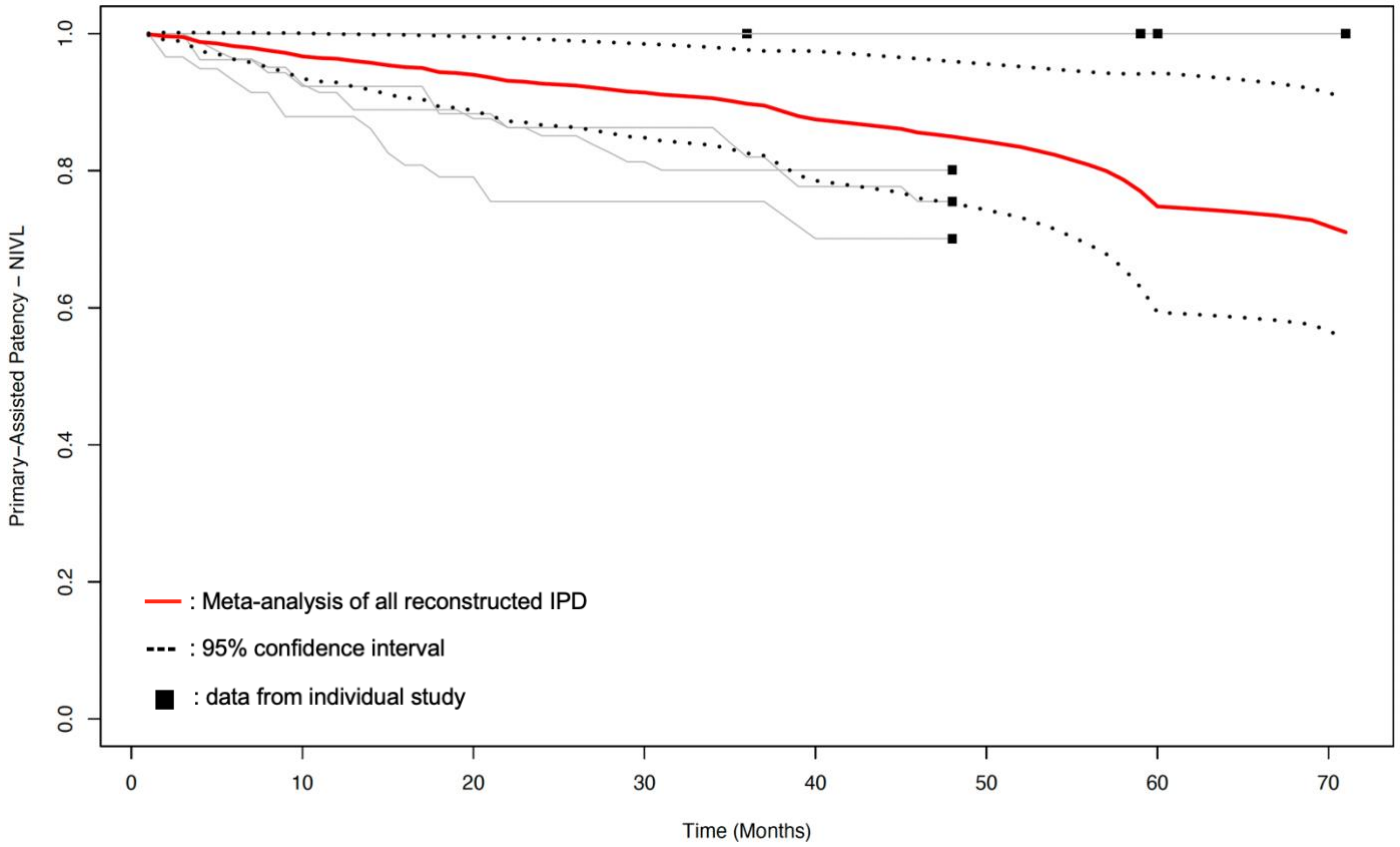
Month	Pooled estimate PAP (%)	Lower bound 95% CI (%)	Upper bound 95% CI (%)
12	91.91	88.21	95.76
18	89.43	85.43	93.61
24	88.09	83.05	93.43
30	86.26	80.06	92.95
36	84.62	78.81	90.86
42	82.87	76.85	89.35
48	80.94	74.56	87.87
54	79.22	72.34	86.76
60	75.58	67.43	84.71

CI: Confidence interval
PAP: Primary-assisted patency

2.3.8 Primary-assisted patency – non-thrombotic iliac vein lesion

PAP for NIVL (n=937) at 12 months, 36 months, and 60 months was 96.3% (95% CI: 92.88 – 99.92), 89.8% (95% CI: 82.55 – 97.62), and 74.8% (95% CI: 59.32 – 94.27) respectively (I^2=28.79). Table 12 shows the pooled PAP for NIVL over time at 6-monthly intervals (n=937, I^2=28.79).

Figure 30: Pooled survival curve for primary-assisted patency of iliac vein stents placed for non-thrombotic iliac vein lesions, utilising reconstructed individual-patient data



IPD: Individual-patient data
NIVL: Non-thrombotic Iliac Vein Lesion

Table 12: Pooled estimate of primary-assisted patency, and associated 95% confidence interval, of iliac vein stents placed for post thrombotic syndrome, utilising reconstructed individual-patient data

Month	Pooled estimate PAP (%)	Lower bound 95% CI (%)	Upper bound 95% CI (%)
12	96.34	92.88	99.92
18	94.38	89.34	99.70
24	92.71	86.66	99.17
30	91.40	84.82	98.50
36	89.77	82.55	97.62
42	86.95	77.88	97.08
48	84.97	75.26	95.94
54	82.32	71.48	94.79
60	74.78	59.32	94.27

CI: Confidence interval
PAP: Primary-assisted patency

2.3.9 Post thrombotic syndrome vs. non-thrombotic iliac vein lesion – primary patency

Pooled survival PP for PTS was significantly lower than NIVL at all assessed timepoints, see Table 13. Pooled RMST for PTS was also significantly lower than for NIVL at the assessed timepoints of 12- and 36-months, see Table 14.

Table 13: Pooled primary patency for post thrombotic syndrome and non-thrombotic iliac vein lesions

Month	PTS Pooled PP (%)	NIVL Pooled PP (%)	p-value
12	86.90 (95% CI: 83.74 – 89.02)	96.76 (95% CI: 95.66 – 97.88)	<0.05
36	73.09 (95% CI: 68.13 – 76.30)	91.08 (95% CI: 88.82 – 93.39)	<0.05
60	61.62 (95% CI: 55.31 – 64.82)	80.45 (95% CI: 75.97 – 85.20)	<0.05

NIVL: Non-thrombotic Iliac Vein Lesion
PP: Primary patency
PTS: Post thrombotic syndrome

Table 14: Pooled restricted mean survival time, primary patency, for post thrombotic syndrome and non-thrombotic iliac vein lesions

Month	PTS RMST PP (months)	NIVL RMST PP (months)	p-value
12	10.58 (95% CI: 10.25 – 10.91)	11.84 (95% CI: 11.77 – 11.91)	<0.05
36	28.61 (95% CI: 27.30 – 29.91)	34.24 (95% CI: 33.40 – 35.29)	<0.05

NIVL: Non-thrombotic Iliac Vein Lesion
PP: Primary patency
PTS: Post thrombotic syndrome
RMST: Restricted mean survival time

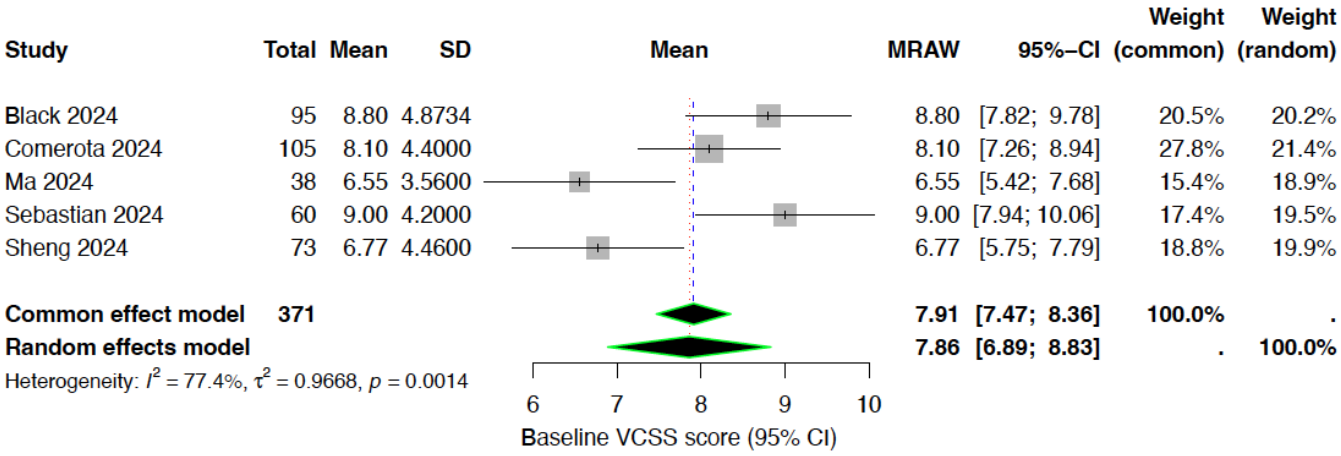
2.3.10 Severity of disease at baseline – post thrombotic syndrome

Baseline venous clinical severity score

A total of 13 study arms (n=447) (181, 184, 208, 211, 216-218, 240, 246, 249, 250, 284, 299) reported at least one VCSS measurement for PTS participants undergoing iliac vein stenting. Of these, six studies reported mean and SD values permitting meta-analysis of baseline VCSS score(181, 184, 208, 211, 246, 250, 286).

Appendix *12* shows the forest plot of the meta-analysis for the six pooled studies with an I^2 value of 99.1% due to inclusion of an outlier value from Moini et al. (mean: 17, SD: 2.72)(250). This study was excluded as it was a significant outlier ($p<0.001$) and a significant source of heterogeneity in the meta-analysis. Figure 31 shows the pooled results for the remaining five studies(181, 184, 208, 211, 246) (n=371), the mean VCSS score was 7.86 (95% CI: 6.89 – 8.83, I^2 =77.4).

Figure 31: Forest plot for baseline venous clinical severity score for post thrombotic syndrome



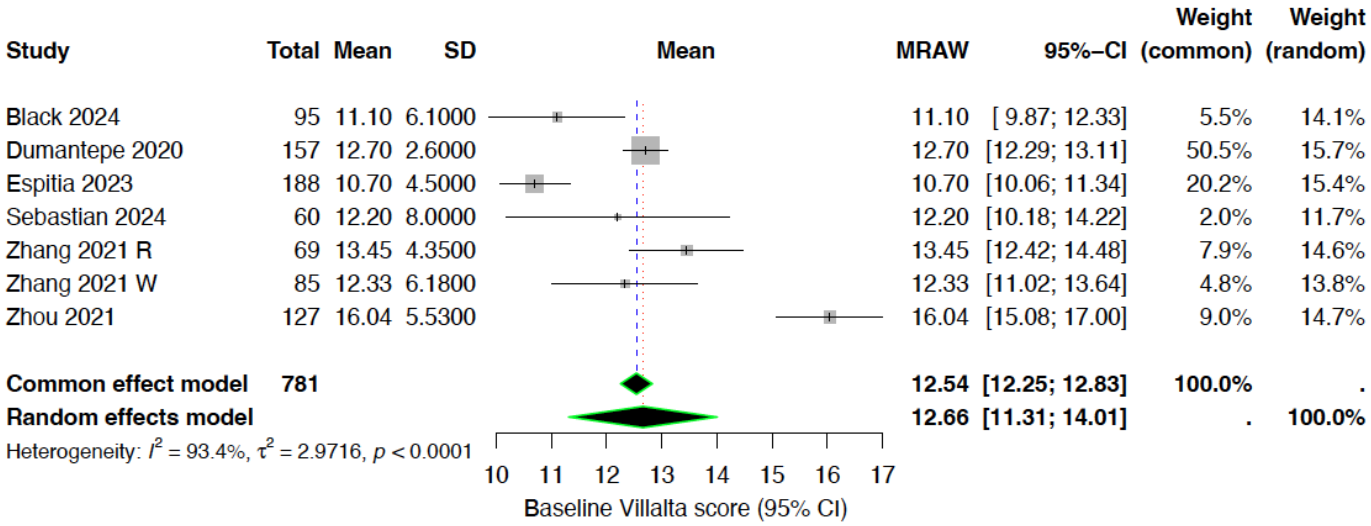
CI: Confidence interval
MRAW: Summary measure of untransformed means
SD: Standard deviation
Total: represents number of participants within each study

Baseline Villalta score

A total of 15 study arms (n=1,373) (181, 208, 209, 216-219, 226, 249, 282, 284, 297, 300, 301) reported at least one Villalta measurement for PTS participants undergoing iliac vein stenting. Eight of which summarised the Villalta score using means and SD, assuming normal distribution of the data(208, 209, 218, 219, 300, 301).

The pooled mean baseline Villalta scores are illustrated in Figure 32, a single study could not be included for a lack of data on the SD. The mean baseline Villalta score was 12.66 (95% CI: 11.31 – 14.01, n=781, I^2=93.4%). The median baseline Villalta scores from the other seven studies(216, 217, 226, 249, 282, 284, 297) can be found in Table 15, there was insufficient data on the inter-quartile range to perform meta-analysis of medians using quantile estimation.

Figure 32: Forest plot for baseline Villalta score for post thrombotic syndrome



CI: Confidence interval
MRAW: Summary measure of untransformed means
SD: Standard deviation
R: Rivaroxaban study arm
W: Warfarin study arm
Total: represents number of participants within each study

Table 15: Median and interquartile range of baseline Villalta score for post thrombotic syndrome

Study	Sample size	Median baseline Villalta score	IQR
de Wolf 2015(216)	40	11.5	NA
de Wolf 2017(217)	70	11	NA
Guillen 2020(226)	42	14	NA
Moeri 2021(249)	150	7	NA
Sarici 2013(282)	52	18	7 – 30
Sebastian 2020(284)	193	8	NA
Ye 2018(297)	45	18	NA

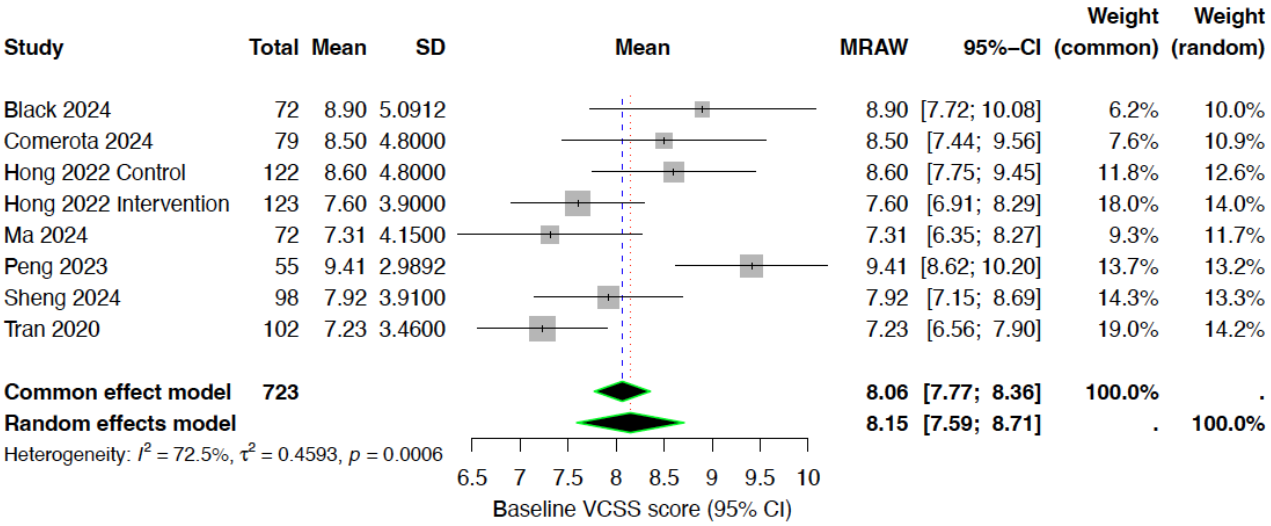
IQR: Interquartile range
NA: Not applicable, missing data

2.3.11 Severity of disease at baseline – non-thrombotic iliac vein lesion

Baseline venous clinical severity score

A total of 13 study arms (n=811) (184, 208, 211, 216, 229, 233, 240, 246, 250, 262, 284, 293) reported at least one VCSS measurement for NIVL participants undergoing iliac vein stenting. Of these, nine study arms(184, 208, 211, 229, 246, 250, 262, 293) reported mean and SD values permitting meta-analysis of baseline VCSS score. Appendix 13 shows the forest plot of the meta-analysis for the nine pooled studies with an I^2 value of 98.0% due to the inclusion of an outlier value from Moini et al. (mean: 14.64, SD: 2.86)(250). This study was again excluded, as it was in the PTS analysis, as it was a significant outlier ($p<0.001$) and a significant source of heterogeneity in the meta-analysis. Figure 33 shows the pooled results for the remaining eight study arms(184, 208, 211, 229, 246, 262, 293) (n=723), the mean VCSS score was 8.15 (95% CI: 7.59 – 8.71, I^2 =72.5).

Figure 33: Forest plot for baseline venous clinical severity score for non-thrombotic iliac vein lesions



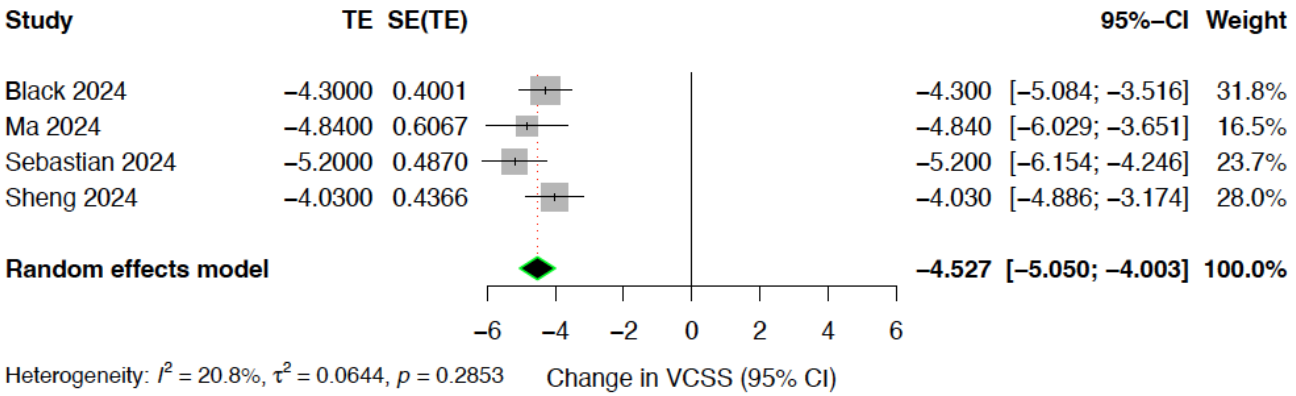
CI: Confidence interval
MRAW: Summary measure of untransformed means
SD: Standard deviation
Total: represents number of participants within each study

2.3.12 Severity of disease treatment response – post thrombotic syndrome

Change in venous clinical severity score

Of the 13 study arms reporting VCSS measurement in PTS participants, nine of them reported a significant reduction ($p<0.05$) in severity of disease after iliac vein stenting(181, 184, 208, 211, 216, 217, 241, 246, 250). Four study arms (n=266) (181, 184, 208, 246) reported sufficient disaggregated VCSS data to permit pooling in a meta-analysis to establish the response to treatment, see Figure 34. The mean reduction in VCSS at last follow-up was 4.52 (95% CI: 4.00 – 5.05, n=266, I^2=20.8%).

Figure 34: Forest plot illustrating the change in venous clinical severity score at last follow-up for post thrombotic syndrome after iliac vein stenting



CI: Confidence interval
TE: Treatment effect
SE: Standard error
VCSS: Venous Clinical Severity Score

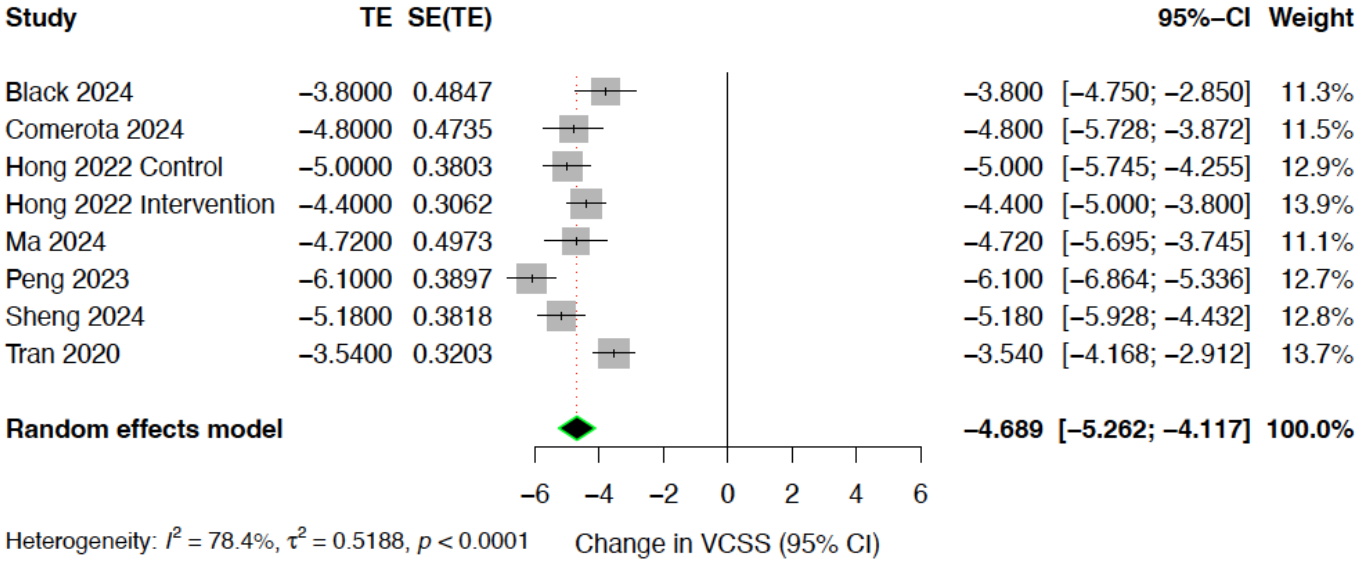
Of the 15 study arms reporting Villalta score measurement in PTS participants, 11 of them reported a significant reduction ($p<0.05$) in severity of disease after iliac vein stenting(181, 208, 209, 216-219, 282, 300, 301). There was insufficient data reported to meaningfully summarise these results either through meta-analysis of means or meta-analysis of medians using quantile estimation.

2.3.13 Severity of disease treatment response – non-thrombotic iliac vein lesion

Change in venous clinical severity score

Of the 13 study arms reporting VCSS measurement in NIVL participants, 10 of them reported a significant reduction ($p<0.05$) in severity of disease after iliac vein stenting(184, 208, 211, 216, 233, 240, 246, 250, 262, 293). Eight study arms (n=723) (184, 208, 211, 229, 246, 262, 293) reported sufficient disaggregated VCSS data to permit pooling in a meta-analysis to establish the response to treatment, see Figure 35. The mean reduction in VCSS at last follow-up was 4.69 (95% CI: 4.12 – 5.26, n=723, I^2=78.4%).

Figure 35: Forest plot illustrating the change in venous clinical severity score at last follow-up for non-thrombotic iliac vein lesions after iliac vein stenting

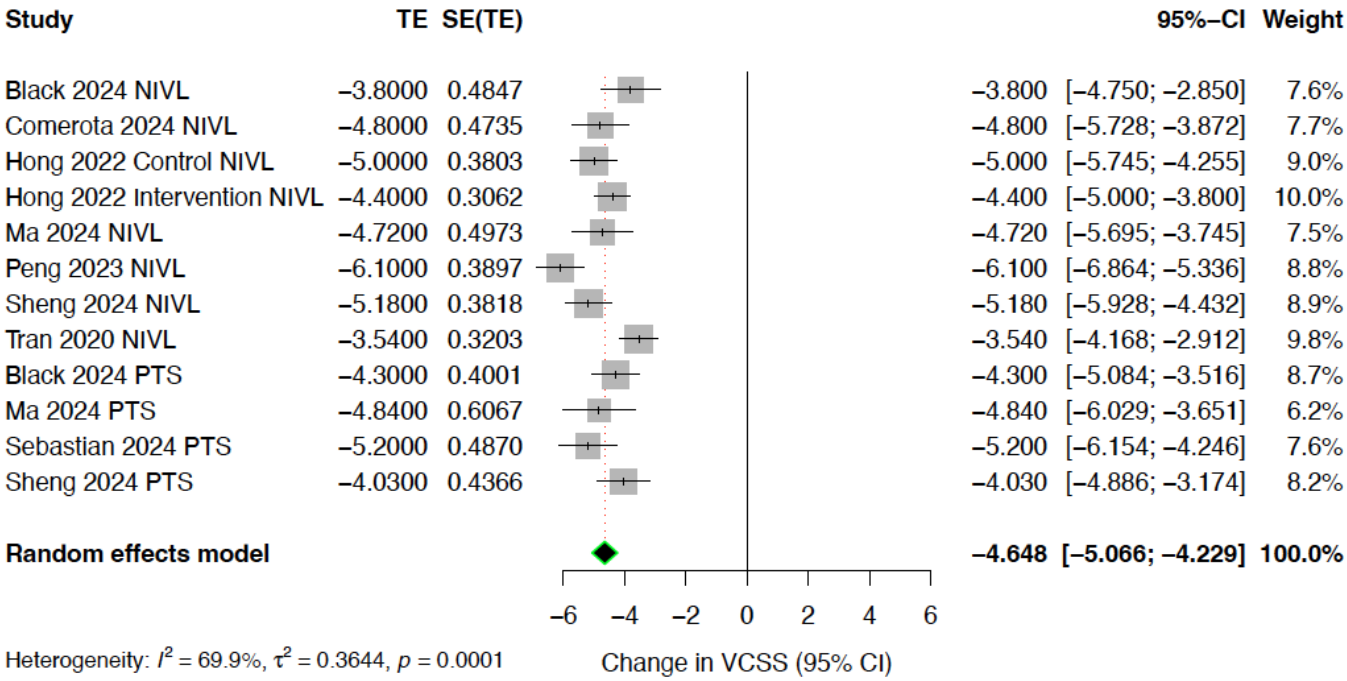


CI: Confidence interval
TE: Treatment effect
SE: Standard error
VCSS: Venous Clinical Severity Score

2.3.14 Severity of disease treatment response – sensitivity analysis for pathology

Meta-regression of the change in VCSS for underlying pathology (PTS vs. NIVL) had an R^2 (amount of heterogeneity accounted for) value of 0.00%, p=0.79. The treatment response in respects to severity of disease was independent of the underlying pathology. Appendix 14 is the Bubble plot of the meta-regression demonstrating the flat regression line for PTS vs. NIVL. The overall reduction in VCSS after iliac vein stenting, incorporating both PTS and NIVL pathologies (n=989), was 4.65 (95% CI: 4.23 – 5.07, n=989, I^2=69.9%), see Figure 36.

Figure 36: Forest plot illustrating the change in venous clinical severity score at last follow-up for both underlying pathologies



CI: Confidence interval
NIVL: Non-thrombotic iliac vein lesion
PTS: Post thrombotic syndrome
TE: Treatment effect
SE: Standard error
VCSS: Venous Clinical Severity Score

2.3.15 Venous ulceration at baseline – post thrombotic syndrome

A total of 14 study arms (n=1,149) (181, 203, 209, 216, 218, 225, 243, 249, 250, 277, 282, 285, 297, 300) reported the number of participants with a venous ulcer status at baseline for PTS. The proportion with active venous ulceration ranged from 9.0% - 55.0%. Appendix 15 shows the forest plot for the meta-analysis of proportion. The pooled proportion for baseline venous ulceration in PTS was 0.18 (95% CI: 0.12 – 0.26, n=1,149, I^2=90.2%).

2.3.16 Venous ulceration at baseline – non-thrombotic iliac vein lesion

A total of 11 study arms(n=1,026) (201, 208, 211, 216, 229, 243, 246, 250, 262, 294) reported the number of participants with a venous ulcer status at baseline for NIVL. The proportion with active venous ulceration ranged from 0.0% - 38.0%. Appendix 16 shows the forest plot for the meta-analysis of proportion. The pooled proportion for baseline venous ulceration in NIVL was 0.08 (95% CI: 0.04 – 0.17, n=1,026 , I^2=84.0%).

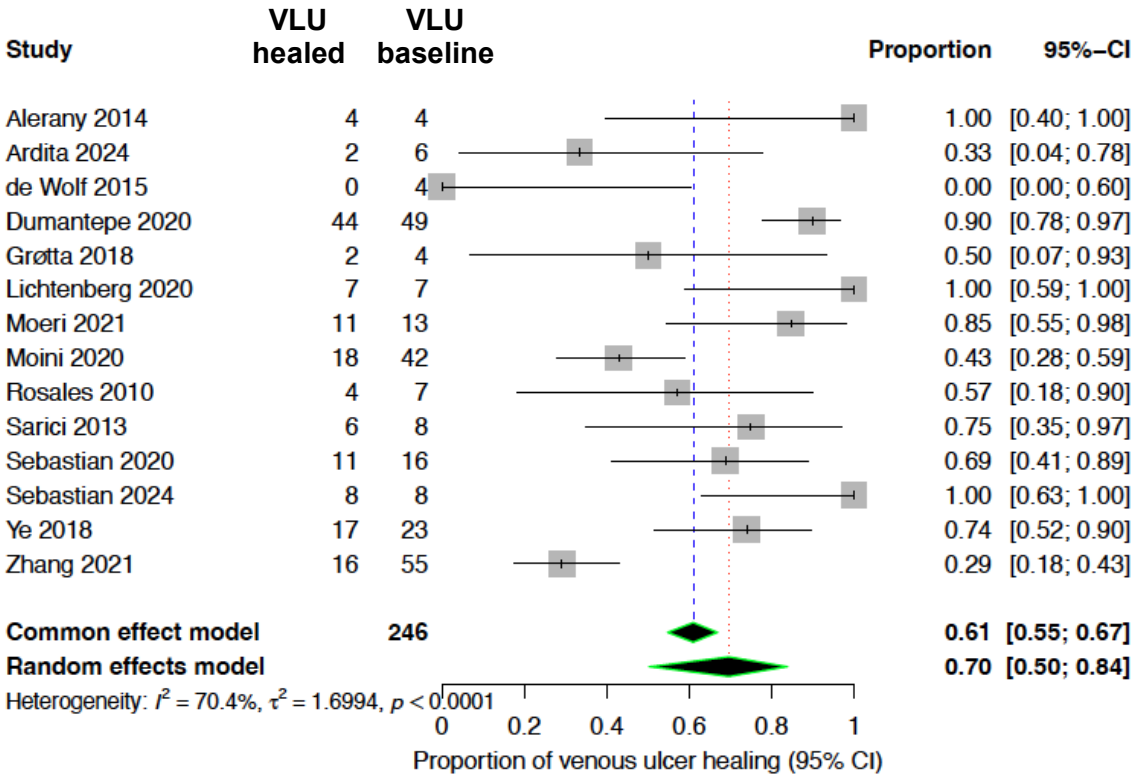
2.3.17 Venous ulceration treatment response – post thrombotic syndrome

The 14 study arms (n=246) (181, 203, 209, 216, 218, 225, 243, 249, 250, 277, 282, 285, 297, 300) reporting venous ulceration at baseline for PTS also reported the rate of venous ulcer status at last follow-up after iliac vein stenting. Proportion of venous ulcer healing ranged from 0.0% - 100.0%. Figure 37 illustrates the forest plot for the meta-analysis of proportions for venous ulcer healing. Pooled venous ulcer healing after iliac vein stenting for PTS was 0.70 (95% CI: 0.50 – 0.84, n=246 , I^2=70.4%). Note this value represents the proportion healing, not an odds ratio of ulcer status.

2.3.18 Venous ulceration treatment response – non-thrombotic iliac vein lesion

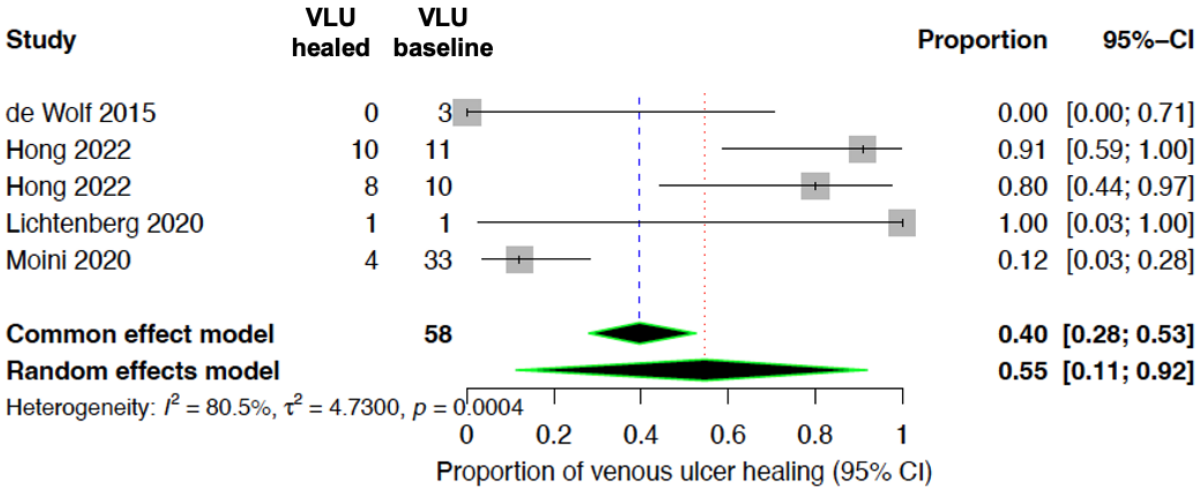
Of the 11 study arms reporting venous ulceration at baseline, five of the studies also reported the rate of venous ulcer status at last follow-up after iliac vein stenting for NIVL (n=58) (216, 229, 243, 250). Proportion of venous ulcer healing ranged from 0.0% - 100.0%. Pooled venous ulcer healing after iliac vein stenting for NIVL was 0.55 (95% CI: 0.11 – 0.92, n=58 , I^2=80.5%), see Figure 38.

Figure 37: Forest plot illustrating the proportion of venous ulcer healing at last follow-up after iliac vein stenting for post thrombotic syndrome



CI: Confidence interval
VLU baseline: number of participants within each study with a venous leg ulcer at baseline
VLU healed: number of participants within each study who had a venous leg ulcer at baseline that then healed after iliac vein stenting at last follow-up

Figure 38: Forest plot illustrating the proportion of venous ulcer healing at last follow-up after iliac vein stenting for non-thrombotic iliac vein lesions

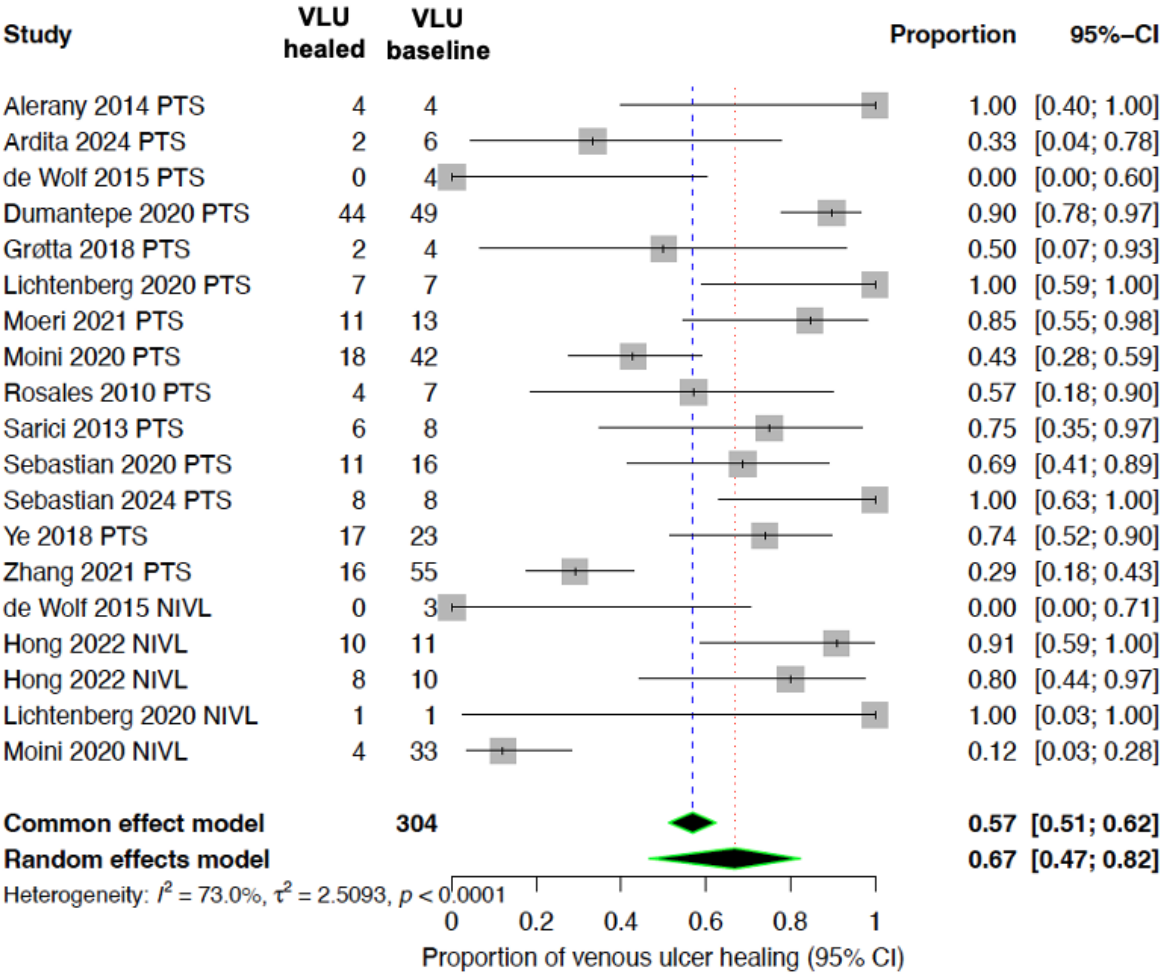


CI: Confidence interval
VLU baseline: number of participants within each study with a venous leg ulcer at baseline
VLU healed: number of participants within each study who had a venous leg ulcer at baseline that then healed after iliac vein stenting at last follow-up

2.3.19 Venous ulceration treatment response – sensitivity analysis for pathology

Meta-regression of the proportion of venous ulcer healing at last follow-up for underlying pathology (PTS vs. NIVL) demonstrated that there was a high level of residual heterogeneity (85.1%), and that the moderator had no significant influence (p=0.80). The treatment response in respects to venous ulcer healing was variable, but independent of the underlying pathology. Pooled venous ulcer healing after iliac vein stenting across both pathologies was 0.67 (95% CI: 0.47 – 0.82, n=304 , I^2=73.0%), see Figure 39.

Figure 39: Forest plot illustrating the proportion of venous ulcer healing at last follow-up after iliac vein stenting for both underlying pathologies



CI: Confidence interval
NIVL: Non-thrombotic syndrome
PTS: Post thrombotic syndrome
VLU baseline: number of participants within each study with a venous leg ulcer at baseline
VLU healed: number of participants within each study who had a venous leg ulcer at baseline that then healed after iliac vein stenting at last follow-up

2.3.20 Venous claudication at baseline – post thrombotic syndrome

Nine study arms (n=641) (206, 216, 217, 225, 250, 277, 282, 294, 295) reported the number of participants with venous claudication at baseline for PTS(206, 216, 217, 225, 250, 277, 282, 294, 295). Venous claudication had no consistent definition or diagnostic criteria. Proportion with venous claudication ranged from 15.0% - 100.0%. Appendix 17 illustrates the forest plot of the pooled proportion for baseline venous claudication, however, the heterogeneity was sufficiently high (I^2=95.2%) that the pooled estimate is not reported. Residual heterogeneity remained despite sensitivity analysis.

2.3.21 Venous claudication at baseline – non-thrombotic iliac vein lesion

Three study arms(216, 250, 295) reported the number of participants with venous claudication at baseline for NIVL. Proportion of participants with venous claudication at baseline ranged from 33.3% - 100.0%. Appendix 18 illustrates the forest plot of the pooled proportion for baseline venous claudication, however, as for PTS, there was a significant degree of variance within the small numbers of studies precluding reporting of the pooled estimate.

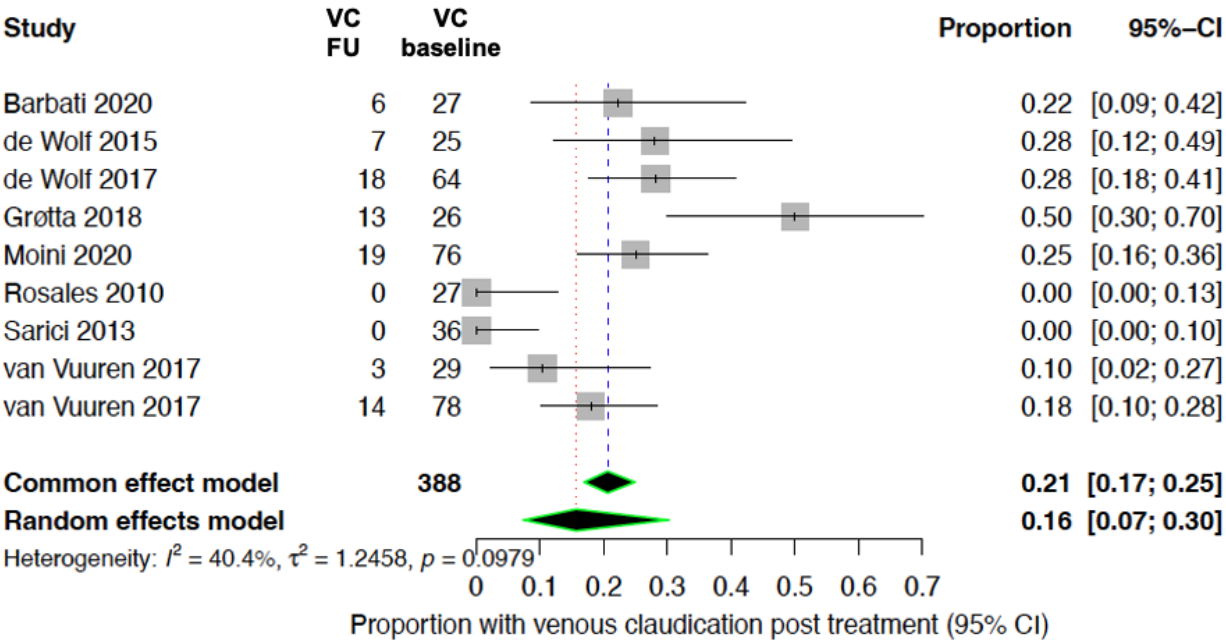
2.3.22 Venous claudication treatment response – post thrombotic syndrome

The nine study arms (n=641) (206, 216, 217, 225, 250, 277, 282, 294, 295) reporting the number of participants with venous claudication at baseline for PTS also reported the number of participants with venous claudication at last follow-up post treatment. Pooled proportion of PTS participants at baseline that still had venous claudication post treatment was 0.16 (95% CI: 0.07 – 0.30, n=641, I^2=40.4%), see Figure 40.

2.3.23 Venous claudication treatment response – non-thrombotic iliac vein lesion

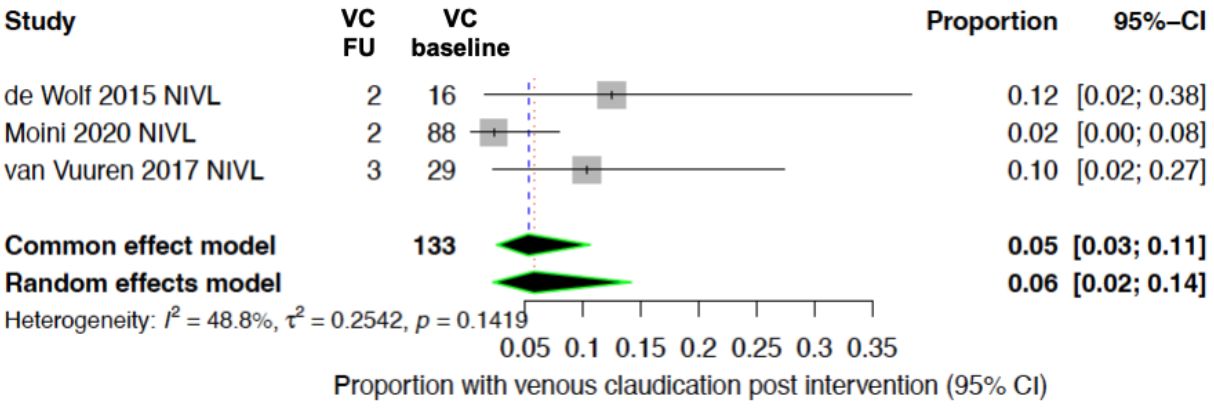
The three study arms (n=133) (216, 250, 295) reporting the number of participants with venous claudication at baseline for NIVL also reported the number of participants with venous claudication at last follow-up post treatment. Pooled proportion of NIVL participants at baseline that still had venous claudication post treatment was 0.06 (95% CI: 0.02 – 0.14, n=133, I^2=48.8%), see Figure 41.

Figure 40: Meta-analysis of proportion of venous claudication post iliac vein stenting for post thrombotic syndrome



CI: Confidence interval
VC baseline: number of participants within each study with venous claudication at baseline
VC FU: number of participants within each study with venous claudication after iliac vein stenting at last follow-up

Figure 41: Meta-analysis of proportion of venous claudication post iliac vein stenting non-thrombotic iliac vein lesions

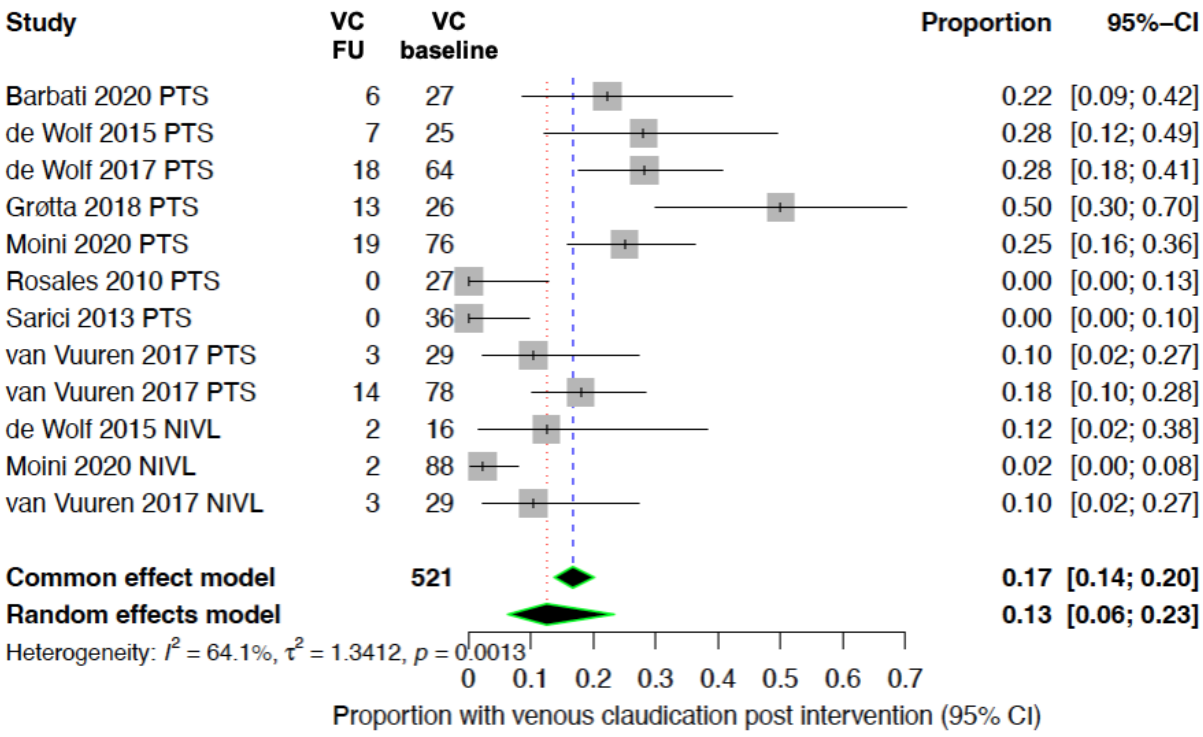


CI: Confidence interval
VC baseline: number of participants within each study with venous claudication at baseline
VC FU: number of participants within each study with venous claudication after iliac vein stenting at last follow-up

2.3.24 Venous claudication treatment response – sensitivity analysis for pathology

Meta-regression of the proportion of participants at baseline that still had venous claudication post treatment at last follow-up for underlying pathology (PTS vs. NIVL) demonstrated the moderator had no significant influence (p=0.15). The treatment response in respects to venous claudication was independent of the underlying pathology. The number of studies reporting disaggregated venous claudication status at follow-up for NIVL was limited to three studies. Pooled proportion of participants at baseline that still had venous claudication post treatment at last follow-up was 0.13 (95% CI: 0.13 – 0.23, n=521, I^2=64.1%), see Figure 42.

Figure 42: Meta-analysis of proportion of venous claudication post iliac vein stenting for both underlying pathologies



CI: Confidence interval
VC baseline: number of participants within each study with venous claudication at baseline
VC FU: number of participants within each study with venous claudication after iliac vein stenting at last follow-up

2.3.25 Quality of life treatment response – post thrombotic syndrome

Quality of life was assessed utilising a range of patient-reported outcome measures including the Venous Insufficiency Epidemiological and Economic Study (VEINES-QOL/Sym) questionnaire, Chronic Venous Insufficiency quality of life Questionnaire (CIVIQ), EuroQol-5 Dimension (EQ-5D) 5 level questionnaire, and the 36-Item Short Form Health Survey (SF-36).

VEINES QOL/Sym

Two studies(208, 218) reported VEINES QOL/Sym results for PTS participants before and after iliac vein stenting, the first an IDE cohort trial(208) and the second a cohort study reporting on hybrid endophlebectomy and stenting procedures(218). Both studies reported a significant increase in VEINES QOL and VEINES Sym score from baseline to last follow-up, see Table 16. The STEVECO trial reported pooled VEINES QOL/Sym values across both PTS and NIVL but provided no separate results(286).

Table 16: VEINES QOL/Sym scores at baseline and last follow-up for post thrombotic syndrome

Study	VEINES QOL baseline	VEINES QOL follow-up	VEINES Sym baseline	VEINES Sym follow-up	Follow-up (months)
Black 2024(208)	49.1	65.7†	49.5	66.6†	36
Dumantepe 2020(218)	49.4	68.7*	47.7	69.6*	12

**: p-value <0.05*
†The overall increase in VEINES QOL/Sym across subgroups was significant (p<0.05) however the p-value was not reported for the PTS subgroup

CIVIQ-20

Three studies(181, 214, 282) reported CIVIQ-20 results for PTS participants before and after iliac vein stenting. Study designs included an IDE cohort trial(214), a prospective cohort trial(181), and a single centre prospective cohort study(282). All three studies reported a significant improvement in CIVIQ-20 scores at last follow-up, see Table 17. Dake 2021 reported that the overall increase in CIVIQ-20 across subgroups was significant ($p<0.05$) however the p-value was not reported for the PTS subgroup(214). No data was reported to assess for significance in the PTS subgroup.

Table 17: CIVIQ-20 scores *at baseline and last follow-up for post thrombotic syndrome*

Study	CIVIQ-20† baseline	CIVIQ-20† follow-up	Follow-up (months)
Dake 2021(214)	52.5	32.0*	36
Sebestian 2024 (181)	45	27*	24
Sarici 2014(282)	64††	83*††	6

†: CIVIQ-20 is reported as the global index across the 20 domains
††: Sarici 2014 scaled the CIVIQ-20 inversely in comparison to the other studies, i.e., an increase in score equates to a better health-related quality of life

EuroQol EQ5D-5L

A single study, the Abre stent IDE trial(208), reported EQ5D-5L results for PTS participants before and after intervention. The EQ5D index value increased from 0.69±0.02 at baseline to 0.76±0.02 at 36 months post intervention. The overall increase in EQ5D across subgroups was significant ($p<0.05$) however the p-value was not reported for the PTS subgroup. Calculation of 95% confidence intervals based on the provided SE suggests that this increase is significant. The STEVECO trial reported pooled EQ5D-5L values across both PTS and NIVL but provided no separate results(286).

2.3.26 Quality of life treatment response – non-thrombotic iliac vein lesion

VEINES QOL/Sym

A single study, the Abre stent IDE trial(208), reported VEINES QOL/Sym results for NIVL participants before and after iliac vein stenting. The VEINES QOL score increased from 46.8±3.0 at baseline to 71.2±3.2 at 36 months post intervention. The VEINES Sym score increased from 48.4±2.9 at baseline to 72.4±3.2 at 36 months post intervention. The overall increase in VEINES QOL/Sym across subgroups was significant ($p<0.05$) however the p-value was not reported for the NIVL subgroup. Interpretation of the SE provided suggests that the increase would be significant based on the 95% confidence intervals.

CIVIQ-20 / CIVIQ-14

Two studies(214, 262) reported CIVIQ questionnaire results for NIVL participants before and after iliac vein stenting, one utilising the 20-domain version and the other using the 14-domain version. Study designs included an IDE cohort trial(214) and a single centre retrospective cohort study(262). Dake et al. reported an improvement in CIVIQ-20 from 45.7 at baseline to 30.3 at 36 months post intervention(214). The overall improvement in CIVIQ-20 across subgroups was significant ($p<0.05$) however the p-value was not reported for the NIVL subgroup. Peng et al. reported a significant improvement in CIVIQ-14 score ($p<0.001$) from 33.70±11.07 at baseline to 20.35± 8.21 at 12 months post intervention(262).

EuroQol EQ5D-5L

A single study, again the Abre stent IDE trial(208), reported EQ5D-5L results for NIVL participants before and after intervention. The EQ5D index value increased from 0.69±0.03 at baseline to 0.79±0.03 at 36 months post intervention. The overall increase in EQ5D across subgroups was significant ($p<0.05$) however the p-value was not reported for the NIVL subgroup. As for PTS, calculation of the 95% confidence intervals based on the provided SE suggests that this increase is significant.

2.3.27 Quality of life treatment response – across both pathologies

There was insufficient data to pool health-related quality of life metrics to compare the treatment response across PTS and NIVL pathologies. The magnitude and direction of response is broadly similar across pathologies in these single-armed studies.

2.3.28 Reintervention rate – post thrombotic syndrome

Nineteen studies (n=1,653) (181, 206, 208, 209, 214-218, 225, 243, 249, 275, 277, 284, 294, 295, 298, 300) reported on the proportion of participants undergoing reintervention after iliac vein stenting for PTS. Rate of reintervention varied from 8.4% - 72.9%. Meta-analysis of 19 studies reporting reintervention at last follow-up demonstrated two significant outlier studies which performed hybrid procedures(217, 294), see Appendix 19. Meta-regression for hybrid procedure status demonstrated a significant moderating effect ($p< 0.0001$). These two study arms were removed to improve the certainty in the estimate. Meta-analysis of 17 study arms provided a pooled estimate for reintervention of 0.185 (95% CI: 0.149 – 0.227, n=1,653, I^2=72.2%) for PTS.

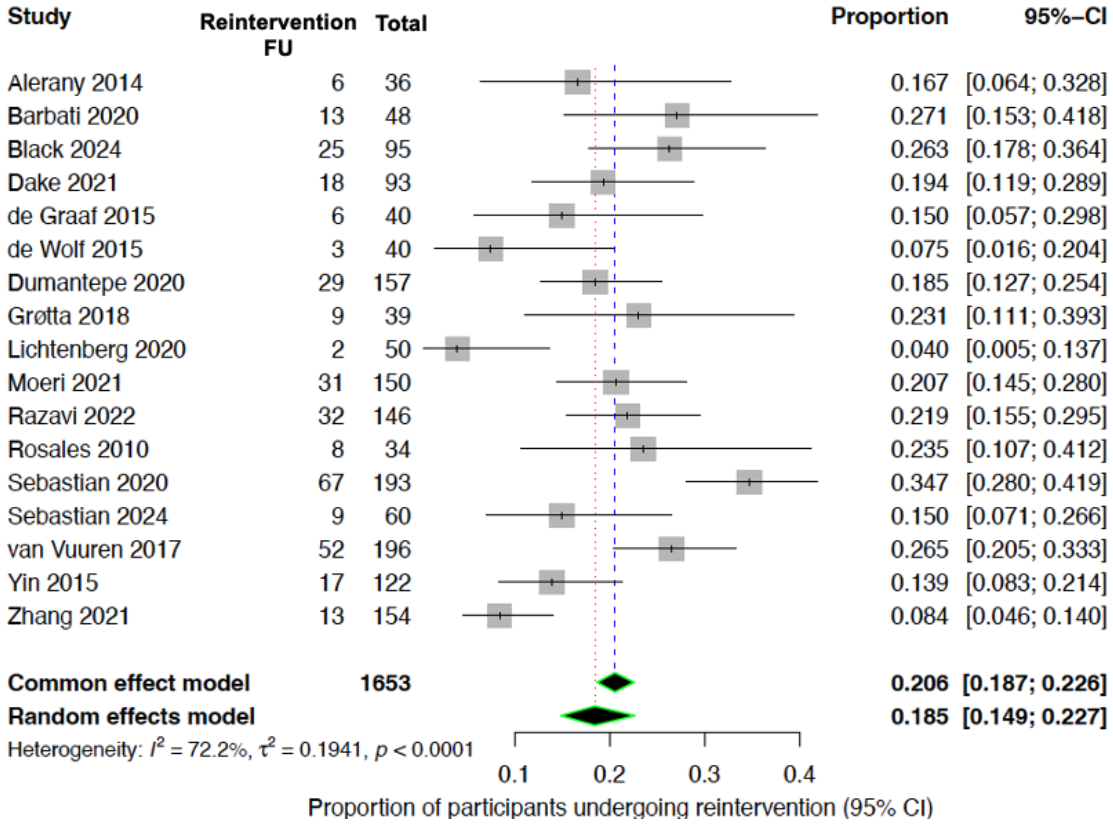
2.3.29 Reintervention rate – non-thrombotic iliac vein lesion

A total of 11 study arms (n=1,224) (201, 208, 214, 216, 229, 243, 275, 284, 293, 295) reported on the proportion of participants undergoing reintervention after iliac vein stenting for NIVL. Proportion of reintervention varied from 0.0% - 8.6%. Meta-analysis of 11 study arms provided a pooled estimate for reintervention of 0.016 (95% CI: 0.007 – 0.035, n=1,224, I^2=35.1%) for NIVL.

2.3.30 Reintervention rate – sensitivity analysis for pathology

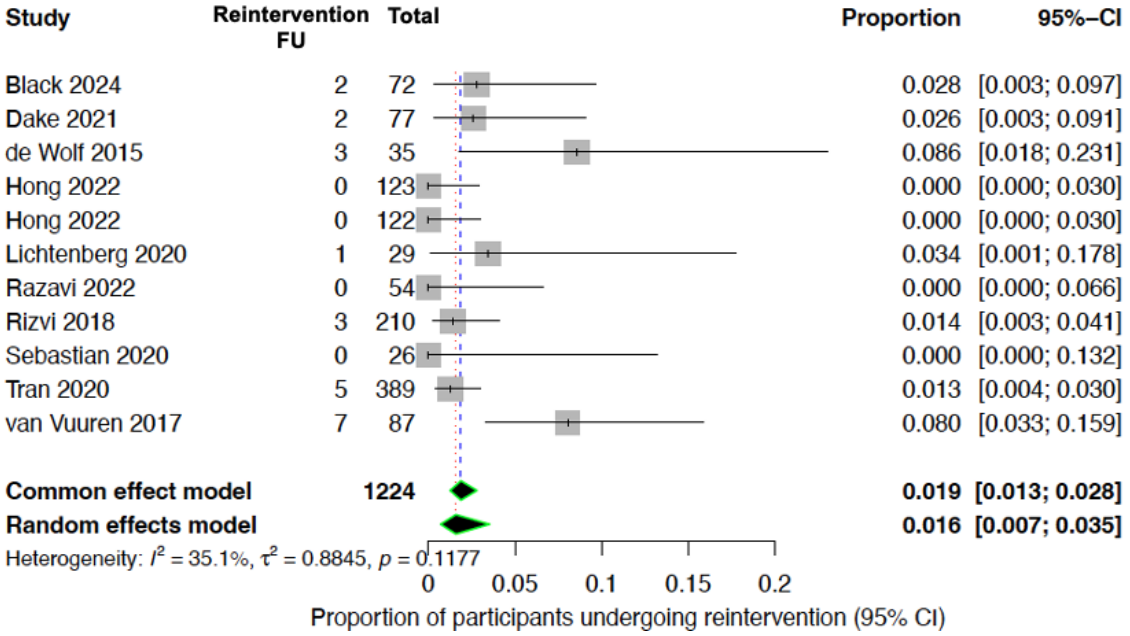
Meta-regression for underlying pathology (PTS vs. NIVL) on the proportion of participants undergoing reintervention after iliac vein stenting demonstrated that the moderator was significantly associated with reintervention($p<0.0001$). Reintervention is significantly influenced by the underlying pathology, therefore the pooled estimate incorporating both pathologies is not reported.

Figure 43: Meta-analysis of proportions for reintervention at last follow-up for post thrombotic syndrome



CI: Confidence interval
Reintervention FU: Number of participants undergoing reintervention by last follow-up
Total: represents number of participants within each study

Figure 44: Meta-analysis of proportions for reintervention at last follow-up for non-thrombotic iliac vein lesions



CI: Confidence interval
Reintervention FU: Number of participants undergoing reintervention by last follow-up
Total: represents number of participants within each study

2.3.31 Major bleeding – post thrombotic syndrome

Seventeen study arms (n=1,594) (181, 184, 203, 208, 209, 216-218, 223, 246, 249, 284, 294, 295, 298, 300, 301) reported on the number of participants that had a major bleeding episode after iliac vein stenting for PTS. Rate of major bleeding varied from 0.0% - 12.8%. Meta-analysis of 17 studies reporting major bleeding demonstrated two significant outlier studies which performed hybrid procedures(217, 294), see Appendix 20. As for reintervention proportion in PTS, meta-regression for hybrid procedure status was a significant covariate ($p< 0.0001$). These two study arms were again removed to improve the certainty in the estimate. Meta-analysis of 15 study arms provided a pooled estimate for major bleeding of 0.009 (0.9%)(95% CI: 0.003 – 0.017, n=1,594 , I^2=29.0%) for PTS, see Figure 45.

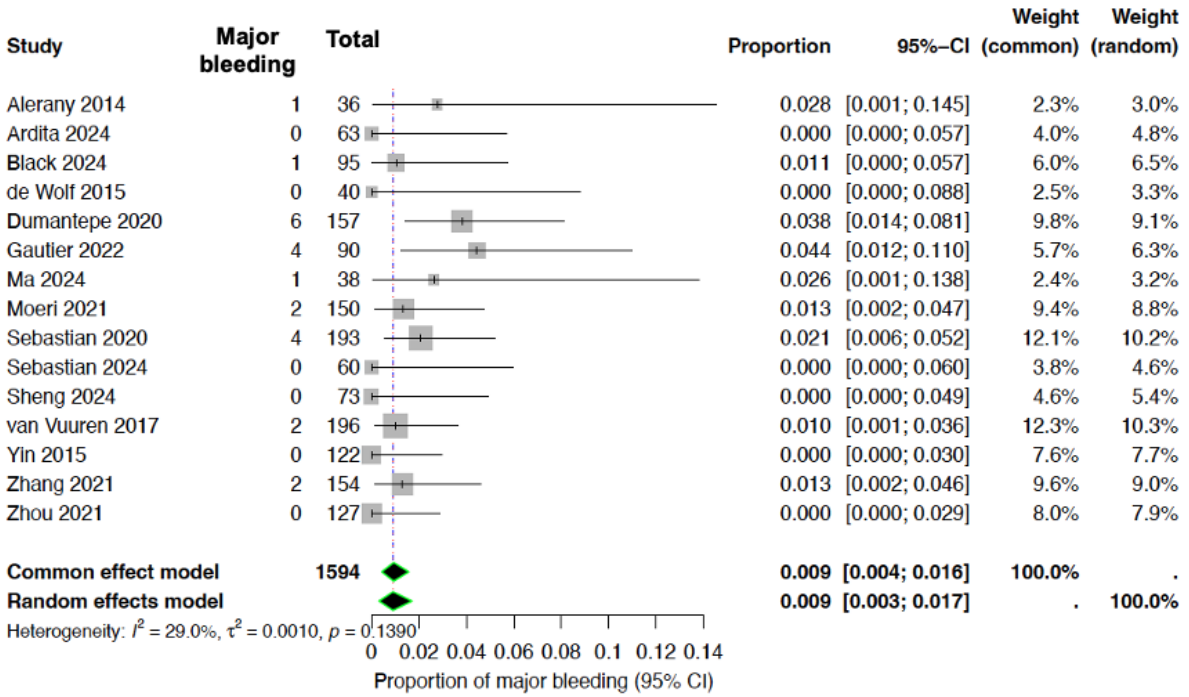
2.3.32 Major bleeding – non-thrombotic iliac vein lesion

Seven study arms (n=499) (184, 208, 216, 246, 262, 285, 295) reported on the number of participants that had a major bleeding episode after iliac vein stenting for NIVL. Rate of major bleeding varied from 0.0% - 4.6%. Meta-analysis of seven study arms provided a pooled estimate for major bleeding of 0.004 (0.4%) (95% CI: 0.000 – 0.019, n=499, I^2=36.9%) for NIVL, see Figure 46.

2.3.33 Major bleeding – sensitivity analysis for pathology

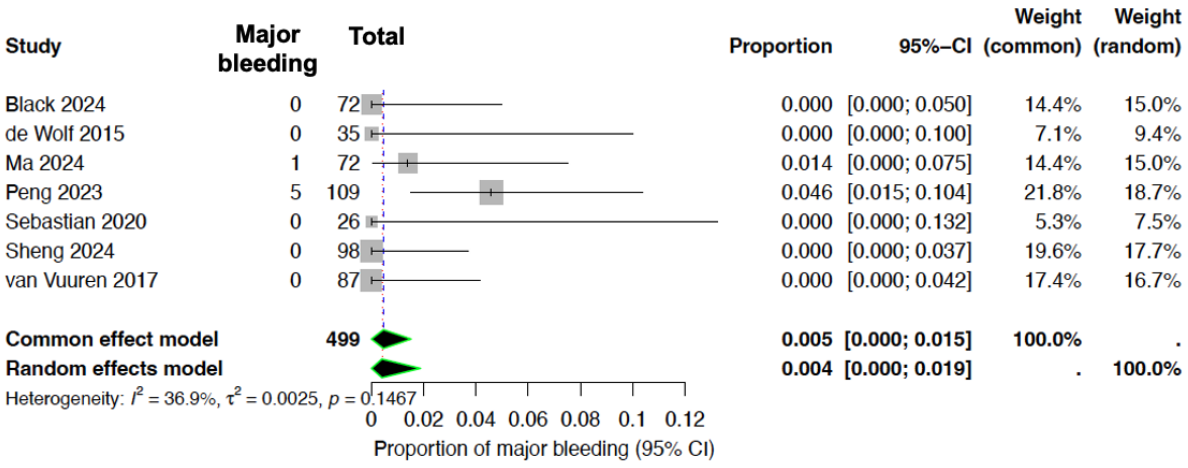
Meta-regression of major bleeding for underlying pathology (PTS vs. NIVL) demonstrated the moderator had no significant influence (p=0.63). Underlying pathology did not influence the rate of major bleeding. Pooled proportion of major bleeding across both pathologies was 0.008 (0.8%) (95% CI: 0.003 – 0.014, n=2,093, I^2=28.9%), see Figure 47.

Figure 45: Meta-analysis of proportions for major bleeding for post thrombotic syndrome



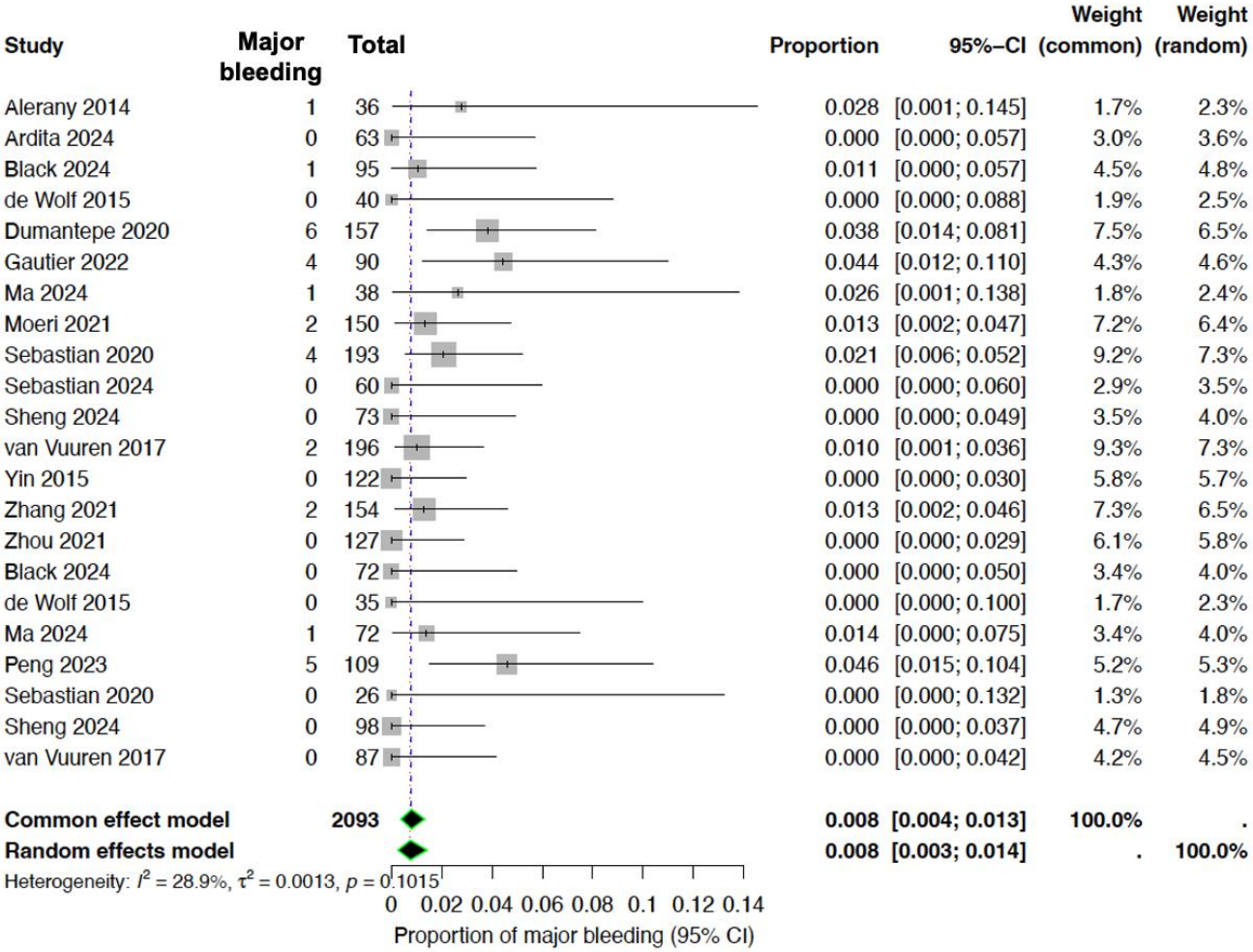
CI: Confidence interval
Major bleeding: number of participants within each study in which major bleeding occurred
Total: represents number of participants within each study

Figure 46: Meta-analysis of proportions for major bleeding for non-thrombotic iliac vein lesions



CI: Confidence interval
Major bleeding: number of participants within each study in which major bleeding occurred
Total: represents number of participants within each study

Figure 47: Meta-analysis of proportions for major bleeding for both underlying pathologies



CI: Confidence interval
Major bleeding: number of participants within each study in which major bleeding occurred
Total: represents number of participants within each study

2.3.34 Stent fracture – post thrombotic syndrome

Sixteen study arms (n=1,837) (203, 208, 209, 214, 216-218, 225, 246, 249, 255, 277, 284, 294, 295, 298) reported the rate of stent fracture post iliac vein stenting for PTS. Stent fracture occurred at a rate of 0.0% - 2.7%. Meta-analysis of the 16 study arms provided a pooled estimate for stent fracture of 0.0 (95% CI: 0.000 – 0.003, n=1,837, I^2=0.0%) for PTS, see Appendix 21.

2.3.35 Stent fracture – non-thrombotic iliac vein lesions

Ten study arms (n=1,230) (184, 208, 214, 216, 229, 246, 255, 284, 295) reported the rate of stent fracture post iliac vein stenting for NIVL. Stent fracture occurred at a rate of 0.0% - 2.9%. Meta-analysis of the 10 study arms provided a pooled estimate for stent fracture of 0.00 (95% CI: 0.000 – 0.000, n=1,230, I^2=0.0%) for NIVL, see Appendix 22.

2.3.36 Stent fracture – sensitivity analysis for pathology

Meta-regression of stent fracture for underlying pathology (PTS vs. NIVL) demonstrated the moderator had no significant influence (p=0.26). Underlying pathology had no influences on the rate of stent fracture.

2.3.37 Stent migration – overall rate

There was insufficient data reported across the PTS and NIVL pathologies to provide discrete estimates for stent migration. A total of 22 study arms(177, 184, 185, 202, 203, 208, 211, 214, 216, 217, 221, 222, 229, 231, 238, 240, 246, 251, 261, 275, 292, 299) across mixed PTS and NIVL cohorts reported on stent migration. With the exception of two studies(211, 275) all other studies reported a 0% rate for stent migration. The rate of stent migration ranged from 0.0% - 1.2%.

2.3.38 Censoring proportion – overall rate

Censoring rates were calculated from reconstructed IPD and then pooled in a meta-analysis, see Appendix 23. Censoring rates ranged from 3% - 95%. Pooled censored proportion was 0.52 (95% CI: 0.41 – 0.62, n=5,909, I^2=95.7%). No significant difference in censoring rates between PTS and NIVL pathologies were identified. Pooled proportions for PTS and NIVL were 0.50 and 0.54 respectively.

Meta-regression against study design demonstrated that prospective cohort trials had a lower rate of censoring in comparison to prospective and retrospective cohort studies (estimate: -1.1798, p=0.0341). Censoring rates for the prospective cohort trials ranged from 8% - 83%.

2.3.39 Factors significantly associated with primary patency – overall cohort

In a univariate meta-regression for the included studies in which IPD could be reconstructed (n=6,185, 61 study arms), several patient- and technical-variables were significantly associated with PP at 12 months, see Table 18. Factors not associated with PP included: baseline disease severity, bilateral venous stenting, BMI, dedicated venous stent use, open cell stent use, sex, and study year.

Pathology had the largest effect estimate for any single variable; therefore, the meta-analysis and meta-regression was undertaken within each pathology subgroup.

Table 18: Factors associated with primary patency at 12 months in a univariate meta-regression

Variable	Estimate	p-value
Age (as continuous measure)	0.822	0.0003
Baseline diameter stenosis (as continuous measure)	-0.3593	0.0294
Hybrid procedure status (dichotomous)	-0.2399	<0.0001
Number of stents (as a continuous measure)	-5.3718	0.0218
Pathology (PTS dichotomous)	-13.7469	<0.0001
Stenting below the inguinal ligament (dichotomous)	-0.1606	0.0026
Thrombophilia (dichotomous)	-0.5339	<0.0001
Total occlusion at baseline (dichotomous)	-0.1398	0.0009

PTS: Post thrombotic syndrome

2.3.40 Factors significantly associated with primary patency – post thrombotic syndrome

The meta-regression for PP within the PTS subgroup (n=3,628, 36 study arms) demonstrated that many of the factors which were significant in the overall cohort were no longer significant variables. Age, hybrid procedure status, and thrombophilia status remained as significant variables for PP at 12 months, see Table 19. Use of open cell stents approached significance for a minor improvement in stent patency (estimate: 0.0688, p=0.059). Factors not associated with PP included: baseline diameter stenosis, baseline disease severity, bilateral venous stenting, BMI, number of stents placed, open cell stent use, sex, stenting below the inguinal ligament, study year and total occlusion at baseline. Meta-regression for 36-month PP (n=2,518, 18 study arms) demonstrated consistent results.

In a multivariate meta-regression, including all significant variables in the univariate analysis, age was no longer found to be a significant variable. There was a significant interaction between hybrid procedure status and age – with increasing age being associated with lower likelihood of having a hybrid procedure.

Table 19: Factors associated with primary patency at 12-months in a univariate meta-regression for post thrombotic syndrome

Variable	Estimate	p-value
Age (as continuous measure)	0.7714	0.0140
Dedicated venous stent status (dichotomous)	0.1353	0.0017
Hybrid procedure status (dichotomous)	-0.2004	0.0004
Thrombophilia (dichotomous)	-0.4881	0.0002

2.3.41 Factors significantly associated with primary patency – non-thrombotic iliac vein lesion

Meta-regression for PP within the NIVL subgroup (n=2,557, 21 study arms) demonstrated that nearly all baseline variables within the NIVL cohort were not associated with PP. Factors not associated with PP included: age, baseline diameter stenosis, baseline disease severity, BMI, dedicated venous stent use, number of stents placed, open cell stent use, sex, stenting below the inguinal ligament, study year, thrombophilia status, and total occlusion at baseline. The only factor that was significantly associated with PP at 12 months was study design, with the prospective cohort trials, including the IDE trials and European industry sponsored registries, being associated with a higher patency (estimate: 3.6383, p=0.046).

2.3.42 Validation with restricted mean survival time

Meta-regression of the pooled RMST for PP across the overall dataset and PTS/NIVL subgroups was also performed to validate the findings from the pooled survival probability. The findings of the meta-regression for survival probability were consistent and replicated.

2.3.43 Comparative evidence of iliac vein stenting in comparison to medical therapy

There are two published RCTs comparing iliac vein stenting to current medical therapy in the treatment of CVOO(185, 286). There is one further RCT which is ongoing, the C-TRACT trial(304). Rossi et al.(185) reports a single centre RCT published 2015, randomising participants, in a double blinded fashion, to either iliac vein stenting in addition to medical therapy or medical therapy alone. Medical therapy constituted aminaphtone 75mg twice daily and class II compression stockings (20 – 30mmHg). For participants with a venous ulcer, compression wraps, and elastic bandages were also prescribed. Participants had at least C3 disease and a greater than 50% lumen area reduction of the iliac vein on IVUS. The randomisation allocation was revealed to the operator while the participant was under general anaesthesia. Wallstent™ stents were used in all cases. The study had multiple reported primary outcomes with no formal sample size calculation.

A total of 51 participants were randomised, 26 to the stenting arm and 25 to the medical therapy arm. Sixteen (31.4%) had PTS, with the remainder having NIVL. As many as 29.4% of participants had an active venous ulcer at baseline. VCSS at baseline was 18.5 for the stent arm and 15 for the medical therapy arm. PP and PAP at 12 months were 92% and 96% respectively. There was a significant reduction in VCSS for the stent arm in comparison to the medical therapy arm, reducing from a mean of 18.5 to 11.0 and 15.0 to 14.0 respectively ($p<0.001$). Ulcer healing occurred more frequently in the stent arm (90%) in comparison to the medical therapy arm (40%) but this failed to reach significance. The SF-36 domains were significantly higher across the four domains in the stent arm at all timepoints.

The STEVECO trial(286) was an industry-funded RCT published in 2023 which closed early due to inadequate recruitment. Participants were randomised to either iliac vein stenting in addition to medical therapy or medical therapy alone in a 2:1 ratio, stratified for pathology (PTS or NIVL). Inclusion criteria described CVOO with debilitating symptoms. Primary outcome was the change in disease-specific quality of life measure VEINES-QoL based on a formal sample size of 130 participants including a minimally important difference of 14 points(305). A total of 63 participants were randomised to either the stent arm (n=42) or medical therapy arm (n=21). Fifty-eight participants had PTS with the remaining 18 having NIVL. There was a significantly greater difference in the mean change of VEINES-QOL and VEINES-Sym scores in the stenting arm in comparison to the medical therapy arm, with a mean difference of 8.07 and 5.99 respectively. There was also a significantly greater change in VCSS in the stenting arm, with a mean difference of –2.93. There was no significant difference in the change in EQ5D index value or Villalta score across the two arms.

2.3.44 Conflict of interest

A total of 66 of the 107 articles had a perceived or declared conflict of interest. Of note, one of the two RCTs, the STEVECO trial outlined above(286), was industry funded. All of the prospective cohort IDE trials were industry funded (174-178).

2.3.45 Risk of bias

The results of the ROBINS-I risk of bias assessment can be reviewed in Appendix 24. As the study designs were broadly similar, the key principles that underpin each bias domain grading will be outlined. With the exception of two RCTs, all studies were either prospective or retrospective 'uncontrolled before and after follow-up studies'. Risk of bias due to confounding was low as there were no comparisons made against a control arm. Risk of bias in selection of participants was generally low as in retrospective studies all comers were included and in the prospective studies the baseline characteristics were broadly similar, furthermore the follow-up started as soon as the intervention had occurred i.e., there was no way of assessing optimal performers other than the baseline characteristics. Risk of bias in classification of interventions was deemed to be low as classification of the intervention could not be influenced by knowledge of the outcome. Similarly, there was no scope of deviation from the intervention as once the iliac vein stent had been placed, it is not possible to reverse this.

The risk of bias was more concerning when reviewing the domains regarding missing data, outcome assessment, and outcome reporting. Risk of bias introduced by missing data was deemed as moderate because the analyses generally did not account for missing data, and it is possible that those lost to follow-up had differing outcomes to those that remained in the study. Risk of bias arising from the measurement of the outcome was serious across all unblinded studies for any subjective measure. There is a strong relationship between the knowledge of the intervention and expected benefit. This domain was the most significant source of bias across all studies included. Risk of bias in selection of the reported results differed across study designs, with most being at moderate risk of bias. The IDE trials differed in that detailed protocols were published outlining which outcomes were measured and what the study intended to report i.e., were deemed to have a low risk of bias in selection of the reported results. VCSS and venous claudication outcomes are subjective and amenable to influence and therefore had a higher risk of assessment bias in comparison to the dichotomous presence of a venous ulcer. Overall, there was a serious risk of bias in the evidence underpinning the VCSS and venous claudication pooled outcome estimates, and a moderate risk of bias associated with the pooled estimate of venous ulcer healing.

The risk of bias in the single completed RCT was low across most domains as it was double blinded up until 6 months. A trial protocol was not published therefore it was deemed to be at moderate risk of bias for selection of reported outcomes. Most concerningly, the certainty in the evidence was limited by a lack of power and limited external validity, reporting on only 51 participants recruited in a single centre consisting of two subgroups across two arms.

2.4 Discussion

This work package represents the most contemporary and comprehensive summary of the literature on the use of iliac vein stenting in the treatment of CVOO to date. Journal submission guidelines generally restrict the word count for review articles to 3,500 – 4,000 words; the result of this is that the volume of work required to sufficiently explore the literature can rarely be reported. This thesis is the first to provide pooled estimates for patency, based on reconstructed IPD from all relevant study arms using rigorous methodology, treatment efficacy measures, and complications.

2.4.1 Post thrombotic syndrome and non-thrombotic iliac vein lesions are different pathologies with different fates

A striking finding from this work is the distinction between PTS and NIVL with respect to how the pathologies interact with iliac vein stenting. Although, on the face of it, it would appear obvious that a thrombotic pathology would have a different trajectory – however the methodologies and reporting prevalent in the literature would suggest they are one and the same. Of the 109 articles included, 78 of them reported on both PTS and NIVL within the same study – the majority of them failed to report the subgroup results for each pathology. This lack of distinction is also reflected in international guidelines with the ESVS 2022 CVD clinical practice guideline providing a level IIa, grade B, recommendation for stenting in “iliac vein outflow obstruction and severe symptoms/signs”(38). Distilling PTS and NIVL down to the same entity, CVOO, obscures the true outcome and treatment effect for each distinct pathology.

The PP and PAP for PTS was significantly lower than in NIVL. This is accompanied by a significantly higher rate of reintervention in PTS. Technical factors, such as the number of stents required, proportion of stenting below the inguinal ligament, and proportion with total occlusions, were also different to NIVL. Despite this, the clinical practice guidelines, and the general sentiment in the venous sphere, offer no tangible differing recommendations or considerations across the two pathologies.

2.4.2 Treatment response with respect to disease improvement was similar

Interestingly, in spite of the difference in interaction between the stent and the pathology as detailed above, the treatment response in terms of disease severity and venous ulcer healing seems remarkably consistent. Reduction in VCSS for PTS and NIVL was 4.53 (95% CI: 4.00 – 5.05) and 4.69 (95% CI: 4.12 – 5.26) respectively, with a sensitivity analysis demonstrating no moderating effect for pathology. Similar results were also observed in venous ulcer healing.

A hypothesis for this consistency could be that the hemodynamic effect of stenting, in restoring patency, reducing luminal resistance, and reducing venous hypertension, has a similar effect across pathologies. The long-term efficacy will differ as the stent has a greater propensity to occlude in PTS, but the initial haemodynamic response is similar. Although, detracting from this hypothesis, studies investigating the haemodynamic impact of stenting report a lack of consistent substantial hemodynamic improvement ascertained by conventional measurements(255).

2.4.3 Disease-specific markers readily improve, but generic markers are less consistent

The disease severity and disease-specific quality of life measures readily improve after stenting. However, this does not seem to be replicated in overall quality of life (such as the EQ5D-5L). The STEVCO trial reported a significant improvement in VCSS for the stenting arm, yet the EQ5D index value improved more in the medical therapy, note that this was not significant(286). Generally, improvements in the EQ5D index value are expected in both arms as when patients seek medical attention, they tend to have just passed a critical activation energy – which is likely a trough point in their disease severity. However, it would be expected that the intervention provides an additive benefit to generic quality of life which has not been demonstrated. The Abre study reported an improvement in EQ5D-5L out to three years, but this was not a controlled comparison.

2.4.4 Pathology was significantly associated with patency

The covariates traditionally associated with stent patency, such as stenting below the inguinal ligament(302) and total stented length(145), had no identifiable independent effect on stent patency. Once underlying pathology was accounted for, these variables were insignificant. It is possible that the dual inclusion of PTS and NIVL as a single pathology in the literature is responsible for this effect. If PTS is not adjusted for from the outset, all of the underlying covariates for PTS appear as significant variables. Other studies have also reported that there is no difference in patency for PTS or NIVL patients when stenting below the inguinal ligament once appropriate adjustments are made(302).

2.4.5 Large proportions of the data are censored

The results in this meta-analysis also draw attention to the certainty in the evidence base and the potential for industry influence. The proportion of censoring in some studies was high, with little to no mention within the body of the manuscript. Pooled censoring rate across all included studies was 52%, with a range from 3% - 95%. This means that for the estimates reported in the literature, the majority of data is censored. The overall rate of censoring was higher in the retrospective and prospective cohort studies. However, the censoring rate for prospective cohort trials, which are single armed ‘trials’ was also higher than would be considered satisfactory.

The censoring rate is rather opaque in the literature, only to be gained by reconstructing all of the data. When compared to the loss-to-follow-up rates in the studies, the censoring rates are higher. An example of such is one of the prospective cohort trials, stating “Subjects with non-clinically driven TLR [target lesion revascularisation] were censored for primary patency end point reporting to eliminate bias caused by non-study device usage after the index procedure of subjects being intervened on for a stenosis percentage on ultrasound that did not correlate with subject symptoms”(176). The trial protocol on ClinicalTrials.gov states “Clinically driven target lesion revascularization will be adjudicated by the CEC [Clinical Endpoint Committee] based on core laboratory adjudicated imaging data and relevant clinical information provided by the site”. Within this particular study, reconstructed IPD suggests that 40 participants were censored across the PTS and NIVL groups, yet the

manuscript reports only 20 leaving the study (including those with acute DVT). This means that a substantial proportion are being censored without clear mention in the manuscript, potentially for having a reintervention that was deemed ‘not clinically driven’. This cohort trial was undertaken in selected high-volume centres which should have rendered non-clinically driven revascularisation unlikely.

Adding further weight to this concern, the majority of evidence that is relied upon to support the use of venous stenting is delivered by researchers that have industry associations, with 66 of the 107 articles having a perceived or declared conflict of interest.

2.4.6 Limitations

This systematic review was limited to peer-reviewed full text publications. While this approach results in the included studies having met a minimum threshold for scientific integrity, it also means that some of the data in the literature has been missed. Furthermore, the searches to retrieve the articles were undertaken in English. Although no limits were imposed on the language of included articles, the search strategy likely missed some studies in which the title or abstract had not been translated into English.

Although rigorous steps were taken in the reconstruction of IPD, an important limitation is that this analysis is not based on the original data from the included studies. Writing to authors to gather original data is the gold standard when undertaking an IPD analysis. However, in practice, it is rarely possible to secure such large volumes of data. This analysis reconstructed data from 63 study arms, this would not have been possible if original data had been sought in its place. Furthermore, the validation studies of the methodology employed in analysis showed that this approach had excellent precision when compared to the original datasets. Any discrepancy between the reconstructed IPD and original data is unlikely to significantly alter the direction or magnitude of any of the associations reported. The use of reconstructed IPD facilitated the largest ever quantitative review of the literature.

Furthermore, the meta-regression performed, while utilising reconstructed IPD for patency outcomes, regressed against aggregate summary values for covariates. This

approach reduces the power in the meta-regression, reducing the number of comparisons down to the number of study arms included and reporting the given covariate. The result of this is that some significant associations have likely been missed. This is evident in the meta-regression for the NIVL population in which only one significant association was identified.

Venous inflow is infrequently reported in the literature but is increasingly considered as the key metric influencing long-term stent patency(306). Unfortunately, due to the lack of available data on inflow, this analysis was unable to incorporate this potentially important variable.

Lastly, the results produced by the meta-analyses are limited by the bias in the underlying data. The included study arms were nearly all single-armed studies that are subject to a number of biases. This is particularly important for patient-reported and clinically rated outcome measures (such as VEINES QOL/Sym and VCSS). Dichotomous objective outcomes such as ulcer healing, reintervention, and major bleeding are less subject to these biasing influences.

2.5 Conclusion

Evidence from non-randomised studies suggests promising early safety and clinical efficacy results. For PTS, long-term patency is relatively poor with a high rate of reintervention. Traditionally associated factors of success, such as stenting below the inguinal ligament, are potentially confounders for the underlying pathology rather than true independent variables. Large volumes of data are censored in the literature, often without sufficient explanation, reducing the certainty in the evidence and raising concerns regarding the validity of published results. There is a lack of high-quality comparative evidence to support the use of venous stenting in CVOO.

3 – WORK PACKAGE B:

Trend analysis of deep venous procedures performed across England from 1998 – 2024 utilising the Hospital Episode Statistics database

CHAPTER 3: WORK PACKAGE B

Trend analysis of deep venous procedures performed across England from 1998 – 2024 utilising the Hospital Episode Statistics database

The work presented in this chapter has been published as a peer-reviewed manuscript in the *Journal of Vascular Society of Great Britain & Ireland(307).*

3.1 Introduction

3.1.1 A changing deep venous landscape

Deep venous practice has changed dramatically over the past three decades, from the sole treatment being compression therapy and/or anticoagulation, to the relatively routine recanalisation of chronic total occlusions and placement of dedicated venous stents(308). These changes have also been mirrored in the acute setting, with the introduction of percutaneous catheter-delivered pharmacomechanical thrombectomy(309) and non-lytic mechanical thrombectomy(310, 311). These interventions are offered within the NHS in trusts/networks offering complex venous services, with designated acute and chronic clinical pathways(312). In parallel with these changes, the UK venous stent market is now estimated to be worth >$30 million(313). Within the venous sphere, from conferences to workshops, deep venous procedures have a prominent presence. However, it is unclear what the true landscape of venous stenting is.

3.1.2 The rates of venous stenting across the United Kingdom

The current rate of iliac vein stenting in the UK is unknown. A previous article utilising the Hospital Episode Statistics (HES) database, published 2015, aimed to ascertain the rate of open and percutaneous deep venous procedures for acute interventions(314). This report also published a figure of combined chronic and acute stenting interventions over a 10-year period from 2005 – 2015. However, the rate of chronic interventions alone was not published. Furthermore, the analysis was limited to inpatient care only.

The British Society of Interventional Radiology© launched the Venous Registry in 2021 which is a voluntary registry aiming to standardised data on all patients referred for consideration of percutaneous mechanical thrombectomy/thrombolysis in the UK. There has yet to be a publication from the registry and attempts to gather data proved unsuccessful. Furthermore, the National Vascular Registry© does not capture deep venous procedures in their audit process.

More recently, the ESVS launched the European Venous Registry (EVeR), including the UK, in late 2024(315). There are no preliminary reports available on the rate of venous stenting in the UK or Europe.

There are nine available stents approved for venous use, with a further dedicated venous stent under investigation. This suggests there is a growing market value that has yet to be consolidated. Venous stent sales are protected commercial information and interrogation of revenue reports provides little extra information on the rate of venous stenting in the UK.

3.1.3 Establishing the current landscape of iliac vein stenting across England

The HES database contains administrative data acquired using standardised data collection and reporting mechanisms from hospitals located in England within the NHS(316). HES was launched in 1989, initially recording every inpatient hospital episode. Its reach was later expanded to cover four domains:

i) Inpatient episodes;
ii) Outpatient episodes;
iii) Emergency department (Accident & Emergency) attendance; and
iv) Critical Care episodes.

Its primary purpose was to facilitate financial reimbursement for NHS trusts under the ‘Payment by Results’ system. However, an important secondary aim is the use of HES in academic research. Research based on HES data is established across medical and surgical specialties(317, 318) and its coverage has been independently validated(317).

HES contains data on diagnoses coded using the International Classification of Diseases, tenth revision (ICD-10), and procedures coded using the Office of Population Censuses and Surveys Classification of Interventions and Procedures, version 4 (OPCS-4). From this, the number of deep venous procedures, along with the underlying pathologies that serve as their clinical indications, can be extracted and analysed to build a picture of the deep venous landscape.

When interpreting the rate of iliac vein stenting for PTS and NIVL, it is important to also understand this in relation to the rate of iliac vein stents placed for acute indications. Dedicated venous stents are licenced for both indications and, as outlined in the chapter 1.2.6, acute DVT, NIVL and PTS are inherently related. Furthermore, these procedures are generally performed in the same centres, by the same teams, hence from a healthcare planning perspective are intrinsically linked.

3.1.4 Aims

The aims of WP B are as follows:-

1) To undertake a trend analysis of deep venous stenting procedures placed for chronic indications;

2) Interpret this trend in the context of:

i) the rate of acute early thrombus removal procedures; and

ii) the rate of the underlying clinical indication for deep venous procedures (PTS, NIVL, and acute DVT).

3.2 Methods

3.2.1 Data retrieval from the Hospital Episodes Statistics database

The HES database covers all Integrated Care Boards across England, previously the Clinical Commissioning Groups often referred to as CCGs(319). Data processing pathways are available through NHS Digital(320). The HES database is published per financial year, generated from regular data submissions by healthcare providers to NHS commissioners for financial reimbursement. NHS England produce the annual official statistic reporting series which are available to access for national monitoring and research purposes.

Each hospital episode is defined as a finished admission under the care of a named consultant. It is represented once within the database, with the primary diagnosis requiring admission and the most resource intensive procedure being selected. Outpatient care episodes include initial and follow-up appointments each year. As for the hospital episodes, they represent a prevalence of disease, rather than an incidence, as the same person can present more than once with the same diagnosis. Each procedure performed is represented once within the database, individual patients only feature once unless they have a further procedure. Ad-hoc data quality checks are performed, and investigations based on information supplied by providers or from feedback from HES data users.

Searches of the HES database for hospital inpatient care and outpatient care episodes were performed on the 29th of September 2022 and then updated on the 6th of January 2025. Records were searched from 1998 up until 2024, spanning a 26-year period.

3.2.2 Rationale for target diagnoses and procedures

There are no ICD-10 codes that can directly define CVOO. PTS has a unique code in the ICD-10 classification system. PTS is most common after proximal iliofemoral DVT, however a proportion of PTS will be due to distal DVT and therefore lack a proximal iliac lesion(321). Therefore, while there is an ICD-10 code for PTS, the PTS group will over-represent the potential number of candidates for iliac vein stenting.

There is no unique diagnostic code for NIVL within the ICD-10 system. The most relevant code pertains to chronic venous insufficiency as a whole “I87.2 Venous insufficiency (chronic)(peripheral)”. Although broad, the other codes available likely mean that its use is reduced down to deep venous pathologies alone. There are several other distinct codes relevant to varicose veins (such as I83.9) and ulceration (L97.9). These are more numerous and easier to identify in comparison to I87.2, which means that for those presenting with superficial venous reflux it is unlikely that the I87.2 code will be utilised as the primary diagnosis. It is more likely to feature as a secondary diagnoses in these instances. Therefore, I87.2 is generally used to represent deep venous pathologies, which are otherwise unrepresented, both obstructing and refluxing of primary eitology (secondary causes would be coded as PTS). As for PTS, the CVI group will over-represent the potential number of candidates for iliac vein stenting.

Acute DVT is represented by a well-recognised set of ICD-10 codes and features in the National Clinical Coding Standards ICD-10, 5th edition, as a case example(322). DVT is categorised by its location: IVC, femoral vein, and deep veins of the lower extremity. Importantly, there are a separate group of codes for superficial venous thrombosis (I80.0). ICD-10 amendments were reviewed in full to assess for changes in coding over time(323).

Deep venous procedures for chronic indications generally describe balloon venoplasty and placement of a stent. Importantly, they lack a descriptor for thrombolysis or thrombectomy. Unlike for arteries, HES lacks an anatomical descriptor for veins when describing venoplasty and stenting procedures. This means that the subclavian vein will be included in the thrombolysis, non-caval stents, and venoplasty codes. There are discrete codes for interventions undertaken to maintain fistula patency for renal dialysis access (I74.3) and for interventions undertaken in the pulmonary circulation. As the primary procedure is coded as the most resource intensive, an early thrombus removal procedure in which there is subsequent placement of a stent is likely to be coded as L99.3 “Percutaneous transluminal venous thrombolysis with reconstruction”. This would reflect an admission in which a patient received a period of catheter-directed thrombolysis (e.g. two days) prior to undergoing stenting for an underlying compression during the same index admission. ICD-10 and OPCS-4 codes were ratified by expert Vascular Surgeons.

3.2.3 Data retrieval – codes extracted

As outlined previously, diagnoses and procedures were retrieved using the ICD-10 and OPCS-4 codes respectively. The Classifications Browser, 5th edition, was used to search for codes relevant to deep venous disease(324). Both primary and secondary codes are available within the dataset. Primary diagnoses and procedure, being the key attribute leading to the hospital episode, were extracted.

Regarding diagnostic codes, a total of five codes were identified to capture PTS, CVI, and DVT diagnoses, see Table 20. Regarding procedure codes, a total of 12 codes were identified to retrieve percutaneous deep venous procedures, see Table 21.

Table 20: International Classification of Diseases (ICD-10) used to retrieve primary diagnoses from the Hospital Episode Statistics database

Category	ICD-10	Diagnosis description
PTS	I87.0	Post thrombotic syndrome
CVI	I87.2	Venous insufficiency (chronic)(peripheral)
DVT	I80.1	Phlebitis and thrombophlebitis of femoral vein
	I80.2	Phlebitis and thrombophlebitis of other deep vessels of lower extremities
	I82.2	Embolism and thrombosis of vena cava

CVI: Chronic venous insufficiency
DVT: Deep vein thrombosis
ICD-10: International Classification of Diseases 10th Edition
PTS: Post thrombotic syndrome

Table 21: Office of Population Censuses and Surveys Classification of Interventions and Procedures, version 4 (OPCS-4) used to retrieve primary diagnoses from the Hospital Episode Statistics database

Category	OPCS-4	Procedure description
Vena cava stent	L79.3	Insertion of stent into vena cava NEC
Percutaneous venoplasty	L94.6	Percutaneous transluminal venoplasty
	L94.7	Percutaneous transluminal balloon angioplasty of vein NEC
	L99.1	Percutaneous transluminal angioplasty of vein NEC
Other venous stent	L94.5	Percutaneous transluminal insertion of stent into vein NEC
	L99.2	Percutaneous transluminal stent reconstruction of vein
Percutaneous early thrombus removal	L96.1	Percutaneous mechanical thromboembolectomy
	L96.2	Percutaneous aspiration thromboembolectomy
	L96.8	Other specified percutaneous removal of thrombus from vein
	L96.9	Unspecified percutaneous removal of thrombus from vein
	L99.3	Percutaneous transluminal venous thrombolysis with reconstruction
	L99.4	Percutaneous transluminal venous thrombolysis NEC

NEC: Not elsewhere classifiable
OPCS-4: Office of Population Censuses and Surveys Classification of Interventions and Procedures, version 4

3.2.4 Statistical analysis

Analysis included simple descriptive statistics of the data in addition to trend testing. Parametric assumptions were not fulfilled, therefore linear regression (with time as predictor), or Pearson correlation coefficient, could not be utilised to assess for significant trends in the data. Quantile-quantile (Q-Q) plots of the residuals from simulated linear regression models across a range of variables were constructed to assess if the residuals were normally distributed. As the residuals were not normally distributed, non-parametric techniques were utilised. In order to assess for the trend of a single non-parametric variable over time, the Mann-Kendall trend test was deployed as has been demonstrated elsewhere in the wider scientific literature(325, 326). Mann-Kendall trend testing was undertaken in R utilising the 'Kendall' package(327).

Appendix 25 contains the pertinent code used to perform the Mann-Kendall test. Importantly, Kendall's tau was not used as the data is an interval time series rather than a test of association between two variables. The Mann-Kendall test compares each datapoint with every datapoint appearing after it in the time series and assigns a positive or negative 'sign' depending on if the data is larger (increasing) or smaller (decreasing).

The first datapoint (x_1) is compared to each datapoint afterwards in succession (x_{n+1}). If $x_1 < x_{n+1}$, then a sign of (+1) is determined. If $x_1 > x_{n+1}$, then a sign of (-1) is determined. These signs are determined for each datapoint, and a total sum of the signs is calculated. The variance of the sum is then calculated which forms the basis of the Z-statistic standardisation(328), see Figure 48.

Figure 48: Equation used to calculate the variance and the associated Z-statistic in the Mann-Kendall test(328)

$$Variance\ (S) = \frac{\big(n\ (n-1)\big)(2n+5)}{18},$$

$$Z = , \frac{S-1}{\sqrt{Variance\ (S)}}, \quad where\ S > 0$$

S: *Sum of the signs*
n: *Number of datapoints*
Z: *Z-statistic*

Additionally, non-parametric regression techniques were used to smooth the data in order to identify an overall pattern. LOcally WEighted Scatterplot Smoothing (LOWESS), as described by Cleveland et al. was also undertaken(325, 326) using the 'lowess' function in R, see Appendix 25 for the code used. LOWESS fits a regression model to each datapoint based on a subset of the data that surrounds that given point. The weights for each point are calculated using a tricube function. This function assigns a higher proportion of the weight to data points that are closer in proximity to the data point being smoothed. The neighbourhood scaling factor, referred to as 'span', is used to determine how closely the smoothed curve will fit the data. A small span means the regression line will fit closer to the data values whereas a larger span will create a smoother, less changing, curve to describe the data. For a given data point being smoothed (x_1), the weight for that point (w_1) can be calculated using the tricube function in Figure 49(329).

Figure 49: Tricube equation used to calculate weight in the LOcally WEighted Scatterplot Smoothing model

$$w_1 = \left(1 - \left|\frac{x_n - x_1}{d}\right|^3\right)^3$$

w_1: weight for point being smoothed
x_1: point being smoothed, x_n: neighbouring datapoint
d: numerical distance to furthest point in neighbour scaling group

Forecasting for future trends was explored utilising the 'forecast' package in R. However, the data was not sufficiently stationary, i.e., the variability was too high, and lacked the required number of timepoints, therefore no forecasting was undertaken.

3.2.5 Ethical approval

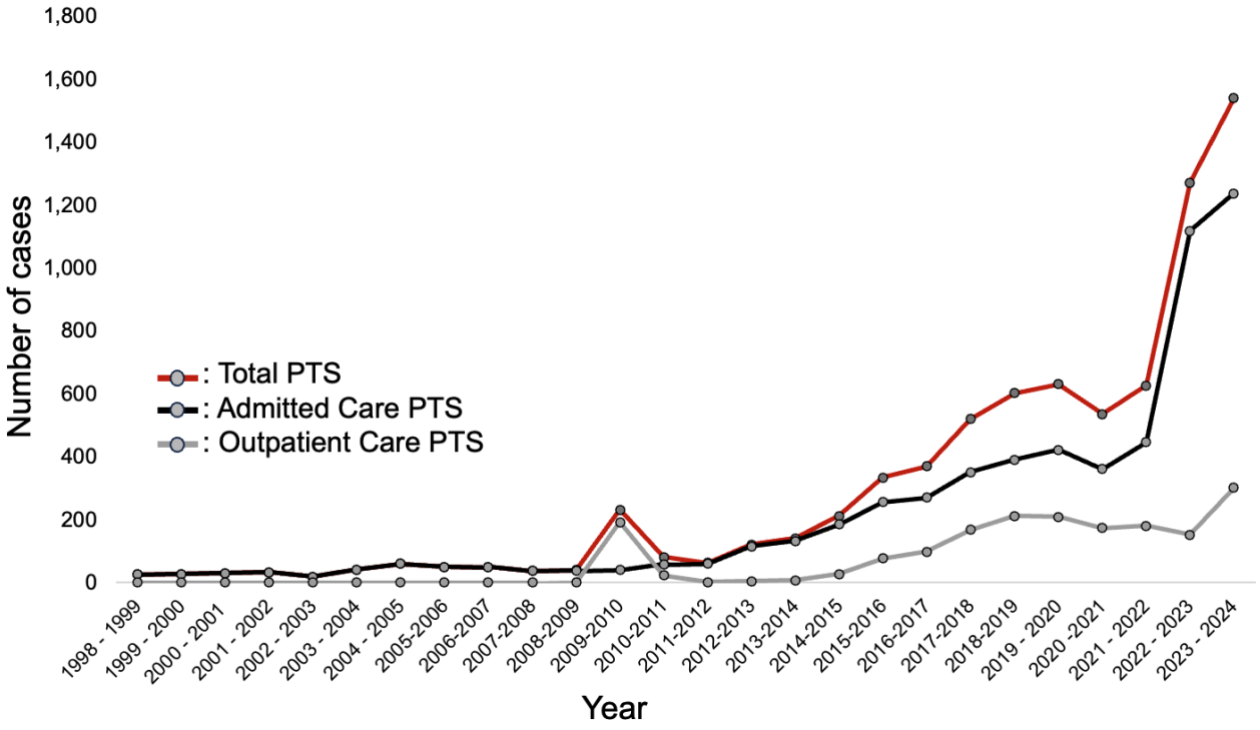
Approval from the Confidentiality Advisory Group and Health Research Authority's Research Ethics Committee was not sought as this analysis utilised anonymised aggregate data that is publicly available through the HES data publishing reports. No identifiable patient data was used or stored in the process of this analysis.

3.3 Results

3.3.1 Rate of care episodes with primary diagnosis of post thrombotic syndrome

Figure 50 illustrates the number of care episodes across both admitted patient care and outpatient care with a primary diagnosis of PTS. Overall PTS care episodes have significantly risen from 1998 (n=26), particularly after 2012 (tau=0.852, p<0.001). The rate of increase is consistent up until 2019 where there is a sharp decline the following year, which is then followed by a rapid increase from 2021 onwards to its peak (n=1,540). Admitted patient care and outpatient care follow a similar pattern, while admitted patient care constituted a greater proportion of the episodes. Both admitted patient care episodes and outpatient care episodes have significantly increased (tau=0.863, p<0.001 and tau=0.742, p<0.001 respectively). PTS is rarely the primary diagnosis in the outpatient setting (maximum value: 303). The overall reported number of episodes for PTS was low across all timepoints, range: 26 – 1540.

Figure 50: Number of episodes with primary diagnosis of post thrombotic syndrome between 1998 and 2024

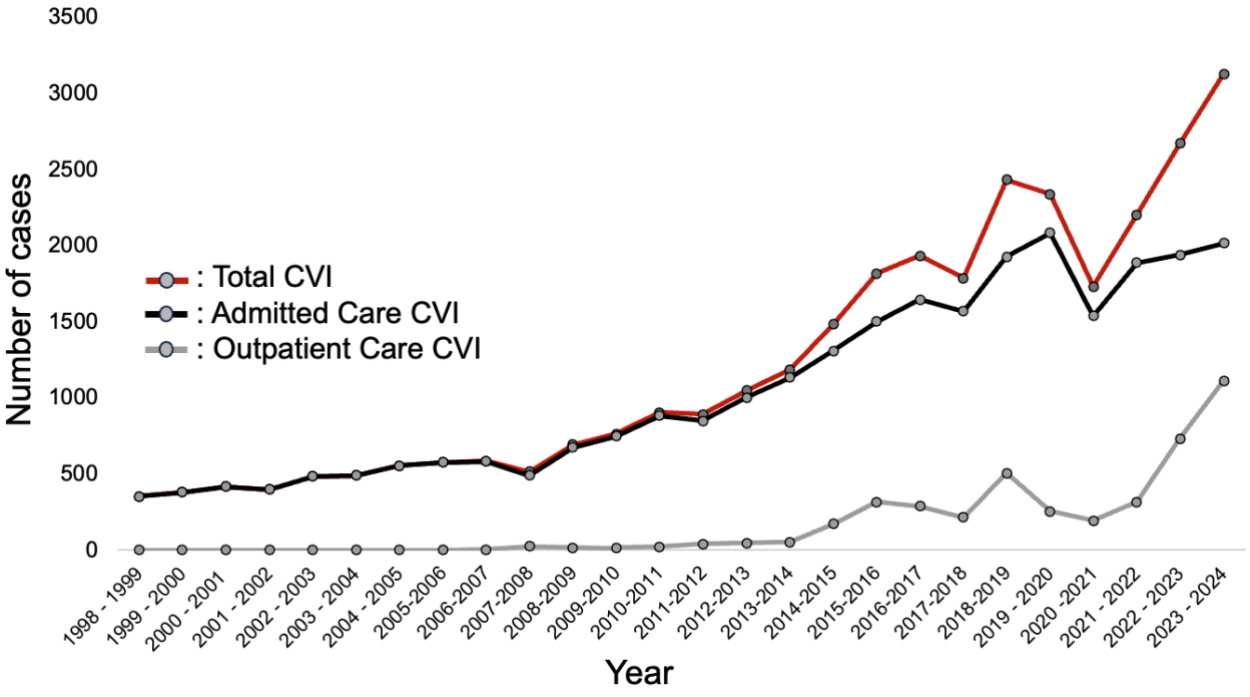


PTS: Post thrombotic syndrome

3.3.2 Rate of care episodes with primary diagnosis of chronic venous insufficiency

Figure 51 illustrates the number of care episodes across both admitted patient care and outpatient care with a primary diagnosis of CVI. Overall CVI care episodes have significantly risen from 1998 (n=354) (tau=0.908, p<0.001). As for PTS, there is a steady rate of increase up until 2019 where there is a sharp decline the following year, which is then followed by a rapid increase from 2021 onwards up to its peak number of diagnoses (n=3,128). Both admitted patient care episodes and outpatient care episodes have significantly increased (tau=0.912, p<0.001 and tau=0.830, p<0.001 respectively). Primary diagnosis of CVI as an outpatient ranged from 0 – 1,112. Primary diagnosis of CVI for all care episodes ranged from 354 – 3,128.

Figure 51: Number of episodes with primary diagnosis of chronic venous insufficiency between 1998 and 2024

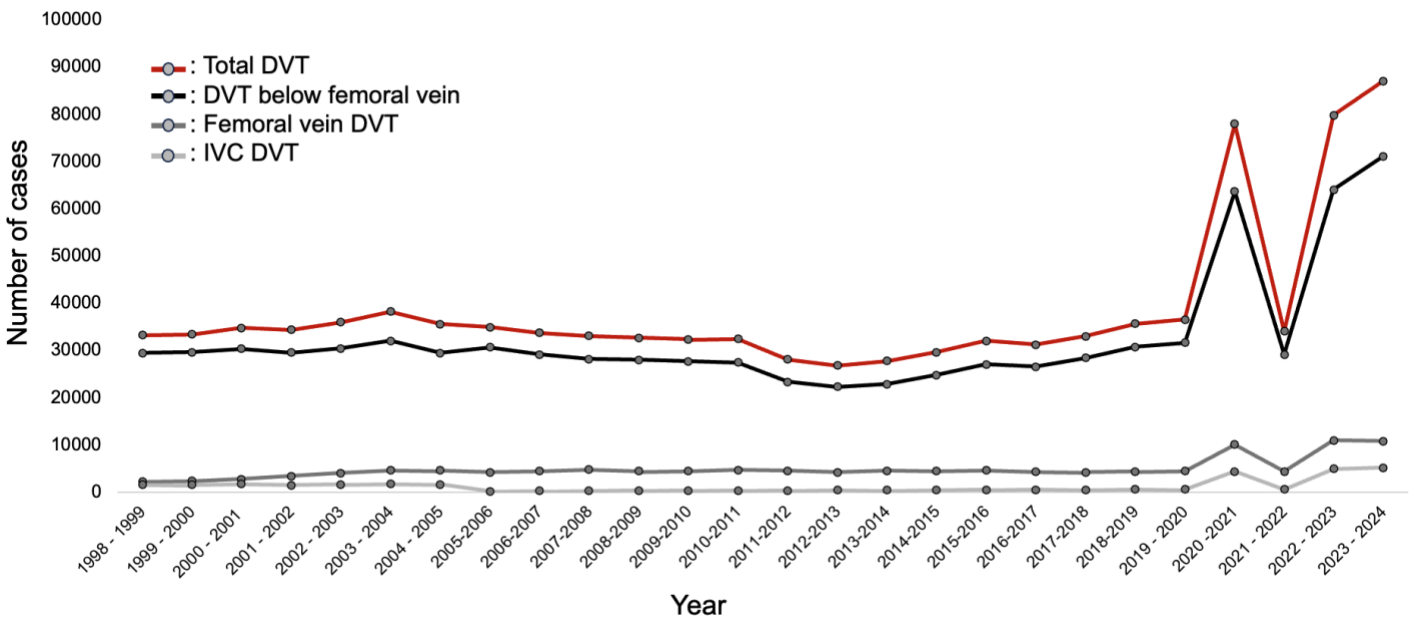


CVI: Chronic venous insufficiency

3.3.3 Rate of care episodes with primary diagnosis of deep vein thrombosis

Figure 52 illustrates the number of care episodes, for both admitted patient care and outpatient care, with a primary diagnosis of DVT. Overall, the DVT rate has not significantly changed since 1998 (n=33,205) (tau=0.04, p=0.791). The rate of DVT pre-2020 i.e., between 1998 – 2020 was decreasing (tau=-0.273, p =0.08), although this did not meet the significance threshold. Since 2019, there has been large fluctuations in the DVT rate, with an initial spike in 2020 before returning to the baseline rate the following year. The rate then increases rapidly again peaking at its highest ever value in 2023 (n=86,959). The rate of outpatient care episodes with a primary diagnosis has significantly increased since 2004 (n=274) to 2023 (n=8,895) (tau=0.724, p<0.001). The relative proportion of IVC, femoral, and lower limb DVT have remained constant over time. The overall reported numbers of episodes for DVT ranged from 26,770 – 86,959.

Figure 52: Number of episodes with primary diagnosis of deep vein thrombosis between 1998 and 2024



DVT: Deep vein thrombosis
IVC: Inferior vena cava

3.3.4 Rate of care episodes with primary procedure of percutaneous deep venous interventions for chronic indications

Figure 53 illustrates the number of care episodes, for both admitted patient care and outpatient care, with a primary procedure code representing a deep venous procedure for a chronic indication. The time series was reduced, extending from 2005 – 2024, as there were no relevant interventions performed between 1998 – 2004. Overall, the rate of procedures for chronic indications has plateaued (tau=0.392). There is an appreciable change in the rate of procedures from 2019 onwards. From 2006 – 2019, the total rate of procedures significantly increased from 516 to its peak maximum number of 1,678 (tau=0.676, p<0.001). Post 2020, overall rates have been lower, (2020: n=1,165) changing the trend over the observation period. Figure 54, illustrating the LOWESS curve, best demonstrates this overall plateau. The rate of outpatient i.e., not admitted care, procedures significantly increased across all timepoints (tau=0.625, p<0.001).

This is a consistent pattern across the different categories of interventions. Overall, balloon venoplasty has plateaued (tau=0.345) whereas prior to 2019 the rate was significantly increasing (tau=0.524, p <0.001). Balloon venoplasty was the most frequent procedure across all timepoints, range: 247 – 828. Vena cava stents demonstrated a non-significant decreasing trend overall (tau=-0.135), whereas prior to 2019 it had essentially plateaued.

The only category of chronic interventions which has persisted to increase throughout all timepoints is the placement of non-caval stents. Overall rate for non-caval stents significantly increased from 2005 – 2024 (tau=0.649, p<0.001). As for other procedures, the number peaked in 2019 (n=525) prior to decreasing down to a lower level in 2020 (n=303). Figure 55 shows the LOWESS curve for non-caval stents which demonstrates how the overall trend has increased. Non-caval stents was one of few variables which demonstrated parametric properties and was suitable for linear regression. Appendix 26 shows the Q-Q plot of the residuals indicating relative normality.

Figure 56 represents the overall increasing trend for non-caval stents as demonstrated by the linear regression model with time as a moderating variable (p<0.01). The rate of non-caval stent ranged from 83 – 525.

Figure 53: Number of episodes with primary procedure code representing interventions for chronic indications between 2005 and 2024

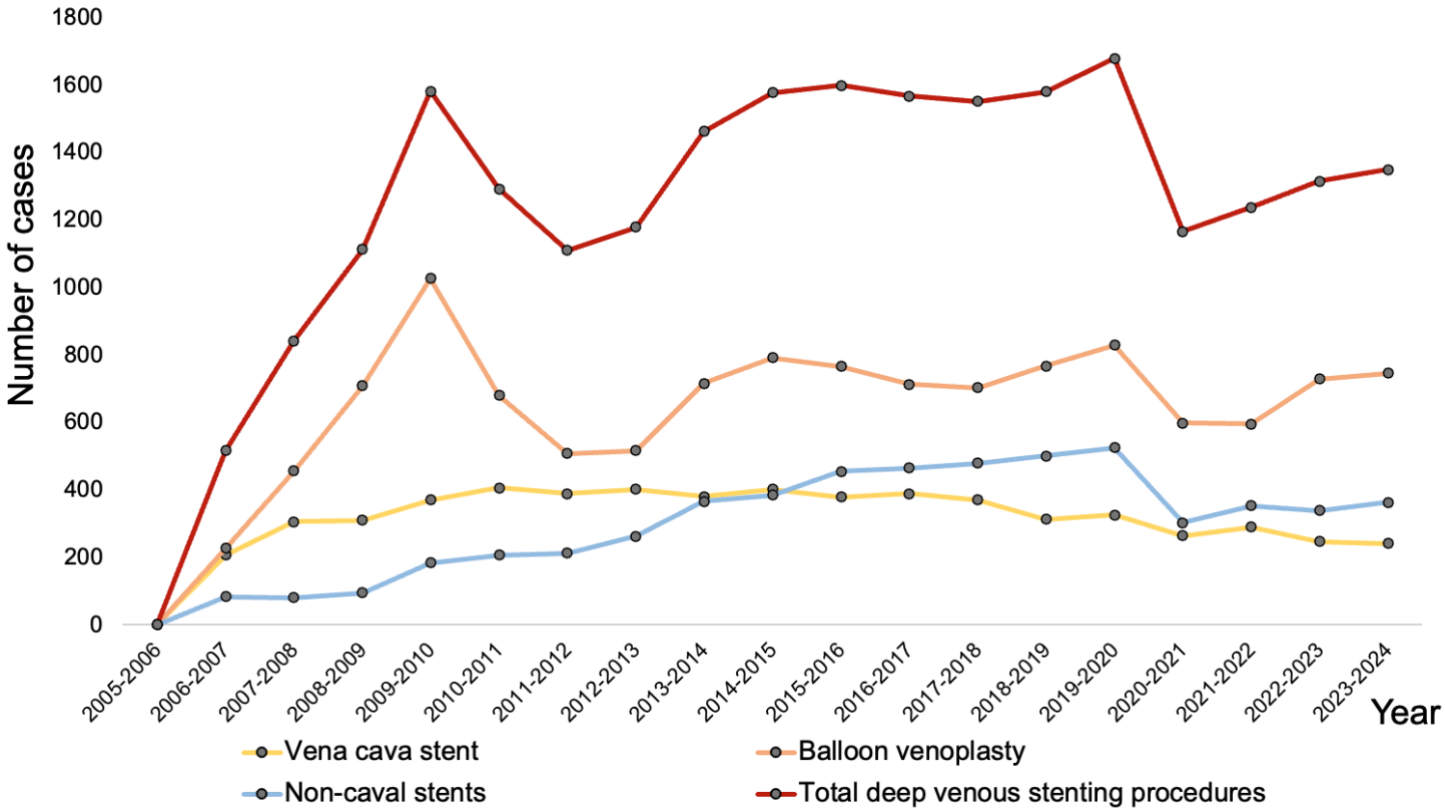
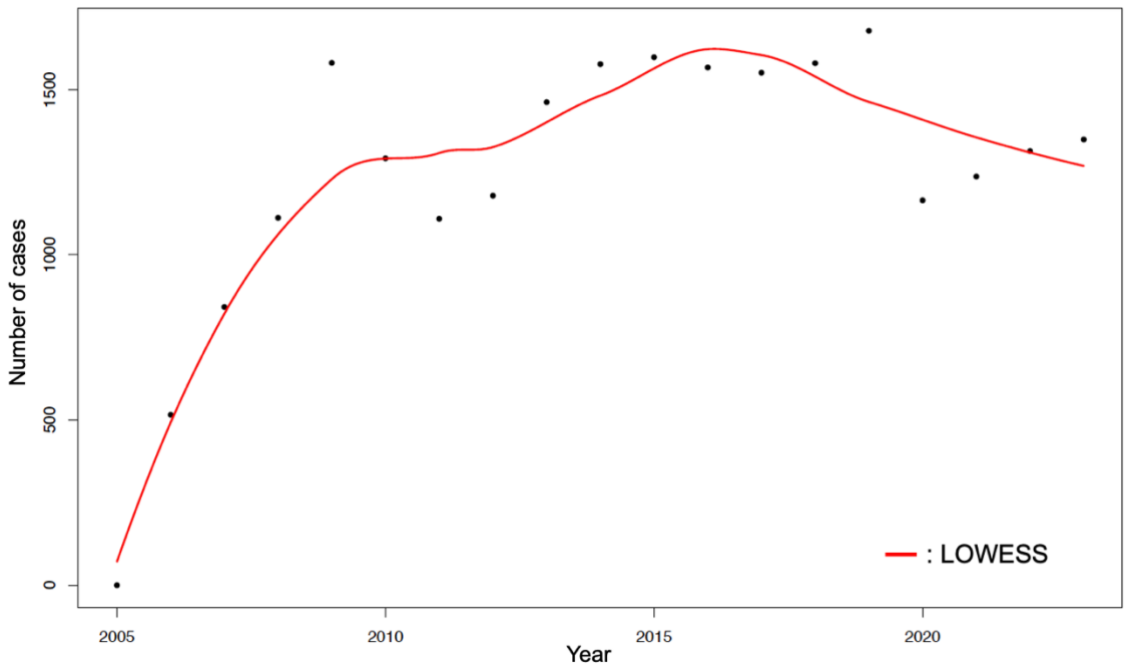
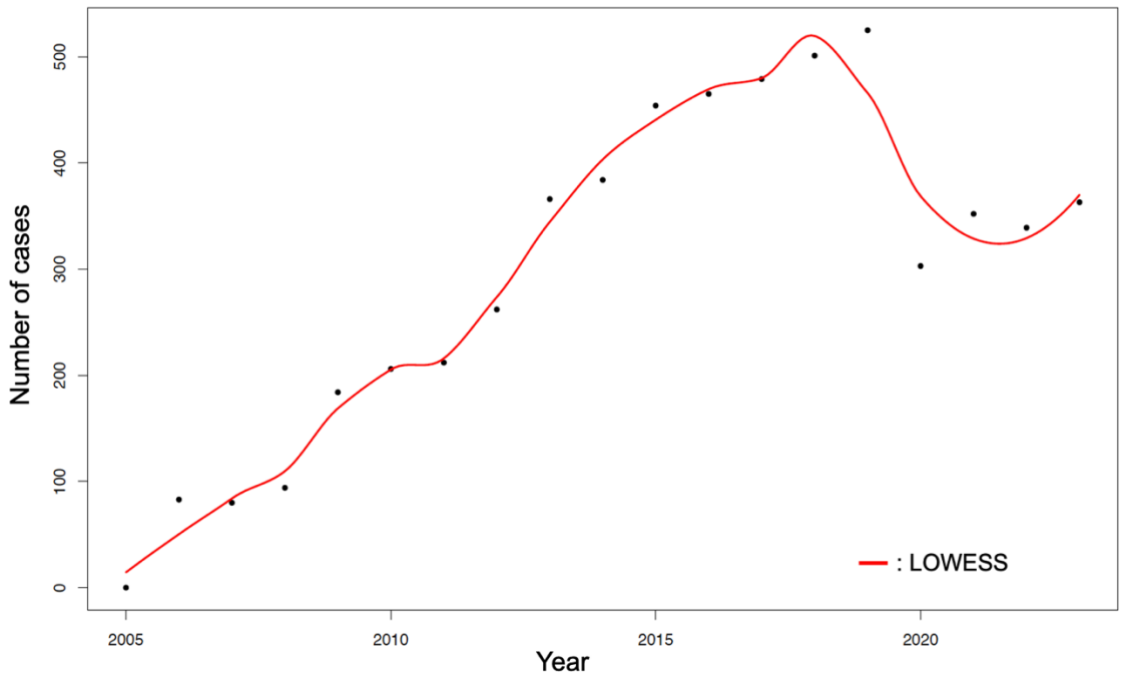


Figure 54: LOcally WEighted Scatterplot Smoothing graph of the number of primary procedures pertaining for chronic indications (all cases) between 2005 and 2024



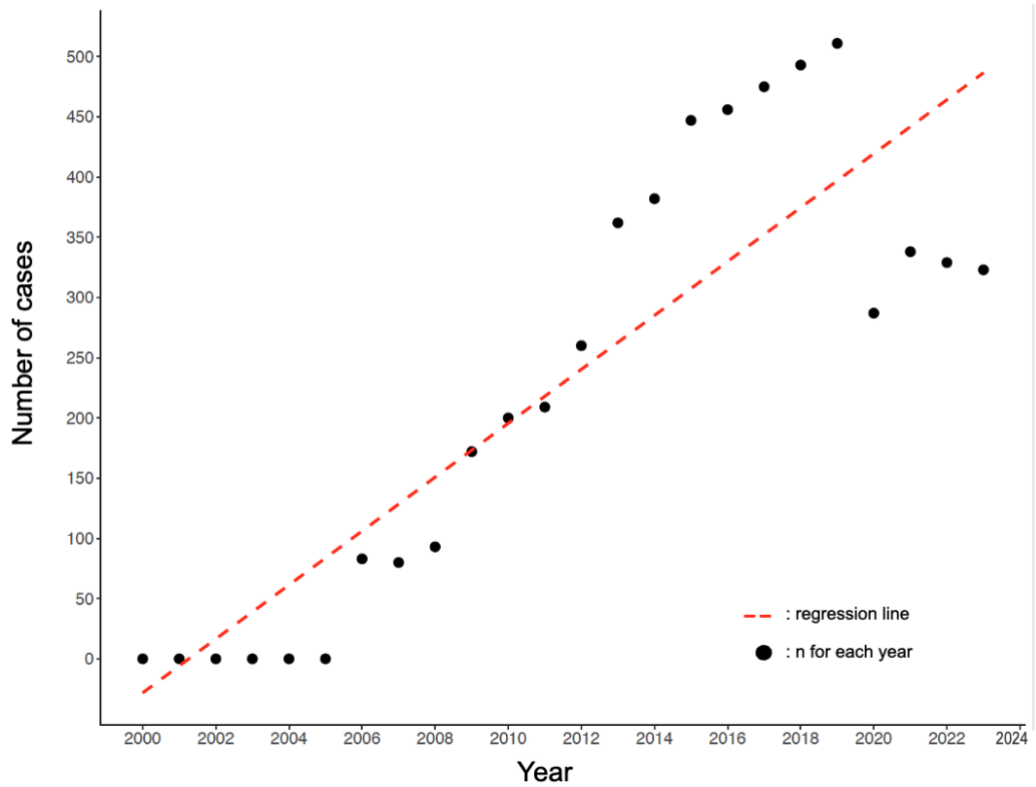
LOWESS: LOcally WEighted Scatterplot Smoothing

Figure 55: Locally Weighted Scatterplot Smoothing graph of the number of primary procedures for non-caval stents (all cases) between 2005 and 2024



LOWESS: LOcally WEighted Scatterplot Smoothing

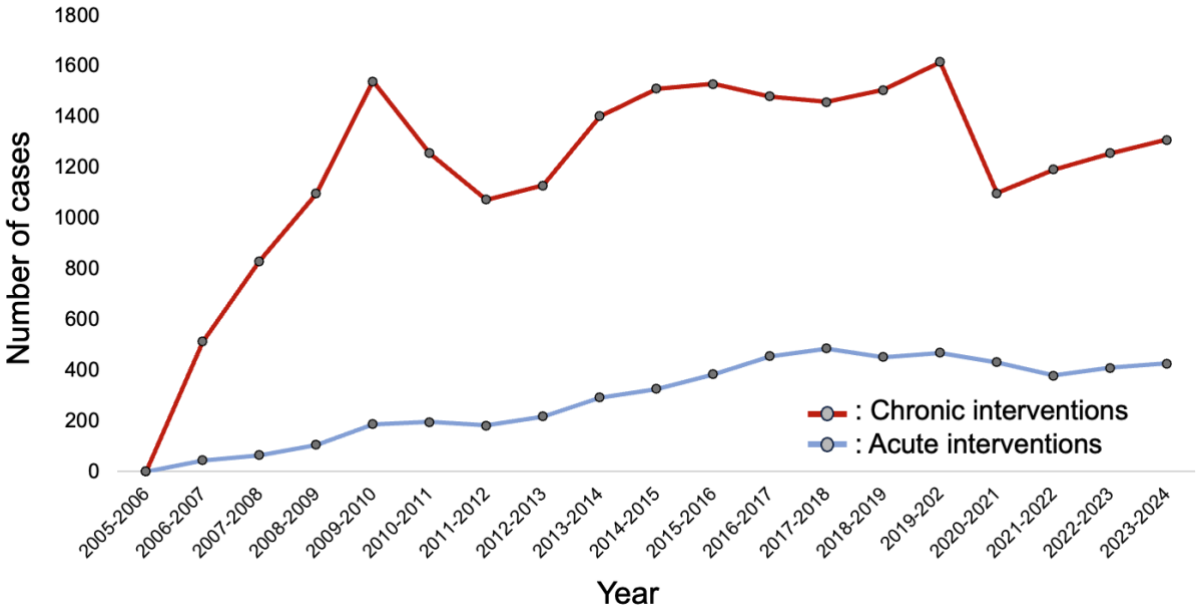
Figure 56: Linear regression for the number of primary procedures for non-caval stents (all cases) between 2005 and 2024



3.3.5 Rate of hospital episodes with primary procedure of early thrombus removal procedures

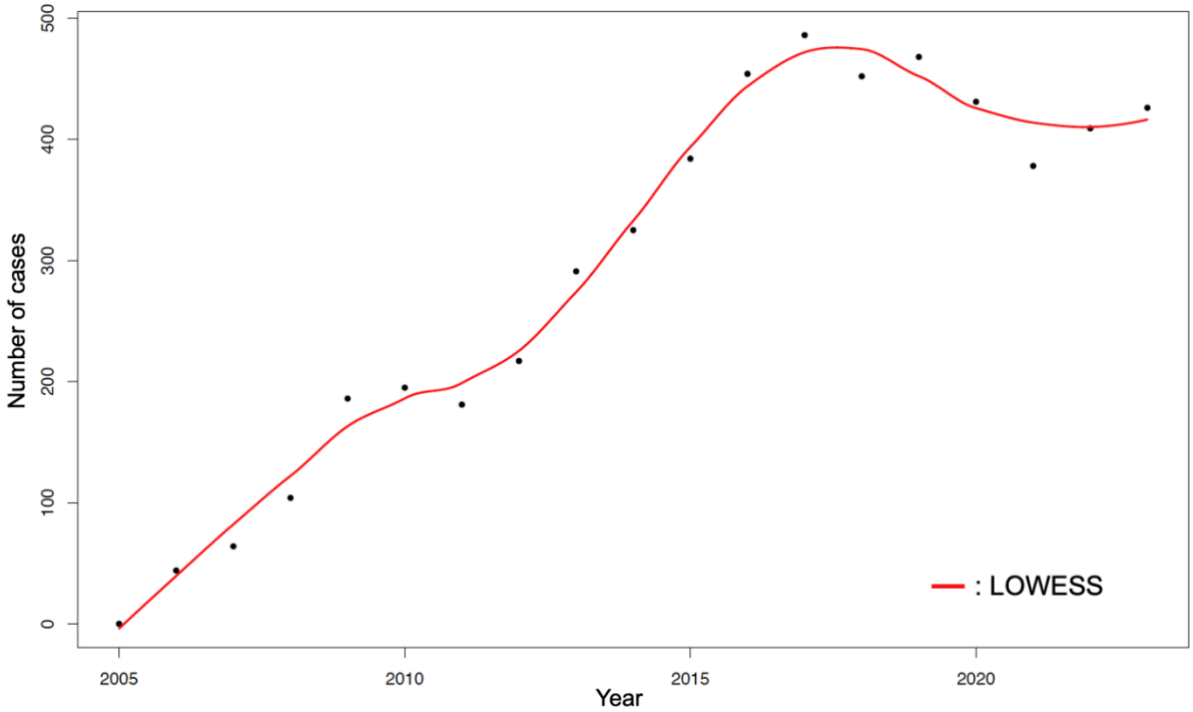
Figure 57 illustrates the total number of procedures performed for early thrombus removal in acute DVT (acute interventions) alongside the total number of procedures performed for chronic indications (chronic interventions) from 2005 - 2024. The rate of acute early thrombus removal procedures has significantly increased (tau=0.708, p<0.001). The number of acute interventions peaked in 2019 at 468 cases. Acute interventions fell modestly after 2019 but not to the same extent as chronic interventions. Thrombolysis with reconstruction (i.e., thrombolysis and stenting) has significantly increased (tau=0.662, p<0.001), peaking in 2020 with 67 cases. Percutaneous mechanical and aspirational thrombectomy demonstrated the strongest upward trend across all timepoints (tau=0.909, p<0.001), with the peak number in 2023 (n=217). Figure 58 shows the LOWESS curve for acute interventions which demonstrates how the overall trend has increased. At all timepoints, the number of chronic interventions is greater than the number of acute interventions.

Figure 57: Number of episodes with primary procedure codes for acute and chronic interventions between 2005 and 2024



Acute intervention: Procedure consisting of thrombolysis or thrombectomy
Chronic interventions: Procedure consisting of venoplasty and/or vein stenting with no mention of thrombectomy or thrombolysis

Figure 58: Locally Weighted Scatterplot Smoothing graph of the number of primary acute thrombectomy / thrombolysis procedures (all cases) between 2005 and 2024.



LOWESS: LOcally WEighted Scatterplot Smoothing

3.4 Discussion

This chapter presents the most comprehensive report to date on the status of deep venous interventions in England using data from a national database over a 26-year period. This analysis was able to show the scale of chronic interventions across the country, the numbers exist in the low thousands (rather than the tens of thousands). This work has several strengths over other studies published in the literature(314), however, still struggles to ascertain the rate of iliac vein stenting due to its limitations. Firstly, care episodes across both inpatient and outpatient settings were retrieved for a comprehensive list of codes covering all percutaneous deep venous procedures. Secondly, thorough statistical considerations were made when interpreting the data, ensuring that the that non-parametric techniques were used. Lastly, a detailed discussion on the limitations of using HES data for vascular pathologies is provided. Where possible, the trends reported will be explored in the wider context of the literature.

3.4.1 The rate of chronic interventions has plateaued

A rapid increase in chronic interventions occurred between 2005 – 2010. As outlined in chapter 1.4.1, stenting of the superior vena cava and subclavian vein were reported in literature in the mid 1990s. This was followed by the two landmark case series for iliac vein venoplasty and stenting published in the year 2000 by the teams at Stanford and Mississippi which showed promising early results for CVOO(129, 257). This likely prompted the relatively rapid uptake of subclavian and iliac vein venoplasty and stenting. Notably, the Veniti Vici Venous Stent© received a CE Mark approval on the 6th of November 2013. The rapid increase in interventions occurred prior to this point, suggesting these procedures represent the placement of Wallstent™ stents in both upper and lower deep veins. The rate of chronic interventions abruptly fell during the coronavirus pandemic. The Vascular Society of Great Britain & Ireland wrote a letter on the 27th of March 2020 to all its members recommending deferring all elective venous surgery. Since the pandemic, the number of chronic interventions has yet to return to its pre-pandemic levels.

The rate of non-caval stenting demonstrated a persistent significant increasing trend. The inference from this is that either subclavian vein and/or iliac vein stenting is increasing. There are only a few reasons to stent the subclavian vein given the treatment for Paget-Schrötter syndrome is largely either conservative management or first-rib resection(330). Therefore, it could be considered that this increase is due to the introduction of dedicated venous stents and an increasing uptake in iliac vein stenting. As outlined in WP A, the two RCTs investigating the use of iliac vein stenting in CVOO did not provide compelling evidence, therefore they are unlikely to have measurably influenced the rate of venous stenting for CVOO at any timepoint.

3.4.2 Increasing trend of early thrombus removal procedures

This analysis has demonstrated that the rate of early thrombus removal procedures has significantly increased. However, the overall number of early thrombus removal procedures remains low. The bulk of evidence in this area concerning lower limb DVT consists of three large RCTs investigating whether early thrombus removal in acute proximal DVT utilising catheter-delivered therapies reduces the risk of subsequent PTS(58, 61, 331). The CaVenT study, published in 2012, was the only RCT to report a significant difference in favour of early thrombus removal for PTS prevention(58). This significant finding corresponds with an increasing rate of percutaneous thrombus removal procedures within the NHS from 2011 to 2017. However, subsequent publication of the ATTRACT trial in 2017, the largest of the three RCTs, conflicted the evidence supporting the efficacy of early thrombus removal finding no significant difference in the overall rate of PTS(61). Most recently, the CAVA trial, published in 2020, utilised ultrasound-accelerated catheter-directed thrombolysis and reported no significant difference in the rate of PTS at 12 months(331). The impact of the ATTRACT and CAVA trials are obscured by the impacts of the coronavirus pandemic. It is unclear if these two trials have restrained the widespread adoption of early thrombus removal procedures due to uncertainty in the evidence.

3.4.3 The trends visualised in the primary diagnoses for post thrombotic syndrome likely reflect code utilisation patterns

Both PTS and CVI increased significantly over the observation period. However, the relative absolute number of diagnoses were low across all timepoints. We can logically conclude that the burden of disease for PTS must be greater than the reported numbers considering the overall population size of 56 million people across England and the rate of DVT. PTS affects ~20% of those with distal DVT and as many as 50% of those with proximal DVT(321). Therefore, the low numbers likely reflect a lack of utilisation of the PTS code rather than a low burden of disease. The rapid increase in PTS from 2020 onwards mirrors the large fluctuations in acute DVT. However, the scale of PTS diagnoses is still a fraction of the likely true prevalence of disease, suggesting that the certainty in the estimate is low.

3.4.4 Acute deep vein thrombosis has increased since the coronavirus pandemic

This analysis demonstrated a downward trend for the rate of DVT from 1998 which approached significance prior to the coronavirus pandemic (which reached the UK in March 2020). It could be hypothesised that this modest decline is due to national initiatives to reduce VTE such as the National Commissioning for Quality and Innovation VTE risk assessment target alongside the launch of a National VTE Prevention Programme by the Department of Health in 2010(332). Hospitals across the UK are now consistently risk assessing >95% of hospital inpatients. The rate of DVT dramatically increased across the year 2020 – 2021 which corresponded to the peak incidence of infections during the COVID-19 pandemic in the UK(333). Incidence of DVT in those testing positive for COVID-19 has been demonstrated to be as high as 16%, coinciding with the 2.4 fold increase reported in this analysis(334).

Rates of IVC thrombosis remain unchanged within the study period. However, there was a stark reduction in 2005, from which there has been a slow increase each year (non-significant). The impact of the number of admissions for IVC filter placement over this period was reviewed, however the decline appears unrelated. Furthermore, this change cannot be explained by changes in coding descriptors i.e., ICD-9 to ICD-10.

Given this sustained increase in DVT, it can be inferred that the number of potential candidates for early thrombus removal procedures has also increased. This in turn, leading to a continued increase in the rate of iliac vein stenting in the acute setting.

3.4.5 Limitations

There are several limitations in the interpretation of this analysis. HES data are collated from service-providers as part of the Commissioning Data Set and are used for monitoring and reimbursement. This data is not collected primarily for research purposes and its accuracy cannot be assured.

The most significant limitation is the unavoidable inclusion of subclavian and superior vena cava procedures. This is due to a lack of granularity in the procedural codes utilised by the HES database. To combat this, the analysis focused on the broad aggregate trend of endovenous procedures over time while contextualising this with the trends of the underlying indications for these procedures. Use of the primary procedure code in retrieval (rather than including secondary procedure codes) will offset this to a degree. For example, if subclavian venoplasty is performed to aid placement of a central line, the primary procedure should be coded as L91.2. Hence, it should not be captured in this dataset. However, the lack of purpose designed codes remains a significant limitation.

It is also not possible to ascertain the clinical indication from the procedure codes. Within this context, the primary procedure performed is often associated with a specific presentation, however, as this is not formally recorded within the HES data, it relies on an inference of standard clinical practice. Additionally, only the most resource intensive procedure is represented as a single primary procedure code. When reviewing the rates, we can likely see this effect at work. The rate of ‘mechanical thrombectomy’ demonstrates a stronger increasing trend in comparison to ‘thrombolysis with reconstruction’. However, this does not mean that the rate of venous stenting in acute DVT is not increasing to the same degree as mechanical thrombectomy, it is just that there is no code for mechanical thrombectomy in addition to reconstruction. In this example, the primary procedure is coded as mechanical thrombectomy rather than thrombolysis with reconstruction given the higher cost of

thrombectomy devices. Therefore, using primary procedures within HES data is likely to under-report the number of iliac vein stenting procedures undertaken.

ICD-10 codes also fail to reflect vascular pathologies with sufficient detail to identify the rates of PTS and NIVL precisely. This analysis is intended to be used to assess the scale and trend of the disease, therefore precise numbers are not mandatory. It shows us that the diagnoses are in the scale of a couple of thousand, not millions.

Given the above limitations, the ICD-10 and OPCS-4 coding structures are not well suited to complex vascular pathologies and specialist procedures.

3.5 Conclusion

Although exact estimates were not possible from this analysis, the scale of deep venous procedures across England lies in the low thousands annually. These numbers would suggest that the practice is established and being routinely performed but has yet to be widely adopted. The overall rate of deep venous procedures for chronic indications has plateaued. Rates of non-caval stents, specifically, have significantly increased despite the coronavirus pandemic. Furthermore, the rate of DVT has demonstrated a non-significant increase since the coronavirus pandemic, this is likely to have future implications in the rate of PTS and number of participants eligible for stenting in the acute and chronic setting. Considering these insights, high-quality evidence to provide certainty of effectiveness for iliac vein stenting in CVOO would be beneficial.

4 – WORK PACKAGE C:

Single centre retrospective cohort study investigating factors associated with successful iliac vein stenting in the management of CVOO

CHAPTER 4: WORK PACKAGE C

Single centre retrospective cohort study investigating factors associated with successful iliac vein stenting in the management of CVOO

4.1 Introduction

4.1.1 Shortfalls with existing cohort studies

There are a total of 56 unique cohort studies published in the literature. Therefore, it is important to ascertain why a further one is required. All of the published results for iliac vein stenting in the UK arise from a single institution. When reviewing the numbers in their published cohorts, in comparison to the scale of procedures identified in WP B, it is clear that this institution is one of the largest volume centres in the UK. This property is also true for many of the other cohorts in the literature, such as the cohorts published from the US and Europe (namely Germany). Reviewing the evidence from WP A suggests that the literature is largely comprised of results from large volume centres performed by international key opinion leaders. It is unlikely that these results are representative for standard clinical practice. This retrospective analysis represents a 'real world' experience in a tertiary vascular centre that has an established venous practice undertaking reasonable numbers of open and endovenous reconstruction for CVOO. Furthermore, long-term data is infrequently reported, and the literature would benefit from cohorts containing data extending out to 5 years post intervention.

4.1.2 The need to establish if the underlying pathology or technical factors are associated with long-term treatment success

The literature is largely composed of studies that report aggregate results including both PTS and NIVL in a single dataset. Often, there is little exploration of factors associated with procedural success and long-term patency. Where there is an analysis of covariates, the variables are infrequently adjusted for underlying pathology. This analysis will extract rich data on technical factors and aim to assess the relationship between these covariates and stent patency. To aid this analysis, the chronic venous obstruction classification system will be used as a marker of venous inflow(306).

4.1.3 The need for resource use data

There is currently no data in the literature on resource use for iliac vein stenting in the treatment of CVOO. As the majority of care for this condition is provided in secondary care, this retrospective analysis will be able to capture the healthcare resource use associated with the long-term post-operative care and stent surveillance. This will serve as important inputs for the cost-effectiveness analysis planned in WP D.

4.1.4 The use of acute deep vein thrombosis as a comparator group for technical covariates

Importantly, acute DVT will not be pooled together with the CVOO cohort as they represent a different pathophysiological process (as is often done in the literature), However, for the purpose of this analysis, acute DVT patients represent a unique reference group as they possess a thrombotic tendency akin to the PTS group but an outflow obstruction pattern similar to the NIVL group. This, again, is underpinned by the interplay between NIVL, acute DVT, and subsequent PTS as outlined in chapter 1.2.6. Therefore, patients undergoing iliac vein stenting in the acute DVT setting can provide a balance of covariates to better elucidate technical factors associated with patency.

4.1.5 Aims

The aims of WP C are as follows:-

1) Investigate technical-, disease-, and patient-related variables associated with iliac vein stenting outcomes;

2) Provide external validation of a newly published classification system for chronic venous obstruction; and

3) Provide inputs on resource use for future cost-effectiveness analysis (WP D).

4.2 Methods

4.2.1 Study design

Study design is that of a single centre retrospective analysis of all patients undergoing iliac vein stenting between January 2005 – December 2019.

4.2.2 Inclusion criteria & cohort identification

All patients undergoing iliac vein stenting for PTS or NIVL with a clinically significant iliac vein lesion were included. Patients undergoing iliac vein stenting for a residual compressive lesion after catheter-directed thrombolysis for acute DVT were also included as a comparator group. All patients were treated at a tertiary vascular centre with an established specialist venous service offering both open and endovenous reconstruction. The hospital audit and quality improvement department provided pseudo-anonymised identification numbers for all those undergoing a venogram during the observation period. Venograms were consistently coded in the department with an excellent capture rate in comparison to known cases.

4.2.3 Data collection

Data was extracted into a password-protected spreadsheet, lacking identifiable information, hosted on a secure trust-based server. Medical records were searched on Cerner™ (Oracle©). Data was extracted up until the defined endpoint of December 2024. As definitions differ in the literature, for clarity, secondary patency (SP) was defined as (once the initial intervention has failed to the level of thrombosis) the durability of the secondary intervention which restores patency.

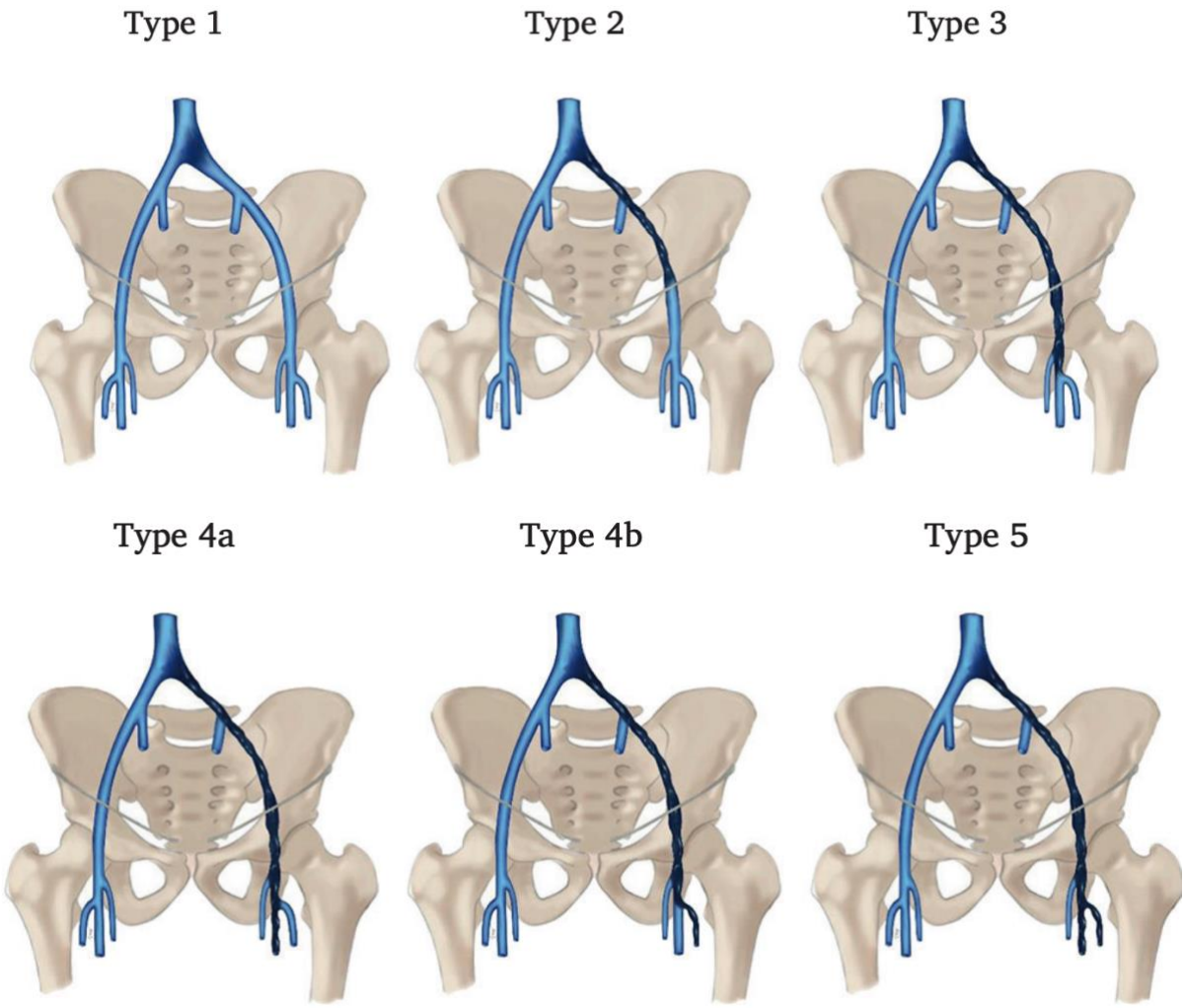
4.2.4 Radiological imaging analysis

All relevant radiological imaging was reviewed for each included participant and treated as source data as a quality control measure against data extracted in the medical notes. Venograms were reviewed to assess inflow and establish if there was evidence of cross-pelvic and para-vertebral collateral vessels in a blinded fashion.

4.2.5 Chronic venous obstruction classification

Chronic venous obstruction classification was classified according to the prognostic classification system based on anatomy of the iliofemoral tract, graded 1 – 5, published by the International Chronic Venous Obstruction Classification Study Group, see Figure 59(306). Multiplanar venography imaging was reviewed and graded in a blinded fashion by an interventional radiologist outside of the study team.

Figure 59: Classification system of venous inflow based on anatomy of the iliofemoral tract



Reproduced with permission from Jalaie et al.(306), see copyright permissions.
1: Non-thrombotic iliac vein lesion
2: Chronic venous obstruction of iliac segments
3: Chronic venous obstruction of iliofemoral segment above the confluence of the common femoral vein
4: Chronic venous obstruction of iliofemoral segment extending down into one of the main inflow veins, 4a) femoral vein, or 4b) deep femoral vein
5: Chronic venous obstruction of the iliofemoral segment involving both main inflow veins

4.2.6 Diagnostic work-up & procedure details

All patients underwent extended duplex ultrasound of the lower limb including the iliac vein, computed tomography with venous-phase contrast (CT venogram), and venography. All procedures were performed by a Consultant Vascular Interventional Radiologist with a specialist interest in venous disease supported by a Consultant Vascular Surgeon. Patients were admitted to hospital in all instances, no cases were performed as a day-case procedure.

Cases were performed in an interventional radiology suite or a hybrid vascular theatre. General anaesthesia was utilised for all PTS cases with either general anaesthesia or sedation used for NIVL cases. Technical aspects differed between cases which are reported in the Results section, see chapter 4.3.2. For acute DVT cases, catheter-directed thrombolysis was used for early thrombus removal in all occurrences. A 'check' venogram to ascertain thrombus clearance was performed every 24 hours. Bilateral access was gained in the majority of cases, with the remainder being performed via retrograde ipsilateral access. Neck access was selectively utilised. A 50% reduction in the diameter, or area when using IVUS, was used as the diagnostic criteria for an obstructing lesion of the iliac vein. IVUS was used in the majority of cases. Intra-procedural unfractionated heparin, 5000 units, was administered in all cases prior to venoplasty. Pre-stent and post-stent venoplasty were undertaken routinely using a balloon size corresponding to the stent size. Veniti Vici© stents were placed in the majority of cases, with Sinus XL stents utilised in cases involving iliocaval reconstruction. Standard practice included a heparin infusion to achieve therapeutic anticoagulation in the immediate post-operative period for the first 24 hours and pre-discharge duplex ultrasonography to ensure technical success.

4.2.7 Standard clinical follow-up

The standard post-operative clinical follow-up included outpatient review with a duplex ultrasound scan at 4 weeks, 3 months, 6 months, and 12 months. The schedule of duplex ultrasound after this point varied, with the unit's typical practice to be at least every 12 months.

4.2.8 Quality improvement

As part of this retrospective analysis, any patients that were identified as lost to follow-up were invited for a further outpatient appointment and duplex scan by their named responsible consultant.

4.2.9 Statistical analysis

Descriptive statistics were used to summarise the dataset with regards to baseline characteristics and outcome reporting (with the exception of survival probability).

Survival probabilities for PP and PAP were calculated using Kaplan-Meier survival estimates, which have been covered in chapter 2, paragraph 2.2.5. Survival probabilities were calculated in R using the package ‘survival’, the code used to perform this function can be found in Appendix 27. In the calculation of survival probabilities, censoring was undertaken if a patient was lost to follow-up despite attempts made to contact them. Censoring was not undertaken for any other reason. Censoring rates will be reported in full.

Logistic regression was used to assess the effect of pre-determined variables on the binary outcome of PP. The logistic regression model was undertaken in R using the ‘glm’ function, the code used is included in Appendix 28. The number of regression variables was limited to those reported due to the small sample size.

4.2.10 Ethical approval and information governance

Institutional agreement for service evaluation and quality improvement was granted by Imperial College Healthcare NHS Trust audit department (registration number 1,056). Approval from the Health Research Authority's Research Ethics Committee was not sought as this analysis was a retrospective review of anonymised routinely collected healthcare data for the purpose of service evaluation. No identifiable patient data was stored in the process of this analysis.

4.3 Results

A total of 65 participants undergoing primary procedures and 47 undergoing reintervention procedures (paired participants) were included in the cohort. Mean follow-up was 61.7 months with 16.9% of all patients lost to follow-up.

4.3.1 Patient (baseline) characteristics

The key baseline characteristics for the 65 included patients, organised by underlying pathology, are illustrated in Table 22. Significant differences in baseline characteristics were identified across pathologies for the following variables: previous DVT, venous ulceration, unilateral disease, and total vessel occlusion. Other baseline characteristics such as hypertension, type 2 diabetes mellitus, hyperlipidaemia, ischaemic heart disease, stroke, and chronic kidney disease were similar across the three pathology groups.

4.3.2 Operative details

Table 23 contains the main operative variables across the three groups. Significant differences were apparent in most of the technical variables collected, including: distal landing zone, stenting below the inguinal ligament, and number of stents placed. All patients were treated with dedicated venous stents in the iliac segment.

General anaesthesia was used in 70.7% of cases, sedation with local anaesthesia was significantly more likely for NIVL cases ($p<0.05$). Procedures were undertaken in the prone position for 53.8% of cases, this was significantly more common for the acute DVT group (76.2%, $p<0.05$). Femoral access was utilised in 53.8%, with the remainder being popliteal – there was no significant differences across pathology subgroups. Bilateral access was deployed in 76.9%. Additional neck access was gained in 27.7%, which was significantly more common in PTS and total occlusion cases ($p<0.05$). Iliocaval reconstruction was undertaken in 27.7% of cases and was more common in the PTS group ($p<0.05$). A single NIVL case had an iliocaval reconstruction as a bail out procedure for a mispositioned stent on the ipsilateral side.

Table 22: Baseline characteristics for included cohort

	PTS	NIVL	Acute DVT	p-value
n	33	11	21	
Age				
Mean	45.4	48.9	41.0	>0.05
SD	14.4	25.2	17.2	
Sex				
Prop female (%)	46.7	81.8	71.4	>0.05
Previous DVT				
Prop (%)	83.3	18.1	33.3	<0.05
Previous PE				
Prop (%)	3.3	0.0	4.7	>0.05
Venous ulcer				
Prop (%)	21.0	0.0	0.0	<0.05
Thrombophilia				
Prop (%)	6.7	0.0	4.8	>0.05
Unilateral disease				
Prop (%)	56.7	100.0	85.7	<0.05
Total vessel occlusion				
Prop (%)	80.0	0.0	42.9	<0.05

DVT: Deep vein thrombosis
NIVL: Non-thrombotic iliac vein lesion
PE: Pulmonary embolism
PTS: Post thrombotic syndrome
SD: Standard deviation

Table 23: Key operative variables for the included cohort

	PTS	NIVL	Acute DVT	p-value
n	33	11	21	
IVUS				
Prop (%)	93.3	90.9	76.2	>0.05
Iliocaval reconstruction				
Prop (%)	42.4	9.1	14.3	<0.05
Distal landing zone				<0.05
Common iliac (%)	3.3	9.1	14.3	
External iliac (%)	13.3	81.8	57.1	
Common femoral (%)	76.7	9.1	23.8	
Profunda origin (%)	3.3	0.0	0.0	
Femoral vein (%)	3.3	0.0	4.8	
Stent below IL				
Prop (%)	83.3	18.2	28.6	<0.05
Number of stents				
Mean	3.77	1.55	2.05	<0.05
SD	2.13	0.69	1.60	
Dedicated venous stent				
Prop (%)	100.0	100.0	100.0	>0.05

DVT: Deep vein thrombosis
IL: Inguinal ligament
IVUS: Intravascular ultrasound
NIVL: Non-thrombotic iliac vein lesion
PTS: Post thrombotic syndrome
SD: Standard deviation

4.3.3 Technical success and pre-discharge stent patency

Technical success in restoring patency was 93.4%. Across subgroups, technical success for PTS, NIVL, and acute DVT was 90.9%, 100.0%, and 100.0% respectively. There were three PTS cases in which a chronic total occlusion could not be successfully crossed in order to restore patency. A pre-discharge post-operative duplex was performed in 58.5% of cases. There were five immediate post-procedural occlusions, all of which occurred in the PTS group ($p<0.05$). All five underwent catheter-directed thrombolysis with post-discharge patency achieved in three. However, patency was unable to be salvaged in two cases. Hence, overall procedural success was achieved in 60 patients (92.3%) at discharge.

4.3.4 Chronic venous obstruction classification

A summary of the chronic venous obstruction classification is included in Table 24. The modal classification for PTS, NIVL, and acute DVT was Type 3, Type 1, and Type 2 respectively. The chronic venous obstruction classification significantly differed across the three pathology groups ($p<0.05$). Although outside of the classification system, the presence of cross-pelvic/paravertebral collateral veins on venography also significantly differed ($p<0.05$).

4.3.5 Post-discharge anticoagulation strategy

Anticoagulation strategy on discharge is shown in Table 25. The most common anticoagulation strategy across the three pathology groups was the prescription of an anticoagulation agent, such as warfarin, in addition to dual antiplatelet therapy (DAPT) (which was aspirin 75mg and clopidogrel 75mg in all cases). NIVL was the only subgroup to include the use of DAPT alone. The anticoagulation strategies significantly differed across the three pathology groups ($p<0.05$).

Table 24: Chronic venous obstruction classification and presence of cross-pelvic collaterals across the three subgroups

	PTS	NIVL	Acute DVT	p-value
n	33	11	21	
CVO classification				<0.05
Prop (%)				
Type 1	3.3	81.8	28.6	
Type 2	20.0	9.1	42.9	
Type 3	53.3	9.1	23.8	
Type 4a	16.7	0.0	4.8	
Type 4b	3.3	0.0	0.0	
Type 5	3.3	0.0	0.0	
Cross-pelvic collaterals				
Prop (%)	86.7	18.2	57.1	<0.05

CVO: Chronic venous obstruction
DVT: Deep vein thrombosis
NIVL: Non-thrombotic iliac vein lesion
PTS: Post thrombotic syndrome

Table 25: Anticoagulation strategies on discharge for the three subgroups

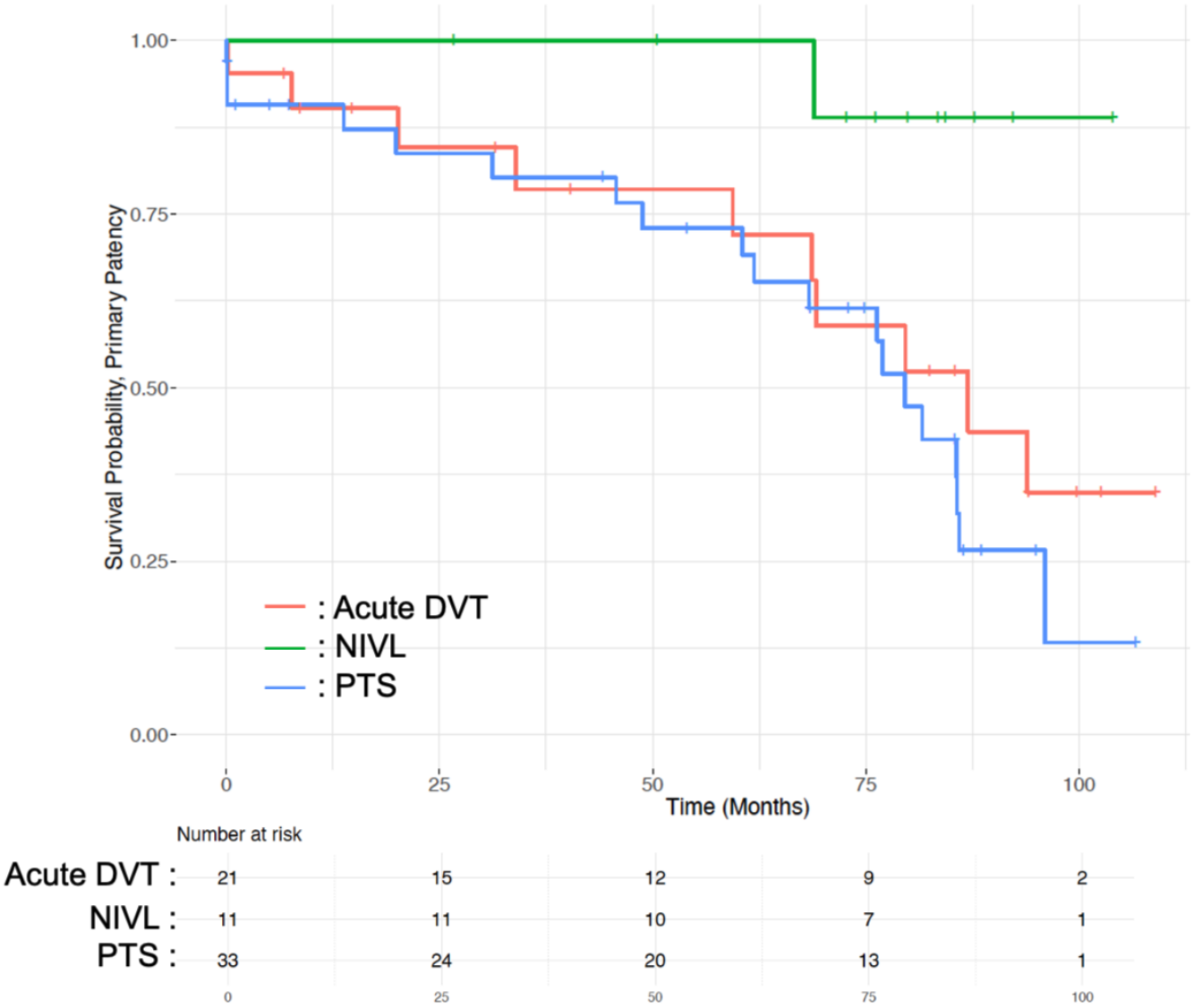
	PTS	NIVL	Acute DVT	p-value
n	33	11	21	
Anticoagulation strategy				<0.05
Anticoagulation alone	3.3	9.1	4.7	
Anticoagulation + SAP	10.0	0.0	23.8	
Anticoagulation + DAPT	86.7	72.7	61.9	
DAPT	0.0	18.2	0.0	

DVT: Deep vein thrombosis
NIVL: Non-thrombotic iliac vein lesion
PTS: Post thrombotic syndrome
SAP: Single antiplatelet
DAPT: Dual antiplatelet

4.3.6 Primary patency

Overall survival probability for PP is illustrated in the Kaplan Meier curve, Figure 60. PP at 84 months for PTS, NIVL and acute DVT was 42.5% (95% CI: 10.1 – 26.7), 88.9% (95% CI: 10.5 – 70.6), and 52.4% (95% CI: 32.8 – 83.5) respectively. PP for PTS and acute DVT was significantly lower than for NIVL ($p<0.05$). 84 months was chosen as it was the point at which the number at risk was <50% for all three pathology groups. PP up to 96 months is illustrated at 6-month intervals in Table 26.

Figure 60: Kaplan-Meier curve for primary patency across the three pathology groups



DVT: Deep vein thrombosis
NIVL: Non-thrombotic iliac vein lesion
PTS: Post thrombotic syndrome

Table 26: Kaplan-Meier survival probability for primary patency across the three pathology groups

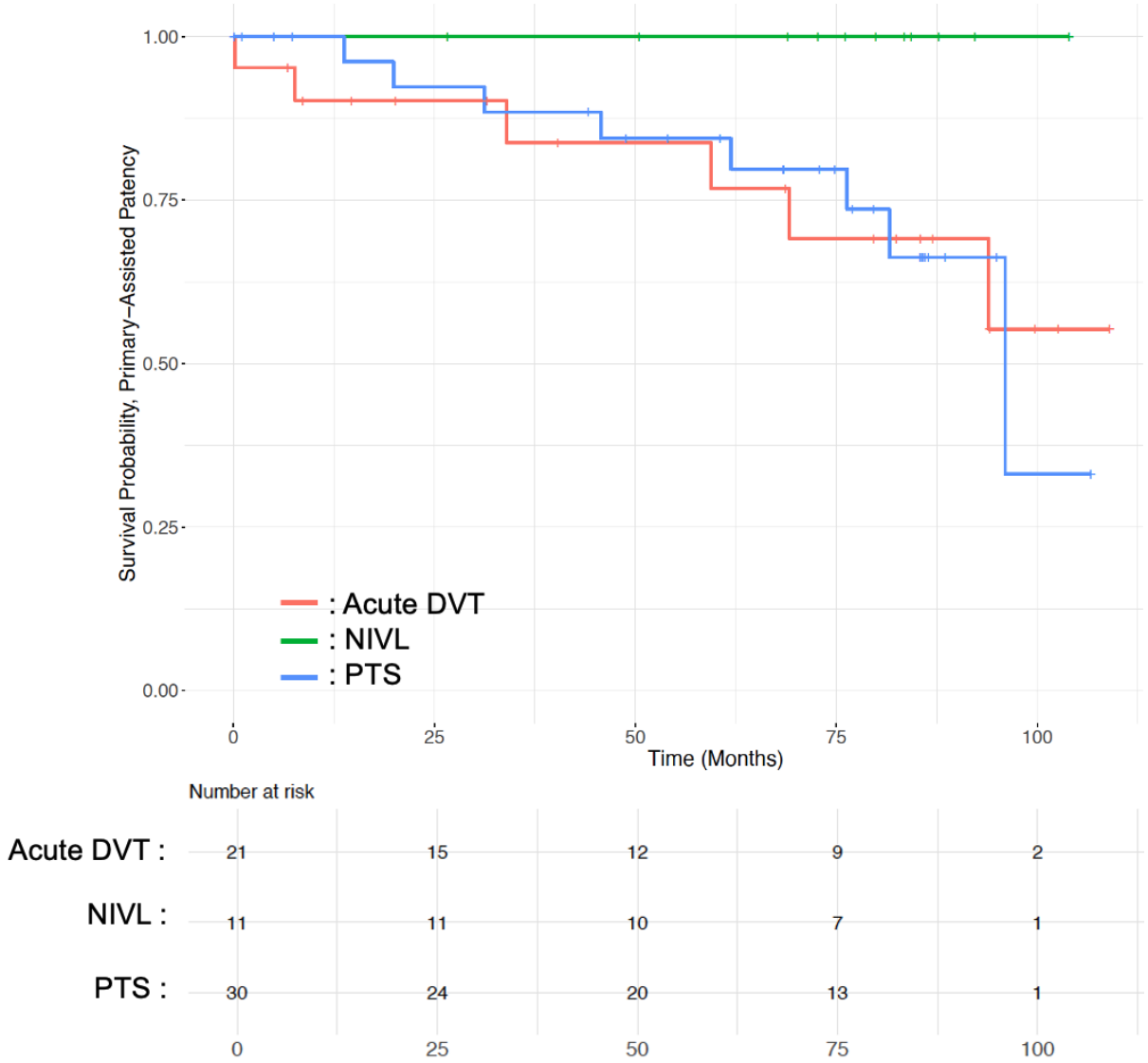
Month	PP PTS (%, 95% CI)	PP NIVL (%, 95% CI)	PP acute DVT (%, 95% CI)
6	90.7 (81.2 – 100.0)	100.0 (100.0 – 100.0)	95.2 (86.6 – 100.0)
12	90.7 (81.2 – 100.0)	100.0 (100.0 – 100.0)	90.2 (78.2 – 100.0)
18	87.2 (76.2 – 99.8)	100.0 (100.0 – 100.0)	90.2 (78.2 – 100.0)
24	83.7 (71.6 – 97.9)	100.0 (100.0 – 100.0)	84.6 (78.2 – 100.0)
30	83.7 (71.6 – 97.9)	100.0 (100.0 – 100.0)	84.6 (69.9 – 100.0)
36	80.2 (67.2 – 95.8)	100.0 (100.0 – 100.0)	78.5 (69.9 – 100.0)
42	80.2 (67.2 – 95.8)	100.0 (100.0 – 100.0)	78.5 (61.8 – 99.8)
48	76.6 (62.8 – 93.5)	100.0 (100.0 – 100.0)	78.5 (61.8 – 99.8)
54	73.0 (58.5 – 91.0)	100.0 (100.0 – 100.0)	78.5 (61.8 – 99.8)
60	73.0 (58.5 – 91.0)	100.0 (100.0 – 100.0)	72.0 (61.8 – 99.8)
66	65.3 (49.8 – 85.5)	100.0 (100.0 – 100.0)	72.0 (53.6 – 96.6)
72	61.4 (45.8 – 82.5)	88.9 (70.6 – 100.0)	58.9 (53.6 – 96.6)
78	52.0 (35.7 – 75.6)	88.9 (70.6 – 100.0)	58.9 (39.3 – 88.3)
84	42.5 (26.7 – 67.8)	88.9 (70.6 – 100.0)	52.4 (39.3 – 88.3)
90	26.6 (13.0 – 54.1)	88.9 (70.6 – 100.0)	43.6 (32.8 – 83.5)
96	13.3 (2.8 – 54.1)	88.9 (70.6 – 100.0)	34.9 (24.2 – 78.6)

CI: Confidence interval
DVT: Deep vein thrombosis
NIVL: Non-thrombotic iliac vein lesion
PP: Primary patency
PTS: Post thrombotic syndrome

4.3.7 Primary-assisted patency

Overall survival probability for PAP is illustrated in the Kaplan Meier curve, Figure 61. PAP at 84 months for PTS, NIVL and acute DVT was 66.3% (95% CI: 47.7 – 92.0), 100.0% (95% CI: 100.0 – 100.0), and 69.1% (95% CI: 49.4 – 96.8) respectively. PAP for PTS and acute DVT was significantly lower than for NIVL ($p<0.05$). PAP up to 96 months at 6-month intervals is illustrated in Table 27. Time to occlusion occurred on average 11.5 months post-procedure, range: 0.03 – 94.7 months.

Figure 61: Kaplan-Meier curve for primary-assisted patency across the three pathology groups



DVT: Deep vein thrombosis
NIVL: Non-thrombotic iliac vein lesion
PTS: Post thrombotic syndrome

Table 27: Kaplan-Meier survival probability for primary-assisted patency across the three pathology groups

Month	PAP PTS (%, 95% CI)	PAP NIVL (%, 95% CI)	PAP acute DVT (%, 95% CI)
6	100.0 (100.0 – 100.0)	100.0 (100.0 – 100.0)	95.2 (86.6 – 100.0)
12	100.0 (100.0 – 100.0)	100.0 (100.0 – 100.0)	90.2 (78.2 – 100.0)
18	96.2 (89.0 – 100.0)	100.0 (100.0 – 100.0)	90.2 (78.2 – 100.0)
24	92.3 (82.6 – 100.0)	100.0 (100.0 – 100.0)	90.2 (78.2 – 100.0)
30	92.3 (82.1 – 100.0)	100.0 (100.0 – 100.0)	90.2 (78.2 – 100.0)
36	88.5 (77.0 – 100.0)	100.0 (100.0 – 100.0)	83.8 (68.3 – 100.0)
42	88.5 (77.0 – 100.0)	100.0 (100.0 – 100.0)	83.8 (68.3 – 100.0)
48	84.4 (71.5 – 99.7)	100.0 (100.0 – 100.0)	83.8 (68.3 – 100.0)
54	84.4 (71.5 – 99.7)	100.0 (100.0 – 100.0)	83.8 (68.3 – 100.0)
60	84.4 (71.5 – 99.7)	100.0 (100.0 – 100.0)	76.8 (58.9 – 100.0)
66	79.7 (65.3 – 97.4)	100.0 (100.0 – 100.0)	76.8 (58.9 – 100.0)
72	79.7 (65.3 – 97.4)	100.0 (100.0 – 100.0)	69.1 (49.4 – 96.8)
78	73.6 (57.1 – 94.9)	100.0 (100.0 – 100.0)	69.1 (49.4 – 96.8)
84	66.3 (47.7 – 92.0)	100.0 (100.0 – 100.0)	69.1 (49.4 – 96.8)
90	66.3 (47.7 – 92.0)	100.0 (100.0 – 100.0)	69.1 (49.4 – 96.8)
96	33.1 (8.0 – 100.0)	100.0 (100.0 – 100.0)	55.3 (31.8 – 96.1)

CI: Confidence interval
DVT: Deep vein thrombosis
NIVL: Non-thrombotic iliac vein lesion
PP: Primary patency
PTS: Post thrombotic syndrome

4.3.8 Secondary patency rate

A total of 10 patients underwent secondary interventions to re-establish patency after occlusion, five of which were from the PTS group and the remaining five from the acute DVT group. SP survival probability for the PTS and acute DVT was 0.0% and 50.0% respectively at last follow-up.

4.3.9 Venous ulcer healing

All seven patients with venous ulceration at baseline had PTS. Only one of these patients achieved long-term ulcer healing at last follow-up (14.3%). For one of the venous ulcer patients, recanalisation was not possible and the ulcer persisted despite compression bandaging. Two patients were lost to follow-up and therefore the ulcer healing status was not possible to ascertain. One patient died ~18 months after the recanalisation and therefore long-term ulcer healing could not be determined. The remaining two patients never achieved ulcer healing, one of whom suffered from stent occlusion.

4.3.10 Reinterventions

Twenty-five patients (40.3%) underwent a reintervention during the observation period. For those undergoing reintervention, the number of reinterventions ranged from 1 – 6, with a modal number of 2 reinterventions. Nearly a quarter of the cohort underwent more than one reintervention (22.6%). The proportion of patients undergoing reintervention for PTS, NIVL, and acute DVT was 50.0%, 27.2% and 33.3% respectively – there was no significant difference between groups. The proportion of patients undergoing multiple reinterventions for the PTS and acute DVT groups were 33.3% and 19.0% respectively. There were no cases of multiple reintervention in the NIVL group. There was a significant difference in the rate of multiple reintervention for PTS and acute DVT in comparison to NIVL ($p<0.05$).

A total of 47 reinterventions were undertaken within the cohort of 65 primary procedures. These were emergent in 37.3% of cases, with the remainder being planned expedited elective procedures. The majority (61.7%) were undertaken for in-

stent stenosis. The mean diameter stenosis on duplex ultrasound that lead to a reintervention for in-stent stenosis was 58.2% (median: 52.5, SD: 17.4).

Regarding procedures performed, the proportion of reinterventions involving balloon angioplasty and stent relining was 68.1% and 8.5% respectively. Catheter-directed thrombolysis was undertaken in 25.5% of cases for total or partial thrombotic stent occlusion. Two patients (6.4%) required open surgery to create an arteriovenous fistula between the common femoral artery and vein to maintain stent patency. A further patient underwent open venous bypass with an adjunctive arteriovenous fistula after failed thrombolysis.

4.3.11 Perioperative complications

The most common perioperative complication was haemorrhage, which occurred in 12.3% of patients – three-quarters of which were in the acute DVT group. Two patients in the PTS group required transfusion (6.0%). There were no bleeding events in the NIVL group.

Three cases (4.6%) met the International Society on Thrombosis and Haemostasis definition of surgical major bleeding (that being extra-surgical site bleeding causing a fall in haemoglobin level of >2 g/dL). These patients were all from the acute DVT group and all suffered from upper gastrointestinal bleeding requiring transfusion of blood products. The remaining cases required transfusion of blood products but did not meet the surgical major bleeding criteria as bleeding was related to the operative site. Two patients (2.3%) developed a clinically apparent haematoma at the access site, both of which were treated with antibiotics alone.

A single patient in the acute DVT group suffered from an acute kidney injury and hospital-acquired pneumonia after being treated with catheter-delivered pharmacomechanical thrombolysis for peri-operative stent thrombosis. A further patient in the acute DVT group undergoing catheter-delivered pharmacomechanical thrombolysis for peri-operative stent thrombosis during their index admission required an open surgical procedure to create an arteriovenous fistula to maintain stent patency.

4.3.12 Complications during follow-up

A total of fifteen patients (23.1%) presented to hospital with a complication during the observation period. Of these, 53.0% of presentations were related to bleeding. These events were spread across the three groups ($p>0.05$). Most of the bleeding episodes did not require treatment. A single patient was admitted to hospital on two occasions for bleeding episodes, the first for an abdominal wall haematoma and the second for persistent menorrhagia. A further patient underwent a colonoscopy as a response to the bleeding as an outpatient.

Two patients from the acute DVT group (3.1%) had thrombotic events distant from the site of the stent, one distal DVT and one PE. A single patient from the PTS group who underwent reintervention for an occluded stent went on to have an open venous bypass as a salvage procedure as part of the same admission. This led to an Intensive Care admission and a prolonged hospital stay due to an infected groin haematoma.

4.3.13 Stent-related adverse events

There were no cases of stent fracture or stent migration observed across the entire cohort.

4.3.14 Resource use

In respects to the index admission, a total of 408 hospital-bed days were occupied across the 65 patient episodes. The length of stay was significantly longer for acute DVT ($p<0.001$). The average length of stay for PTS and NIVL was 5.4 and 1.5 days respectively. A total of 173 dedicated venous stents were placed, the number of average stents placed for PTS, NIVL, and acute DVT was 3.77, 1.55, and 2.05 respectively.

There was a total of 751 outpatient appointments across the observation period. The average number of outpatient appointments and duplex ultrasounds per year was 2.38 and 2.02 respectively. There was no significant difference in the number of outpatient appointments or duplex ultrasounds over time across the three pathology groups ($p>0.05$).

Reinterventions led to an additional 47 procedures and 203 hospital-bed days. Angioplasty for in-stent stenosis was generally undertaken as a day-case procedure, however, in-stent thrombosis requiring catheter-directed thrombolysis resulted in extended hospital stays.

4.3.15 Censoring rates over time

The proportion of patients censored at 84 months for PTS, NIVL, and acute DVT was 30.0%, 45.0% and 30.0% respectively. There was no significant difference in the censoring rate across the three groups ($p>0.05$). Number of patients censored at each timepoint is illustrated in Table 28.

Table 28: Number of participants censored for loss to follow-up at each timepoint across the three pathology groups

Month	PTS Censoring (n)	NIVL Censoring (n)	DVT Censoring (n)
6	1	0	1
12	3	0	0
18	0	0	2
24	0	1	0
30	0	0	1
36	0	0	0
42	1	0	0
48	0	1	0
54	0	0	1
60	1	0	0
66	0	1	0
72	3	1	0
78	0	1	0
84	1	0	2
% Prop	30.0%	45.0%	30.0%

DVT: Deep vein thrombosis
NIVL: Non-thrombotic iliac vein lesion
PTS: Post thrombotic syndrome

4.3.16 Validation of the chronic venous obstruction classification

As outlined in Table 24, the chronic venous obstruction classification significantly differed across pathology groups at the time of intervention, with PTS having a higher grade of obstruction.

Chronic venous obstruction classification was significantly associated with stent patency. With Type 1 utilised as the reference category, there was decreasing stent patency as outflow obstruction worsened. Table 29 shows the results of the logistic regression. A grade-effect dose-response can be seen with increasing degree of obstruction. Type 4b and Type 5 were excluded from the analysis as only a single patient had these gradings and it increased the level of factors in the analysis unnecessarily. When also accounting for pathology as a moderating variable, NIVL was a significant moderator ($p<0.001$). When the analysis was repeated without NIVL, a similar trend in the effect estimate was observed but it failed to reach significance.

Table 29: Logistic regression estimates for chronic venous obstruction classification and stent patency, including data from all three pathology groups

CVO classification	Effect estimate	Standard error
Type 1 (reference)	+1.47	0.64
Type 2	-1.22	0.82
Type 3	-1.47	0.77
Type 4a	-3.08	1.27

CVO: Chronic venous obstruction

4.3.17 Factors associated with stent patency

In a logistic regression model, underlying pathology was significantly associated with patency ($p=0.028$), PTS had the largest negative effect on stent patency.

Total vessel occlusion at baseline was significantly (negatively) associated with stent patency ($p=0.020$). However, this effect was eliminated when accounting for pathology. Stenting below the inguinal ligament approached significance as an associated variable ($p=0.065$), however, this was diminished when accounting for pathology. The same relationship was observed with the total number of stents placed in each case.

Distal stent landing zone was significantly associated with stent patency, with stents ending in the external iliac vein having a better patency (p=0.048), this relationship was also eliminated by accounting for pathology. Iliocaval reconstruction, with unilateral stenting as the reference category, was not associated with stent patency (p=0.141).

Anticoagulation strategy had no effect on stent patency (p=0.994). This relationship was sustained when accounting for pathology as a moderating variable. Length of stay was significantly associated with worsening stent patency (p=0.018), this relationship was also diminished when accounting for pathology.

4.4 Discussion

This retrospective analysis is a deep dive into the 'real world' experience of iliac vein stenting in a tertiary vascular centre. It provides some unique insights that have yet to be explored in the literature. The follow-up duration is one of the longest in the literature and the reported patency rates have the lowest censoring rates seen for these timepoints. The detailed data extraction has enabled a comprehensive description of technical factors associated with stent patency across PTS, NIVL, and acute DVT pathologies. Furthermore, it reports on an aggressive anticoagulation strategy utilised in attempt to improve stent patency and mitigate against in-stent restenosis.

4.4.1 Long-term patency for post thrombotic syndrome is poor

At 8 years post procedure, more than half of stents placed for PTS had occluded despite reintervention efforts. Given the average age of 45 in this group, this demonstrates that most stents will occlude within a patient's lifetime. The procedure is not durable in the long-term, with a persistent rate of occlusion over time. The PP was as low as 42.5% at 84 months, some may argue this is appreciably lower than observed in the wider literature. This analysis had a reasonably high proportion of patients undergoing iliocaval reconstruction rather than a standard unilateral iliac stent, however, this was not a significant factor in the regression analysis. When reviewing the pooled survival probabilities at similar timepoints from WP A, this rate is largely consistent with the pooled evidence estimate. Furthermore, this decline in patency is not limited to single centre cohort studies, medium-term data published by the IDE trials also shows a concerning rate of stent occlusion in the PTS group(208, 211, 303), with ~30% loss of patency at 36 months.

4.4.2 Long-term patency decline follows differing failure patterns across pathologies

The NIVL group in this cohort, although small in number, responded well to reintervention and sustained a PAP of 100% at long-term follow-up (84 months). This group appears to lack a consistent decline in stent patency which is observed in the PTS and acute DVT groups.

This pattern is partly supported by the evidence gathered in WP A, where the Kaplan-Meier curve shows some studies with 100% PAP at long-term follow-up, with the average pooled patency being reduced by a distinct set of studies that fail to achieve this. This differs to the Kaplan-Meier curves for PTS in which every study demonstrates a consistent decline in PAP over time, with the gradient of that decline varying between studies. This further supporting the hypothesis that the interaction of NIVL with the stent is entirely different to that of PTS.

4.4.3 Conventional technical factors associated with stent patency are confounders for pathology and venous inflow

As observed in the meta-regression results in chapter 2, WP A, conventional factors associated with stent patency, such as stenting below the inguinal ligament, number of stents used, and need for iliocaval reconstruction, were not associated with stent patency when accounting for pathology. PTS was the significant factor in these relationships. The observation that the factors were associated with stent patency prior to adjustment for underlying pathology, and that these factors significantly differed across the different pathology groups, suggests that they are confounding covariates for the PTS pathology. Patency declined with worsening chronic venous obstruction classification both across and within pathologies. Although within the PTS pathology this was not significant, this was likely due to a lack of power – the larger inception study showed that the patency rates within PTS declined with obstruction grade(306). The relationship between obstruction grade and patency is also confounded by these previously reported factors. For higher grades of obstruction, an increased number of stents, with extension below the inguinal ligament, is required to land the stent in an adequate healthy vein.

4.4.4 Chronic venous obstruction classification is a predictor of stent patency

This analysis was able to externally validate the chronic venous obstruction classification published in the literature(306). In the original validation study, NIVL was always classified as Type 1. Its inclusion of NIVL Type 1 lesions seems somewhat redundant as it is likely that this will be a confounding factor given that the classification significantly differs across pathology groups (as illustrated in this cohort). This analysis

demonstrated a significant dose-response reduction in stent patency with grade of obstruction across both NIVL and PTS, with the same trend seen in PTS alone without reaching significance.

4.4.5 Aggressive anticoagulation strategies increase the risk of bleeding without improving stent patency

This cohort is the only report in the literature to utilise an antithrombotic / anticoagulation strategy comprising of three agents: an anticoagulation, such as warfarin, in addition to DAPT (aspirin 75mg and clopidogrel 75mg). Antithrombotic strategies in clinical practice are highly variable(335, 336). International and national Delphi studies suggest that the most commonly opted initial post-operative strategy is anticoagulation alone, with a proportion of clinicians adding in a single antiplatelet drug. This observation is supported by the general literature reviewed in WP A.

This analysis demonstrated that a more aggressive antithrombotic strategy failed to change the fate of stents, with comparable survival probabilities to the pooled rates in WP A. However, it did increase the rate of bleeding events. Other studies have reported no difference in stent patency with respects to the antithrombotic strategy utilised, however, these analyses are subject to confounding by indication(337). This cohort had a largely consistent approach to antithrombotic strategy with no detectable difference in patency. Further comparative evidence, in the form of an RCT, is required.

4.4.6 Iliac vein stenting is associated with substantial resource use and poses a burden to patients

The resource use in the placement of an iliac vein stent, and the associated post-operative aftercare, is high. This particularly so when considering the indefinite nature of stent surveillance. There is no high-quality evidence in the literature investigating the cost of iliac vein stenting. There is a reasonable volume of evidence for catheter-directed thrombolysis in acute DVT stemming from the associated RCTs, such as the ATTRACT trial(338). Although distinct, the scale of the cost per patient during the index admission was $21,509 for catheter-directed thrombolysis.

The admission for PTS is significantly shorter in duration and lacks the need for the catheter-directed thrombolysis which will result in less resource utilisation. However, the cost of the index admission for PTS is still likely to be high given the average 5-day hospital-bed days and the cost of three stents per patient. The unit in this analysis provided, on average, two vascular outpatient appointments and two duplex ultrasounds per year per patient. Once a unit has treated several hundred patients, even when considering the rate of long-term failure, this could constitute a significant proportion of its workload and resource use, akin to surveillance after endovascular aneurysm repair.

From a patient's perspective, this resource use represents a considerable burden. Patients attended on average, 13 outpatient appointments, 10 duplex ultrasound scans, and were readmitted to hospital once during the observation period. Optimal medical care, in the context of not having a venous ulcer, is likely to be associated with substantially less healthcare burden. This burden could be captured through quality of life and survivorship metrics. However, there are currently no studies reporting long-term generic quality of life outcome measures after iliac vein stenting. The STEVECO trial demonstrated equivalent EQ5D index values across the stent and control arms. Within the venous space, this level of patient-experienced burden has yet to be explored.

4.4.7 Limitations

The main limitation of this work is the relatively small sample size, particularly when considering the number within each pathology group. The small sample size will undoubtedly introduce uncertainty into the reported figures in this chapter. Larger sample sizes, with the same granularity of reporting, would strengthen this work. The small sample size limited the number of regression variables in this analysis. Careful consideration was paid to the variables chosen, with the aim of avoiding of failing to reach convergence for too few events per variable. Larger datasets would permit the inclusion of many more variables in a regression model, adding an increasing nuance to the interpretation of the data.

Healthcare records are not designed for service evaluation or research use. There is no data quality control measures or auditing for the precision of data. This means it is not possible to ascertain if the absence of recording equates to the absence of a variable or simply missed recording. Patency status is relatively robust as it is ascertained by duplex ultrasound, the reports of which are uploaded into the medical records. However, past medical history and clinical evaluation is often incomplete. Another consequence of utilising healthcare records is that this analysis chiefly focused on stent patency and procedural success, it lacked measures of disease severity or quality of life. VCSS and quality of life measures, such as EQ5D, are rarely undertaken as part of routine clinical practice and is therefore not recorded in the medical notes. There are examples of retrospective cohort studies based on medical notes elsewhere in the literature with this data(252), however, unfortunately this was not possible in this analysis. Disease severity was limited to the presence of venous ulceration alone.

Furthermore, as for all cohort studies in the literature, no comparative evidence is provided in this analysis. Therefore, it adds little to guiding clinicians on the additive benefit of iliac vein stenting in the treatment of CVOO.

4.5 Conclusion

The long-term patency of iliac vein stents placed for PTS and acute DVT is poor and there is a persistent decline in stent patency over time. Iliac stents placed for NIVL had promising long-term patency and underwent fewer reinterventions. The results from this analysis, in addition to the wider literature, suggests that the long-term decline in stent patency for NIVL differs to that of PTS. Underlying pathology accounted for many of the technical factors associated with stent patency, supporting the hypothesis that PTS has a different long-term pathophysiological interaction with the iliac vein stent. The chronic venous outflow obstruction classification is associated with long-term stent patency and may also explain the relationship for some of the confounding variables. The use of a more aggressive antithrombotic strategy involving anticoagulation in addition to DAPT showed no signal for efficacy but was associated with a higher risk of bleeding complications. Future research is required to assess if this classification system can aid patient selection and improve the overall performance of iliac vein stenting. Iliac vein stenting for PTS is associated with substantial resource use and poses a substantial burden to patients which is underexplored in the literature.

5 – WORK PACKAGE D:

Development of a multi-level Markov-state transition model to evaluate the cost-effectiveness of iliac vein stenting in the treatment of CVOO

CHAPTER 5: WORK PACKAGE D

Development of a multi-level Markov-state transition model to evaluate the cost-effectiveness of iliac vein stenting in the treatment of CVOO

5.1 Introduction

5.1.1 There is a lack of cost-effectiveness evidence in the literature

There is currently a lack of data on the cost-effectiveness of iliac vein stenting in the management of CVOO. Iliac vein stenting is an expensive intervention requiring long-term surveillance associated with substantial resource use. A single study exists in the reported literature which reported the cost-effectiveness of iliac vein stenting in venous ulceration based on data from 26 participants across a three-year time horizon(339).

The work undertaken in this thesis so far (WP A and WP C) has provided useful inputs in order to undertake a meaningful cost-effectiveness analysis. In order to undertake a cost-effectiveness analysis, a measure of health gain, or utility, is required. This is commonly expressed through the EQ5D index utility value calculated from the EQ5D-5L / 3L quality of life measure. WP A has demonstrated a relative lack of information on generic quality of life measures in the literature, there instead is a relative abundance of disease-severity measures (such as VCSS). The STEVECO trial is the only RCT to collect both EQ5D and VCSS data across both study arms. This represents a unique opportunity to calculate a function of EQ5D from VCSS, thus being able to calculate the utility gained utilising the large body of VCSS evidence in the literature.

5.1.2 The need for cost-effective analysis

There is a finite number of resource in the NHS with an accompanying utilitarian requirement to maximise the benefit of this resource. The National Institute for Health and Care Excellence (NICE) has a non-binding threshold of £20,000 per quality-adjusted life-year (QALY) at which it deems an intervention to be cost-effective(340). Importantly, this is not the gross cost, but the cost per QALY compared to current

medical care. In order to incorporate the cost-effectiveness of current medical care, the incremental cost-effectiveness ratio (ICER) is calculated.

NICE considers deeming an intervention cost-effective if the ICER lies in the range of £20,000 – £30,000 providing there is sufficient uncertainty in the quality of life gained or if an intervention adds a distinct benefit that may not have been adequately captured in the measurement of quality of life.

A lack of proven cost-effectiveness will limit the widespread adoption of iliac vein stenting as NICE will refrain from providing a strong recommendation for its use. Furthermore, if it fails to be cost-effective, then drivers of this should be explored in order to establish how to improve the intervention.

Given the differing fates of iliac vein stents placed for PTS in comparison to NIVL, it is imperative that separate models are constructed for each pathology.

5.1.3 Aims

The aims of WP D are as follows:-

1) Establish the relationship between VCSS and EQ5D-5L to produce a quality-of-life function for disease severity through analysis of primary data from the STEVECO RCT; and
2) Determine the ICER for iliac vein stenting in the treatment of CVOO through development of a multi-level Markov state-transition model.

This work was undertaken in collaboration with the Department of Applied Economics, University of Granada, and the Stent Versus Conservative Treatment in Patients with Deep Venous Obstruction (STEVECO) trial team.

5.2 Methods

5.2.1 Model structure

Distinct Markov state transition models were composed to compare the cost-effectiveness of iliac vein stenting in PTS and NIVL in comparison to standard medical therapy. The health utility outcome was quality of life as ascertained by EQ5D-5L.

Iliac vein stenting is undertaken for improvements in severity of disease. It is not a prophylactic procedure. The disease state at the point of intervention likely represents when medical therapy has been trialled and failed to make sufficient improvements. Therefore, the following assumptions are made by the model:

1. Iliac vein stenting offers improvement in severity of disease, capturing an improved likeliness of ulcer healing, aligning with that seen in the single-armed studies in the literature;
2. For a patient who has undergone iliac vein stenting, that then suffers from stent occlusion, they will be placed in the same pathophysiological haemodynamic circumstances that were present prior to stenting, meaning that the severity of disease returns to the pre-stent severity; and
3. Those not undergoing iliac vein stenting will have a disease severity that regresses around the mean at which they currently are, neither significantly improving or worsening.

Three health states were developed, see Figure 62. The health states are as follows:-

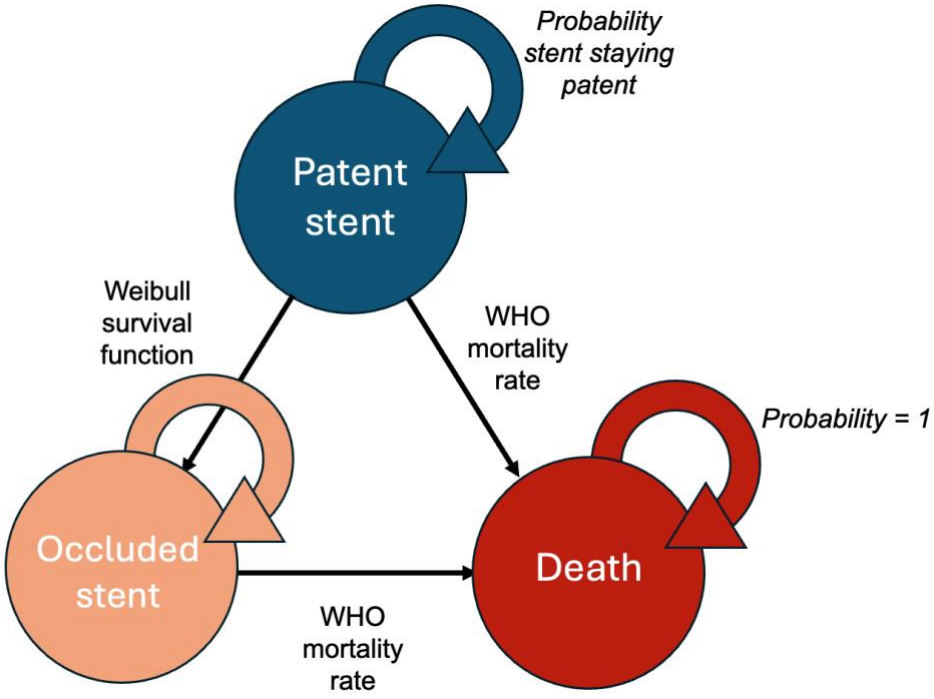
1. Reconstructed patent iliac system (including those undergoing reintervention achieving PAP) with reduced (improved) VCSS, increased ulcer healing ratio, and increased quality of life;
2. Occluded iliac system with increased (worsened) VCSS, reduced ulcer healing ratio, and decreased quality of life equal to that of their pre-stenting disease state; and
3. Death, which had no associated utility value or costs.

The Markov state transition model was undertaken utilising a bespoke package 'Heemod' in R(341). The code used to define the model parameters, state transition probabilities, health states, and model architecture, alongside the subsequent sensitivity analyses can be reviewed in Appendix 29.

Time-varying properties, including stent patency and mortality, were all input as functions making the model more dynamic and closer to the real-world trajectory of the patients treated. Stent patency, PAP, across cycles was inputted as a function to mirror the survival probabilities from WP A, produced through a Weibull distribution model, see 5.2.7. Reintervention across cycles was also input as a function over time. This was calculated by finding the difference between PP and PAP which were reported in WP A. Age- and sex-matched mortality rates were input as a function using data from the World Health Organisation, country-specific, mortality data(342).

One QALY represents one year lived in perfect health (with an index utility value of 1.0.). The mean ICER was calculated, in the conventional way, as the difference in cost between the medical arm and stent arm divided by the difference in QALY between the medical arm and stent arm. Costs and QALYs were discounted at 3.5% per year.

Figure 62: State transitions within the Markov model



WHO: World health organisation

5.2.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was undertaken to moderate the confidence in the estimates for the inputs into the model and determine the probability of cost-effectiveness for different willingness-to-pay thresholds. PSA was undertaken across the 1000 cycles and utilised conservative SD values for cost and utility data. The output of this was used to construct cost-effectiveness acceptability curves for PTS and NIVL in reference to the NICE willingness-to-pay thresholds. During the PSA, the Weibull survival function was changed to a flat average rate of stent failure.

5.2.3 Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) was performed to assess the sensitivity of the model outputs to changes in the underlying parameters. DSA was performed for initial procedure cost, long-term care costs including stent surveillance and reintervention, stent patency rates, and change in EQ5D index utility value. DSA was undertaken to estimate the value of the parameter in which the ICER would exceed £30,000. This is distinct from PSA, which looks at the effect of general uncertainty on the results, in that it assesses the impact of changes in individual parameters on the ICER.

5.2.4 Data from the stent versus conservative treatment in patients with deep venous obstruction randomised controlled trial

The STEVECO was an industry-funded RCT based in the Netherlands at Maastricht University Medical Center(305). The trial closed early due to poor recruitment with a total of 65 participants enrolled. The primary outcome for the STEVECO trial was VEINES QOL/Sym, with secondary outcomes including VCSS and EQ5D-5L. A collaboration was established between Imperial College London Department of Surgery & Cancer and the STEVECO trial team in order to build a cost-effectiveness model with inputs from the original data collected in the trial. Multiple imputation was undertaken on the STEVECO trial dataset for missing values. However, it introduced substantial uncertainty into the data, therefore a complete case analysis was performed.

5.2.5 Statistical analysis - establishing the relationship between EuroQol EQ5D-5L and venous clinical severity score

Firstly, the normality of VCSS was assessed by plotting histograms, Q-Q plots, and undertaking the Shapiro-Wilk Test. Histograms demonstrated a normal distribution, Q-Q plots showed little deviation, and the W statistic calculated equated to 0.968 (p=0.117). Therefore, normality of VCSS, and its ability to be treated as a continuous measure, was adequately demonstrated. Grubb's test, also known as the maximum normalized residual test, was utilised to identify outliers in the EQ5D-5L and VCSS data. Three data points lied significantly outside of the normality of the data, they were examined and appeared to be transcription errors. These outliers were removed.

The correlation, a priori, between EQ5D-5L and VCSS would be expected to be invariant over time and to be independent of treatment received. Therefore, the relationship between the two variables can be assessed at all timepoints across both the stenting and medical arms, commonly referred to as having a long data structure.

Linear mixed models were deployed to assess the relationship between EQ5D-5L and VCSS for their ability to handle correlated data (repeated measures from the same participants) and influence from independent variables. Linear mixed models are less likely to identify false-positive associations in comparison to other techniques such as ANOVA(343).

Linear mixed models were undertaken using the specialist package 'lme4' in R(344), the code utilised to undertake this function can be reviewed in Appendix 30. Fixed effect covariates included intervention, pathology, BMI, and sex. Random variables included participant identification number.

5.2.6 Source data for the model

Inputs for stent patency, baseline VCSS, baseline ulceration, change in VCSS and change in ulceration, were gathered from the relevant meta-analyses in WP A as this represents the most comprehensive source in the literature. Resource use in terms of hospital bed-days, device use, and stent surveillance were taken from the analysis in WP C. Resource use in the care of venous ulceration is available in the literature from existing RCTs(345).

5.2.7 Statistical analysis – establishing a time-varying function for stent patency

Pooled survival estimates calculated on reconstructed IPD using the bespoke package 'metaSurv' from WP A, were used to create a Weibull survival function of stent patency over time. Weibull survival functions permit extrapolation of the survival probabilities beyond the observed data(346). This facilitates modelling of longer time horizons. It also includes a shape parameter which means that the hazard does not have to be constant over the horizon. The Weibull survival function is shown in Figure 63. The parameters are ascertained from performing the Weibull model.

Figure 63: Equation used to calculate Weibull survival function

$$S(t) = e^{[-(\lambda_{est}\, t)^{p_{est}}]}$$

λ_{est}: Lambda parameter
p_{est}: Shape parameter
S: Survival
t: Time

This Weibull survival function describes the survival probability at a given time, i.e. that the stent has remained patent up until that timepoint. The Markov model utilises state-transition probabilities which represent the probability of succumbing to that defined event within each cycle (which are one year each in duration). Therefore, the Weibull survival function needs to be converted to an instantaneous hazard at each timepoint, which would be equal to the state transition probability. The probability of survival across a timepoint can be calculated by dividing the survival at the next interval ($t + 1$) by the current survival up to that interval (t). To calculate the risk of non-survival, this is subtracted from 1. The equation for this is shown in Figure 64. The calculated function of survival included those that had undergone reintervention to achieve PAP. This function of an instantaneous hazard, with the corresponding lambda (λ) and shape parameter (p) values for PTS and NIVL, were input as a state-transition probability for stent occlusion.

Figure 64: Equation used to calculate instantaneous hazard from Weibull survival function

$$Instantenous\ hazard\ (t) = 1 - \frac{S_{(t+1)}}{S_{(t)}}$$

$$1 - \frac{S_{(t+1)}}{S_{(t)}} = 1 - \frac{e^{[-(\lambda_{est}\ t+1)^{p_{est}}]}}{e^{[-(\lambda_{est}\ t)^{p_{est}}]}}$$

λ_{est}*: Lambda parameter*
p_{est}*: Shape parameter*
S*: Survival*
t*: Time*

5.2.8 Statistical analysis – establishing a function for reintervention

It is assumed, a priori, that the only difference in survival between PP and PAP is reintervention. The survival probability for PP of a stent is the probability of the stent being patent without the need for reintervention. The survival probability for PAP is the probability of the stent being patent with the aid of additional reintervention. Therefore, we can use the difference as an estimate of reintervention probability at any given time. Censoring will occur equally across both groups - if a participant is censored from the PP data, they will also be censored from the PAP data and vice versa. The difference in pooled survival estimates calculated on reconstructed IPD using the specialist package 'metaSurv' were used to model reintervention over time. This relationship is outlined in Figure 65. Year-to-year rates of reintervention was then calculated and analysed to assess if the rate was constant.

Figure 65: Relationship defining reintervention using the survival probabilities of primary patency and primary-assisted patency

$$Reintervention\ (t) = S(t)PAP - S(t)\ PP$$

PAP*: Primary-assisted patency*
PP*: Primary patency*
S*: Survival*
t*: Time*

Reinterventions were assumed to be day-case interventions performing intravascular venogram, IVUS, and balloon angioplasty. This was the modal reintervention across both pathologies recorded in WP C. Rarely, stent relining will be required which will not be captured by the model/

5.2.9 Assigning cost values to resource use

Resource use cost will be ascertained primarily by collecting procurement costs from NHS trusts. Stent, IVUS and balloon angioplasty device costs were the price paid in 2024. Where this data is not available, the 2023 – 2025 NHS national tariff data(347) were used.

5.2.10 Ethical approval and information governance

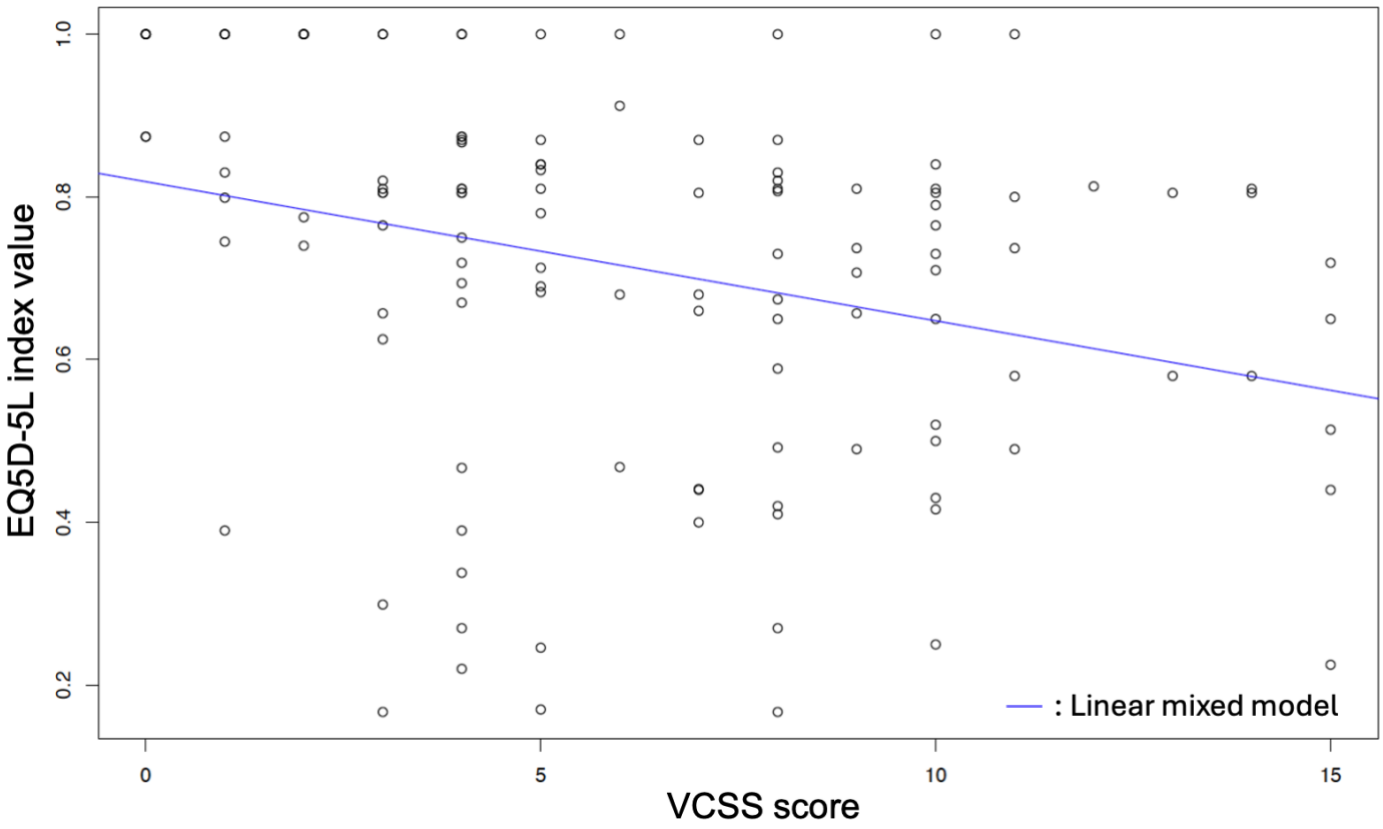
The STEVECO trial team were granted approval from the study sponsor to share anonymised data with Imperial College London Department of Surgery & Cancer. As outlined in WP C, institutional agreement for service evaluation and quality improvement by Imperial College Healthcare NHS Trust audit department (registration number 1,056) was gained for information pertaining to resource use. Approval from the Health Research Authority's Research Ethics Committee was not sought as this analysis was a retrospective review of anonymised routinely collected healthcare data. No identifiable patient data was stored in the process of this analysis.

5.3 Results

5.3.1 EuroQol EQ5D-5L as a function of venous clinical severity score

After three outliers were removed, 190 comparisons for EQ5D index utility value and VCSS were analysed. EQ5D-5L index utility value was significantly correlated with VCSS (estimate = -0.018, [SE: 0.0058], p=0.002). The fixed effects (intervention, pathology, BMI, and sex) in the model were not significant (p>0.05). Figure 66 illustrates the correlation for EQ5D index utility value and VCSS.

Figure 66: Scatterplot of EQ5D index utility value and venous clinical severity score with linear mixed model output



EQ5D-5L: Standardised measure of health-related quality of life developed by the EuroQol Group
VCSS: Venous clinical severity score

5.3.2 Mapping EuroQol EQ5D-5L to change in venous clinical severity score after iliac vein stenting

Pooled estimates from the literature are reported in WP A. For PTS, the mean baseline VCSS score was 7.86 (95% CI: 6.89 – 8.83). The mean reduction in VCSS for PTS at last follow-up was 4.53 (95% CI: 4.003 – 5.050). Therefore, best estimates from the pooled results of the literature show that VCSS decreases from 7.86 down to 3.33 after iliac vein stenting. The improvement in EQ5D-5L index utility value equates to 0.084.

For NIVL patients, the mean baseline VCSS score was 8.15 (95% CI: 7.59 – 8.71). The mean reduction in VCSS for NIVL at last follow-up was 4.69 (95% CI: 4.12 – 5.26). Therefore, best estimates from the pooled results of the literature show that VCSS decreases from 8.15 down to 3.46 after iliac vein stenting. The improvement in EQ5D-5L index utility value equates to 0.087.

5.3.3 Time-varying function for stent patency – post thrombotic syndrome

Weibull modelling was performed on the pooled survival probabilities from WP A for PTS. The lambda and shape parameters were 0.056597 and 1.068083 respectively. The resulting Weibull survival function for stent patency for PTS over time is shown in Figure 67. A visual representation of the Weibull survival function can be reviewed in Appendix 31.

Figure 67: Weibull survival function for stent patency in Post Thrombotic Syndrome

$$Stent\ patency\ S(t) = e^{\left[-(0.056597\ .\ t)^{1.068083}\right]}$$

S: Survival
t: Time

5.3.4 Time-varying function for stent patency – non-thrombotic iliac vein lesion

Weibull modelling was performed on the pooled survival probabilities from WP A for NIVL. The lambda and shape parameters were 0.051719 and 1.305782 respectively. The resulting Weibull survival function for stent patency for NIVL over time is shown in Figure 68. A visual representation of the Weibull survival function can be reviewed in Appendix 32.

Figure 68: Weibull survival function for stent patency in Non-thrombotic Iliac Vein Lesion

$$Stent\ patency\ S(t) = e^{[-(0.033447\ .\ t)^{1.150380}]}$$

S: Survival
t: Time

5.3.5 Reintervention function – post thrombotic syndrome

Reintervention probability over time was calculated and the year-to-year rate was defined. The average yearly rate of reintervention was 3.41% (SE: 0.57) across the population. This is consistent with the aggregate pooled rates in WP A.

5.3.6 Reintervention function – non-thrombotic iliac vein lesion

As for PTS, reintervention probability over time was calculated and the year-to-year rate was defined. The PP and PAP did not sufficiently diverge until 2 years to get a stable estimate, therefore the probability difference was undertaken from 2 years onwards. The average yearly rate of reintervention was 0.89% (SE: 0.29) across the population.

5.3.7 Venous ulceration – post thrombotic syndrome

Pooled estimates from the literature are reported in WP A. The baseline venous ulceration in PTS was 0.18 (95% CI: 0.12 – 0.26). The pooled proportion for venous ulcer healing was 0.70 (95% CI: 0.50 – 0.84). Hence, for PTS, the baseline venous ulcer rate in the model was set at 18.0%, reducing down to 5.4% after iliac vein stenting.

5.3.8 Venous ulceration – non-thrombotic iliac vein lesion

Baseline venous ulceration in NIVL was 0.08 (95% CI: 0.04 – 0.17). The pooled proportion for venous ulcer healing was 0.55 (95% CI: 0.11 – 0.92). Hence, for NIVL, the baseline venous ulcer rate in the model was set at 8.0% reducing down to 3.6% after iliac vein stenting.

5.3.9 Costs associated with index iliac vein stenting procedure for post thrombotic syndrome

Table 30 contains the resource use and associated costs relevant to the index admission for iliac vein stenting in PTS. The total cost equates to £14,385.64.

Table 30: Costs included in the Markov model for the index stenting procedure in post thrombotic syndrome

Resource	Units per procedure	Unit cost (£)	Total cost (£)
Pre-operative CT (A)	1.0	103.00	103.00
Pre-operative venogram (A)	1.0	859.00	859.00
Dedicated venous stent (B)	3.77	1,920.00	7,238.40
High-pressure angioplasty balloon (B)	1.0	269.64	269.64
IVUS catheter (B)	1.0	2,001.60	2,001.60
Theatre/procedure cost (A)	1.0	2,070.00	2,070.00
Pre-discharge duplex ultrasound (B)	1.0	120.00	120.00
LOS (days) (A)	5.0	431.00	1,724.00

A: NHS national tariff data
B: Procurement cost for the NHS trust

5.3.10 Costs associated with index iliac vein stenting procedure for non-thrombotic iliac vein lesions

Table 31 contains the resource use and associated costs relevant to the index admission for iliac vein stenting in NIVL. The total cost equates to £8,830.24.

Table 31: Costs included in the Markov model for the index stenting procedure in non-thrombotic iliac vein lesions

Resource	Units per procedure	Unit cost (£)	Total cost (£)
Pre-operative CT (A)	1.0	103.00	103.00
Pre-operative venogram (A)	1.0	859.00	859.00
Dedicated venous stent (B)	1.55	1,920.00	2,976.00
High-pressure angioplasty balloon (B)	1.0	269.64	269.64
IVUS catheter (B)	1.0	2,001.60	2,001.60
Theatre/procedure cost (A)	1.0	2,070.00	2,070.00
Pre-discharge duplex ultrasound (B)	1.0	120.00	120.00
LOS (days) (A)	1.0	431.00	431.00

A: NHS national tariff data
B: Procurement cost for the NHS trust

5.3.11 Costs associated with stent surveillance across both post thrombotic syndrome and non-thrombotic iliac vein lesion groups

Table 32 contains the resource use and associated costs for stent surveillance of both PTS and NIVL groups. The total cost equates to £465.60 per year, with an additional varying cost for venous ulceration.

Table 32: Costs included in the Markov model in respect to stent surveillance for those with a patent stent

Resource	Frequency (per year)	Unit cost (£)	Total cost (£)
Vascular outpatient appointment (A)	2.4	94.00	225.60
Duplex ultrasound scan (B)	2.0	120.00	240.00
Venous ulcer care (C)	Variable	1032.16	Variable

A: NHS national tariff data
B: Procurement cost for the NHS trust
C: Epstein et al.(345)

5.3.12 Costs associated with reintervention across both post thrombotic syndrome and non-thrombotic iliac vein lesion groups

Table 33 contains the resource use and associated costs for reintervention to maintain stent patency for both PTS and NIVL groups. These costs are based on a day-case reintervention in which a patient undergoes intravascular venography, IVUS, and balloon angioplasty. The total cost equates to £4,149.00.

Table 33: Costs included in the Markov model in respect to reintervention to maintain stent patency for those with a clinically relevant in-stent stenosis

Resource	Units per procedure	Unit cost (£)	Total cost (£)
High-pressure angioplasty balloon (B)	1.0	269.64	269.64
IVUS catheter (B)	1.0	2,001.60	2,001.60
Theatre/procedure cost (A)	1.0	1,447.00	1,447.00
LOS (days) (A)	1.0	431.00	431.00

A: NHS national tariff data
B: Procurement cost for the NHS trust

5.3.13 Costs associated with medical care for post thrombotic syndrome not undergoing iliac vein stenting

Table 34 contains the resource use and associated costs for medical care of participants with PTS treated conservatively. The annual cost equates to £339.79.

Table 34: Costs included in the Markov model in respect to medical care for those with post thrombotic syndrome not undergoing iliac vein stenting

Resource	Frequency (per year)	Unit cost (£)	Total cost (£)
Vascular outpatient appointment (A)	1.0	94.00	94.00
Duplex ultrasound scan (B)	0.50	120.00	60.00
Venous ulcer care (C)	0.18	1,032.16	185.79

A: NHS national tariff data
B: Procurement cost for the NHS trust
C: Epstein et al.(345)

5.3.14 Costs associated with medical care for non-thrombotic syndrome not undergoing iliac vein stenting

Table 35 contains the resource use and associated costs for medical care of participants with NIVL treated conservatively. The annual cost equates to £236.57.

Table 35: Costs included in the Markov model in respect to medical care for those with non-thrombotic iliac vein lesions not undergoing iliac vein stenting

Resource	Frequency (per year)	Unit cost (£)	Total cost (£)
Vascular outpatient appointment (A)	1.0	94.00	94.00
Duplex ultrasound scan (B)	0.50	120.00	60.00
Venous ulcer care (C)	0.08	1,032.16	82.57

A: NHS national tariff data
B: Procurement cost for the NHS trust
C: Epstein et al.(345)

5.3.15 Cost-effectiveness analysis for iliac vein stenting in post thrombotic syndrome in comparison to standard medical therapy

A Markov state-transition model (n=1,000) was conducted over 50 cycles, each cycle equating to one year, for iliac vein stenting and medical therapy in PTS. Figure 69 illustrates the trajectory for each health state over time. The total utility accrued for iliac vein stenting, across the model, equated to 16,702.55 at a cost of £31,974,020. The total utility accrued for standard medical therapy, across the model, equated to 15,433.44 at a cost of £12,746,577. The total cost difference was £19,227,440, equating to £19,227.44 per simulated patient. This corresponds to an ICER for iliac vein stenting of £15,150.37. The cost-effectiveness acceptability curve, produced from the probabilistic sensitivity analyses, is illustrated in Figure 70.

Figure 69: Markov trace showing the number of simulated patients in each health state across Markov cycles for the post thrombotic syndrome model

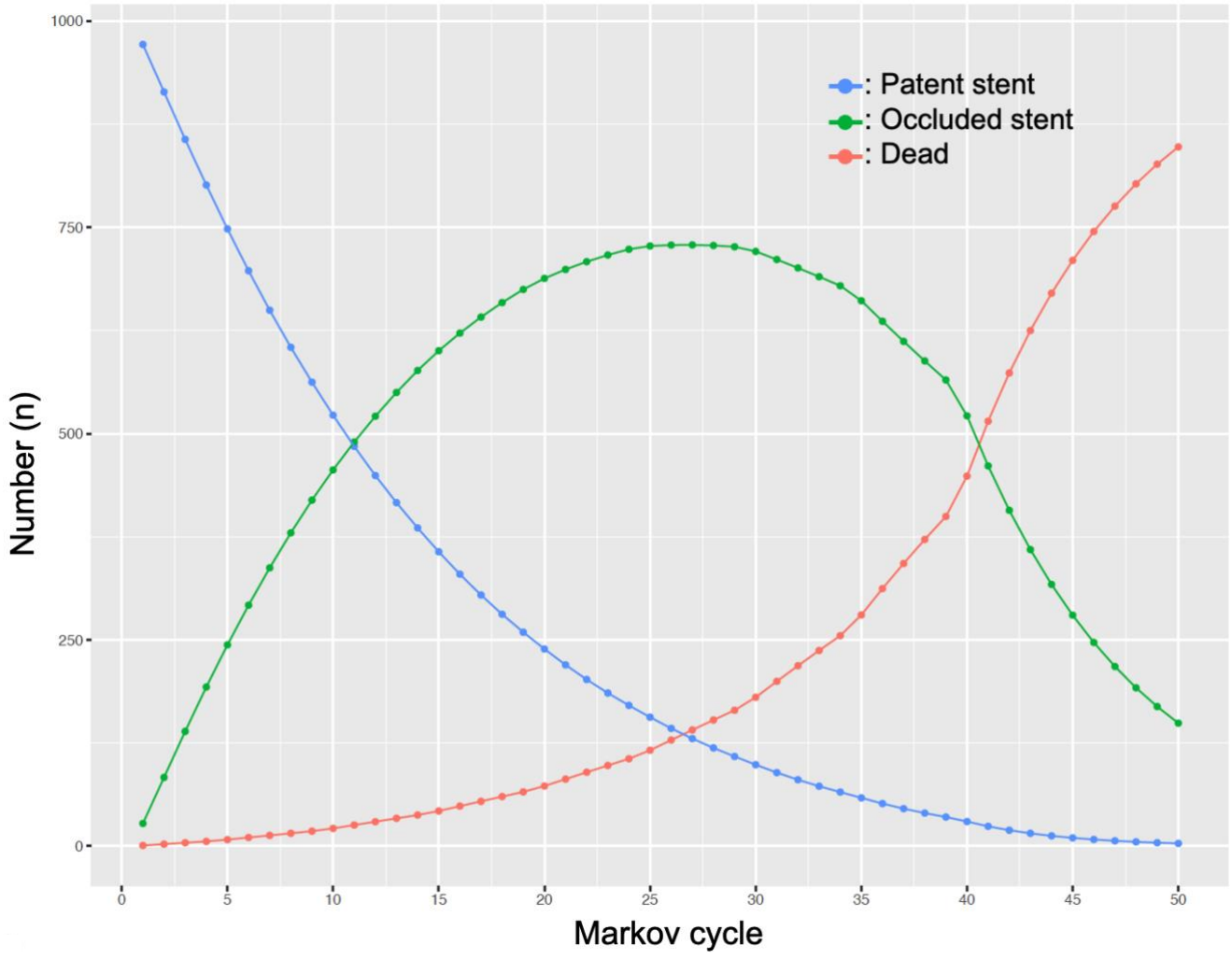
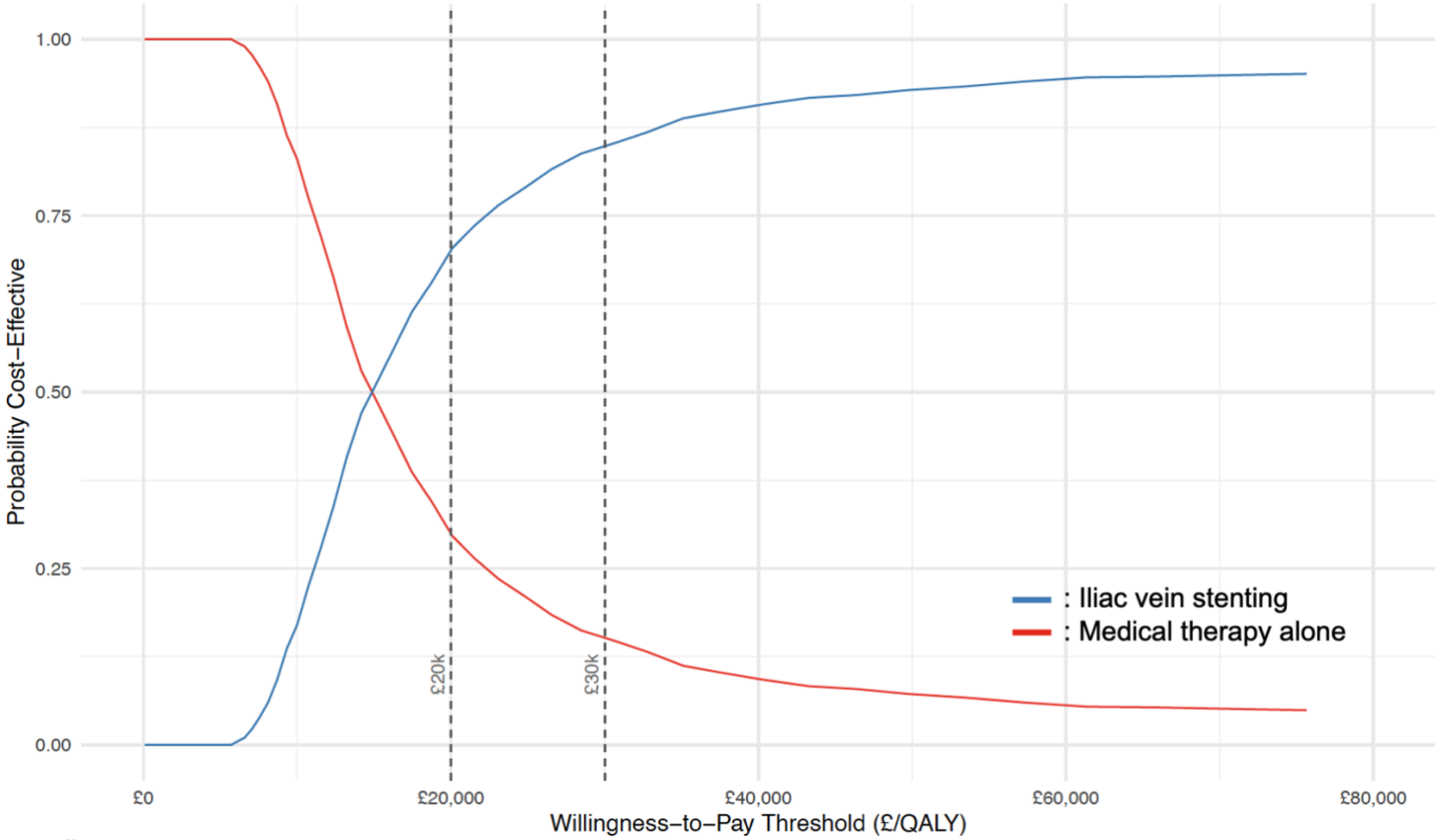


Figure 70: Cost-effectiveness acceptability curve for iliac vein stenting in comparison to standard medical therapy for post thrombotic syndrome



k: kilo, unit of one thousand
QALY: Quality-adjusted life year
Marked thresholds equate to national institute for health and care excellence willingness-to-pay thresholds (£20,000 - £30,000)

5.3.16 Deterministic sensitivity analysis for iliac vein stenting in post thrombotic syndrome in comparison to standard medical therapy

EQ5D-5L index utility was the most influential factor in the deterministic sensitivity analysis for PTS. EQ5D-5L is estimated to increase from 0.700 to 0.784 after iliac vein stenting. The willingness-to-pay threshold of £30,000 was met when the post-stenting EQ5D-5L index utility declined to 0.722. At this value, the total utility accrued equated to 16,024.92 at a cost of £30,492,809, with an ICER of £30,000. If the lower willingness-to-pay threshold of £20,000 is considered, this was met when the EQ5D-5L index declined to 0.755.

With respects to chronic care costs, including stent surveillance and reintervention, the £30,000 willingness-to-pay threshold was met when the annual cost exceeded £1,992.68. Given the cost of reintervention is approximately £4,149.00, the rate of reintervention would need to increase up to 36.8% annually.

The index admission, including cost of procedure, stents, IVUS, and balloon angioplasty, met the £30,000 willingness-to-pay threshold at £33,640.98. At this cost, the same accrued utility of 16,702.55 is gained at a cost £50,819,789 – corresponding to an ICER of £30,000.

5.3.17 Cost-effectiveness analysis for iliac vein stenting in non-thrombotic iliac vein lesions in comparison to standard medical therapy

As for PTS, a Markov state-transition model (n=1,000) was conducted over 50 cycles, each cycle equating to one year, for iliac vein stenting and medical therapy in NIVL. Figure 71 illustrates the trajectory for each health state over time, with NIVL having an improved survival function for stent patency. The total utility accrued for iliac vein stenting, across the model, equated to 17,036.96 at a cost of £24,026,235. The total utility accrued for standard medical therapy, across the model, equated to 15,433.44 at a cost of £8,874,475. The total cost difference was £15,151,760, equating to £15,151.76 per simulated patient. This corresponds to an ICER for iliac vein stenting of £9,449.07. The cost-effectiveness acceptability curve, produced from the probabilistic sensitivity analyses, is illustrated in Figure 72.

Figure 71: Markov trace showing the number of simulated patients in each health state across Markov cycles for the non-thrombotic iliac vein lesion model

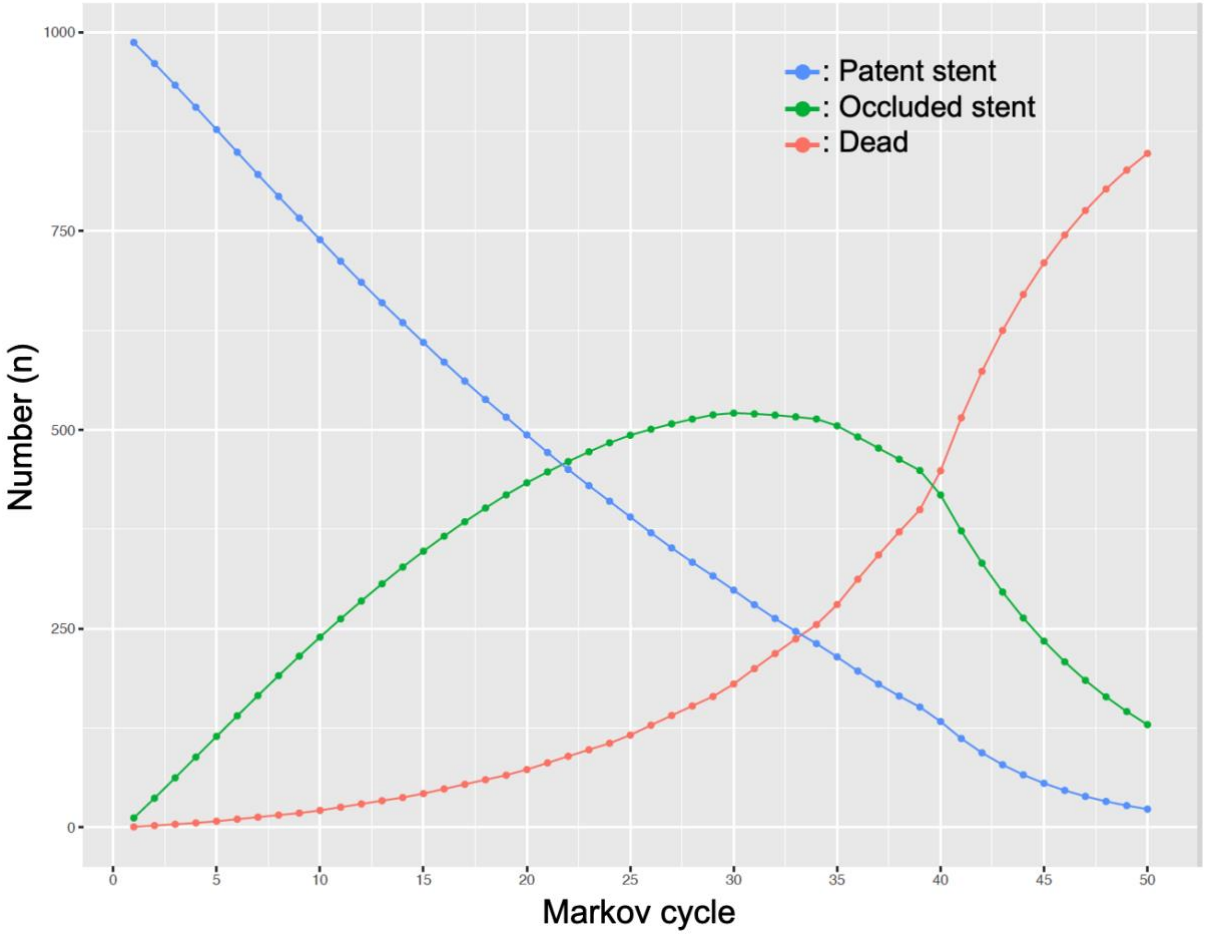
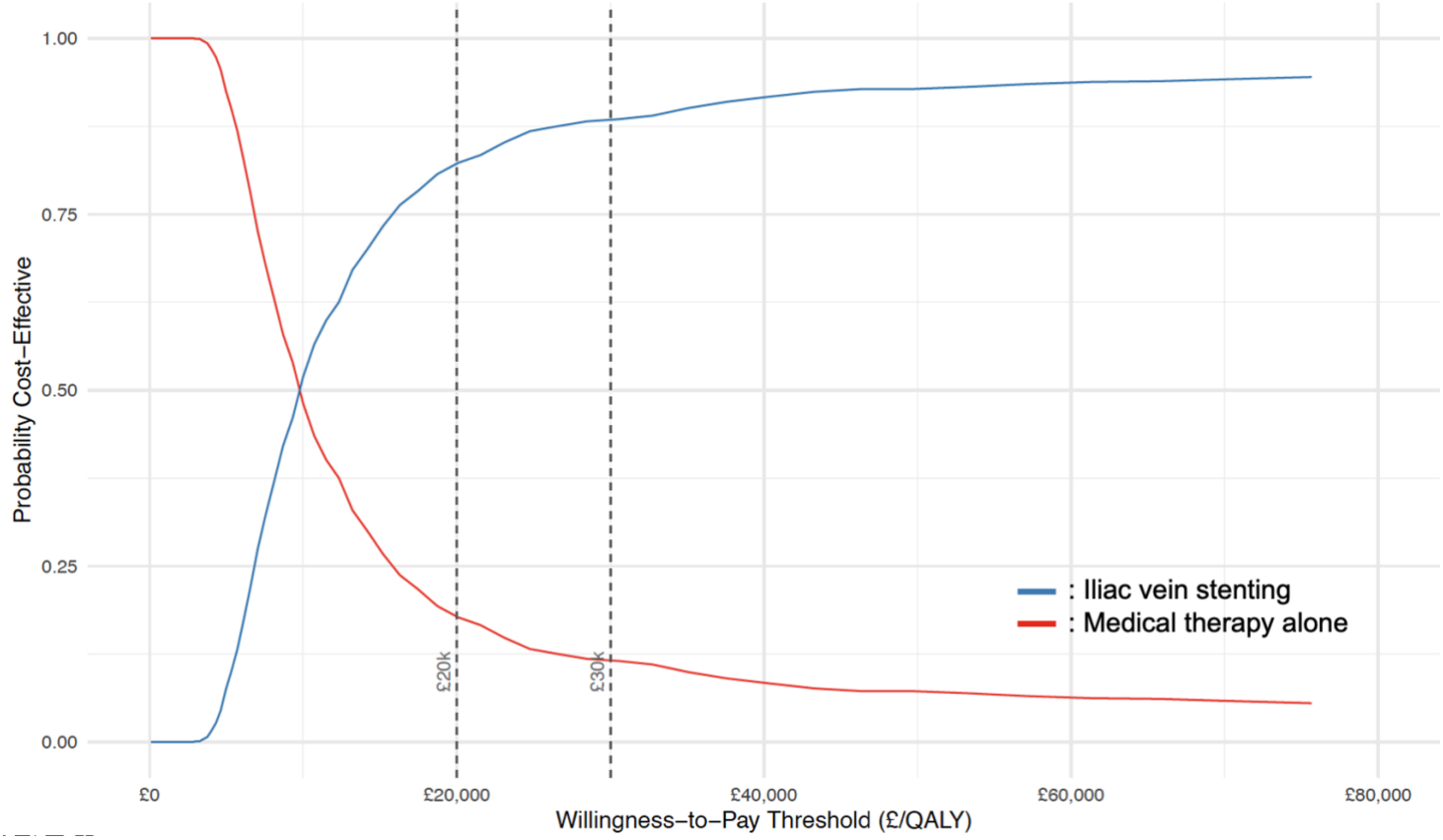


Figure 72: Cost-effectiveness acceptability curve for iliac vein stenting in comparison to standard medical therapy for non-thrombotic iliac vein lesions



k: kilo, unit of one thousand
QALY: Quality-adjusted life year
Marked thresholds equate to national institute for health and care excellence willingness-to-pay thresholds (£20,000 - £30,000)

5.3.18 Deterministic sensitivity analysis for iliac vein stenting in post thrombotic syndrome in comparison to standard medical therapy

As for PTS, EQ5D-5L index utility was the most influential factor in the deterministic sensitivity analysis for NIVL. EQ5D-5L is estimated to increase from 0.700 to 0.788 after iliac vein stenting. The £30,000 willingness-to-pay threshold was met when the post-stenting EQ5D-5L declined to 0.709. At this value, the total utility accrued equated to 15,916.46 at a cost of £23,365,423, with an ICER of £30,000.

With respects to chronic care costs, including stent surveillance and reintervention, the £30,000 willingness-to-pay threshold was met when the annual cost exceeded £2,143.96. The rate of reintervention would need to increase up to 51.7% to amass a total cost of £56,980,203 in order to get to the ICER of £30,000.

The index admission met the £30,000 willingness-to-pay threshold at £41,373.66. At this cost, the same accrued utility of 17,036.96 is gained at a cost £56,980,083 – corresponding to an ICER of £30,000.

5.4 Discussion

This chapter presents the first Markov state transition model in the literature evaluating the cost-effectiveness of iliac vein stenting in PTS and NIVL. The key consideration when designing the model was to utilise high-quality data inputs within a structurally simple Markov model over an extended time horizon. Data from the vast literature was leveraged in the model's creation, establishing functions for stent patency and survival, and providing robust pooled estimates on the improvement of disease severity and venous ulcer healing. Iliac vein stenting was shown to be cost-effective for both PTS and NIVL pathologies. The analysis produced some interesting results, the impact and limitations of which will be explored.

5.4.1 Venous clinical severity score and EuroQol EQ5D are correlated

Firstly, VCSS is a graded measure with the score expressed as a sum of its domains. This would be classified as an ordinal measure, akin to Glasgow Coma Scale or Cancer staging. However, due to the number of domains (with a maximum score of 30) and considered design, it behaves like a continuous measure. All but one study reporting VCSS from WP A treated it as a continuous measure, yet none of the studies reported any proof of the normality of VCSS. This chapter successfully demonstrated the normality of VCSS and therefore was able to employ parametric measures in attempt to assess its relationship with EQ5D.

Within the CVOO population, this is the first time a function of EQ5D from VCSS has been defined. This permits the extrapolation of data from the numerous single armed studies demonstrating that there is a consistent improvement in VCSS after iliac vein stenting. Reassuringly, the modelled EQ5D index utility increase from pooled VCSS mirrors the EQ5D gains seen in the Abre IDE trial(208). Further external validation of the correlation between VCSS and EQ5D is required to increase the certainty in the relationship.

5.4.2 Cost-effectiveness of iliac vein stenting hinges on improvement in quality of life rather than any cost-saving effect

Iliac vein stenting was not a cost-saving procedure despite reducing the rate of venous ulceration. The associated cost of the index procedure and stent surveillance was greater than the cost of medical therapy even when accounting for the increased rate of venous ulceration in the medical therapy arm. The result of this is that the intervention hinges on its ability to provide utility. Furthermore, it is not a prophylactic procedure undertaken to prolong life, as is the case for abdominal aortic aneurysm repair. The length of life in the venous stenting arm is arguably the same as the medical therapy arm. The increased rate of venous ulceration in the medical arm is associated with a modest increased risk of mortality(348), which can be weighed against the damaging health effects of undergoing repeat surgical procedures and bleeding complications in a proportion of the stenting arm. Therefore, no QALYs are gained from improving overall survival.

The improvement in QALY has to arise from an improvement in quality of life above and beyond that experienced in the medical therapy arm. Quality of life has been modelled from the pooled estimate for improvement in disease severity. This area of the analysis likely has the highest degree of uncertainty as it required mapping from one variable to another. This could be problematic as the sensitivity analysis in PTS demonstrated that the EQ5D utility index value would only have to drop to 0.755 prior to the £20,000 willingness-to-pay threshold being met. Likewise, if the index utility value in the medical arm improved by just 0.029, the £20,000 willingness-to-pay threshold would be breached.

More problematic is the assumption that changes in quality of life remain the same in the medical therapy arm rather than improving with medical care. There is no randomised evidence to support this. Justifying this concern, the STEVECO trial demonstrated a greater improvement in EQ5D in the medical therapy arm at 12 months in comparison to the stenting arm. This is particularly important as the point of seeking medical treatment is likely a trough in the disease severity experienced. Just by regressing to the mean, the medical therapy arm could improve. Evidence from a blinded RCT is required to demonstrate how the quality of life varies over time for both treatment strategies.

5.4.3 Treating post thrombotic syndrome is more expensive

The cost of treating PTS was consistently higher in comparison to NIVL. The ICER for PTS and NIVL was £15,150.37 and £9,449.07 respectively. PTS had a higher index procedural costs due to the increased number of stents required and a longer length of stay. The length of stay used in the model for PTS, an input from WP C, could be criticised for being overly long. The length of stay is rarely reported in the literature, two studies reported length of stay for PTS in WP A, with the average values ranging from 1.5 – 3.0. The sensitivity analyses demonstrated there was a significant margin within the cost of the index procedure. Hence, this single variable is unlikely to influence the outcome. The cost of stent surveillance and stent maintenance was also greater in the PTS cohort due to the higher rate of reintervention. This is an interesting finding as there is currently no evidence in the literature to suggest that PTS is more resource intensive to treat in comparison to NIVL other than the reported number of stents placed.

Lastly, from WP A, it was observed that the reduction in VCSS after stenting in PTS is slightly lower than for NIVL. This resulted in different post-stenting EQ5D index utility values of 0.784 and 0.787 for PTS and NIVL respectively. As the utility gained from iliac vein stenting in PTS was slightly lower than for NIVL, this also increased the ICER.

5.4.4 Iliac vein stenting appears to be cost-effective in respect to current willingness-to-pay thresholds in the United Kingdom

Based on the estimates produced by this model, iliac vein stenting for both PTS and NIVL appears to be below the NICE willingness-to-pay threshold of £20,000. The deterministic sensitivity analysis demonstrated that for most variables, except for quality of life, it was likely that iliac vein stenting would produce an ICER below the upper limit of the £30,000 willingness-to-pay exceptional circumstances margin. The existing Markov state transition model in the literature assessing iliac vein stenting in venous ulceration for PTS reported an ICER of €12,388 (£10,699) per QALY. Reassuringly, the rate of ulcer healing used was similar to that used in this model.

5.4.5 Limitations

Mapping variables is an established, and sometimes unavoidable, methodology in cost-effectiveness analyses as it is rarely possible to gather all the necessary information from a single population. The mapping of EQ5D onto VCSS introduces a level of uncertainty into the analysis for the most influential input. The 95% confidence interval for the correlation between VCSS and EQ5D could not be used in the function in the model as the difference was amplified creating unfeasible values – which itself demonstrates the significance of uncertainty in the mapping variable. Mapping facilitated the leverage of a substantial amount of VCSS data from the literature. However, to improve the certainty in the analysis, all of the data sources would have been primarily sourced – the best examples of this originate from adequately powered purpose-designed RCTs.

The effect of reintervention on quality of life is unknown. Although its effect would have been captured to a degree in the STEVECO dataset, the number of participants undergoing reintervention was low due to the limited follow-up duration. Logically, having multiple reinterventions, associated with hospital admissions, pain, and suspension of normal societal function, would be associated with a diminished quality of life. The quality of life was discounted over time, but this occurred equally across the two arms. For PTS, the lifetime rate of reintervention is likely to have a significant effect on quality of life which was not captured by the model.

Lastly, the uncertainty for the cost and utility variables was estimated for the probabilistic sensitivity analysis. For example, the cost of the stent surveillance has a degree of uncertainty which is unquantifiable with the current information. A conservative SD value was utilised in the function to estimate the uncertainty, however, in reality this could be higher or lower than used in the model.

This model has optimised the available data in attempt to provide a meaningful estimate of the cost-effectiveness of iliac vein stenting in CVOO, however, it is limited by the lack of comparative evidence in the literature. As for many cost-effectiveness analyses, the result should be interpretated with caution due to the assumptions made and the uncertainty present in the estimates included.

5.5 Conclusion

Given it is not a cost-saving intervention, the cost-effectiveness of iliac vein stenting hinges on its ability to improve quality of life. Based on current estimates, iliac vein stenting for PTS and NIVL appears to be below the NICE willingness-to-pay threshold of £20,000. Additional evidence is required to validate the relationship between VCSS and EQ5D as this evidence currently originates from a single study. Furthermore, a RCT is required to provide certainty in the utility gained from iliac vein stenting across the two pathologies in comparison to medical treatment. There were again differences observed between the PTS and NIVL pathologies – PTS was more expensive, accrued a lower total utility, and had a higher ICER in comparison to NIVL.

6 – WORK PACKAGE E:

An international assessor-blinded multicentre randomised controlled trial investigating the use of iliac vein stenting in comparison to best medical therapy for the treatment of CVOO

CHAPTER 6: WORK PACKAGE E

An international assessor-blinded multicentre randomised controlled trial investigating the use of iliac vein stenting in comparison to best medical therapy for the treatment of CVOO

6.1 Background

Considering the lack of comparative evidence, an adequately powered RCT was paramount to assess efficacy and cost-effectiveness of venous stenting in PTS and NIVL.

Through collaboration with key stakeholders and patient public partners, the "**B**est **E**ndovenous treatment, including **ST**enting, versus best non-endovenous treatment in chronic proximal deep venous disease – the BEST multi-centre randomised controlled trial" was developed. The patient public involvement (PPI) work undertaken in the development of the trial is covered in 6.2.1. Non-commercial funding for the trial was secured through a multi-round competitive funding application to the British Heart Foundation on the 7th of July 2021. The trial was supported by a variety of key stakeholder groups, including Thrombosis UK, British Society of Interventional Radiology, Circulation Foundation, Society of Vascular Nurses, and the Vascular Society of Great Britain and Ireland.

The aims of the BEST trial were to establish whether:-

1. Undertaking deep venous procedures, including venoplasty and venous stenting, improves clinical measures of chronic venous disease and quality of life;
2. Undertaking deep venous procedures, including venoplasty and venous stenting, is safe; and
3. Undertaking deep venous procedures, including venoplasty and venous stenting, is cost-effective.

As this chapter will cover, the BEST trial was unsuccessful in fulfilling its aims. It closed prior to reaching the pre-defined sample size due to futility.

6.2 Patient public involvement

6.2.1 Patient public involvement in the funding application

Several patients and the public guided the development of the BEST trial. The PPI lead is an expert patient and Executive Officer of Thrombosis UK and had been a part of the study team since study conceptualisation. Two of the co-applicants had lived experience of DVT, one of whom had considered iliac vein stenting as a potential treatment.

The PPI lead also provided key input into the design of a survey undertaken by the venous patient community to ascertain further public views of the proposed BEST trial. The online survey included a description of the potential trial and was shared with members of the venous patient community through Thrombosis UK. A total of 102 people responded to the survey, with 60 answering all of the questions posed. The responses can be summarised as follows:-

- All responders believed it was important to investigate the treatments for CVOO;
- 95% (n=57) stated that the number of follow-ups with the research team was acceptable;
- 77.0% (n=47) thought that the trial, including randomisation, was ethical; and
- 93.7% (n=59) stated that the trial summary describing the trial was clear.

In the long form open questions exploring barriers to enrolment, there was a mix of preferences for intervention balanced against preferences for medical therapy. To gain an insight into these preferences, the following quotes are included below:

- *“I would be nervous about the stent option unless I really needed it as it feels much more invasive, so would probably hope I wasn't randomised to that option. This looks like an important study though.”*
- *“I don’t much like the idea of having a stent put in if it is not actually needed. Presumably it could cause problems (blockage, movement?) which were not there in the first place? But perhaps there is no reason to worry; I just need more information.”*
- *“What would stop you enrolling?” “Preference for intervention.”*

There was a consistent theme of patients wanting more information on how venous stenting would improve specific symptoms and their quality of life. For example, would their swelling improve, or would benefits be isolated to the clinical signs of CVD. When asked what they would like the trial to explore, one response included *"The participants' experience over time, like a diary of their symptoms in daily life*.".

In the long form open questions exploring potential barriers, there was general acceptance that an RCT is required. There were some responses which expressed a degree of hesitance, however, even these fundamentally confirmed equipoise, such as *"I wonder whether these patients who are at the end of their tether would be willing to be randomised. Otherwise, I accept that many vascular surgeons are in equipoise and therefore I would be very happy to take part*".

A further survey was undertaken to explore a patients' willingness to be randomised, to which there were 36 responses. More than three-quarters of patients (78%) felt that there was not enough information in relation to venous stenting available to patients to decide about interventional treatment. Over half, 58%, of respondents would be happy to be randomised into a study like BEST. Additionally, the PPI co-applicants were also a source of key discussion on the acceptability of randomisation. These responses suggested that the proposed research topic was a priority for this patient group and the study design would not be an insurmountable barrier to recruitment.

PPI co-applicants reviewed all participant-facing materials, including the participant information pack, to ensure comprehension and clarity. They also provided guidance on the costings for PPI activities, advising what they believe are reasonable reimbursements for attending PPI activities.

6.2.2 Patient public involvement in the trial management

In order to help guide the course of the trial, one of the PPI co-applicants was invited to be part of the trial steering committee (TSC) and attended every TSC held. The PPI lead would also attend the trial management group (TMG) meetings when key decisions were required regarding changes to the study delivery or design.

6.3 Methods

6.3.1 Trial design

The BEST trial was an international multicentre assessor-blinded RCT investigating the additional benefit of iliac vein stenting in the treatment of CVOO.

6.3.2 Intervention and comparator:

The intervention and control arm can be summarised as follows:-

- Intervention arm: best endovenous reconstruction AND best medical therapy;
- Control arm: best medical therapy alone.

The intervention arm included ‘best’ endovenous reconstruction in addition to best medical treatment. The mantra for the trial was that the procedure would be optimised by utilising widely accepted best practice techniques, namely utilising IVUS to guide the placement of a dedicated venous stent performed in a centre with a specialist venous practice.

The control arm included optimal best medical treatment alone which constituted compression therapy and antithrombotic therapy where indicated. There was no placebo or ‘sham’ procedure.

An intention-to-treat analysis was planned for the primary outcome, this included crossover from best medical therapy to the intervention arm. Crossover was recorded with a subsequent per protocol analysis planned to aid interpretation of the results.

6.3.3 Eligibility criteria

Inclusion criteria

1. Adult patients with chronic venous disease secondary to chronic proximal thrombotic or non-thrombotic stenosis or occlusion
2. Disease in iliac and/or caval deep venous system(s)
3. CEAP clinical C3, C4, C5, C6 or symptoms of venous claudication
4. Anatomically suitable for endovenous reconstruction

Exclusion criteria

1. Contraindications to stenting (e.g., anatomically unsuitable, contrast allergy)
2. Contraindications to prolonged anticoagulation
3. Caval occlusion at or proximal to the level of the renal veins
4. Open / hybrid open-endovascular deep venous intervention
5. Pregnancy
6. Inability to provide consent
7. Need to place stent caudal to common femoral vein confluence to achieve suitable inflow
8. Participants that have tested positive for coronavirus within the last 3 months

6.3.4 Description of the interventions

The intervention arm consisted of best endovenous reconstruction in addition to best medical treatment. The control arm consisted of best medical therapy alone.

Endovenous reconstruction encompassed balloon venoplasty and venous stenting. A dedicated venous stent was used in all cases, the particular device was left to the individual operating surgeon to decide. IVUS was mandated in all cases. To optimise the prospect of technical and procedural success, this trial was undertaken in tertiary vascular centres with competency in the procedure.

Best medical therapy consisted of graduated compression therapy in addition to antithrombotic therapy where clinically indicated. For the purpose of the trial, class II and class III GCS were used, with the aim of providing class III if tolerated. Antithrombotic therapy was used throughout the study period in both arms and stopped at the discretion of the treating clinician. Some participants remained on anticoagulation treatment life-long due to recurrent VTE. The duration of compression and antithrombotic therapy was recorded throughout the trial.

6.3.5 Primary outcome

The primary outcome was the change in VCSS from baseline to 6 months. After considerable discussion with PPI representatives, specialists, and trialists, VCSS was considered to be the most appropriate, consistent and responsive outcome measure for this patient population. This is largely echoed in the wider literature as the most commonly reported disease severity marker. The primary outcome was timed to capture maximal therapeutic benefit. There are several examples of the responsiveness of VCSS after iliac vein stenting from cohort studies(216, 240). VCSS was also observed to decrease after iliac vein stenting in the single centre RCT(185).

Secondary outcomes

- VEINES-QoL/Sym: Disease-specific quality of life measure;
- Villalta score and Ginsberg score (PTS scores): Villalta score has been used extensively in the literature investigating patients with PTS;
- Stent patency: assessed by duplex ultrasound at follow-up as specified in the study flow diagram;
- Symptom resolution: assessed through a symptom diary, days per week without significant limitation – PPI driven outcome measure;
- Venous ulceration (dichotomous outcome for ulcer healing);
- Generic quality of life measures (EQ-5D-5L & SF-36): EQ5D-5L is a key metric for calculating cost-effectiveness and has been widely validated, SF-36 is often reported in the medical literature and can be used to aid calculation of cost-effectiveness; and
- Cost-effectiveness, ICER for iliac vein stenting in comparison to the control arm.

Figure 73: Flowchart illustrating the intended overview of the BEST trial

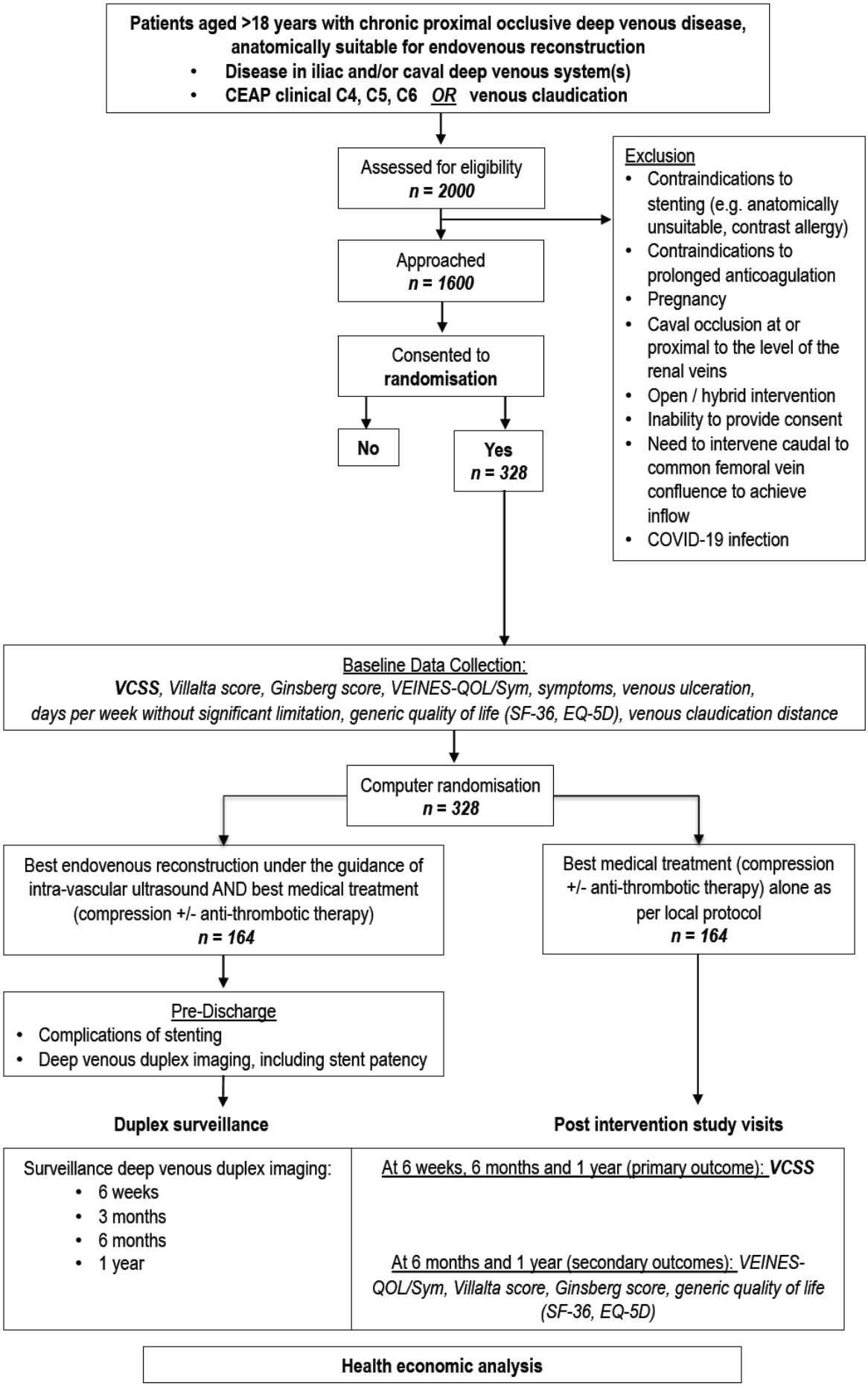


Figure 73 footnotes:
CEAP: Clinical-Eitology-Anatomy-Pathophysiology classification
COVID-19: Coronavirus disease, SARS-CoV-2 2019
VCSS: Venous clinical severity score
VEINES QOL/Sym: Venous Insufficiency Epidemiological and Economic Study questionnaire
EQ5D-5L: 5-level EQ-5D version, EuroQol Group, 2009
SF-36: 36-Item Short Form Health Survey

6.3.6 Study duration

The total project duration was designed to be 48 months, consisting of:-

- 6 months site set up;
- 24 months recruitment;
- 12 months follow-up with database lock; and
- 6 months close down with parallel data analysis.

6.3.7 Study sites, in alphabetical order:

1. Bedfordshire Hospitals NHS Foundation Trust, England;
2. Cambridge University Hospitals NHS Foundation Trust, England;
3. Guy's and St Thomas' NHS Foundation Trust, England;
4. Hull and East Yorkshire Hospital NHS Trust, England;
5. Imperial College Healthcare NHS Trust, England;
6. Leeds Teaching Hospitals NHS Trust, England;
7. London North West University Healthcare NHS Trust, England;
8. Newcastle Upon Tyne Hospitals NHS Foundation Trust, England;
9. North Bristol NHS Trust, England;
10. Oxford University Hospitals NHS Foundation Trust, England;
11. Royal Free London NHS Foundation Trust, England; and
12. University Hospital Galway, Ireland.

6.3.8 Recruitment and randomisation

Participants were recruited from outpatient clinics within tertiary vascular centres. A competent Consultant Vascular Surgeon, detailed on the delegation log, deemed participants eligible prior to enrolment. Computer randomisation (1:1) within REDCap© was used for allocation of intervention, stratified by pathology (PTS vs NIVL).

6.3.9 Blinding

Allocations were single blinded with blinding of outcome assessors only. Within each site centre, at least two research personnel were required to ensure one could remain blinded. Participants were instructed to not reveal their allocation when attending for assessments. It has previously been demonstrated that VCSS can be undertaken in a blinded fashion(185, 349). The participants were not blinded as blinding through a sham procedure was deemed not to be acceptable in the trial consultation period.

6.3.10 Follow-up

Participants in the intervention and control arms were followed up in parallel. Outpatient follow-up with clinical review to ascertain primary and secondary outcomes, with additional stent surveillance lower limb venous duplex imaging was undertaken at the following timepoints: pre-discharge, 6 weeks, 6 months, and 12 months. Lower limb venous duplex scans to check stent patency was undertaken at these timepoints to mirror standard practice in those undergoing venous stenting procedures. Venous duplex at these timepoints was an additional research activity in those that were randomised to the control arm.

The primary outcome was assessed at 6 weeks, 6 months, and 12 months. Whereas secondary outcomes were assessed at 6 months and 12 months only. This was to minimise the research burden on participants during the early 6 week follow-up when quality of life would likely still be impacted by the hospital admission in the intervention arm.

6.3.11 Sample size calculation

At 90% power and a 5% level of significance on the primary outcome of change over baseline VCSS at 6 months, the study could detect the minimally important clinically significant mean change of 4 units, assuming a SD of 8 units. This figure was based on the improvements reported in previous cohort studies(216, 240) and the single centre RCT(185). The large SD permitted a range of disease severities and would have facilitated a subgroup analysis of PTS and NIVL. This base case would require 85 per group, or 170 in total. An anticipated 10% crossover (which could only have been from best medical care alone to best endovenous treatment, since everyone gets best medical care and once a stent has been placed this is irreversible) increased this to 105 per group or 210 in total. To allow for clustering in the surgical group, an intra-class correlation (ICC) coefficient of 0.03 was assumed, increasing the sample size in this arm by around 33% (assuming equal sized centres). Likewise, to allow for clustering due to different standard of care in the control group, an ICC of 0.01 was assumed, increasing the sample size in this arm by around 11%, (again assuming equal sized centres). The two arms were of equal size rather than randomising in a ratio; hence both groups were inflated by the larger design effect of 1.33 (so 210 inflates to 279). A total of 15% was allowed for loss to follow up. The total sample, randomised 1:1 between the two groups, was 328 (or 164 per group). This total sample size was similar to the sample size required for adequate power if VEINES QoL/Sym were the primary outcome. This would have allowed sufficient power to evaluate disease-specific quality of life. When considering effect sizes, a 4-unit change in VCSS was deemed to represent a clinically meaningful change.

The single centre RCT reported that mean VCSS decreased from 11.52 at baseline to 5.77 at 6 months, a unit change of 5.75 with a SD at baseline of 3.54(185). A conservative SD of 8 units was assumed in the power calculation for the overall sample size. Importantly, the SD for each pathology was likely to be lower and lie closer to 4 units SD. When considering the SD of 8, it considered that the overall variability is made up of the two contributing pathologies. The sample size would be sufficiently powered to detect a 4-unit treatment effect in the PTS patients alone (or NIVL patients alone) – assuming equal enrolment and that the relevant SD is under 6 (again a conservative estimate).

6.3.12 Data collection and confidentiality

The principal means of data collection from participant visits were Electronic Data Capture (EDC) using a REDCap database system via the internet. Data was entered into the EDC system via site personnel. All source data recorded in the case report forms was signed by the Investigator or the appropriate designee.

All changes made following the electronic signing had an electronic audit trail with a signature and date. A record of all access to data was maintained on the Data Sharing Log. All study data was archived in accordance with the sponsor's standard operating procedures. The Edinburgh Clinical Trials Unit was responsible for the database build and maintenance alongside system validation aligning with their standard operating procedures.

6.3.13 Statistical analysis

All statistical analyses were intended to be governed by a comprehensive Statistical Analysis Plan, authored by the study statistician (Professor John Norrie) and agreed by the independent TSC. The main analysis was planned to be according to the intention-to-treat principle and set to compare the changeover baseline VCSS at 6 months, using a repeated measures ANOVA, adjusting for baseline VCSS and any other pre-specified strongly prognostic baseline covariates, and centre as a random effect. Randomisation was stratified on pathology type to ensure equal number of those with PTS and NIVLs across the intervention and control arms.

Repeated measures of the outcome were measured at 6 weeks, 6 months and 12 months. It was planned for the findings to be assessed for robustness against any missing data, first using multiple imputation assuming this data is missing at random and, if appropriate and the data permits, further sensitivity analyses for any plausible missing data mechanisms not missing at random. Secondary outcomes were to be analysed in a similar fashion with generalised linear models appropriate to the distribution of the outcome.

6.3.14 Internal pilot of feasibility

The trial was continually monitored for safety and would have been stopped at any time on the recommendation of the DMC if there was marked clinical harm resulting in a lack of equipoise and it being deemed unethical to continue the trial.

The internal pilot of feasibility looked to establish (i) recruitment feasibility (at 6 months) and (ii) confirm/re-estimate sample size (at 12 months). With a staggered set up of the total 10 study sites at 2 sites per month, by 6-months of the internal pilot the study was required to have all 10 sites activated and have randomised 60 participants. The corresponding actions from the internal pilot were set out as follows, illustrated in Figure 74. If there were 46 or more participants recruited, this was within sampling variability of the target of 60 (Green) and the study continues. Between 30 and 45 participants, this would have been below the target but addressable with alterations to the recruitment strategy (Amber). Lastly, if less than 30 participants were recruited, consideration was to be made of terminating the study due to infeasibility (Red).

Figure 74: Internal pilot of feasibility at 6-months recruitment, equating to month 12 of the study

Progression criteria	**Red**	**Amber**	**Green**
% Threshold	<50	50 – 99.9%	≥100
Recruitment rate / site / month	<1	1 – 1.49	≥1.5
Number of sites opened	<5	5 - 9	≥10
Total number of participants recruited	<30	31 - 59	≥60

6.3.15 Cost-effectiveness analysis

The trial set out to collect the following variables which were to be used in the health economic analyses:

- Procedure resource use (staff, days in hospital, devices and consumables), costed using manufacturers' list prices, national UK reference costs and other literature
- Primary clinical outcome, VCSS
- EQ-5D-5L, scored using the index recommended by NICE in the UK
- Healthcare resource use during follow-up (hospital visits, re-admissions, re-interventions, primary and community care, wound care), collected from case notes and patient diaries
- Physiotherapy and other health professional interventions
- Social care and home help (paid and unpaid)
- Patient out-of-pocket expenses related to these conditions
- Days lost from work and normal activities

Two types of analyses were planned to compare the cost-effectiveness of iliac vein stenting versus no stenting. First, a within-study economic analysis at 6 months, using the data collected during the trial. Second, a Markov state–transition decision model allowing consideration of the probability of clinical events and reinterventions over the longer term to quantify the impact on patient health (quality-adjusted life years) and resource use. Both types of analyses were to be performed from the perspective of the NHS and Personal Social Services, with secondary analyses from a societal perspective.

6.3.16 Data monitoring, safety and quality control

An independent TSC including, as a minimum, an independent chair, independent clinician, independent statistician/trial methodologist, oversaw the trial. The role of the TSC was to provide overall supervision of trial conduct and progress. The independent Data Monitory Committee (iDMC) comprised an independent chair, independent clinician, and independent statistician. The role of the iDMC was to oversee the safety of the trial participants.

6.3.17 Ethical approval

The BEST trial was reviewed in full and granted ethical approval by the West Midlands South Birmingham Research Ethics Committee (REC) (22/WM/0067). Health Research Authority (HRA) approval was granted on the 5th of April 2022. The study also received confirmation of capacity and capability from each participating NHS Trust. The study was conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. All amendments to the protocol were submitted to the sponsor for review before gaining approval from the REC and the HRA. Informed consent was gained for all participants with freedom to withdraw at any time without reason.

6.4 Results

6.4.1 Internal pilot of feasibility – study set-up

The overall trial duration was planned to be 48 months, comprising of 6 months set-up, 24 months recruitment, 12 months follow-up, and 6 months closedown. Delays were encountered in the acquisition of regulatory approvals for the trial and the commencement of funding was delayed for 8 months after the initial anticipated start date.

The revised timeline is illustrated below:

- May 2022 – October 2022 (6 months set-up)
- November 2022 – October 2024 (24 months recruitment) with internal pilot of feasibility after 6 months of recruitment ending April 2023
- November 2024 – October 2025 (12 months follow-up)
- November 2025 – April 2026 (6 months closedown and parallel data analysis)

Hence, the internal pilot of feasibility finished at the end of April 2023, with review from the funder commencing thereafter. As of the end of the internal pilot of feasibility, six of the 10 sites had been activated and were recruiting. The full list of sites and their date of activation is shown in Table 36.

Table 36: Date of activation for included study sites

Recruitment centre	Date initiated	Date Activated
Imperial College Healthcare NHS Trust	03/05/2022	01/09/2022
Bedford University Hospitals NHS Foundation Trust	28/09/2022	16/01/2023
Newcastle Hospital NHS Foundation Trust	03/05/2022	01/02/2023
Guy's and St Thomas' NHS Foundation Trust	03/05/2022	14/04/2023
London North West University Healthcare NHS Trust	03/05/2022	17/04/2023
Oxford University Hospitals NHS Trust	03/05/2022	15/05/2023
Royal Free London NHS Foundation Trust	03/05/2022	Not activated
Cambridge University Hospitals	03/05/2022	Not activated
University College Hospital, Galway	03/05/2022	Not activated
University Hospitals of Leicester NHS Trust	16/01/2023	Not activated
Leeds Teaching Hospitals NHS Trust	03/05/2022	Not activated
Hull University Teaching Hospitals NHS Trust	03/05/2022	Not activated
North Bristol NHS Trust	21/02/2023	Not activated

6.4.2 Internal pilot – recruitment

The planned recruitment period for the trial was scheduled from 1st of November 2022 – 31st of October 2024 (24 months). The formal internal pilot of feasibility phase ended on the 31st of April 2023, marking the end of the first 6 months of recruitment, the corresponding green-amber-red criteria applied to this point in time. The monthly recruitment figures for each active site during the internal pilot of feasibility can be reviewed in Appendix 34. A single site (Imperial College Healthcare NHS Trust) commenced recruitment ahead of schedule thus explaining why the recruitment tracker begins in September 2022. A single site recruited three-quarters of the participants into the trial. A total of 10 participants were recruited into the study by the end of the internal pilot.

Across the 6-month recruitment period, 15.5 centre-months were accumulated across the active study sites, this equating to centres recruiting on average 0.6 participants per active centre-month. The accrued centre-months and number of participants recruited are illustrated in Figure 75. This was below the target threshold of ≥1.5 participants per active centre-month.

The projected cumulative accrued centre-months at the end of the internal pilot was 35 (based on a staggered site set-up of 2 sites / month over 6 months). Due to the delays in achieving site-set-up, the trial was able to amass less than half the volume of centre activity during the internal pilot (15.5 centre-months).

A total of 36 potential participants had been screened for enrolment into the trial. Approximately 25% of the potential participants screened were subsequently recruited into the trial. Seven potential participants were awaiting a confirmatory diagnostic venogram. The reasons for the remaining 29 screening failures are included in Table 37. The ‘Other’ category on the screening log consisted of patients who were inappropriately screened and hence do not represent true screen failure i.e., ‘distal venous disease’. The number of participants screened was lower than had been originally anticipated, this was due to a low participant throughput in outpatient clinics.

At the end of the internal pilot phase, the trial failed to meet either the recruitment rate or recruitment number targets. In response to these results, the TMG formulated several interventions to improve recruitment ahead of the feasibility assessment.

Figure 75: Actual vs. Predicted centre-months accrued and participant recruitment for the BEST trial after 6 months of recruitment (equating to 12 months post funding commencement)



Table 37: Reasons for screening failures for potentially eligible participants

Reasons for ineligibility	n
CVD not meeting inclusion criteria	3
Anatomically not suitable for reconstruction	4
Preference for intervention	7
Preference for conservative management	2
Open hybrid procedure required	1
Not willing to take part in trial follow-up	2
Subsequently not suitable for intervention (poor inflow)	3
Other	7

6.4.3 Adaption strategies to improve deliverability

Additional set-up of UK-based sites

Increasing the number of centres was explored in order to increase the total volume of centre-months accrued, therefore reducing the required recruitment rate. Within the UK, this could be achieved at a nominal additional cost (site set-up and archiving fee was £600 per site). However, the highest volume centres within the UK were already involved in the study. Upon approaching several potential sites, it was established that case volumes would not be sufficient. Therefore, opening high volume international centres was the only feasible option to increase the number of sites.

Additional set-up of European sites

There are several high-volume European sites which could have significantly contributed to overall recruitment. However, this was associated with an additional cost above which would be incurred for UK centres. An example of such a centre would be Maastricht University Medical Centre, which had undertaken the STEVECO trial. This centre had existing trial protocols alongside an experienced research team. Furthermore, the University Hospital Aachen has previously recruited for the ABRE venous stent registry.

We explored opening these two high-volume European centres to complement the existing UK centres with Rede Optimus, a pan-European Clinical Research Organisation based in Switzerland. Rede Optimus were supportive of the trial and confirmed that they could facilitate the submission to central and local Ethics Committees, complete specific local submission documents, and act as the competent authority for the two additional trial sites across the Netherlands and Germany. Given the BEST trial was a non-commercial trial, the price was negotiated at a significant discount.

6.4.4 Revised sample size

A re–estimation of the sample size was planned after 12 months of recruitment. This would have included updating the assumptions made around the variability, namely the SD, overall crossover rate, size of clustering effect, and the loss to follow up rate. The timing of this sample size re-estimation was to maximize the number of randomised participants with mature 6-month follow up data, which in turn increases the power of the sample size re-estimation while keeping it in the shortest feasible time to allow the maximum impact on remaining recruitment schedules.

The sample size re-estimation was brought forward in light of new data becoming available which provided clarity on the variance for VCSS in a similar study. The intended purpose was to update the sample size estimate using external data from the STEVECO trial (n=63) which closed early due to COVID-19 and poor recruitment. As outlined in Chapter 5, the primary outcome was VEINES QOL/Sym, however, VCSS was a key secondary outcome measure. The STEVECO trial observed a mean difference in VCCS at 12 months of ~3 units, with an observed SD for the change from baseline of ~4 units.

The original sample size calculation assumed an SD of 8 units for the change in VCSS from baseline to 6 months. STEVECO reported an SD half the value of this, at just 4 units. The included population is very similar across the two trials, with an eligibility criteria that differs only in the clarification of a minimum disease state in BEST (namely, at least C3 disease). It was therefore deemed justifiable to consider a substantial reduction in the assumed SD which was set conservatively high.

If maintaining the same 90% power, 5% level of significance, ICC of 0.03 (intervention group) and 0.01 (control group), and 10% total crossover, with 1:1 randomisation, 15% loss to follow up, a reduction in the assumed SD from 8 units to 4 units results in an overall sample size reduction from 328 to 70. If a slightly higher SD of 5 was assumed, then the required sample size equates to 106. The effect of the SD on the sample size was dramatic. The re-estimation of the sample size was undertaken in conjunction with the iDMC. In light of the aforementioned considerations, the re-estimation of the sample size assumed an SD of 5 units, while maintaining the mean difference of 4 units. The revised sample size required equated to 106 in total.

6.4.5 Result of the internal pilot and proposed trial adaptions

To summarise, at the time of the internal pilot assessment, a total of 10 participants had been successfully recruited with 15.5 active centre-months accumulated, equating to centres recruiting on average 0.6 participants per centre-month. This was below the 'Red' criteria for both total number of participants (<30) and recruitment rate (<1). The adaption strategies to improve deliverability and recruitment in the context of the revised sample size were costed and proposed to the funder. However, after critical review from the funder, the BEST trial funding support was withdrawn on the 4th of July 2023. The trial activities were halted immediately to minimise the cost liabilities incurred by the funder, with all financial support ceasing in October 2023.

6.4.6 Trial redesign and relaunch

In response to the result of the internal pilot of feasibility, and the feedback gained from the funder's critical review process, the trial was re-designed to improve deliverability and recruitment. An overview of the re-designed trial is illustrated in Figure 76. In summary, the following elements were changed in the trial:-

1. Narrow the trial's scope to solely include participants with PTS;
2. Sample size re-estimation with SD data from STEVECO trial;
3. Removal of surveillance duplex scans in the control arm; and
4. Removal of 6-week study visit.

Inclusion of post thrombotic syndrome participants only

Given the intention to re-estimate the sample size utilising the lower SD value of 5, the inclusion of both PTS and NIVL was critically reviewed. The STEVECO trial included both PTS and NIVL patients, therefore the SD of 4 is applicable to both pathologies. However, it was not powered for a subgroup analysis. With the reduction of the SD from 8 to 5, the concern was that a powered subgroup analysis would not be possible. Therefore, in order to improve the deliverability of the trial, we would either have to make a conclusion regarding CVOO as a whole or choose one of the pathologies to investigate independently. Given the differences in long-term outcomes, it was decided that PTS alone would be investigated.

This concern regarding the sample size re-estimation was shared by the funder's critical review panel "…if a total of 106 patients could be recruited, the results of a trial of this size would be unlikely to impact clinical practice". Whereas, if the trial investigated PTS alone, this would be more likely to impact clinical practice for this pathology.

Sample size re-estimation

As outlined earlier, through collaboration with the STEVECO trial management group, we were able to access the primary STEVECO VCSS data providing more certainty in the predicted effect size and SD for the primary outcome. This, in combination with the sole inclusion of those with PTS, enabled a sample size re-estimation to reduce the overall sample size from 328 down to 106 while maintaining power. Re-estimation of the sample size was performed by the lead statistician and reviewed by the independent statistician from the DMC.

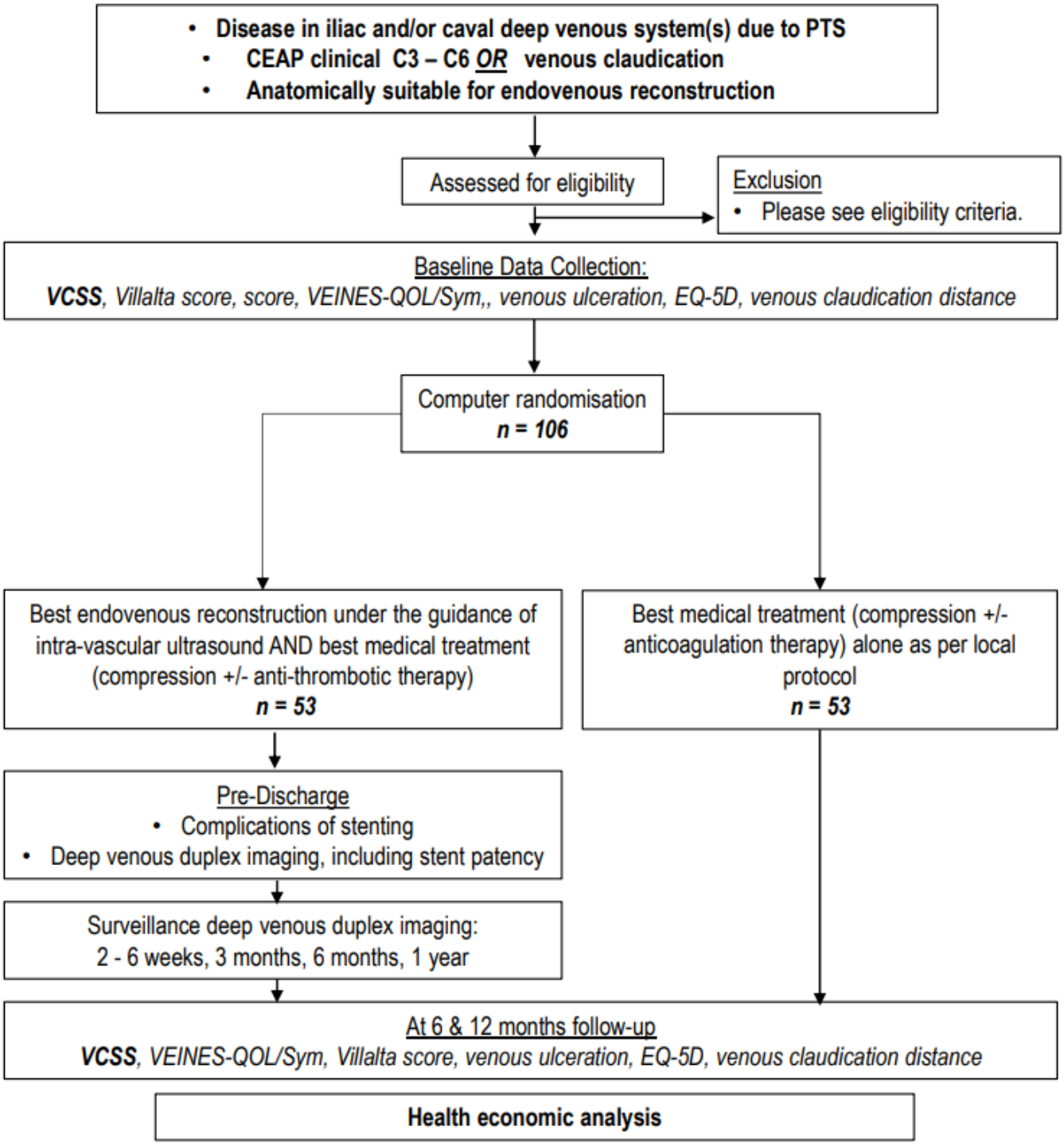
Removal of surveillance duplex scans in the control arm

In order to reduce burden for participants, burden to sites, and financial costs to the study funder, the duplex surveillance scans in the control arm were removed. These scans were included upon request of the original funder in attempt to reduce performance bias, with the belief that those having additional scans would be more likely to receive other forms of optimising medical care. This was disputed by the TMG as the stent surveillance scans are localised to the groin and are not used to guide additional superficial venous interventions. The control arm scans became a condition of funding and were adopted into the trial protocol. However, they were a source of significant resource use at a site level and were the main cost driver in the control arm. These were removed as part of the trial re-design after review from the DMC.

Removal of 6-week study visit

The 6-week study visit was designed to capture the early effect of intervention and be a suitable timepoint for resource use data collection for the peri-operative period. However, given the significant financial pressures on the study, it was decided by the TMG that long-term efficacy outcomes were a priority. Sites were being asked to run the study at a loss, and therefore each study visit needed to be vital to the aims of the study. The 6-week study visit was removed after review by the DMC.

Figure 76: Flowchart illustrating the intended overview of the re-designed BEST trial



CEAP: Clinical-Eitology-Anatomy-Pathophysiology classification
COVID-19: Coronavirus disease, SARS-CoV-2 2019
VCSS: Venous clinical severity score
VEINES QOL/Sym: Venous Insufficiency Epidemiological and Economic Study questionnaire
EQ5D-5L: 5-level EQ-5D version, EuroQol Group, 2009
SF-36: 36-Item Short Form Health Survey

6.4.7 Re-launch of the BEST trial

The updated trial design received sponsor approval in October 2023 and was subsequently granted HRA approval. Funding for the re-designed trial was secured through a National Institute for Health and Care Research investigator grant awarded to the chief investigator. The BEST trial was relaunched in February 2024 and the new trial site agreements were negotiated with each site. Unfortunately, during the renegotiation of trial site agreements, three sites withdrew from the study citing a lack of financial viability to deliver the study.

6.4.8 Closure of the BEST trial

From February 2024, recruitment remained active at a single centre. There was ongoing pursuit of the updated trial site agreement at two additional sites. By October 2024, the total number recruited into the trial was just 12 participants, this initiated a further review of the trial deliverability with a pause to recruitment. The TMG met and critically reviewed the prospect of deliverability. After consultation, the trial was closed in March 2025.

6.4.9 Results of the included participants

The consort diagram from the included studies is illustrated in Appendix 35. Of the 12 participants enrolled, one participant withdrew from the study after a multi-disciplinary team decision recommended against iliac vein stenting due to concerns regarding venous inflow. A further patient in the control arm was lost to follow-up and failed to attend their research study visits. A summary of the baseline characteristics for the limited number of participants enrolled is displayed in Table 38. The baseline and 12-month VCSS values are shown in Table 39. The change in VCSS at 12 months for the intervention arm and control arm is not shown as the there was insufficient participant numbers within each group.

Table 38: Baseline characteristics for participants recruited into the BEST trial

	n	%
Eitology		
PTS	9	75.0%
NIVL	3	25.0%
Sex		
Female	9	75.0%
CEAP (C)		
3	6	50.0%
4	4	33.3%
5	1	8.3%
6	1	8.3%
	Mean	**SD**
Age	48.3	13.4
BMI	28.4	5.7
VCSS	9.8	1.0

CEAP: Clinical-Eitology-Anatomy-Pathophysiology, clinical classification
BMI: Body mass index
PTS: Post thrombotic syndrome
NIVL: Non-thrombotic iliac vein lesion
VCSS: Venous clinical severity score

Table 39: Baseline and 12-month venous clinical severity for participants recruited into the BEST trial

	Mean	SD
VCSS Baseline (overall)	9.8	0.96
VCSS 12 months (overall)	8.7	1.11

VCSS: Venous clinical severity score

6.5 Discussion

The BEST trial was designed and developed through collaboration with a variety of key stakeholders, involving patients and experts, to produce a much-needed RCT. The lack of evidence was viewed as a research priority in the venous sphere and the trial was supported by Vascular Surgeons during its development. Despite this, the trial was undeliverable and has failed to provide comparative evidence as to whether iliac vein stenting provides additional benefit for those with CVOO. The main barriers to the trial will be explored and, where possible, reflection provided on as to what could have been done differently.

6.5.1 There was a marked delay in achieving local approvals from study sites

There was a substantial delay in achieving confirmation of capacity and capability (CCC) from study sites. CCC is a required step in the activation of a study site prior to any recruitment. It assesses an NHS organisation's available resource and capacity to undertake the research study. The NHS Research & Development teams generally aim to confirm CCC within 40 days of receipt of the local information pack which contains all of the relevant study documents. Seven of the 12 sites receiving the local information pack issued CCC. Four sites were reviewing the status of the trial for >365 days, for these sites the study set-up was abandoned. For the seven sites issuing CCC, it took on average 196 days (range: 64 – 336 days). As the study involved "image-guided procedures undertaken whilst the patient is enrolled in the study", Ionising Radiation (Medical Exposure) Regulations (IR(ME)R) approval at each study site was required. This process involves combined review from the Medical Physics Expert and Practitioner Clinical Radiation Expert at each site. There was a delay in granting the IR(ME)R approval across all sites included in the trial.

Once CCC was issued by sites, the central study team was able to activate the study site in less 14 days in all instances. The severe delays in gaining CCC from sites resulted in a reduction in the active centre-months accrued. All of the included sites provided a preliminary capacity agreement during the funding acquisition. Anecdotally, from speaking with research teams, delay of issuing CCC is often deliberate in order to avoid missing locally set recruitment targets. There is a lack of publicly available data on CCC times nationally.

In order to combat this in the future, a greater duration of time for site set-up could be assigned to reflect the delays occurring within research teams in the NHS. However, this significantly increases the cost and duration of the trial which renders it unlikely to be funded within the current budget constraints of non-commercial research funding. More work is required on how best to measure the capacity at potential sites in the funding acquisition process as the current accepted standard of assessment is inadequate.

6.5.2 Participant preference for intervention hampered recruitment

As illustrated earlier in this report, see Table 37, participant preference for one of the two study arms was a significant cause of eligible participants not enrolling into the trial. A total of 36 potentially eligible participants were approached regarding entry into the study, 26 were subsequently not enrolled. Patient preference for a given treatment was responsible for 9 (35%) of all screening failures - 70% of which expressed a wish for intervention. Hence, a preference for intervention accounted for 26.9% of screening failures. The PPI work undertaken prior to funding acquisition suggested a reasonable proportion of patients would have a pre-defined desire for intervention, however, this was thought to be surmountable with sufficient throughput of eligible participants.

As an alternative, a patient preference trial was explored. In a patient preference trial, there are essentially four groups occurring from three populations: 1) randomised willingly to the intervention arm, 2) randomised willingly to the control arm, 3) opted (not randomised) for the intervention arm, and 4) opted (not randomised) for the control arm. The three populations include those that have no preference who are willing to be randomised, those that are keen for intervention, and those that are keen to avoid intervention. The patient preference trial facilitates improved recruitment, as those with a preference are willing to enrol as randomisation is removed. However, the key evidence still originates from the randomised comparison, the other two groups are biased(350). Desired treatment allocation has a significant treatment effect in pooled meta-analysis(351). The preference groups are used to externally validate the findings in the randomised comparison at a cost lower than a separate study. However, if the single-arm biased evidence already exists, the preference arms add little benefit and increases the complexity of the trial.

For example, if BEST was delivered as a patient preference trial, the number randomised would still be 12 participants. However, there would be an additional nine participants in separate parallel groups. This would not represent value for information. The IDE trials have already provided the non-randomised evidence(183, 208, 275, 303, 352). The randomised comparison is required to improve the certainty in the evidence. The same holds true for partially randomised preference trials. Randomised cross-over trials can help to mitigate against preference effects however this would not be possible for surgical interventions.

Proposed models of how participants develop treatment preferences describe how the patient fosters ‘expectancies’ prior to undertaking an ‘expectancy value calculation’ regarding randomisation(353). Expectancy is influenced by a number of information provision sources, including ‘professional preference’ which stems from the interaction with medical professionals. Identifying participants at the most appropriate point in their clinical journey, and effective communication of the trial, seems key in avoiding solidification of these expectancies. For many CVOO patients, their clinical journey comprises of the following:-

1. Attending their local general practitioner, and after assessment being treated with conservative management;
2. Re-presenting to their general practitioner after persisting symptoms;
3. Referral to their local secondary care unit and undergoing diagnostics – each of which with an associated waiting list;
4. Subsequent referral to a tertiary venous centre for review by a Consultant with a specialist interest; and
5. Repeat investigations with a view to plan for iliac vein stenting.

This process can take years to progress through, and at several points there is the admission from the treating clinician to the patient that they have failed to make them better, but the onward referral will. This shaping their ‘expectancies’. At the point of being meaningfully considered for intervention, the patient has a solidified expectation for iliac vein stenting. This clinical journey is streamlined for those presenting initially to a tertiary vascular centre with a specialist interest, and anecdotally from my own experience, these patients seem more amenable to randomisation.

Therefore, approaching potential participants earlier on in the clinical pathway, or streamlining the pathway to reduce solidification of expectations, may hold the key to reducing patient preference for intervention. This is not to deny patients of information, it simply means presenting the balanced information to enable them to form their own opinions, maximising autonomy, before developing an unshakable belief that iliac vein stenting is the only possible outcome.

6.5.3 Delay in radiological investigations for potential participants were as a result of the lesser prioritisation of venous disease

A further 7 potential participants were awaiting confirmatory radiological diagnostic investigations at the time of the internal pilot, amounting to 19.4% of eligible participants. These patients had a known lesion on duplex ultrasound but were awaiting a diagnostic venogram. Vascular Surgery units across the UK classify CVD as a lower clinical priority in comparison to arterial disease (priority 3 vs. priority 2). The result of this is that arterial angiograms are prioritised ahead of venograms, this results in delays to confirmatory imaging. Prioritisation of arterial angiograms is clinically appropriate given the risk of limb loss in chronic limb threatening ischaemia(354). However, it reflects a lack of resource in the NHS to provide investigations for CVD in a timely fashion. In order to address this, the highest recruiting centre was successful in organising an additional interventional radiology list once per fortnight to create additional capacity.

In the future, to combat the lack of available resource available to CVD patients, if the financial situation permitted, the trial could provide support to permit additional interventional radiology capacity on a private, perhaps out of hours, basis.

6.5.4 Commercial trials provide higher value per participant reimbursement

The NHS received on average £9,000 per patient recruited to a commercial clinical trial(355). Commercial studies provided an income of £355 million in the year 2018 – 2019 while accounting for less than 2% of the total participants recruited into trials within the NHS(355, 356).

While it is not possible to provide a direct comparison to a commercial trial in this context, the per participant reimbursement for all study encounters, including baseline assessment, consent, interventional study visit, and the 6-week, 6-month and 12-month follow-up visits, came to a total of ~£600 for the BEST trial. The BEST trial was one of the lowest reimbursing trials in the included sites' portfolios. The result of this was a general lack of prioritisation, the trial essentially ran at a loss while being bolstered by higher paying commercial studies. The BEST trial costings were too lean, which likely contributed to its poor recruitment.

6.5.5 Throughput of eligible participants was lower than anticipated

There is an incongruence in the number of patients screened, which is a proportional marker of the number reviewed in the Vascular Surgery outpatient clinic, and the predicted burden of disease. This particularly so for PTS.

WP C demonstrates that the annual rate of DVT across England alone is 86,959. Traditional estimates suggest one-third of these will be iliofemoral (~29,000). HES data cited in WP C indicates that ~16,000 DVTs affect the IVC – femoral vein annually. If approximately one-third of these patients fail to recanalise(52, 69, 70, 357) resulting in a complete iliac vein occlusion, there is between ~5,000 – 10,000 additional potential PTS cases each year. WP C also demonstrates that as few as ~300 of these patients are undergoing early thrombus removal procedures. PTS is a chronic condition, and the population prevalence will accumulate over time. The total number of outpatient appointment provided by Vascular Surgery in the NHS across the year 2023 – 2024 was 47,786(358). PTS management should make up a significant proportion of Vascular Surgery's outpatient workload – yet its relatively rare. This is reflected in just 36 participants being screened over the 6-month recruitment period. The logical explanation for this is that most patients are treated by their primary care physician or in secondary care under the Haematology team and are never referred to Vascular Surgery. A proposed solution to this is to have paired Haematology-Vascular clinics and a strong collaborative relationship between the two specialties. However, in centres with joint clinics, the number is still relatively few.

The rate of residual vein occlusion is reasonably well evidenced, which makes possible over-estimation of disease burden unlikely. It seems probable that these patients are being care for in primary care, and future studies should consider primary care participant identification centres.

6.5.6 Lack of clinical equipoise amongst clinicians was a key contributing factor to the failure of the trial

Capturing a lack of clinical equipoise utilising formal methodologies can be challenging. When a lack of equipoise is occurring, the screening log is often neglected, and the cause of a low recruitment rate may not be forthcoming. A sensitive marker for the presence of a lack of clinical equipoise is a stark imbalance in recruitment rates across sites in the absence of other causative factors (such as staffing or resourcing) and a high crossover rate. There was a stark imbalance across recruitment centres in the trial, the centres caseload was incongruent with the number recruited. This was reflected in the feedback received from the funder's critical review at the internal pilot of feasibility "In particular, they were concerned that the strategies presented were unlikely to address the problem of lack of equipoise…". Equipoise was not formally raised as a barrier by sites at any time; however, it was palpable in the trial's activity. Informally, it became apparent over time that the BEST trial did suffer from a lack of clinical equipoise. Clinicians held a strong belief in the intervention and were unwilling to randomise participants to medical therapy.

When developing the trial, all of the sites taking part acknowledged the importance of the question and confirmed equipoise. As a community, it is important to establish the driving forces behind this phenomena as the success of RCTs hinges on clinical equipoise. The explanation underpinning this is more likely to relate human behaviour, than of clinical evidence. A separate thesis is warranted in the exploration of the societal and economic factors that encourages clinicians to enrol in trials that they have no 'real' intention of recruiting into. This is consistently seen across RCTs, for every trial there is always some sites recruiting just a handful of participants.

From a societal perspective, social desirability bias is likely to play a role. Social desirability bias describes the response-bias in which there is a tendency to answer questions in a manner that will be viewed favourably by wider society(359). Academics

generally want to appear collaborative across institutions. Collaboration has been key to the success of several international RCTs in vascular surgery including, but not limited to, ECST, ACAS, DREAM, EVAR-1, EVAR-2, UK SAT, MASS, and IMPROVE trials(360). Collaboration is an increasing and necessary practice in vascular research(361). Being a collaborative researcher is a socially desirable trait that is reflected in a potential investigator's response to a call for involvement in an RCT. This can be mitigated, but not eliminated, by making responses anonymous(359). Other literary devices, such as outlining the likely social desirability factors and framing dishonesty within the survey as an unattractive trait, have been shown to help reduce response bias(359). Qualitative preparatory work is heavily relied upon when assessing the feasibility of a study(362), however the methodological rigour of it is rarely assessed by funders. This is paired with a financial incentive anticipated by the study development teams meaning they register the reassuring responses with a blinded optimism.

There are also tangible career pressures that may influence potential investigators. The sum of grant funding secured by an academic is allocated significant weight in the academic community, even in situations when that grant funding was not awarded to their host institution. Review of the selection criteria for various senior academic roles at UK leading universities provides descriptions such as "ability to attract research funding" and "a significant track record of winning competitive research funding". This is understandable as without funding, there is no research. However, the reward for being part of a research team securing funding is independent of the end result – there are few consequences for failing to provide to a study. To provide balance, there is also little reward for local investigators outside of the research process itself. The non-commercial clinical research system relies heavily on the uncosted time of local investigators who are highly skilled and in scarce supply.

The factors influencing clinical equipoise are vast and complex. The success of a trial is dependent on the human behaviour of those involved, this is an under-researched and under-appreciated component in trial design and feasibility assessment.

6.6 Conclusion of the BEST trial

The BEST trial serves, among many other failed RCTs, as a cautionary tale for those embarking on a trial of a complex intervention. The lessons learnt are largely generalisable to other surgical disciplines. Future work is required to better elucidate the barriers to delivering a RCT in this clinical area, focusing on clinical equipoise and patient preferences specifically. A non-commercial RCT is still required to provide unbiased evidence to demonstrate that iliac vein stenting confers additional benefit in comparison to medical therapy alone.

7 – DISCUSSION & FUTURE WORK

CHAPTER 7: DISCUSSION & FUTURE WORK

This thesis has produced an array of interesting findings and has added some key contributions to the field of iliac vein stenting in CVOO. The main themes encountered will now be explored in greater detail and, wherever possible, suggestions made on how future work can overcome the shortfalls in the current evidence base.

7.1.1 Post thrombotic syndrome and non-thrombotic iliac vein lesions are different diseases

PTS and NIVL are distinct and discrete pathologies that share the same conceptual hemodynamic consequence. This statement would be redundant if it were not so commonplace in the literature for studies to pool the results of PTS and NIVL patients. Pooling the results of PTS and NIVL is tempting as they are consistently described together as CVOO. However, it confuses the evidence base by having two such different pathologies reported as one.

This difference is best illustrated in the long-term stent patency, with the 60-month patency rate for PTS being significantly lower at 61.6% in comparison to 80.5% in NIVL. The pattern of decline also differed across the two pathologies. This is best illustrated in WP A, with the shape of the two Weibull model functions differing, and with the additional data from WP C. There seems to be a persistent decline in PTS patency rates over time, despite reintervention, stents seem to occlude each year. This is suggestive of an underlying chronic inflammatory process that perpetuates a recurring scarring phenomena in which the stenosing scar tissue is broken with balloon angioplasty but then persistently reoccurs, akin to removing hypertrophic scars with their likely recurrence. NIVL comprises of spurs, that once broken, seem less likely to recur. No NIVL cases underwent multiple reintervention from WP C. When reviewing the survival data for patency in WP A, there are examples of studies that achieved a 100% PAP rate beyond 48 months for NIVL(186). There is clearly a different pathophysiological response to the stent in this cohort in comparison to PTS.

The differing patency rates across PTS and NIVL are well known in the venous sphere – the reported data on this, although robustly shown, is not a novel finding. Of the 78 unique studies including both PTS and NIVL, 53.8% of them failed to report disaggregated data for the two pathologies – the majority of studies reported the data as a combined summary. Therefore, the question must be posed as to why studies pool the data in this way. Studies may do this to increase the total population size, e.g. when they are unable to report PTS or NIVL separately due to low number of participants in a given group. Cynically, with the acknowledgement that this is conjecture, this reporting strategy could also be used as a rhetorical device. When combined, iliac vein stenting has an acceptable patency, neglecting to highlight that PTS patency rates are lower.

7.1.2 The long-term patency of iliac vein stents placed for post thrombotic syndrome is poor

From WP A, the median survival time for PTS PP was 74.3 months. This increasing to 98.9 months (just over eight years) when considering reintervention. The pooled average age in the literature for patients with PTS undergoing iliac vein stenting was 47.7. Given the nature of the persistent decline in patency seen with the PTS pathology, this means that the vast majority of PTS undergoing iliac vein stenting will succumb to stent occlusion within their lifetime. This decline in patency was not restricted to the single centre cohort studies utilising Wallstents™, it was also observed in the IDE prospective single-armed trials deploying dedicated venous stents, with the principal investigators of the Abre IDE study acknowledging the need for improvement(363).

In attempt to improve patency, the industry-funded “Perivenous Dexamethasone Therapy: Examining Reduction of Inflammation After Thrombus Removal to Yield Benefit in Subacute and Chronic Iliofemoral DVT trial”, referred to as the DEXTERITY-SCI trial (NCT04858776)(364), is currently assessing the use of perivenous dexamethasone injection after recanalisation using a micro-infusion device. Dexamethasone is infused to prevent the inflammatory process driving re-occlusion. Modulation of the immune system may hold the key to improving long-term PP in PTS.

7.1.3 Iliac vein stenting has reasonable probability of being cost-effective

The estimated ICER for iliac vein stenting for PTS and NIVL was £15,150.37 and £9,449.07 respectively. Despite the reduction in venous ulceration, due to the cost of stent surveillance and stent maintenance, iliac vein stenting is not a cost-reducing intervention. It relies on providing a clinical improvement through quality-of-life gains. Given the promising patency results observed in NIVL, and the low number of stents required, it is logical that iliac vein stenting in NIVL is cost-effective.

The cost-effectiveness for PTS may seem contradictory in light of the long-term patency issues outlined above. However, as there is a significant cost associated with stent surveillance and stent maintenance, and there is a depreciating quality of life with age, long-term patency is not a requirement in providing a reasonable ICER. The patent stent is costing more than it is saving at any point in time, when it occludes, this increased cost expenditure stops with it. The quality of life is diminishing over time irrespective of stent patency; therefore, the majority of health utility gains are in the relative youth of the patient. Hence, providing that the health utility gained in the first few years of patency is more than the index procedural cost (at a cost of <£20,000 per QALY), it is likely that the procedure will be cost-effective.

This gain of health utility hinges on the ability of iliac vein stenting to improve quality of life above and beyond that of medical therapy. There is currently substantial doubt as to whether this is the case in light of the results from the STEVECO trial(286), where there was no significant difference in the change in EQ5D across the stenting and medical arm. Future work needs to either provide external validation of the relationship between VCSS and EQ5D or increase the utilisation of EQ5D as an outcome measure. An RCT is required to establish if there are additional health utility gains in comparison to medical therapy alone.

7.1.4 A randomised controlled trial is still required

The failure of the BEST trial does not preclude the necessity for an adequately powered RCT in the future for both PTS and NIVL pathologies. There is a vast volume of evidence from single-armed studies, the result is that there is reasonable degree of certainty in respects to safety and long-term patency. The efficacy outcomes in the single-armed studies are all subject to significant bias which limits our ability to provide clear recommendations on the added benefit of iliac vein stenting.

The launch of the European Venous Registry, EVeR(315), will likely have a positive impact by permitting the monitoring of international practice ensuring early detection of safety concerns across both devices and treatment centres. However, it will not improve the level of evidence. Key opinion leaders have recently suggested that the existing IDE trials and newly established registries will be sufficient in substituting the need for an RCT. In a publicised discussion from BIBA Medical CX Symposium, sponsored by industry, a key opinion leader stated that the publication of the STEVECO trial results would lead to an increase in the level of evidence recommendation in the ESVS guidelines for iliac vein stenting from B to A. The definition of grade A evidence is “Data derived from multiple randomised trials or meta-analyses of randomised trials”, publication of RCTs that closed prior to meeting their sample size should not fulfil this definition.

This attitude is mirrored, in part, elsewhere in the venous space. In a recent invited commentary published in the “European Journal of Vascular and Endovascular Surgery”, a key opinion leader compares the pursuit of a RCT in CVOO akin to Don Quixote’s attack on windmills in Miguel de Cervantes' "Don Quixote"(365). In this novel, ‘Don Quixote de la Mancha’ is the persona occupied by a retired man who becomes infatuated with ideas of chivalry, knighthood and honour. In attempt to fulfil a heroic act, suffering from delusions, Don Quixote mistakes a group of windmills for giants and attempts to attack them in an act of nobility. Upon attacking the inanimate objects, he is struck down by the windmill. In this conceptual metaphor, the pursuit of an RCT is being viewed as a symbol of Don Quixote's futile battle against an unchangeable reality, mirroring his impractical idealism. This is concerning as it diminishes the level of evidence required to that of an idealistic virtue rather than a scientific standard to meet.

The need for a RCT is imperative. There have been a number of examples of surgical interventions demonstrating promising results in the single arm studies, and even unblinded RCTs, prior to the treatment effect being shown to be a combination of biased assessments and placebo effect in double-blinded RCTs(366-372). An example that can be drawn from, mirroring CVOO, is that of knee arthroscopy in osteoarthritis. Knee osteoarthritis is a chronic condition, and it is likely that patients have received medical therapy for some years, including analgesia, weight loss, and physiotherapy. It could be argued that these patients are unlikely to significantly

improve further on a treatment that they have already trialled. Knee arthroscopy resulted in symptomatic improvement in single arm studies(373-375). This is the current state of evidence for iliac vein stenting in PTS and NIVL. A double-blinded RCT, published in the New England Journal of Medicine, randomly assigned 180 participants to either arthroscopic debridement or placebo sham surgery. Primary outcome was a disease-specific pain score at 24 months(367). There was no difference in disease-specific pain between the intervention and control arms.

Potentially even more pertinent to iliac vein stenting is the percutaneous coronary intervention in stable angina (ORBITA) trial published in the Lancet. This was a double-blinded RCT which randomised 230 patients with stable angina to either percutaneous coronary intervention or a placebo sham procedure(366). There was no significant difference in the exercise time increment between the intervention arm and control arm – both groups improved.

After closure of the STEVECO and BEST trials, the C-TRACT trial remains the only active RCT investigating iliac vein stenting. It launched in July 2018 and remains open to recruitment seven years on. A publication in June 2022 reported that less than one-third of the target 374 participants had been recruited(186). It is currently unclear if C-TRACT will make the distance and if the adaptions made along its way to improve its deliverability will have hampered its impact. The level of evidence for iliac vein stenting will not progress until a RCT is completed.

7.1.5 Timing of an RCT, the ‘Goldilocks’ phenomena

It is postulated that the perfect time to do a RCT is late enough that the intervention is sufficiently adopted in that the learning curve has been diminished and adequate recruitment can be sustained, while early enough that adoption is not so widespread that it prevents randomisation from a lack of equipoise. However, in reality it is often more complex than this. An example of when the desire to be part of an RCT stimulated the necessary adoption, i.e., the trial was too early using the Goldilocks’ phenomena, was the Immediate Management of Patients with Rupture: Open Versus Endovascular Repair (IMPROVE) trial. The IMPROVE trial defined a minimum caseload in which centres made active efforts to attain(376). The trial was successful, recruiting a total of 613 ruptured abdominal aortic aneurysms across 30 vascular

centres. Recruitment started in 2009, the year prior to which as few as 6 centres in the UK were performing ruptured endovascular aneurysm repair and only 23% of vascular centres had an on-call interventional radiologist.

On the other hand, the ‘ulcer surgery as adjuvant to compression bandaging for leg ulcers’ (USABLE) trial closed in 2003 due to a lack of clinical equipoise – the treatment was already established. The USABLE trial aimed to randomise patients with active venous ulcers to either superficial venous surgery or compression bandaging(377). It started recruitment in 2001 and folded 18 months later due to poor recruitment. It concluded “failure of the USABLE trial has informed both surgeons and health care providers that simple venous surgery may not have a major role in managing patients with gaiter leg ulcers”. A decade later in 2013, with the same lead investigator and the same study sponsor, the Early Venous Reflux Ablation (EVRA) trial commenced recruitment(18). After successful completion, it showed that early endovenous ablation lead to quicker venous ulcer healing. Treatment of superficial venous reflux, in addition to compression bandaging, is now key in the management of venous ulcers.

These examples demonstrate that the willingness to be part of a RCT, and clinical equipoise, is shaped by wider influences. WP C suggests that the scale of iliac vein stenting across England is still relatively sparse. Future widespread adoption of iliac vein stenting, with increasing numbers of clinicians offering stenting as a treatment, may alter the general opinion on clinical equipoise and willingness to randomise.

7.1.6 The use of novel trial designs in place of a traditional randomised trial

Generally, a well-designed and competently delivered RCT limits the bias in a pre-determined comparison sufficiently to establish a cause-and-effect relationship for a given treatment and subsequent outcome. Observational studies, however, have inherent biases that, under simple examination, limit their findings to associations alone. This is reflected in leading clinical scientific journals restricting causal vocabulary to randomised study designs, directing the use of ‘correlation’ and ‘association’ for any non-randomised comparison. However, the cause-and-effect relationship for two variables is present regardless of the study design employed, the problem lies with meaningfully demonstrating it through the mitigation of bias. A classic example of such attempt in clinical research is the propensity score matching using

regression analysis approach. More contemporary approaches include causal inference models which are theoretical frameworks that rely on assumptions about the underlying relationships of variables to establish a causal relationship between an independent and dependent variable.

Drawing causal conclusions using causal inference models from observational data is not a novel phenomenon in the ecological and social science fields where the possibility of randomisation is rare(378). However, its application in clinical research is one of contemporary discussion with some of the leading clinical scientific journals publishing frameworks for causal inferences reporting just last year in 2024(379). The use of causal inference in clinical research could help to fill the void of evidence where RCTs have failed to deliver.

There are a multitude of causal inference methodologies (including the widely utilised propensity score matching), each requiring a different set of assumptions regarding the underlying data. For example, one of the key limitations of propensity score matching is the assumption that there is no unmeasured confounding – this is generally unlikely and hence the approach is typically met with a degree of scepticism. Other methodologies, such as instrument variable and difference-in-difference analyses, do not require this assumption regarding unmeasured confounding meaning that these approaches may be well suited to clinical research.

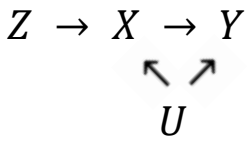
These causal inference models sit outside the scope of this thesis, but we will explore the instrument variable analysis to illustrate the possible applications of causal inference models in the investigation of iliac vein stenting in the treatment of either PTS or NIVL.

Instrument variable analysis is viewed as the mirror image of propensity scoring, where the chosen instrument variable has no direct effect on the outcome or known confounders, but instead has an effect on the treatment outcome alone(379, 380). In the case of venous stenting, the instrument variable would be significantly associated with the treatment of iliac vein stenting but not the severity of disease afterwards. Certain assumptions regarding the relationship between the instrument variable, treatment variable, and outcome variable are required in order to demonstrate causation.

The assumptions can be summarised as follows(381):-

1. The instrument variable (Z) has a causal effect on the treatment variable (X);
2. The instrument variable (Z) affects only the outcome variable (Y) through the treatment variable (X) (i.e., it has no direct effect on the outcome variable);
3. The instrument variable (Z) has no relationship with confounders (U) that are associated with the outcome variable (Y); and
4. The instrument variable (Z) has no effect on the relationship between the treatment variable and outcome measure ($X \rightarrow Y$) (referred to as the homogeneity assumption).

Figure 77: Instrument variable relationship for the treatment variable and outcome variable providing the required assumptions hold



Z: Instrument variable
X: Treatment variable
Y: Outcome variable
U: Confounding variables
Adapted from published manuscript (382)

Based on this relationship, any effect seen (correlation) between the instrument variable (Z) and the outcome variable (Y) must contain within it the relationship between the treatment variable and outcome variable ($X \rightarrow Y$), in addition to the effect of the instrument variable on the treatment variable ($Z \rightarrow X$). The effect of the instrument variable on the treatment variable ($Z \rightarrow X$) can then be removed by finding the correlation between the two variables, this is possible as the instrument variable is independent of confounders and effectively 'randomly' assigned across all of the data.

In the case of iliac vein stenting, the clinician (operator) preference for venous stenting could be used as an instrument variable. Clinician preference for intervention is an established instrument variable in the literature(381, 383). The clinician preference for stenting will have a direct effect on the treatment choice, but has no direct effect on

the outcome measure of severity of disease. It will not be associated with baseline characteristics as the clinician will apply their favourable belief consistently across the population – that is not to say that they will offer treatment to every patient but their predisposition to offer it is consistent. However, the homogeneity assumption may not be satisfied. It is entirely possible that the success of venous stenting in improving disease severity could be influenced by the enthusiasm of the operator, particularly in terms of case numbers and technical proficiency. There is an exception to this assumption that relies on monotonicity, often referred to as the no 'defiers' assumption(383). That is, the clinicians involved behave as assumed consistently, and do not defy this assumption for different cases. For example, a clinician that does not recommend venous stenting, consistently applies this approach throughout the observation study. This may be more achievable but would require supplementary qualitative research to demonstrate(383). This example illustrates the key limitation of the instrument variable approach, finding an instrument variable that holds against the required assumptions can be challenging.

This study design would require the prospective collection of observational data across the two arms (iliac vein stenting versus medical treatment), likely based on different treatment centres, to a similar extent as seen in an RCT, but with greater numbers required. This in turn necessitating an increase in the total duration of the study and number of centres involved in comparison to a traditional RCT. Supplementary qualitative research to demonstrate clinician behaviour may also be required. Therefore, the causal inference models do not necessarily represent a cheaper or shorter option. Causal inference models hold the potential to provide more robust evidence from observational data in the deep venous space, however, such approaches also confer substantial challenges in their design and delivery which are likely to be costly to deliver.

7.1.7 More non-commercial research is required

Of the 107 included articles in WP A, a total of 66 studies (61.7%) had a perceived or declared conflict of interest. All of the IDE trials were, understandably, industry funded(183, 208, 275, 303, 352). The European prospective cohort studies were either industry-funded or possessed conflicts of interest(181, 216, 240, 242). The most recently published STEVECO RCT was also industry funded(286). Not least, the newly formed European Venous Registry, EVeR, is also industry sponsored, with seven of the leading industry companies being industry partners(315). It is unclear how involved the industry partners will be, the ESVS stated that “EVeR maintains full scientific independence”.

Acquisition of non-commercial funding is undoubtedly difficult. Securing the non-commercial funding for the BEST trial took years of work and several attempts. There is a sparse resource that must be shared across all healthcare research.

Industry partners therefore serve a vital purpose in facilitating research that otherwise would not happen. However, there is always a balance to strike. Industry fund research, sponsor registries, pay researchers through honorarium or consulting fees, sponsor conferences, sponsor training events, alongside providing educational and networking opportunities. It has been repeatedly found that industry funding is associated with an increased likelihood of a study reporting positive findings(384, 385). In light of this, as a vascular community, it is important we leverage support for non-commercial research funding in CVOO to provide balance in the literature.

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APPENDICES

Appendix 1: Revised venous clinical severity score

Clinical descriptor	Absent (0)	Mild (1)	Moderate (2)	Severe (3)
Pain	None	Occasional	Daily not limiting	Daily limiting
Varicose veins	None	Few	Calf or thigh	Calf and thigh
Venous oedema	None	Foot and ankle	Below knee	Knee and above
Skin pigmentation	None	Limited peri-malleolar	Diffuse lower 1/3rd calf	Wider above lower 1/3rd calf
Inflammation	None	Limited peri-malleolar	Diffuse lower 1/3rd calf	Wider above lower 1/3rd calf
Induration	None	Limited peri-malleolar	Diffuse lower 1/3rd calf	Wider above lower 1/3rd calf
No. active ulcers	None	1	2	3 or more
Ulcer duration	None	<3 months	3-12 months	>1 year
Active ulcer size	None	<2 cm	2-6 cm	>6 cm
Compression therapy	None	Intermittent	Most days	Fully compliant

Original table using information from published report(22)

Appendix 2: Code performing Guyot's algorithm for the reconstruction of individual patient data, adapted from Guyot et al. (188)

```
library("MASS")
library("splines")
library("survival")

###FUNCTION INPUTS
path<-"FILEPATH"
digisurvfile<-" FILEPATH_2.csv" #Input survival times/ from graph reading
nriskfile<-"nt_34p.csv" #Input reported number at risk
KMdatafile<-"KMdata study2 figA arm1 time1 ne.txt" #Output file events and cens
KMdataIPDfile<-"KMdataIPD study2 figA arm1 time1 ne.txt" #Output file for IPD
tot.events<- "NA" #tot.events = total no. of events reported. If not reported, then
tot.events="NUMEVENTS"
arm.id<-1 #arm indicator


###END FUNCTION INPUTS
#Read in survival times read by digizeit
digizeit<- read.csv(paste(path,digisurvfile,sep=""),header=TRUE)
t.S<-digizeit[,1]
S<-digizeit[,2]

#Read in published numbers at risk, n.risk, at time, t.risk, lower and upper
# indexes for time interval
pub.risk<-read.csv(paste(path,nriskfile,sep=""),header=TRUE)
t.risk<-pub.risk[,2]
lower<-pub.risk[,3]
upper<-pub.risk[,4]
n.risk<-pub.risk[,1]
n.int<-length(n.risk)
n.t<- upper[n.int]

#Initialise vectors
arm<-rep(arm.id,n.risk[1])
n.censor<- rep(0,(n.int-1))
n.hat<-rep(n.risk[1]+1,n.t)
cen<-rep(0,n.t)
d<-rep(0,n.t)
KM.hat<-rep(1,n.t)
last.i<-rep(1,n.int)
sumdL<-0
if (n.int > 1){
  #Time intervals 1,...,(n.int-1)
  for (i in 1:(n.int-1)){
    #First approximation of no. censored on interval i
    n.censor[i]<- round(n.risk[i]*S[lower[i+1]]/S[lower[i]]- n.risk[i+1])
    #Adjust tot. no. censored until n.hat = n.risk at start of interval (i+1)
```

```
while((n.hat[lower[i+1]]>n.risk[i+1])||((n.hat[lower[i+1]]<n.risk[i+1])&&(n.censor[i]>0))){
      if (n.censor[i]<=0){
        cen[lower[i]:upper[i]]<-0
        n.censor[i]<-0
      }
      if (n.censor[i]>0){
        cen.t<-rep(0,n.censor[i])
        for (j in 1:n.censor[i]){
          cen.t[j]<- t.S[lower[i]] +
            j*(t.S[lower[(i+1)]]-t.S[lower[i]])/(n.censor[i]+1)
        }
        #Distribute censored observations evenly over time. Find no. censored on each
time interval.
        cen[lower[i]:upper[i]]<-hist(cen.t,breaks=t.S[lower[i]:lower[(i+1)]],
                                     plot=F)$counts
      }
      #Find no. events and no. at risk on each interval to agree with K-M estimates
read from curves
      n.hat[lower[i]]<-n.risk[i]
      last<-last.i[i]
      for (k in lower[i]:upper[i]){
        if (i==1 & k==lower[i]){
          d[k]<-0
          KM.hat[k]<-1
        }
        else {
          d[k]<-round(n.hat[k]*(1-(S[k]/KM.hat[last])))
          KM.hat[k]<-KM.hat[last]*(1-(d[k]/n.hat[k]))
        }
        n.hat[k+1]<-n.hat[k]-d[k]-cen[k]
        if (d[k] != 0) last<-k
      }
      n.censor[i]<- n.censor[i]+(n.hat[lower[i+1]]-n.risk[i+1])
    }
    if (n.hat[lower[i+1]]<n.risk[i+1]) n.risk[i+1]<-n.hat[lower[i+1]]
    last.i[(i+1)]<-last
  }
}
#Time interval n.int.
if (n.int>1){
  #Assume same censor rate as average over previous time intervals.
  n.censor[n.int]<- min(round(sum(n.censor[1:(n.int-1)])*(t.S[upper[n.int]]-
                                                t.S[lower[n.int]])/(t.S[upper[(n.int-1)]]-
t.S[lower[1]])), n.risk[n.int])
}
if (n.int==1){n.censor[n.int]<-0}
if (n.censor[n.int] <= 0){
  cen[lower[n.int]:(upper[n.int]-1)]<-0
  n.censor[n.int]<-0
```

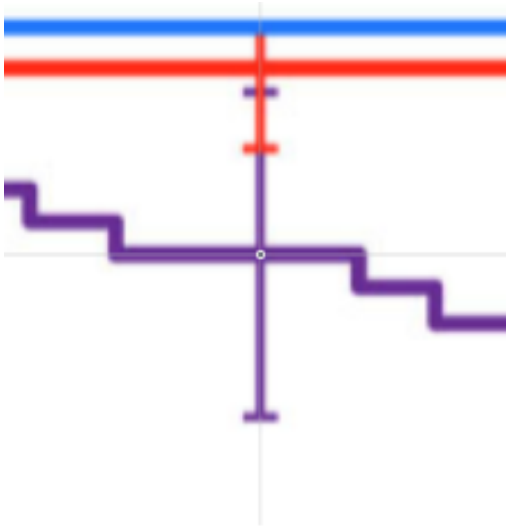
```
}

if (n.censor[n.int]>0){
  cen.t<-rep(0,n.censor[n.int])
  for (j in 1:n.censor[n.int]){
    cen.t[j]<- t.S[lower[n.int]] +
      j*(t.S[upper[n.int]]-t.S[lower[n.int]])/(n.censor[n.int]+1)
  }
  cen[lower[n.int]:(upper[n.int]-1)]<-hist(cen.t,breaks=t.S[lower[n.int]:upper[n.int]],
                                           plot=F)$counts
}
#Find no. events and no. at risk on each interval to agree with K-M estimates read
from curves
n.hat[lower[n.int]]<-n.risk[n.int]
last<-last.i[n.int]
for (k in lower[n.int]:upper[n.int]){
  if(KM.hat[last] !=0){
    d[k]<-round(n.hat[k]*(1-(S[k]/KM.hat[last])))} else {d[k]<-0}
  KM.hat[k]<-KM.hat[last]*(1-(d[k]/n.hat[k]))
  n.hat[k+1]<-n.hat[k]-d[k]-cen[k]
  #No. at risk cannot be negative
  if (n.hat[k+1] < 0) {
    n.hat[k+1]<-0
    cen[k]<-n.hat[k] - d[k]
  }
  if (d[k] != 0) last<-k
}
#If total no. of events reported, adjust no. censored so that total no. of events
agrees.
if (tot.events != "NA"){
  if (n.int>1){
    sumdL<-sum(d[1:upper[(n.int-1)]])
    #If total no. events already too big, then set events and censoring = 0 on all further
time intervals
    if (sumdL >= tot.events){
      d[lower[n.int]:upper[n.int]]<- rep(0,(upper[n.int]-lower[n.int]+1))
      cen[lower[n.int]:(upper[n.int]-1)]<- rep(0,(upper[n.int]-lower[n.int]))
      n.hat[(lower[n.int]+1):(upper[n.int]+1)]<- rep(n.risk[n.int],(upper[n.int]+1-
lower[n.int]))
    }
  }
  #Otherwise adjust no. censored to give correct total no. events
  if ((sumdL < tot.events)|| (n.int==1)){
    sumd<-sum(d[1:upper[n.int]])
    while ((sumd > tot.events)||((sumd< tot.events)&&(n.censor[n.int]>0))){
      n.censor[n.int]<- n.censor[n.int] + (sumd - tot.events)
      if (n.censor[n.int]<=0){
        cen[lower[n.int]:(upper[n.int]-1)]<-0
        n.censor[n.int]<-0
      }
```

```
      if (n.censor[n.int]>0){
        cen.t<-rep(0,n.censor[n.int])
        for (j in 1:n.censor[n.int]){
          cen.t[j]<- t.S[lower[n.int]] +
            j*(t.S[upper[n.int]]-t.S[lower[n.int]])/(n.censor[n.int]+1)
        }
        cen[lower[n.int]:(upper[n.int]-1)]<-hist(cen.t,breaks=t.S[lower[n.int]:upper[n.int]],
                                          plot=F)$counts
      }
      n.hat[lower[n.int]]<-n.risk[n.int]
      last<-last.i[n.int]
      for (k in lower[n.int]:upper[n.int]){
        d[k]<-round(n.hat[k]*(1-(S[k]/KM.hat[last])))
        KM.hat[k]<-KM.hat[last]*(1-(d[k]/n.hat[k]))
        if (k != upper[n.int]){
          n.hat[k+1]<-n.hat[k]-d[k]-cen[k]
          #No. at risk cannot be negative
          if (n.hat[k+1] < 0) {
            n.hat[k+1]<-0
            cen[k]<-n.hat[k] - d[k]
          }
        }
        if (d[k] != 0) last<-k
      }
      sumd<- sum(d[1:upper[n.int]])
    }
  }
}
write.table(matrix(c(t.S,n.hat[1:n.t],d,cen),ncol=4,byrow=F),paste(path,KMdatafile,se
p=""),sep="\t")
### Now form IPD ###
#Initialise vectors
t.IPD<-rep(t.S[n.t],n.risk[1])
event.IPD<-rep(0,n.risk[1])
#Write event time and event indicator (=1) for each event, as separate row in t.IPD
and event.IPD
k=1
for (j in 1:n.t){
  if(d[j]!=0){
    t.IPD[k:(k+d[j]-1)]<- rep(t.S[j],d[j])
    event.IPD[k:(k+d[j]-1)]<- rep(1,d[j])
    k<-k+d[j]
  }
}
#Write censor time and event indicator (=0) for each censor, as separate row in t.IPD
and event.IPD
for (j in 1:(n.t-1)){
  if(cen[j]!=0){
    t.IPD[k:(k+cen[j]-1)]<- rep(((t.S[j]+t.S[j+1])/2),cen[j])
    event.IPD[k:(k+cen[j]-1)]<- rep(0,cen[j])
```

```
    k<-k+cen[j]
  }
}
#Output IPD
IPD<-matrix(c(t.IPD,event.IPD,arm),ncol=3,byrow=F)
write.table(IPD,paste(path,KMdataIPDfile,sep=""),sep="\t")
#Find Kaplan-Meier estimates
IPD<-as.data.frame(IPD)
KM.est<-survfit(Surv(IPD[,1],IPD[,2])~1,data=IPD,type="kaplan-meier",)
plot(KM.est)
summary(KM.est, time=seq(0, 100, 1))
```

Appendix 3: Electronic photograph illustrating digitisation of a Kaplan Meier curve, the point selected shows the survival probability at 6 months to five decimal places.



x: 6.00128, **y:** 0.92241

X-AXIS Linear

X1 0

X2 12

Y-AXIS Linear

Y1 0

Y2 1

Appendix 4: Code used to perform meta-analysis of single-arm survival studies with random effects

```
data <- read_excel("~/meta_analysis/PAP_MTS_Pseudo_IPD_MetaSurv.xlsx")


#load library
library(metaSurvival)
#attach data
attach(data)

Study <- data$Study
Time <- data$Time
Survival <- data$Survival
NbRisk <- data$NbRisk

#Computation of summary survival with continuity correction.
results <- msurv(Study, Time, NbRisk, Survival, confidence="Greenwood", correctionFlag =
T,correctionVal = c(0.25,0.5))

#Plot the estimates summary survival
RandomEffectSummary<- results$summary.random

plot(Time, Survival, type="n", col="black", ylim=c(0,1),xlab="Time (Months)",
    ylab="Primary-Assisted Patency - NIVL")
for (i in unique(sort(Study))){
  lines(Time[Study==i], Survival[Study==i], type="l", col="grey")
  points(max(Time[Study==i]),
         Survival[Study==i & Time==max(Time[Study==i])], pch=15)
}

lines(RandomEffectSummary[,1], RandomEffectSummary[,2], type="l",
     col="red", lwd=3)
points(RandomEffectSummary[,1], RandomEffectSummary[,3], type="l",
       col="black", lty=3, lwd=3)
points(RandomEffectSummary[,1], RandomEffectSummary[,4], type="l",
       col="black", lty=3, lwd=3)
```

Appendix 5: Code used to calculate restricted mean survival time, i.e. integration of the survival function, for each survival curve

```
library(survRM2)
library(azRMST)

data <- read.csv(file = “FILEPATH,” header = TRUE)

RMST <- rmst2(time = data$time,
        status = data$status,
        arm = D=data$arm,
        tau=36)  #TIME HORIZON IN MONTHS

capture.output(RMST, file = "FILEPATH")
```

Appendix 6: Code used to perform meta-analysis of continuous and dichotomous outcomes

```
library(meta)
library(ggplot2)
M <- read.csv(file = “FILEPATH”, header = TRUE)


## 12 MONTHS PP
met <- metamean(
  data = M,
  n =M$Number, # Total number of participants
  mean=M$PP_12M_IPD, # MEAN
  sd = M$PP_12M_IPD_SD, # SD
  studlab = M$Study_Label, # Study labels
  exclude = NULL,
)
met


met <- metaprop(
  event = M$Num_Ulcer_Healed,     # Number of successes (healed)
  n=M$Pre_Ulcer_Num,          # Total number of participants
  data = M,        # Your dataset
  studlab = M$Study_Label,    # Study labels
)

met
```

Appendix 7: Code used to perform meta-analysis for change in continuous outcome measure before and after an intervention

```
library(meta)
data <- read.csv(file = "FILEPATH", header = TRUE)

# Calculate the mean change (effect estimate)
data$TE <- data$mean_post - data$mean_pre

# Calculate the standard error for the change score
data$seTE <- sqrt((data$sd_pre^2 + data$sd_post^2 - 2 * data$r * data$sd_pre * data$sd_post) / data$n)

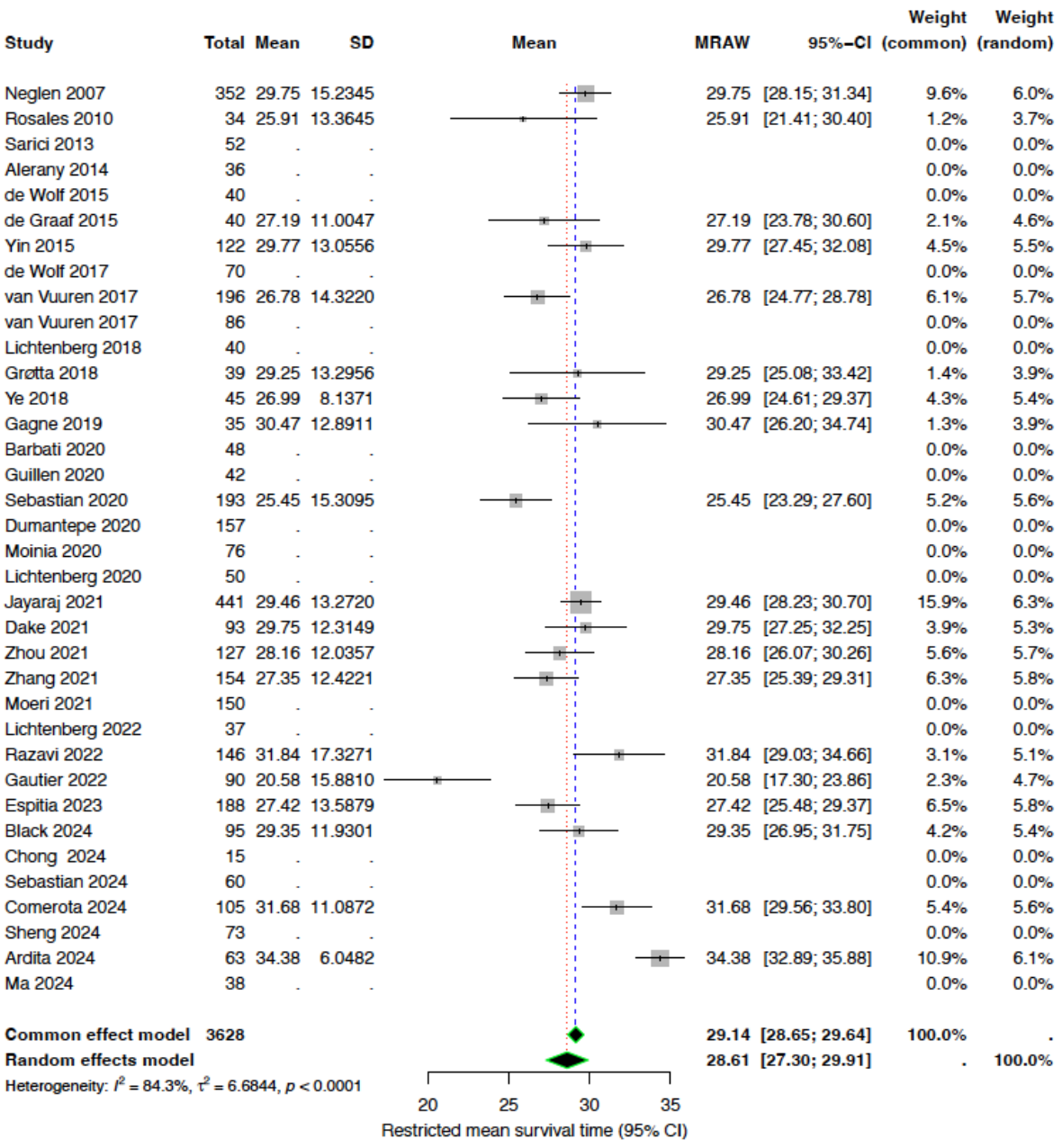
View(data)

meta_result <- metagen(TE = TE,
                       seTE = seTE,
                       studlab = study,
                       data = data,
                       common=FALSE,      # TRUE if you want to see fixed effect estimates too
                       random = TRUE,
                       method.tau="REML")



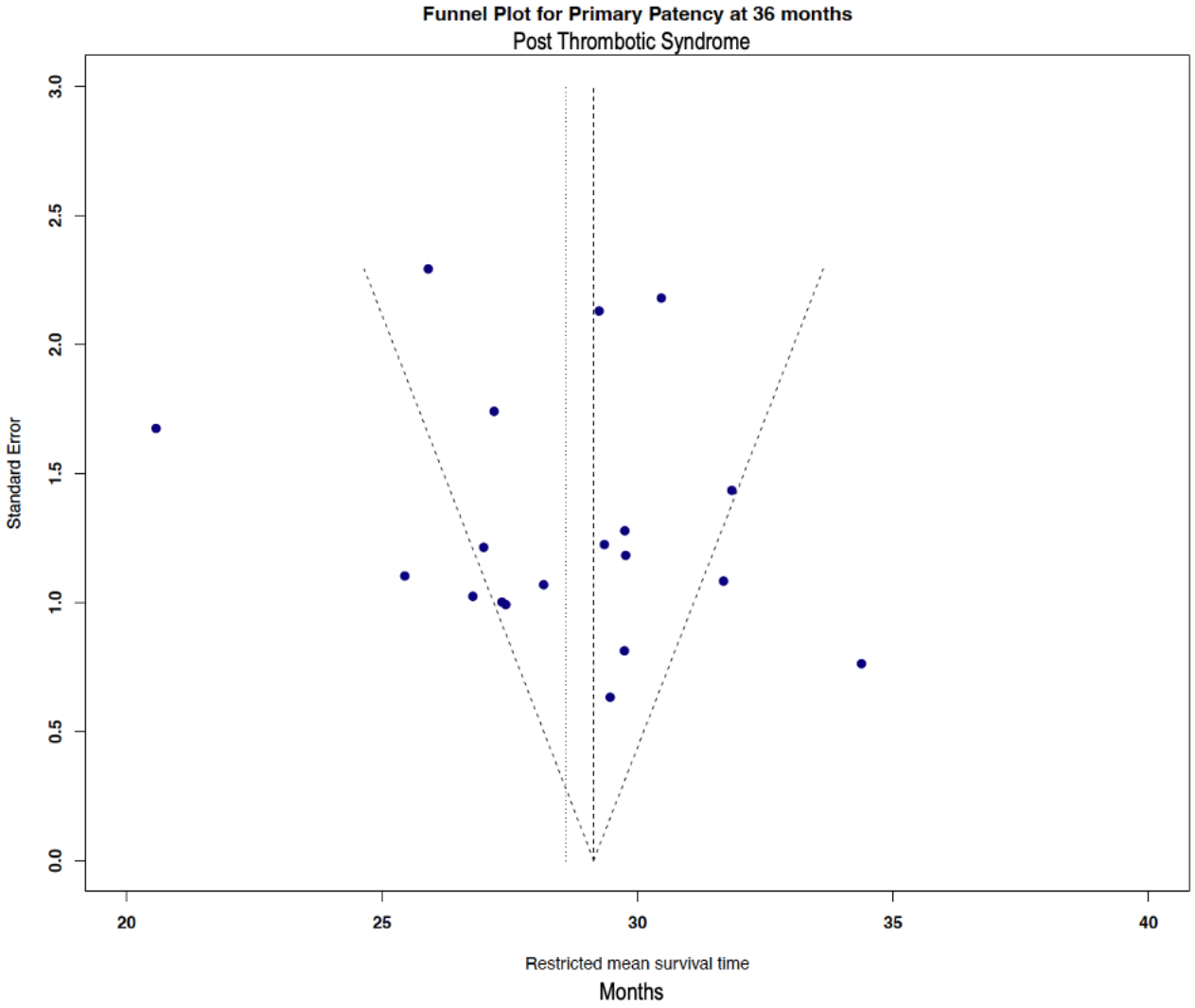
print(meta_result)
```

Appendix 8: Meta-analysis of the restricted mean survival time, primary patency, of iliac vein stents placed for post thrombotic syndrome, utilising reconstructed individual-patient data, at 36 months

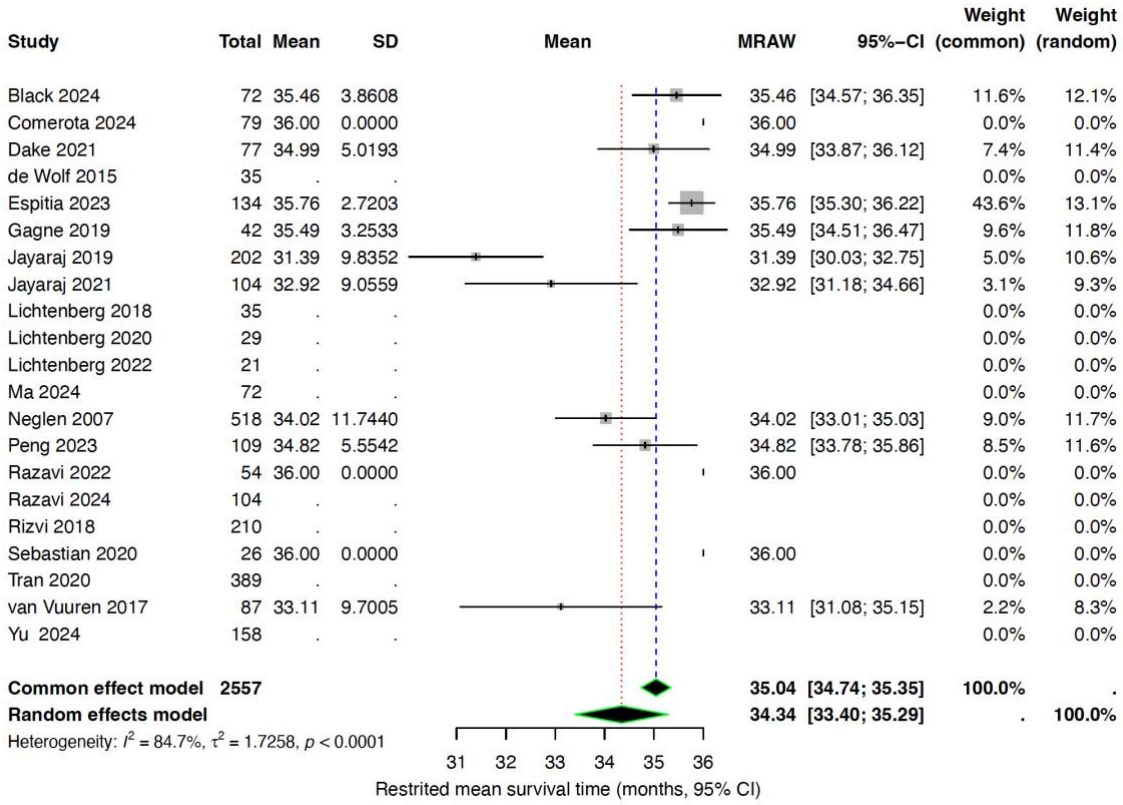


CI: Confidence interval
SD: Standard deviation
MRAW: Summary measure of untransformed means
Total: Represents number of participants within each study

Appendix 9: Funnel plot of with standard error plotted against restricted mean survival time, primary patency, at 36 months for post thrombotic syndrome

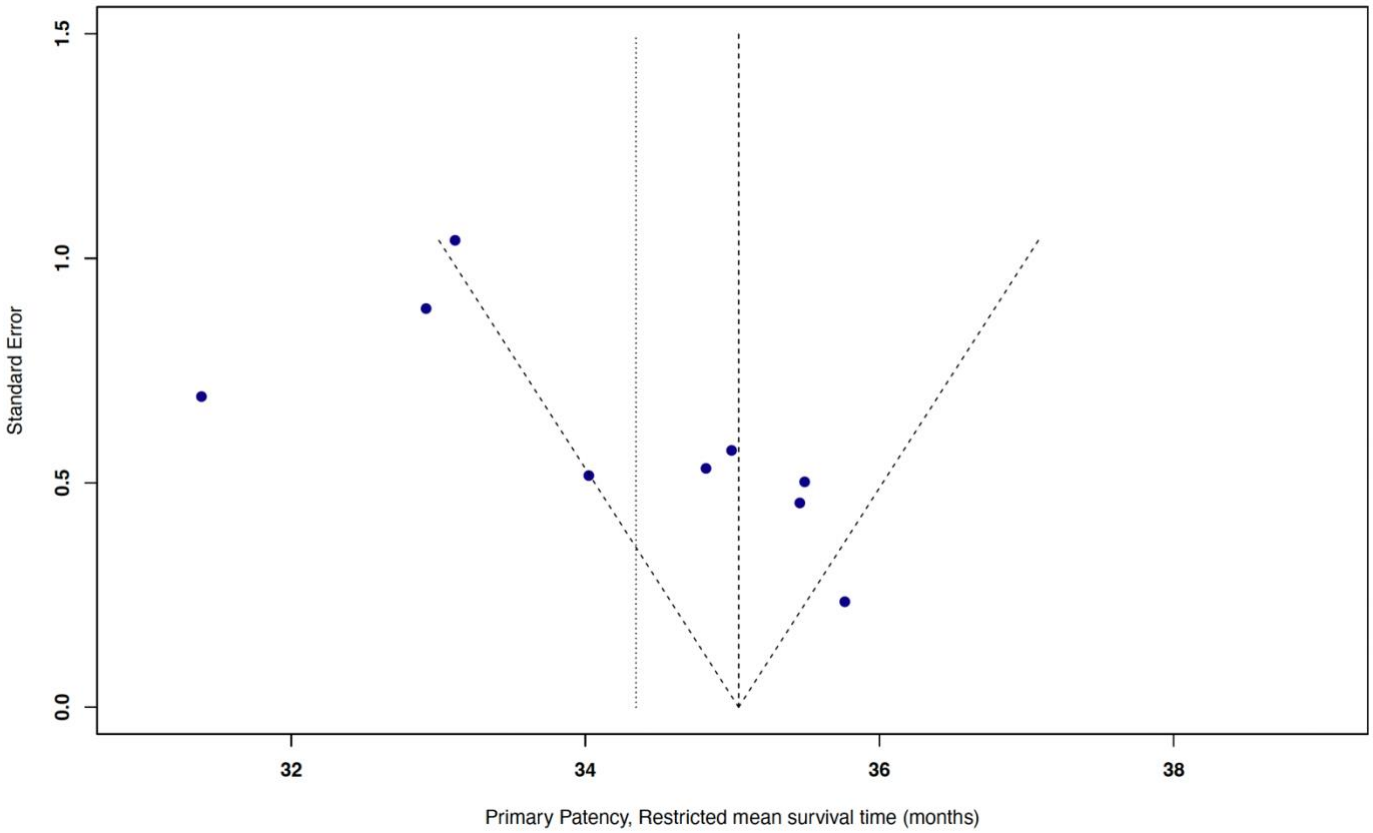


Appendix 10: Meta-analysis of the restricted mean survival time, primary patency, of iliac vein stents placed for non-thrombotic iliac vein lesions, utilising reconstructed individual-patient data, at 36 months

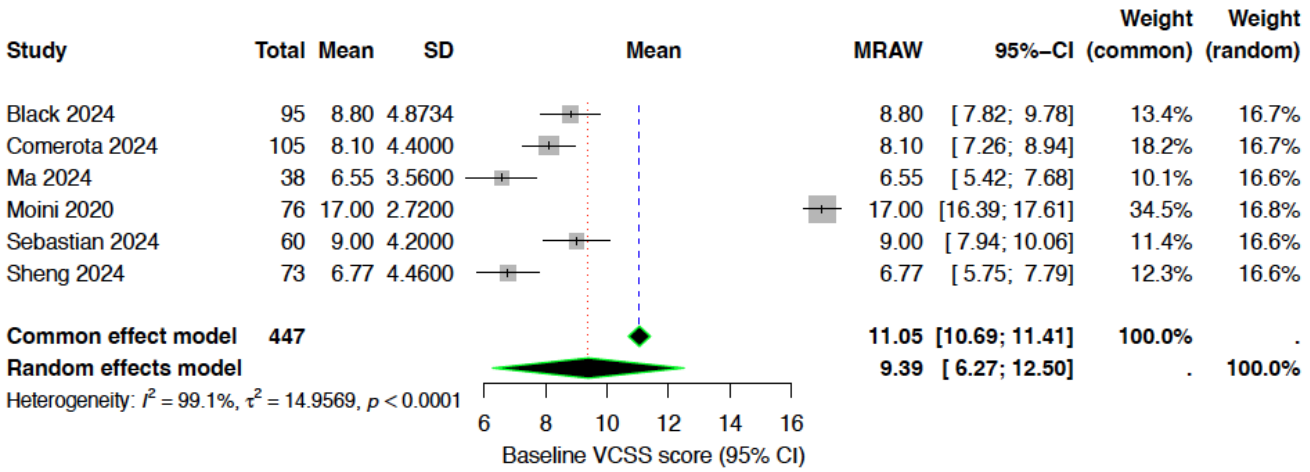


CI: Confidence interval
SD: Standard deviation
MRAW: Summary measure of untransformed means
Total: Represents number of participants within each study

Appendix 11: Funnel plot with standard error plotted against restricted mean survival time, primary patency, at 36 months for non-thrombotic iliac vein lesions

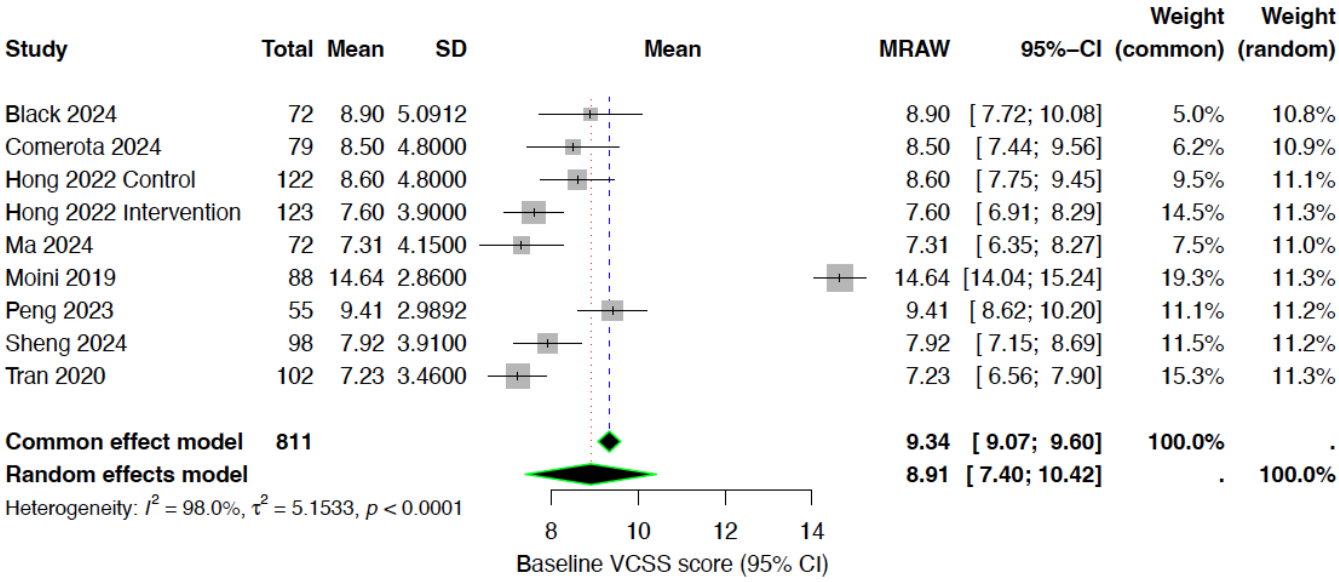


Appendix 12: Meta-analysis of baseline venous clinical severity score for post thrombotic syndrome, including Moini 2024 et al. which was subsequently excluded from the analysis



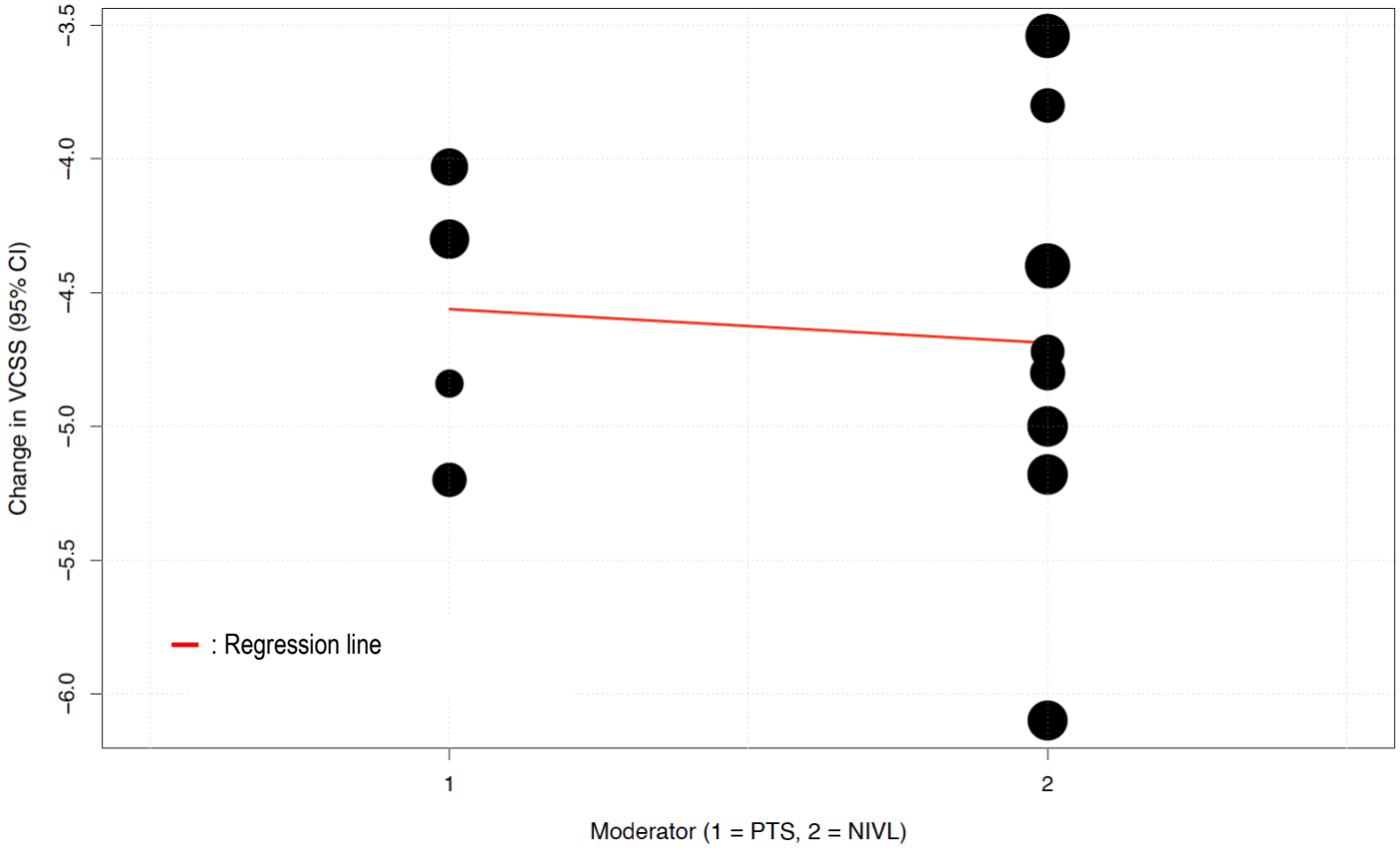
CI: Confidence interval
SD: Standard deviation
MRAW: Summary measure of untransformed means
Total: Represents number of participants within each study

Appendix 13: Meta-analysis of baseline venous clinical severity score for non-thrombotic iliac vein lesions, including Moini 2024 et al. which was subsequently excluded from the analysis



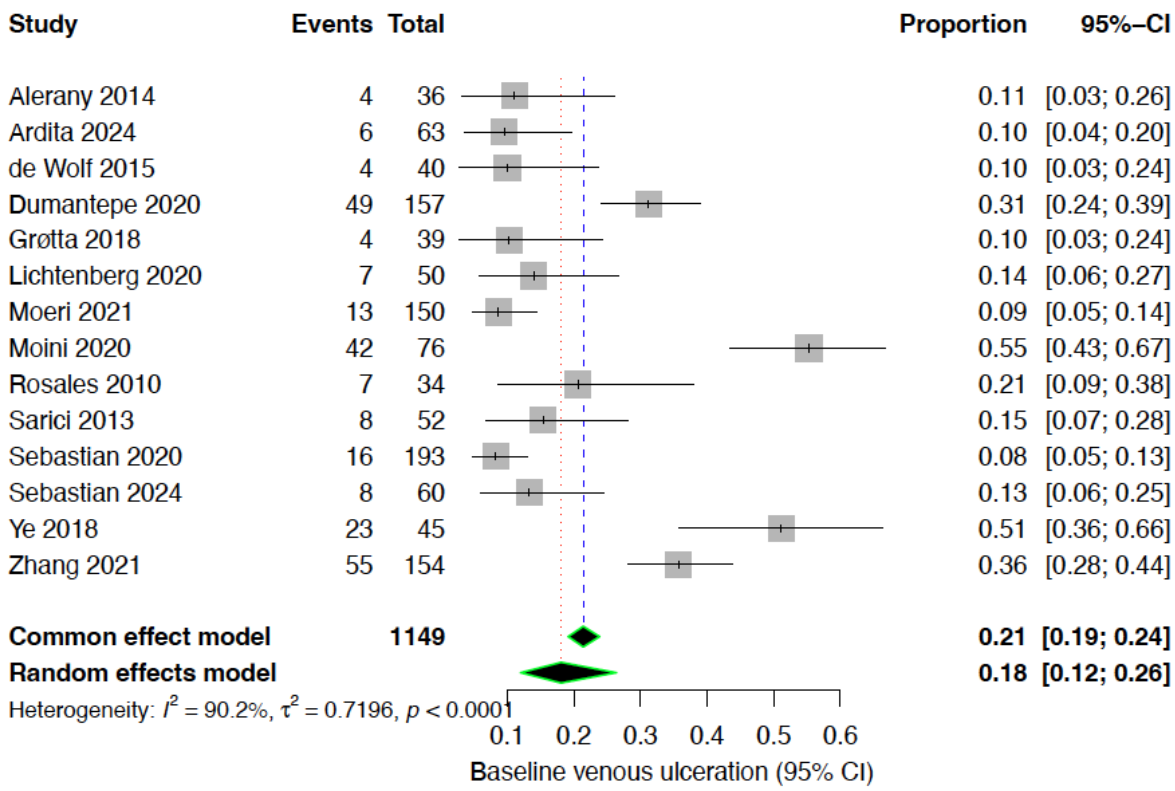
CI: Confidence interval
SD: Standard deviation
MRAW: Summary measure of untransformed means
Total: Represents number of participants within each study

Appendix 14: Bubble plot illustrating the meta-regression of underlying pathology as a moderator for the meta-analysis of change in venous clinical severity score at last follow-up



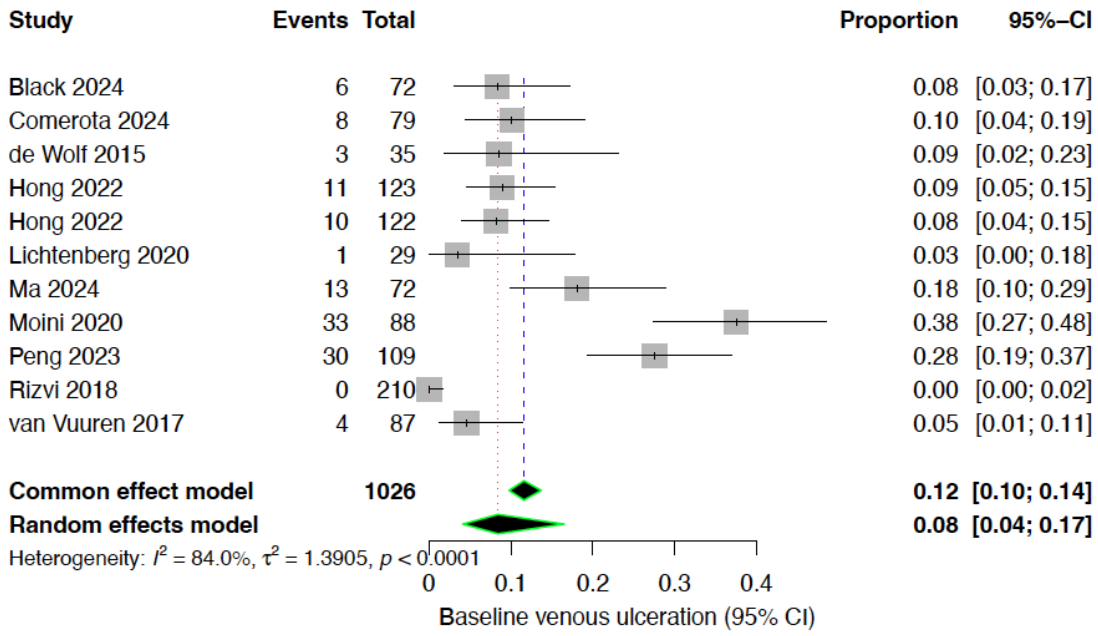
VCSS: Venous clinical severity score
CI: Confidence intervals
PTS: Post thrombotic syndrome
NIVL: Non-thrombotic iliac vein lesion

Appendix 15: Forest plot for the proportion of baseline venous ulceration in post thrombotic syndrome



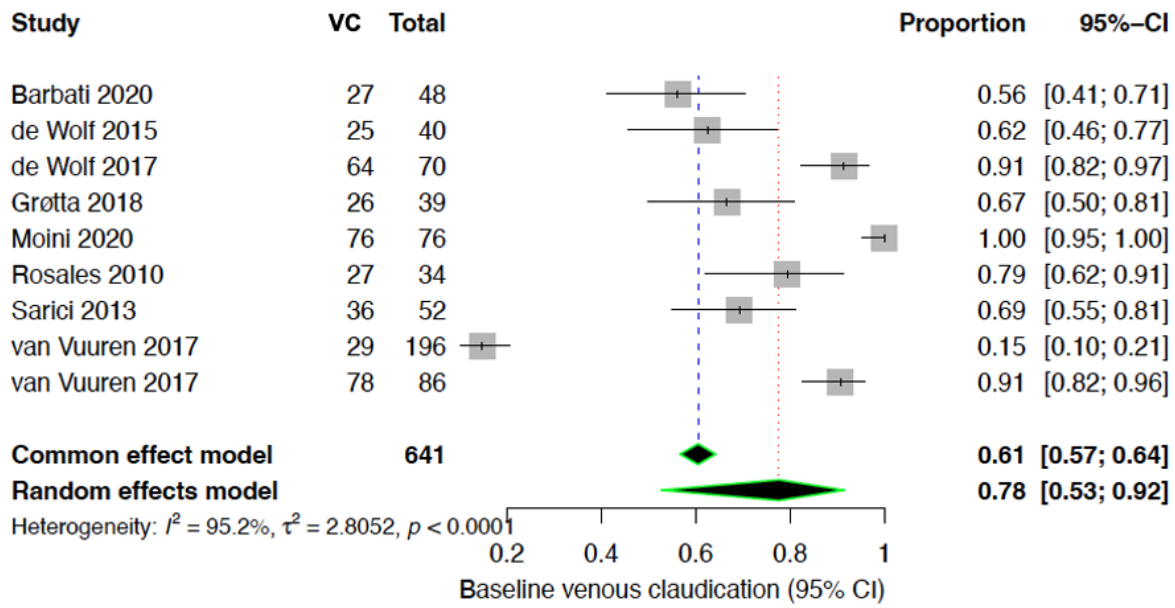
CI: Confidence interval
Total: Represents number of participants within each study

Appendix 16: Forest plot for the proportion of baseline venous ulceration in non-thrombotic iliac vein lesions



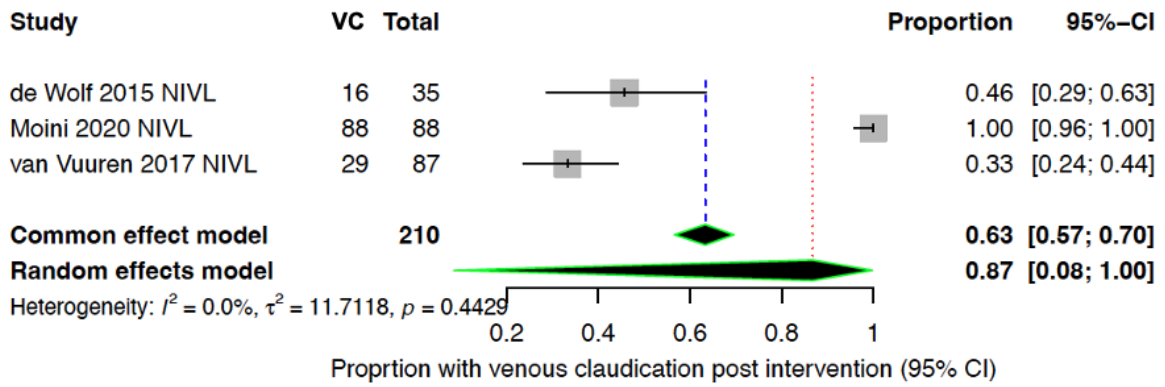
CI: Confidence interval
Total: Represents number of participants within each study

Appendix 17: Forest plot for the proportion of baseline venous claudication in post thrombotic syndrome



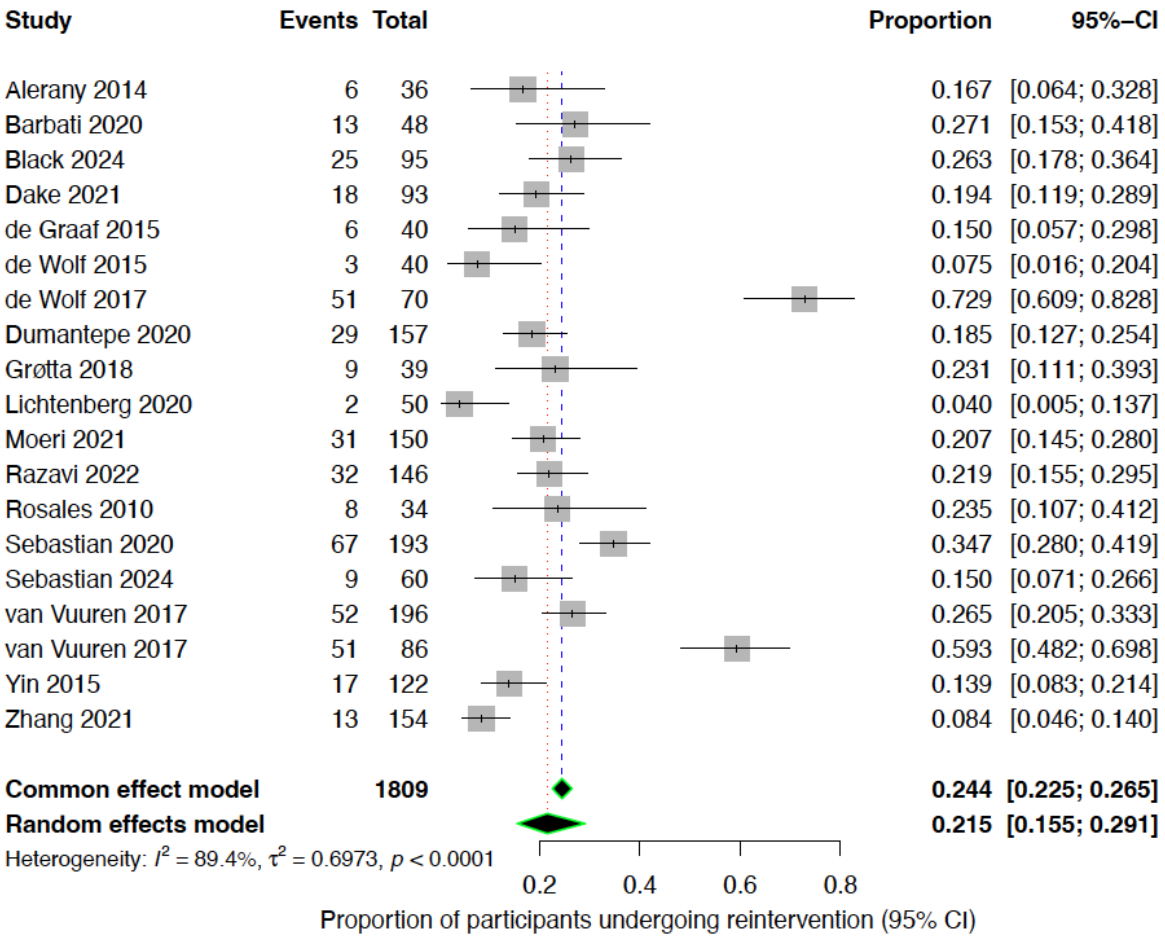
CI: Confidence interval
VC: Venous claudication
Total: Represents number of participants within each study

Appendix 18: Forest plot for the proportion of baseline venous claudication in non-thrombotic iliac vein lesions



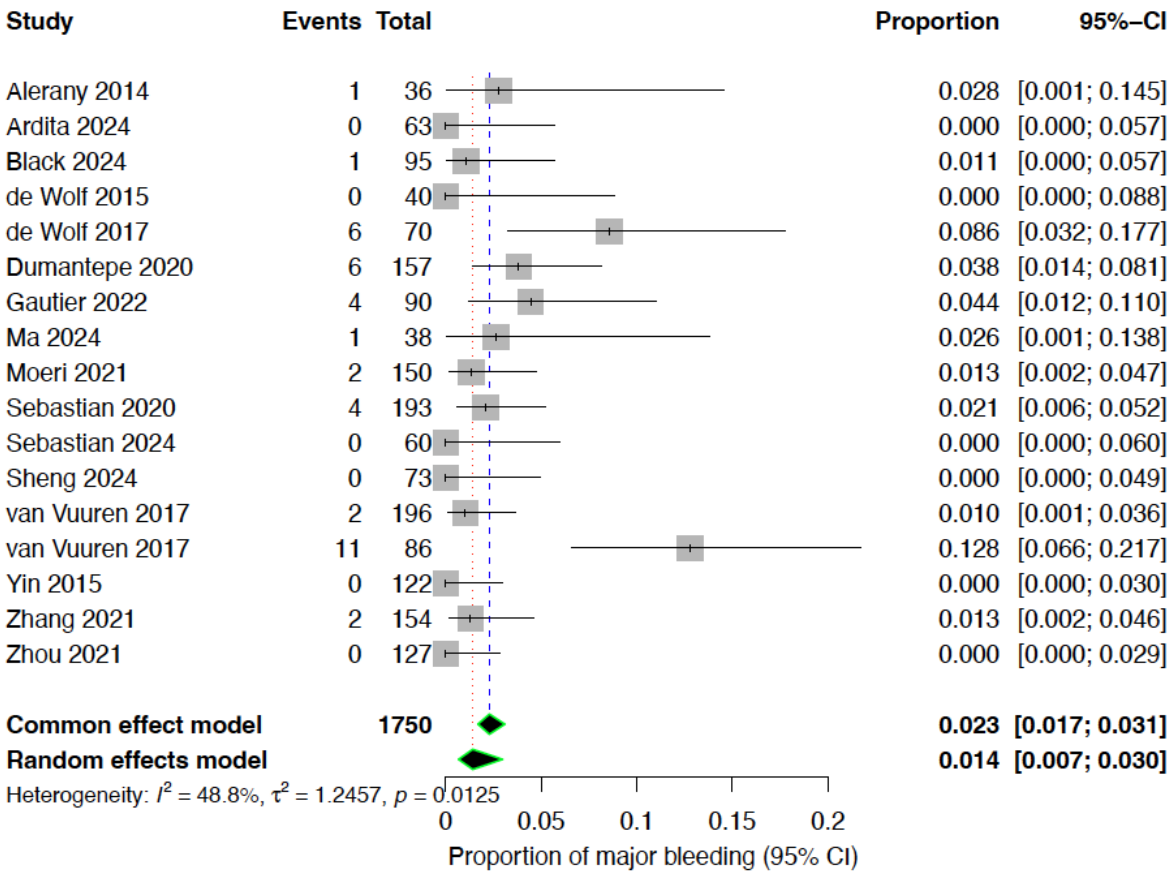
CI: Confidence interval
VC: Venous claudication
Total: Represents number of participants within each study

Appendix 19: Meta-analysis of reintervention post iliac vein stenting at last follow-up for post thrombotic syndrome, including cohorts undertaking hybrid procedures which were subsequently excluded from the analysis



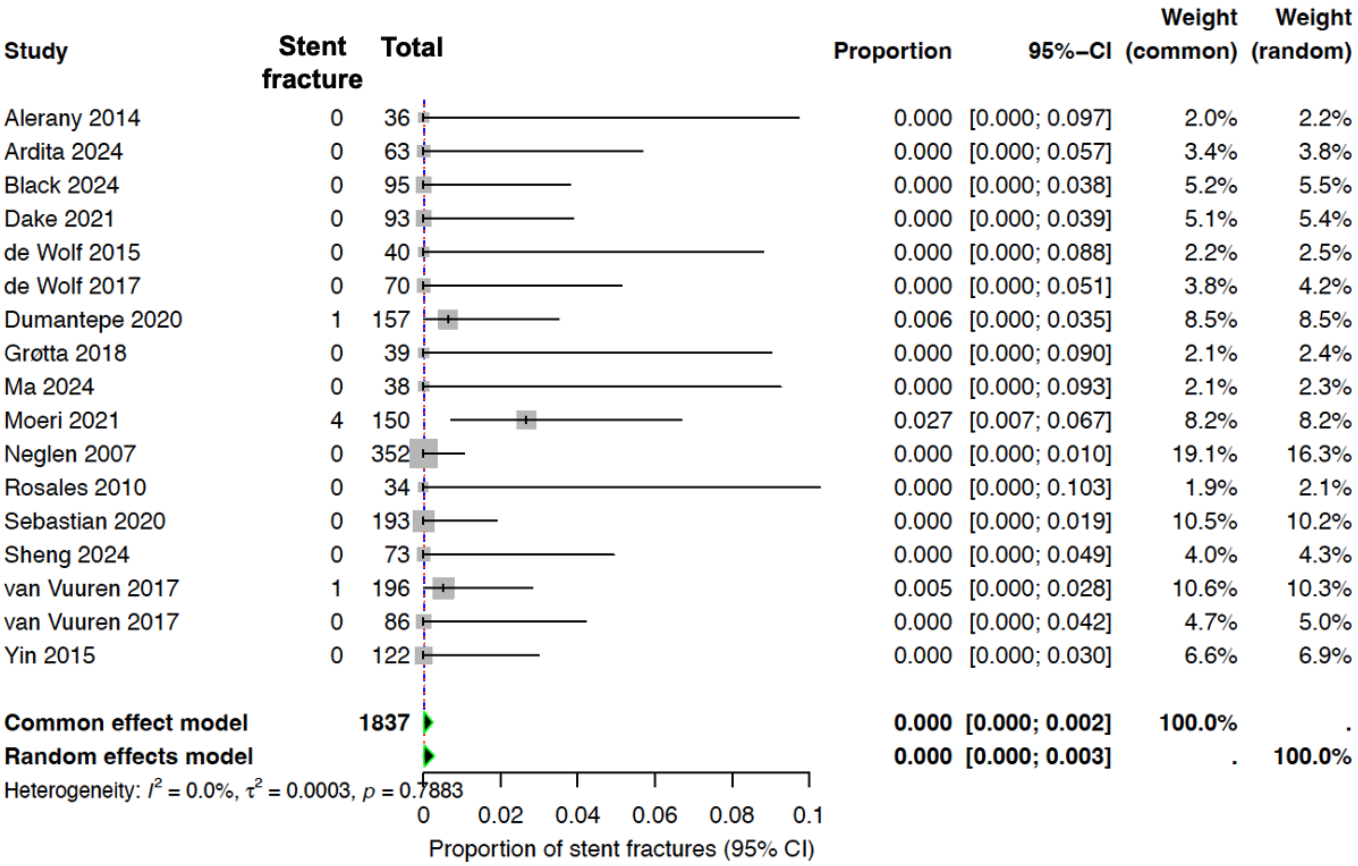
CI: Confidence interval
Total: Represents number of participants within each study

Appendix 20: Meta-analysis of major bleeding post iliac vein stenting at last follow-up for post thrombotic syndrome, including cohorts undertaking hybrid procedures which were subsequently excluded from the analysis



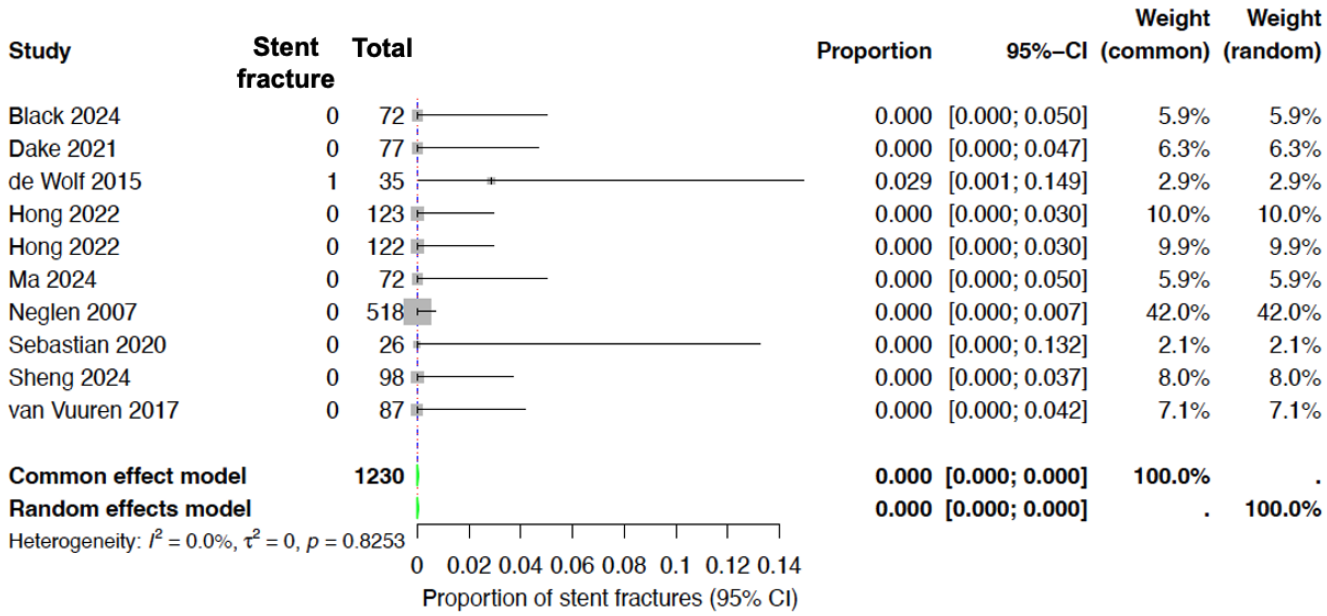
CI: Confidence interval
Total: Represents number of participants within each study

Appendix 21: Meta-analysis of stent fracture post iliac vein stenting for post thrombotic syndrome



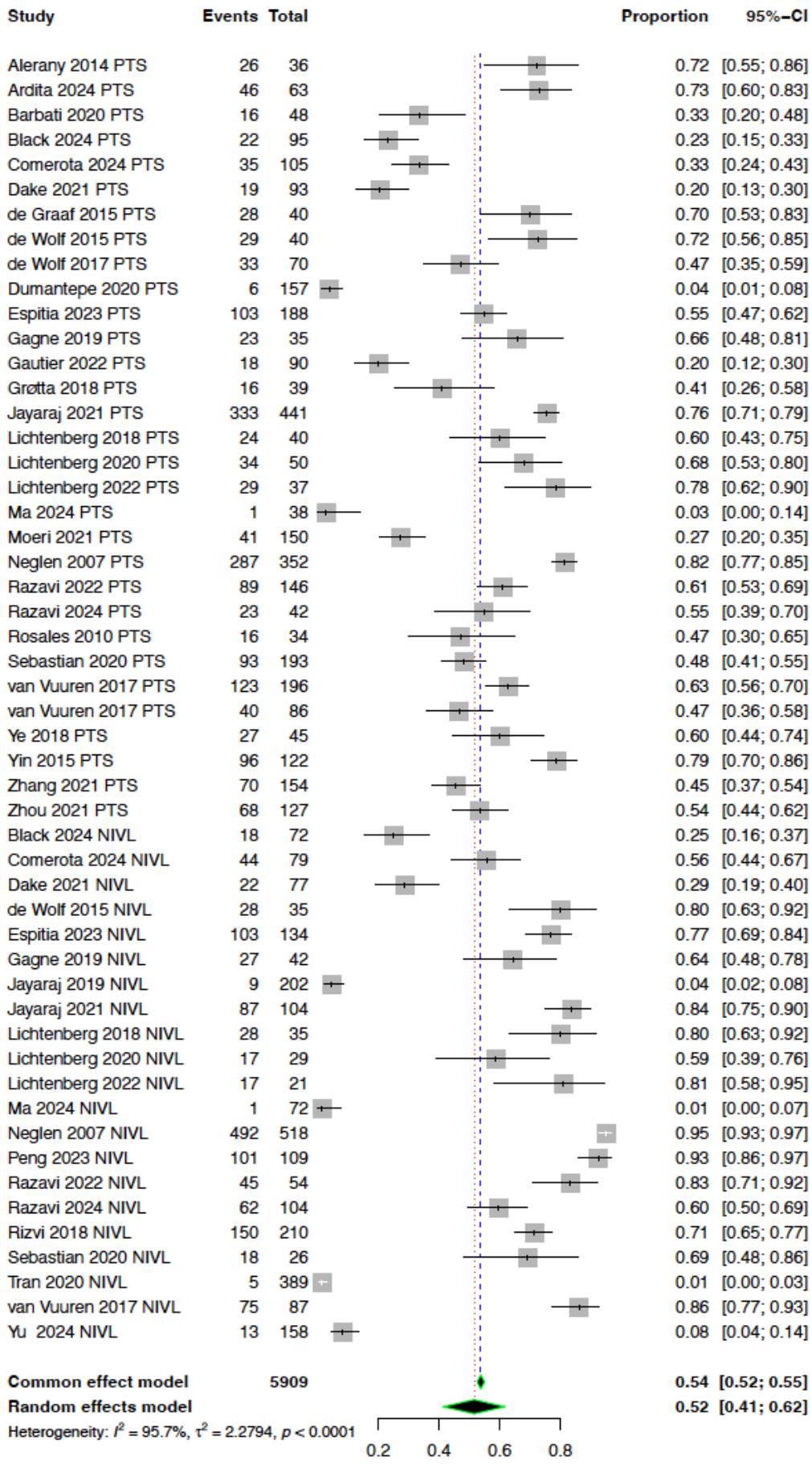
CI: Confidence interval
Total: Represents number of participants within each study

Appendix 22: Meta-analysis of stent fracture post iliac vein stenting for non-thrombotic iliac vein lesions



CI: Confidence interval
Total: Represents number of participants within each study

Appendix 23: Meta-analysis of proportions for the censoring rate occurring in all included studies with data available



Appendix 24: ROBINS-I risk of bias assessment for the pooled outcome measures

Risk of bias domain	VCSS	Venous ulceration	Venous claudication
Domain 1: Risk of bias due to confounding	Low	Low	Low
Domain 2: Bias in selection of participants into the study	Low	Low	Low
Domain 3: Bias in classification of interventions	Low	Low	Low
Domain 4: Risk of bias due to deviations from intended interventions	Low	Low	Low
Domain 5: Risk of bias due to missing data	Moderate	Moderate	Moderate
Domain 6: Risk of bias arising from measurement of the outcome	Serious	Moderate	Serious
Domain 7: Risk of bias in selection of the reported result	Moderate	Moderate	Moderate
Overall risk of bias	Serious	Moderate	Serious

VCSS: Venous clinical severity score

Appendix 25: Code used to perform Mann-Kendall trend testing and LOcally WEighted Scatterplot Smoothing in R using the package 'Kendall'

```
#LOAD LIBRARIES
library(forecast)
library(Kendall)

#IMPORT DATA
data <- read.csv(file = FILEPATH.csv", header = TRUE)


#DATA SET UP
year <- data$Year
stent <- data$non_caval_stent

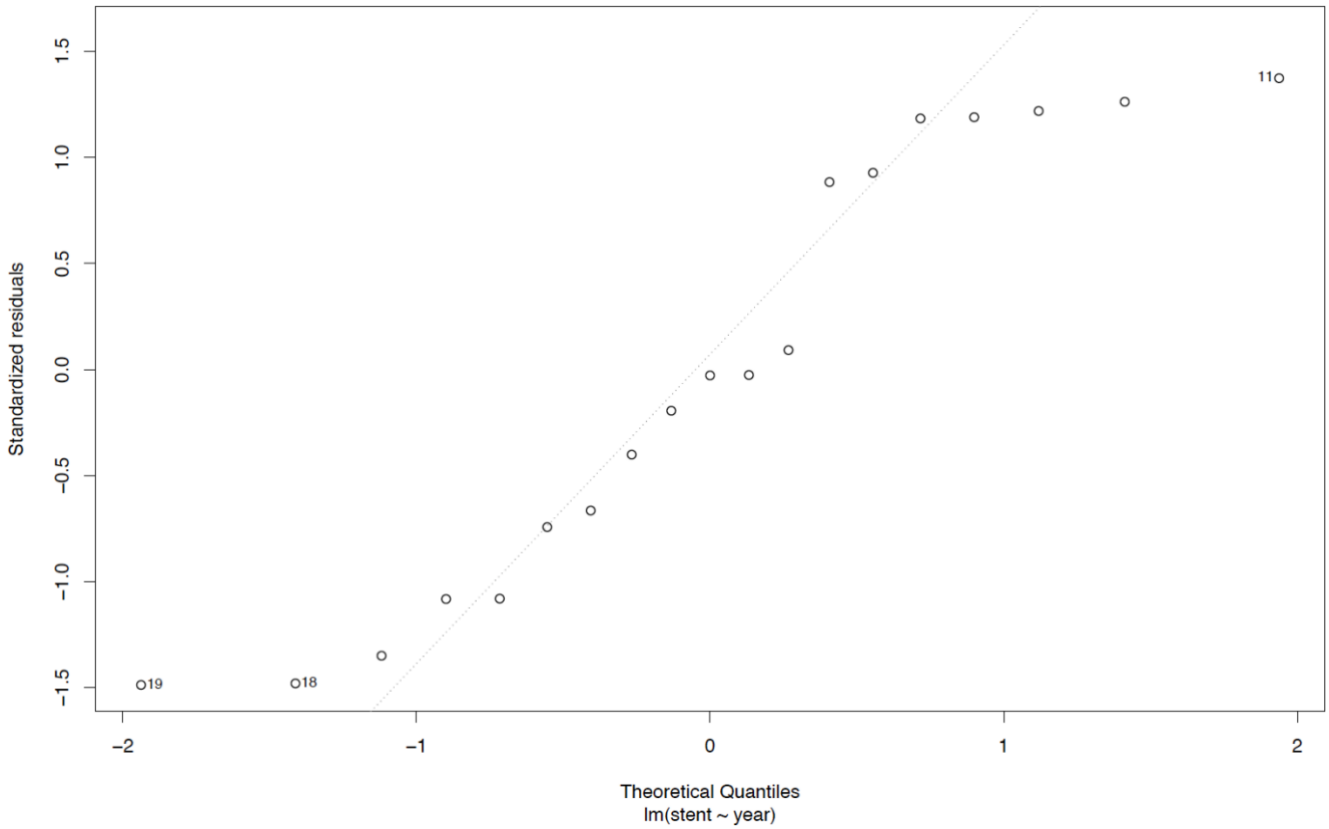
data <- data.frame(year, stent)

result <- MannKendall(data$stent)
print(result)
capture.output(result, file = " FILEPATH")

#LOWESS function
fit <- loess(stent ~ year, span=0.8)
x_new <- seq(min(year), max(year), length.out = 200)
y_pred <- predict(fit, newdata = data.frame(year = x_new))

# Plot
plot(year, stent, main="LOESS Fit", pch = 20)
lines(x_new, y_pred, col = "red", lwd = 2)
```

Appendix 26: Q-Q plot for the residuals of the linear regression model for non-caval stents with time as the moderating variable



Lm: Linear regression model
Stent: Non-caval stents as the dependent variable

Appendix 27: Code used to calculate Kaplan-Meier probability for primary and primary-assisted patency

```
#Loading libraries and importing data file
data <- read.csv(file = “FILEPATH.csv", header = TRUE)
library(survival)
library(survminer)
library(ggplot2)


#Fit the Kaplan-Meier survival curves
km_fit <- survfit(Surv(data$Time, data$Event) ~ data$Group, data = S)


#Plot the KM curve based on probabilities calculated using ‘ km_fit’ function

ggsurv <- ggsurvplot(km_fit,
          data = S,
          risk.table = TRUE,      # display the number at risk table
          pval = FALSE,           # display the p-value
          conf.int = FALSE,        # display confidence
          ncensor.plot = FALSE,      # plot the number of censored
          ncensor.plot.height = 0.25,
          xlim = c(0,120),
          xlab = "Time (Months)",
          ylab = "Survival Probability, Primary-Assisted Patency",
        ggtheme = custom_theme,
          title = "Kaplan-Meier Survival Curves for Primary-Assisted Patency, grouped
by Pathology")

custom_theme <- theme_minimal() +
  theme(
    panel.grid.major = element_line(color = "grey90", size = 0.25),
    panel.grid.minor = element_line(color = "grey90", linetype = "dotted")
  )
ggsurv


#Create data frame from KM function to calculate censoring rate

km_summary <- summary(km_fit)

df_censor <- data.frame(

  time = km_summary$time,

  n.censor = km_summary$n.censor,

  strata = km_summary$strata

)
```

```
# CENSORING RATE

print(df_censor)

df_censor$interval <- cut(df_censor$time, breaks = seq(0, max(df_censor$time), by =
6), right = FALSE)

censor_by_interval <- aggregate(n.censor ~ interval + strata, data = df_censor, sum)

print(censor_by_interval)
```

Appendix 28: Code used to perform logistic regression for a dichotomous outcome

```
df <- read.csv(file = FILEPATH.csv", header = TRUE)

#CATEGORISE VARIABLES
#Baseline characteristics
data$Age <- as.numeric(data$Age)
data$Sex <- as.factor(data$Sex)
data$Indication <- as.factor(data$Indication)

#Techinical / procedural factors
data$Occluded_Pre <- as.factor(data$Occluded_Pre)
data$Unilateral <- as.factor(data$Unilateral)
data$B_IL <- as.factor(data$B_IL)
data$CVO <- as.factor(data$CVO)

#OUTCOMES
data$PP <- as.factor(data$PP)
data$PAP <- as.factor(data$PAP)
data$SP <- as.factor(data$SP)

model <- glm(data$PP ~ data$Anticoag_strategy +
               data$Indication,
             data = data,
             family = binomial()
)


#QUALITY CONTROL CHECKS

plot(model)

residuals(model)

data$resid <- resid(model)

plot(data$year, data$resid, main="Residuals over Time",
```

Appendix 29: Code used to perform Markov state-transition model in bespoke package 'Heemod' in R

```
library(heemod)
library(ggplot2)

#PTS PARAMETERS
param <-  define_parameters(
  age_init = 45,
  sex = 0,
  var_cost = 7759,
  # age increases with cycles
  age = age_init + model_time,
  # age-related mortality rate
  sex_cat = ifelse(sex == 0, "FMLE", "MLE"),
  mr = get_who_mr(age, sex_cat, local = TRUE),
  #We need to incorporate the rate of stent occlusion
  #This is done by fitting a parametric curve to the step-wide decline of the KM
  # Weilbull model
  pso = 1 - exp((0.033447 * model_time)^1.150380 - (0.033447 * (model_time +
1))^1.150380),
  psp=(1 - pso - mr),
  psd = (1 - mr),
  # state values
  u_PatentStent_ImprovedVCSS = .787,
  u_OccludedStent_DecreasedVCSS = .70,
  u_Dead = .0,
  c_PatentStent_ImprovedVCSS = 550.15,
  c_OccludedStent_DecreasedVCSS = 236.57
  #c_PatentStent_ImprovedVCSS = ((length(PatentStent)*0.117)*7600) + 530,
  #c_OccludedStent_DecreasedVCSS = ((length(OccludedStent)*0.175)*7600) + 145
)
param

#STENT ARM STATES
mat_standard <- define_transition(
  state_names = c("PatentStent", "OccludedStent", "Dead"),
  psp, pso, mr,
  0, psd, mr,
  0, 0, 1
)
mat_standard


PatentStent <- define_state(
  utility = discount(u_PatentStent_ImprovedVCSS, .03),
  cost = c_PatentStent_ImprovedVCSS
)
PatentStent
```

```
OccludedStent <- define_state(
  utility = discount(u_OccludedStent_DecreasedVCSS, .03),
  cost =   c_OccludedStent_DecreasedVCSS
)
OccludedStent

Dead <- define_state(
  utility = 0,
  cost = 0
)
Dead

strat_stent <- define_strategy(
  transition=mat_standard,
  PatentStent = PatentStent,
  OccludedStent = OccludedStent,
  Dead = Dead,
  starting_values = define_starting_values(cost = var_cost)
)
strat_stent


#### BEST MEDICAL THERAPY ARM
#Changing initial state allocations as none of them have improved VCSS


mat_medical <- define_transition(
  state_names = c("PatentStent", "OccludedStent", "Dead"),
  0, psd, mr,
  0, psd, mr,
  0, 0, 1
)
PatentStent <- define_state(
  utility = 0,
  cost = 0
)
PatentStent

OccludedStent <- define_state(
  utility = discount(u_OccludedStent_DecreasedVCSS, .03),
  cost =   c_OccludedStent_DecreasedVCSS
)
OccludedStent

Dead <- define_state(
  utility = 0,
  cost = 0
)
Dead
```

```
strat_med <- define_strategy(
  transition=mat_medical,
  PatentStent = PatentStent,
  OccludedStent = OccludedStent,
  Dead = Dead,
  starting_values = define_starting_values(cost = 0)
  )



###RUNNING COMBINED MODEL
res_mod <- run_model(
  medical = strat_med,
  stent = strat_stent,
  parameters = param,
  cycles = 50,
  cost = cost,
  effect = utility
)


#PSA Analysis
psa <- define_psa(
  c_PatentStent_ImprovedVCSS ~ gamma(mean=626.29, sd = 50),
  c_OccludedStent_DecreasedVCSS ~ gamma(mean=339.79, sd = 30),
  u_PatentStent_ImprovedVCSS ~ beta(shape1 = 78.7, shape2 = 21.6),
  u_OccludedStent_DecreasedVCSS ~ beta(shape1 = 70, shape2 = 30)
)

res_psa <- run_psa(
  model = res_mod,
  psa = psa,
  N=1000
)

#Plotting the PSA analysis as Probability of cost effectiveness
library(ggplot2)
plot(res_psa, type = "ac") +
  geom_vline(xintercept = c(20000, 30000), linetype = "dashed", color = "gray40") +
  annotate("text", x = 20000, y = 0.1, label = "£20k", angle = 90, vjust = -0.5, color =
"gray40") +
  annotate("text", x = 30000, y = 0.1, label = "£30k", angle = 90, vjust = -0.5, color =
"gray40") +
  scale_x_continuous(
    labels = scales::dollar_format(prefix = "£", big.mark = ","),
    limits = c(0, 80000),
    name = "Willingness-to-Pay Threshold (£/QALY)"
  ) +
  ylab("Probability Cost-Effective") +
  scale_color_brewer(
```

```
    name = "Strategy",
    palette = "Set1"
  ) +
  theme_minimal(base_size = 14) +
  theme(
    legend.position="bottom",
    plot.title = element_text(face = "bold")
  ) +
  ggtitle("Cost-Effectiveness Acceptability Curve (CEAC)")
View(res_psa)

#deterministic sensitivity analysis (DSA
#Defining differing state transisition probabiltiies
dsa <- define_dsa(
  pso, 0.01, 0.85      # vary occlusion rate
  #u_PatentStent_ImprovedVCSS, .709232, .78
  #c_PatentStent_ImprovedVCSS, 626.29, 2143.96
  #var_cost, 15000, 41373.66
)

res_dsa <- run_dsa(
  model = res_mod,
  dsa = dsa
)
res_dsa
```

Appendix 30: Code used to perform linear mixed models to assess the association between two continuous variables

```
# VCSS AND EQ5D, correlation, invariant over time, LONG data structure, not wide
#Load libraries
library(lme4)
library(caret)

#Import dataset
data <- read.csv(file = "FILEPATH", header = TRUE)


#Baseline variables
PTS <- as.factor(data$PTS)
Limb <- as.factor(data$Diseased.limb.side)
Sex <- as.factor(data$Gender)
Stented <- as.factor(data$Intervention)
ID <- as.factor(data$Subject_code)
Kg <- data$Weight
BMI <-data$BMI
Patency <- as.factor(data$Patency)

#Disease severity markers
VCSS <- data$VCSS
Villalta <- data$Villalta
Claudication <- as.factor(data$Claudication)
CEAP <- as.factor(data$CEAP)

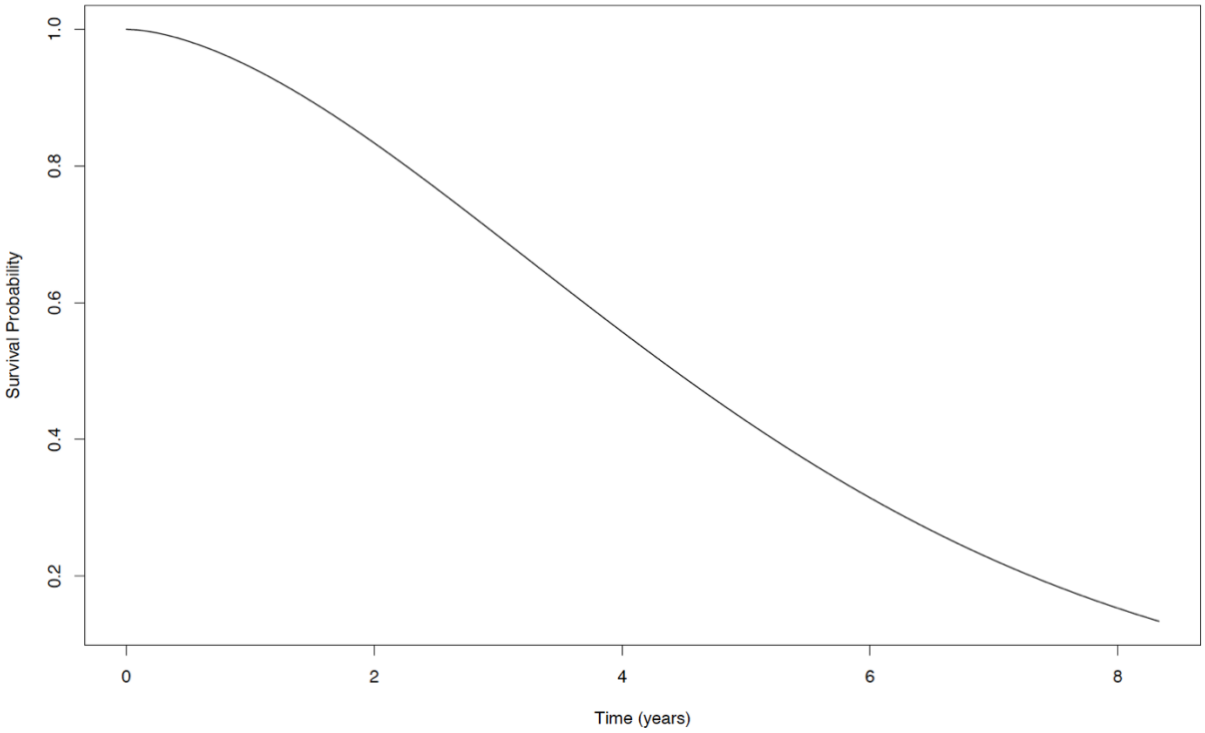
#QoL, EQ5d-5L
EQ5D1 <- data$EQ5D_Mob
EQ5D2 <- data$EQ5D_Self
EQ5D3 <- data$EQ5D_Daily
EQ5D4 <- data$EQ5D_Pain
EQ5D5 <- data$EQ5D_Stem
EQ5DIndex <- data$EQ5D_Index
EQ5DVAS <- data$EQ5D_Vas


#Linear mixed model

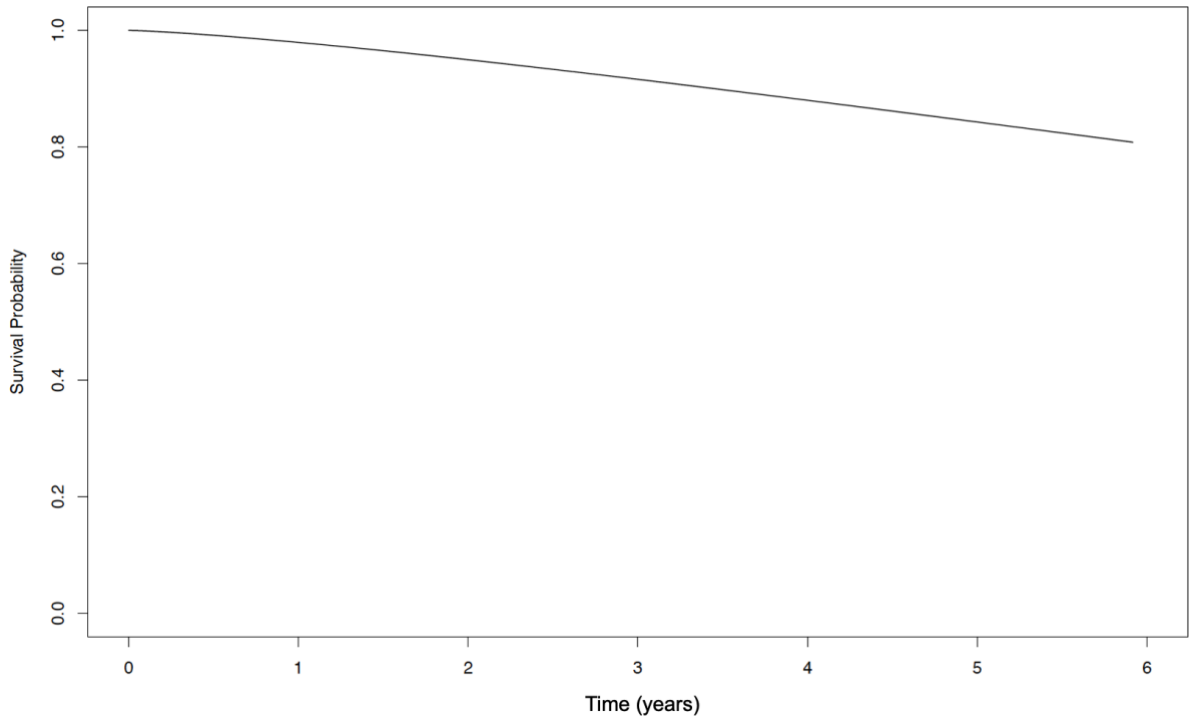
model <- lmer(EQ5DIndex ~ VCSS + Stented + PTS + BMI + Sex + (1|ID), data =
data)

summary(model)
```

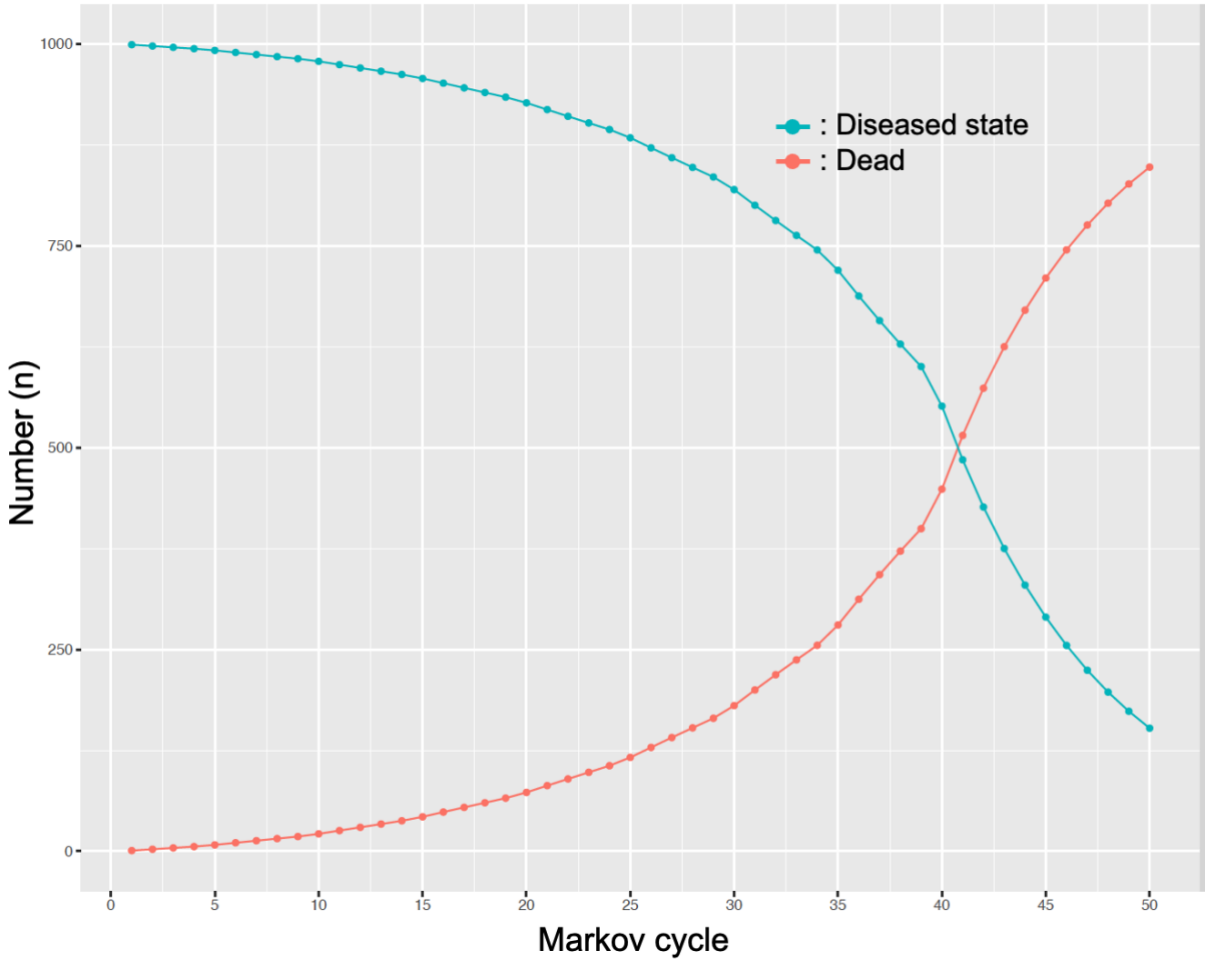
Appendix 31: Weibull survival function for primary-assisted patency of stents placed for Post Thrombotic Syndrome utilising pooled survival probabilities from reconstructed individual patient data



Appendix 32: Weibull survival function for primary-assisted patency of stents placed for Non-Thrombotic Iliac Vein Lesions utilising pooled survival probabilities from reconstructed individual patient data



Appendix 33: Number of simulated participants in the different states over Markov cycle observed in the Markov state transition model, standard medical therapy arm



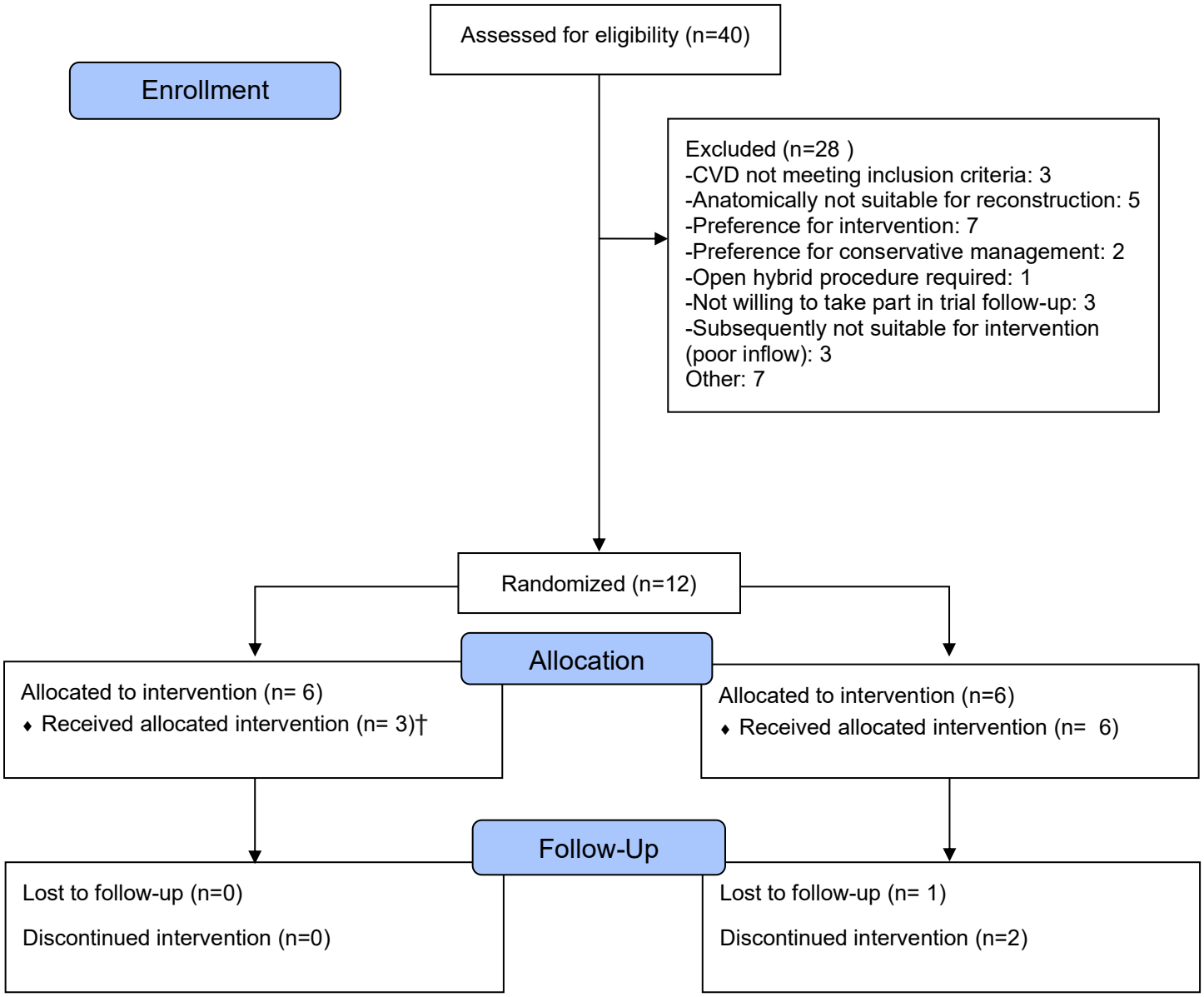
Appendix 34: Monthly recruitment rate per active site during the internal pilot of feasibility for the BEST trial

Site	Date Activated	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Apr-23	May-23	Total
Imperial College Healthcare NHS Trust	01/09/2022	1	4	2	0	0	0	0	0	1	8
Bedford University Hospitals NHS Foundation Trust	16/01/2023					0	0	0	0	1	1
Newcastle Hospital NHS Foundation Trust	01/02/2023						0	0	0	1 (+1)*	1
Guy's and St Thomas' NHS Foundation Trust	14/04/2023								0	0	0
London North West University Healthcare NHS Trust	17/04/2023								0	0	0
Oxford University Hospitals NHS Trust	15/05/2023									0	0

*Consent for enrolment awaiting post COVID-19 infection time duration to elapse prior to randomisation.

Appendix 35: Consort diagram of the BEST trial

CONSORT 2010 Flow Diagram



†: Three participants did not receive an iliac stent after randomisation:

- Deemed to have inadequate inflow on treatment visit;
- Contracted COVID-19 prior to intervention causing procedure delay, participant then withdrew; and
- Withdrew by the principal investigator after randomisation.

PUBLICATIONS

The following manuscripts were published during the thesis period of 2022 – 2025:

1. Machin M, Smith S, Nandhra S, et al. Best Endovenous Treatment, Including Stenting, versus Best Nonendovenous Treatment in Chronic Proximal Deep Venous Disease—The BEST Multicenter Randomized Controlled Trial Protocol. Journal of Vascular Surgery: Venous and Lymphatic Disorders 2022;10(2):573.

2. Birmpili P, Benson RA, Gwilym B, et al. Outcomes following vascular and endovascular procedures performed during the first COVID-19 pandemic wave. EJVES Vascular Forum: Elsevier; 2024:64-71.

3. Machin M, Wanhainen A, D'Oria M, et al. A Core Outcome Set for Intact Abdominal Aortic Aneurysm Repair. European Journal of Vascular and Endovascular Surgery 2024.

4. Machin M, Whittley S, Norrie J, et al. Evaluating pharmacological THRomboprophylaxis in Individuals undergoing superficial endoVEnous treatment across NHS and private clinics in the UK: a multi-centre, assessor-blind, randomised controlled trial—THRIVE trial. BMJ open 2024;14(2):e083488.

5. Turner BR, Machin M, Salih M, et al. An Updated Systematic Review and Meta-analysis of the Impact of Graduated Compression Stockings in Addition to Pharmacological Thromboprophylaxis for Prevention of Venous Thromboembolism in Surgical Inpatients. Annals of Surgery 2024;279(1):29-36.

6. Esposito D, Rawashdeh M, Onida S, et al. Systematic review and meta-analysis of elective open conversion versus fenestrated and branched endovascular repair for previous non-infected failed endovascular aneurysm repair. European Journal of Vascular and Endovascular Surgery 2024;67(3):393-405.

7. Javed A, Machin M, Gwozdz AM, et al. Meta-analysis of lytic catheter-based intervention for acute proximal deep vein thrombosis in the reduction of post-thrombotic syndrome. Journal of Vascular Surgery: Venous and Lymphatic Disorders 2023;11(4):866-875. e1.

8. Machin M, Van Herzeele I, UbbinkD, Powell JT. Shared decision making and the management of intact abdominal aortic aneurysm: a scoping review of the literature. European Journal of Vascular and Endovascular Surgery 2023;65(6):839-849.

9. Machin M, Peerbux S, Whittley S, et al. Examining the benefit of graduated compression stockings in the prevention of hospital-associated venous thromboembolism in low-risk surgical patients: a multicentre cluster randomised controlled trial (PETS trial). BMJ open 2023;13(1):e069802.

10. Machin M. Developing core outcome sets for vascular conditions across Europe, Not as easy as it sounds. EJVES Vascular Forum: Elsevier; 2023:1-4.

11. Turner BR, Thapar A, Jasionowska S, et al. Systematic review and meta-analysis of the pooled rate of post-thrombotic syndrome after isolated distal deep venous thrombosis. European Journal of Vascular and Endovascular Surgery 2023;65(2):291-297.

12. Turner BR, Machin M, Jasionowska S, et al. Systematic review and meta-analysis of the additional benefit of pharmacological thromboprophylaxis for endovenous varicose vein interventions. Annals of Surgery 2023;278(2):166-171.

13. Turner BR, Jasionowska S, Machin M, et al. Systematic review and meta-analysis of exercise therapy for venous leg ulcer healing and recurrence. Journal of Vascular Surgery: Venous and Lymphatic Disorders 2023;11(1):219-226.

14. Jasionowska S, Turner BR, Machin M, et al. Systematic review of exercise in the management of post-thrombotic syndrome. Phlebology 2022;37(10):695.

RESEARCH GRANT FUNDING

The following grants were secured during the thesis period of 2022 – 2025:

1. NIHR HTA Funding Application, 2022 - £2,103,070.31, “The THRIVE Trial - THRomboprophylaxis in Individuals undergoing superficial endoVEnous treatment (THRIVE) – a multicentre assessor-blind randomised-controlled trial”, named co-applicant 5% FTE.
2. NIHR HTA Funding Application, 2023 - £2,673,754.60, “Inpatient GRAduated Compression stocking use as an adjunct to Extended duration pharmacoprophylaxis for venous thromboembolism prevention – the GRACE multi-centre randomised controlled trial”, named co-applicant 5% FTE.
3. NIHR HTA Funding Application, 2023 - £3,058,779.08, “Thromboprophylaxis in Lower Limb Immobilisation (TiLLI)”, named co-applicant 5% FTE.
4. Aortic Dissection Charitable Trust Project Grant - £6,249.52, Development of a Core Outcome Set in Type B Aortic Dissection, Lead Applicant.

The following grants were secured in preparation for the PhD programme, 2021:

5. NIHR HTA Funding Application, 2021 - £2,416,390.79 "Examining the benefit of graduated compression stockings in the Prevention of vEnous Thromboembolism in low-risk Surgical patients: a multicentre cluster-randomised controlled trial (PETS Trial)", named co-applicant 5% FTE.
6. BHF Clinical Study Grant, 2021 - £737,451.35, "Best Endovenous treatment, including STenting, versus best non-endovenous treatment in chronic proximal deep venous disease – the BEST multi-centre randomised controlled trial", named co-applicant 5% FTE.

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