THE EPIDEMIOLOGY OF HEREDITARY HAEMORRHAGIC TELANGIECTASIA AND PULMONARY ARTERIOVENOUS MALFORMATIONS

Dr James W Donaldson BA, MBBS, MRCP

Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

November 2016

TABLE OF CONTENTS

ABSTRACT vii

ACKNOWLEDGEMENTS xi

PUBLICATIONS ARISING FROM THIS THESIS xii

LIST OF FIGURES xiii

LIST OF TABLES xviii

ABBREVIATIONS xxi

CHAPTER 1: INTRODUCTION 1

1.1 Definitions 1

1.1.1 Hereditary haemorrhagic telangiectasia 1

1.1.2 Arteriovenous malformations 1

1.1.3 Telangiectasia 2

1.2 Clinical presentation and progression 3

1.3 Diagnosis 6

1.4 Genetics 7

1.5 Screening for arteriovenous malformations 11

1.6 Treatments 13

1.7 Objectives 16

CHAPTER 2: DATABASES AND METHODOLOGY 17

2.1 The Health Improvement Network 18

2.1.1 Structure of THIN data 19

2.1.2 Data collection 21

2.1.3 Data quality in THIN 21

2.1.4 Validity and generalisability of the THIN database 22

2.1.5 Strengths and limitations of the THIN database 25

2.1.6 Ethical approval 26

2.2 Hospital Episode Statistics 27

2.2.1 Strengths and limitations of the HES database 28
2.2.2 Ethical approval 28
2.3 The Office for National Statistics and death certificate data 29
2.3.1 Strengths and limitations of ONS death certificate data 29
CHAPTER 3: THE PREVALENCE OF HEREDITARY HAEMORRHAGIC TELANGIECTASIA IN THE UK 30
3.1 Introduction 31
3.2 Methods 33
3.2.1 Study population 33
3.2.2 Definition of disease 33
3.2.3 Statistical methods 33
3.3 Results 34
3.3.1 Overall prevalence of HHT 35
3.3.2 Prevalence by sex and year 35
3.3.3 Prevalence by sex and age group 37
3.3.4 Prevalence by deprivation status 40
3.3.5 Prevalence by health authority 41
3.3.6 Sensitivity analysis 42
3.4 Discussion 47
3.4.1 Summary of results 47
3.4.2 Strengths and limitations 48
3.4.3 Interpretation of results 49
3.4.4 Comparison with existing literature 52
3.4.5 Implications 53
CHAPTER 4: COMPLICATIONS AND COMORBIDITIES ASSOCIATED WITH HHT: A POPULATION-BASED STUDY 55
4.1 Introduction 56
4.2 Methods 57
4.2.1 Case-control set 57

4.2.2 Data extraction and processing 58
4.2.3 Data analysis 58
4.3 Results 59
4.3.1 Sensitivity Analysis 62
4.4 Discussion 67
4.4.1 Summary 67
4.4.2 Complications 67
4.4.3 Strengths and limitations 69
4.5 Conclusion 70
CHAPTER 5: MORTALITY IN PATIENTS WITH HHT: A CASE-CONTROL STUDY 71
5.1 Introduction 72
5.2 Methods 72
5.2.1 Data extraction and processing 73
5.2.2 Data analysis 73
5.3 Results 74
5.3.1 Survival analysis 74
5.3.2 Sensitivity analysis 80
5.4 Discussion 81
5.4.1 Summary 81
5.4.2 Data interpretation 81
5.4.3 Strengths and limitations 84
5.4.4 Conclusion 85
CHAPTER 6: THE SAFETY AND SUCCESS RATES OF PERCUTANEOUS EMBOLISATION FOR PULMONARY ARTERIOVENOUS MALFORMATIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS 86
6.1 Introduction 87
6.2 Materials and Methods 88
6.2.1 Data sources and searches 88

6.2.2 Study selection 89
6.2.3 Data extraction and quality assessment 90
6.2.4 Data synthesis and analysis 93
6.3 Results 94
6.3.1 Results: meta-analysis of clinical characteristics 99
6.3.2 Results: meta-analysis of peri-procedural complications 115
6.3.3 Results: meta-analysis of long-term complications 135
6.3.4 Results: meta-analysis of embolisation success rate 142
6.3.5 Results: meta-analysis of reperfusion mechanism 151
6.4 Discussion 163
6.4.1 Summary 163
6.4.2 Interpretation of results 163
6.4.3 Strengths and limitations 166
CHAPTER 7: EMBOLISATION FOR PULMONARY ARTERIOVENOUS MALFORMATIONS ACROSS ENGLAND OVER THE LAST DECADE: AN OBSERVATIONAL EPIDEMIOLOGICAL STUDY USING HOSPITAL EPISODES STATISTICS DATA 171
7.1 Introduction 172
7.2 Methods 172
7.2.1 Study design, setting and source of data 172
7.2.2 Data management and analysis 174
7.3 Results 175
7.3.1 Procedure demographics 175
7.3.2 Mortality 180
7.4 Discussion 183
7.4.1 Summary 183
7.4.2 Strengths and limitations 183
7.4.3 Interpretation of results 184
7.4.4 Conclusion 185

CHAPTER 8: CONCLUSIONS AND FUTURE RESEARCH 186

8.1 Summary 187

8.2 Ongoing work 190

8.3 Recommendations for future research 192

REFERENCES 200

APPENDICES 224

10.1 APPENDIX 1 - OPCS-4 codes for interventional procedures that may have been undertaken as treatment of pulmonary arteriovenous malformations. 224

10.2 APPENDIX 2 - Read codes used to identify potential complications of HHT and associated cardiovascular comorbidities and malignancies 226

10.3 APPENDIX 3 - Selected bias assessment plots (funnel plots) for assessment of publication bias in meta-analysis 253

10.4 APPENDIX 4 - THIN Ethics approval letter 265

10.5 APPENDIX 5 – Genetic study: ethical approval and sponsor letter 268

10.6 APPENDIX 6 - Genetic study: patient information leaflet, consent form and patient questionnaire 271

ABSTRACT

Background

Hereditary haemorrhagic telangiectasia (HHT) is a dominantly inherited genetic disorder of blood vessel development characterised by mucocutaneous telangiectasia and arteriovenous malformations (AVMs). There are no recent epidemiological studies of the prevalence of HHT in the UK, and no population-based studies investigating the burden of disease complications and mortality in this country.

Some of the most devastating complications of HHT such as stroke and cerebral abscess arise as a result of AVMs developing in the pulmonary circulation. Current evidence for the management of pulmonary AVMs using percutaneous embolisation derives from relatively small cohorts published by specialist centres worldwide. No studies have attempted to pool this published literature to summarise the complication rates and efficacy of embolisation. Additionally, there is uncertainty as to whether the apparent low mortality associated with treatment of PAVMs (published in the worldwide literature) is also replicated in the experiences of UK centres currently undertaking the procedure.

Methodology

This research project used large-scale, representative primary care (The Health Improvement Network - THIN) and secondary care (Health Episode Statistics - HES) databases to investigate the prevalence, comorbidities and mortality related to HHT, and the mortality related to treatment for pulmonary AVMs. We further used epidemiological methods to summarise the worldwide published literature regarding the safety and efficacy of percutaneous embolisation as a treatment for pulmonary AVMs.

The specific questions addressed in the studies were;

1. What is the current UK prevalence of HHT and how does this vary with respect to sociodemographic factors?

Using a primary care database (THIN), prevalence rates and adjusted prevalence rate ratios were calculated for HHT and pulmonary AVMs stratified for age group, sex, calendar year, socioeconomic status and geographical location.

2. What are the significant complications and comorbidities associated with HHT?

A case-control study using THIN examined the common complications associated with a diagnosis of HHT and looked at commoner cardiovascular and malignant comorbidities that may be associated with a diagnosis of HHT.

3. What is the mortality related to HHT in the UK?

A case-control study in THIN compared mortality between over 600 cases of HHT with age, sex and primary care practice matched controls, analysing mortality trends by age, sex and socioeconomic status.

4. What is the safety and effectiveness of percutaneous embolisation as a treatment for pulmonary arteriovenous malformations?

A systematic review and meta-analysis of published studies worldwide looking at safety and effectiveness of embolisation was undertaken.

5. What are the current mortality trends in England for patients undergoing percutaneous embolisation for treatment of pulmonary arteriovenous malformations?

Using an extract from the HES database linked to Office for National Statistics death data we investigated mortality associated with embolisation for arteriovenous malformation in England over a 15 year period.

Results

1. The minimum prevalence of diagnosed HHT in the UK was calculated to be 1 in 9,400, with the disease more commonly diagnosed in the female sex, those from older age groups, those from higher socioeconomic groups and patients from certain geographical areas of the UK.

2. A variety of haemorrhagic and neurological complications were commoner in HHT than matched controls including stroke (odds ratio (OR) 1.81) , cerebral abscess (OR 30), epistaxis (OR 11.6) and gastrointestinal haemorrhage (OR 6.08). The odds of cardiac failure (OR 2.36) and colon cancer (OR 2.76) were significantly higher in those with HHT when compared to controls.

3. The hazard ratio for death in HHT cases was twice as high as their matched controls. The median age at death in HHT cases was three years younger than their matched controls.

4. Percutaneous embolisation appears to be a safe procedure for embolisation of pulmonary arteriovenous malformations with a major complication in less than 1% of procedures undertaken. It is effective in 84% of patients who undergo embolisation, or in 90% of lesions treated.

5. The mortality associated with percutaneous embolisation between 1997 and 2011 in England is very low and may be zero.

Conclusions

HHT has a UK prevalence in line with that described in studies from other countries worldwide, though as this prevalence is only in those with diagnosed disease, the true prevalence is likely to be significantly higher. HHT is associated with significant haemorrhagic and neurological complications and HHT cases have a higher mortality than their matched controls. Percutaneous embolisation

appears to be a safe and effective treatment for pulmonary AVMs worldwide and is associated with a very low mortality in England.

ACKNOWLEDGEMENTS

This work was made possible through a combined grant from the University of Nottingham and Nottingham University Hospitals NHS Trust. I am grateful to all those in the Division of Epidemiology and Public Health at Nottingham University who provided me with training in epidemiological methods and statistical expertise, whilst remaining endlessly calm and supportive as I experienced the joys of "getting to grips" with Stata.

My most sincere thanks go to my main supervisors Andrew Fogarty and Tricia McKeever. Andrew had the foresight and vision to turn what was initially to be a brief abstract at a national conference into what subsequently became an entire PhD thesis and Tricia has been an ever smiling and thoroughly supportive hunter out of my statistical errors in work submitted. In addition, I must thank Professor Richard Hubbard who has kept an eye out for the trajectory of my thesis and has offered some invaluable insights in to methodological approaches to the research and to Professor Ian Hall who has been unfailingly helpful in assisting me in the genetic aspects of the research. I am also grateful to Clinical Geneticists Dr Rachel Harrison and Dr Ajoy Sarkar for allowing me to access to their HHT cohort.

Thanks also to my fellow PhD students; Helen Powell, Emma O'Dowd, Graeme Docherty and John Hutchinson who have done much to lighten the mood in the office and preserve my sanity over the time I spent in research.

Finally, to Graeme who tolerated my absences and occasional short temper with good humour and a fine selection from the local vintner and to my family who never tired of asking irrelevant questions about my research - all the while appreciating that it was more important to be interested than to be informed! I am very grateful to all.

PUBLICATIONS ARISING FROM THIS THESIS

Papers

1. Donaldson JW, McKeever TM, Hall IP, Hubbard RB, Fogarty AW. (2014). The UK prevalence of hereditary haemorrhagic telangiectasia and its association with sex, socioeconomic status and region of residence: a population-based study. Thorax 2014;69:161-167

2. Donaldson JW, McKeever TM, Hubbard RB, Hall IP, Fogarty AW. (2015). Complications and mortality associated with hereditary haemorrhagic telangiectasia: A population-based, case-control study. Neurology 2015 (in press).

Conference abstracts

1. Donaldson JW, McKeever TM, Hall IP, Hubbard RB, Fogarty AW. The UK prevalence of hereditary haemorrhagic telangiectasia and its association with sex, socioeconomic status and region of residence: a population-based study. AJRCCM 187;2013:A6117

2. Donaldson JW, Hall IP, Hubbard RB, Fogarty AW, McKeever TM. Peri-procedural complications associated with transcutaneous embolisation for pulmonary arteriovenous malformations: A systematic review and meta-analysis. Hematol Reports 2013: C067

3. Donaldson JW, McKeever TM, Hall IP, Hubbard RB, Fogarty AW. Hereditary haemorrhagic telangiectasia is associated with significant comorbidity and a reduced life expectancy: A prospective controlled study. AJRCCM 2014: A4708

LIST OF FIGURES

Figure 1.1. Diagrammatic representation of a) normal subcutaneous vascular structures and b) a mucocutaneous telangiectatic lesion 2
Figure 1.2. Telangiectasia of a) the tongue and lips, and b) the hands 3
Figure 1.3. Gene interactions in downstream signaling in HHT 9
Figure 2.1. Comparison of THIN population and UK QOF population of males in 2009 with respect to age and gender 23
Figure 2.2. Comparison of THIN population and UK QOF population of females in 2009 with respect to age and gender 23
Figure 3.1. Standardised UK prevalence of HHT by year and sex (2000-2010). 36
Figure 3.2. UK prevalence of HHT by age group in 2010 38
Figure 3.3. Standardised UK prevalence of HHT by Townsend score 40
Figure 3.4. The crude prevalence of hereditary haemorrhagic telangiectasia (per 10,000) by UK health authority area (2000-2010) 41
Figure 3.5. Standardised UK prevalence of HHT/PAVMs by year and sex 43
Figure 3.6. UK prevalence of HHT/PAVMs by age group in 2010 44
Figure 3.7. Standardised UK prevalence of HHT/PAVMs by Townsend score (2000-2010) 46
Figure 5.1. Survival in HHT cases versus controls 75
Figure 5.2 Log-minus-Log plot of survival in HHT cases compared to matched controls 75
Figure 5.3. Histogram detailing age of death in cases with HHT 77
Figure 5.4. Histogram detailing age of death in matched controls without HHT 77
Figure 5.5. Kaplan-Meier plot of survival amongst HHT cases stratified by sex. 78
Figure 5.6. Kaplan-Meier plot of overall survival amongst all HHT cases stratified by Townsend score 78
Figure 5.7. Kaplan-Meier plot of survival amongst HHT cases aged under 60 years at date of diagnosis versus those over 60 years at date of diagnosis. 79

Figure 5.8. Kaplan-Meier plot of survival amongst HHT cases diagnosed pre-2000 versus those diagnosed post-2000. 79
Figure 5.9. Kaplan-Meier plot of survival amongst contemporaneous cases of HHT versus historically diagnosed cases. 80
Figure 6.1. Literature search strategy 89
Figure 6.2. PRISMA flowchart for identifying studies included in meta-analysis 95
Figure 6.3. Proportion of patients evaluated for embolisation diagnosed with HHT 101
Figure 6.4. Proportion of patients evaluated for embolisation with a history of epistaxis 102
Figure 6.5. Proportion of patients evaluated for embolisation with a history of telangiectasia 103
Figure 6.6. Proportion of patients evaluated for embolization with a history of dyspnoea 104
Figure 6.7. Proportion of patients evaluated for embolisation with a history of cyanosis 105
Figure 6.8. Proportion of patients evaluated for mbolization with a history of migraine 106
Figure 6.9. Proportion of patients evaluated for embolisation with a history of clubbing 107
Figure 6.10. Proportion of patients evaluated for embolisation with a history of stroke or transient ischaemic attack 108
Figure 6.11. Proportion of patients evaluated for embolisation with a history of transient ischaemic attack 109
Figure 6.12. Proportion of patients evaluated for embolisation with a history of stroke 110
Figure 6.13. Proportion of patients evaluated for embolisation with a history of haemoptysis 111

Figure 6.14. Proportion of patients evaluated for embolisation with a history of cerebral abscess 112
Figure 6.15. Proportion of patients evaluated for embolisation with a history of seizure 113
Figure 6.16. Proportion of patients evaluated for embolisation with a history of haemothorax..... 114
Figure 6.17. Proportion of embolised patients experiencing pleuritic chest pain/pleurisy 117
Figure 6.18. Proportion of embolised patients experiencing ischaemic chest pain 118
Figure 6.19. Proportion of embolised patients with 'other' complications 119
Figure 6.20. Proportion of embolised patients developing haemoptysis 120
Figure 6.21. Proportion of embolised patients developing pulmonary infarcts 121
Figure 6.22. Proportion of embolised patients with uncatheterisable/unoccludable pulmonary arteriovenous malformations 122
Figure 6.23. Proportion of embolised patients with device embolism..... 123
Figure 6.24. Proportion of embolised patients with device migration..... 124
Figure 6.25. Proportion of embolised patients developing stroke 125
Figure 6.26. Proportion of embolised patients developing arrhythmia 126
Figure 6.27. Proportion of embolised patients developing transient ischaemic attack 127
Figure 6.28. Proportion of embolised patients developing a groin haematoma 128
Figure 6.29. Proportion of embolised patients developing symptoms of air embolism..... 129
Figure 6.30. Proportion of embolised patients developing a venous thromboembolic event..... 130
Figure 6.31. Proportion of embolised patients developing haemopericardium. 131
Figure 6.32. Proportion of embolised patients with ectopic device deposition. 132
Figure 6.33. Proportion of deaths in embolised patients..... 133

Figure 6.34. Proportion of patients experiencing a transient ischaemic attack over long-term follow-up post-embolisation 137
Figure 6.35. Proportion of patients with cerebral abscess diagnosed over long-term follow-up post-embolisation..... 138
Figure 6.36. Proportion of patients experiencing haemoptysis over long-term follow-up post-embolisation 139
Figure 6.37. Proportion of patients developing stroke over long-term follow-up post-embolisation 140
Figure 6.38. Proportion of total deaths over long-term follow-up post-embolisation 141
Figure 6.39. Overall embolisation success rate (by patient)..... 144
Figure 6.40. Overall embolisation success rate (by PAVM)..... 145
Figure 6.41. Embolisation success rate (by PAVM) when coils alone were used 146
Figure 6.42. Embolisation success rate (by PAVM) when follow-up protocol included CT thorax or pulmonary angiography, follow-up exceeded 12 months, and < 20% of patients were lost to follow-up 147
Figure 6.43. Overall recanalisation rate (by PAVM)..... 148
Figure 6.44. Reperfusion rate (by PAVM) 153
Figure 6.45. Recanalisation rate (by PAVM)..... 154
Figure 6.46. Untreated feeder vessel (by PAVM) 155
Figure 6.47. Systemic-to-pulmonary reperfusion (by PAVM)..... 156
Figure 6.48. Pulmonary-to-pulmonary reperfusion (by PAVM)..... 157
Figure 6.49. Recanalisation (by PAVM) 159
Figure 6.50. Untreated feeder vessel (by PAVM) 160
Figure 6.51. Systemic-to-pulmonary reperfusion (by PAVM)..... 161
Figure 6.52. Pulmonary-to-pulmonary reperfusion (by PAVM)..... 162
Figure 7.1. Annual number of percutaneous embolisation procedures performed between 1997 and 2010 in England 176

Figure 7.2. Patient age at first embolisation procedure 177
Figure 7.3. Geographical map by postcode area of patient residence of those undergoing percutaneous embolisation (by number of patients). 178

LIST OF TABLES

Table 1.1. Complications arising in patients with Hereditary haemorrhagic telangiectasia 4
Table 1.2. The Curaçao criteria 6
Table 2.1. THIN population (2009) by Townsend quintile 24
Table 3.1. Summary of prevalence studies of HHT (including data from this thesis) 32
Table 3.2. Prevalent cases of HHT identified between 2000-2010 from the THIN database summarised by Read code 34
Table 3.3. Total prevalent cases of HHT by year (2000-2010) 36
Table 3.4. Prevalent HHT cases by age group and sex in 2010 38
Table 3.5. Crude prevalence rates and prevalence rate ratios of HHT derived from Poisson regression modelling using The Health Improvement Network dataset in 2010 39
Table 3.6. Standardised prevalence of hereditary haemorrhagic telangiectasia by UK health authority area (2000-2010) 42
Table 3.7. Total prevalent cases of HHT/PAVMs by year (2000-2010) 43
Table 3.8. HHT/PAVM cases by age group and sex (2010) 44
Table 3.9. Crude prevalence rates and prevalence rate ratios of HHT/PAVMs derived from Poisson regression modelling using The Health Improvement Network dataset in 2010 45
Table 3.10. Standardised prevalence of HHT/PAVMs by UK health authority area (2000-2010) 47
Table 4.1. Characteristics of cases and controls 60
Table 4.2. Crude and adjusted odds ratios of complications in HHT cases versus controls 61
Table 4.3. Characteristics of cases and controls with contemporaneously diagnosed HHT 63

Table 4.4. Characteristics of cases and controls with historically diagnosed HHT 64
Table 4.5. Crude and adjusted odds ratios of complications in HHT cases with contemporaneously diagnosed HHT versus controls 65
Table 4.6. Crude and adjusted odds ratios of complications in HHT cases with historically diagnosed HHT versus controls 66
Table 4.7. Comparison of our prevalence estimates for complications of HHT with those made in other studies (excluding any that confirmed the presence of pulmonary arteriovenous malformations) 69
Table 5.1. A summary of studies of survival in HHT 82
Table 6.1. Methodological quality assessment scale for case series 92
Table 6.2. Study characteristics of all papers included in the separate meta-analyses 96
Table 6.3. Papers excluded from the meta-analyses due to potential overlap in patient recruitment 98
Table 6.4. Meta-analysis of clinical characteristics of patients with pulmonary arteriovenous malformations considered for embolisation 100
Table 6.5. Meta-analysis of peri-procedural complications of percutaneous embolisation for pulmonary arteriovenous malformations in 19 studies with 974 patients 116
Table 6.6. Sensitivity analysis: peri-procedural complications 134
Table 6.7. Meta-analysis of long-term complications occurring in patients with pulmonary arteriovenous malformations post-embolisation 136
Table 6.8. Meta-analysis of procedural success rate of percutaneous embolisation for pulmonary arteriovenous malformations (by patient and by PAVM) 143
Table 6.9. Sensitivity analysis: procedural success rate 149
Table 6.10 (continued). Sensitivity analysis: procedural success rate 150

Table 6.11. Meta-analysis of causes for reperfusion of previously embolised pulmonary arteriovenous malformations (denominator as total number of embolised PAVMs). 152
Table 6.12. Meta-analysis of causes for reperfusion of previously embolised pulmonary arteriovenous malformations (denominator as total number of reperfused PAVMs)..... 158
Table 6.13. Comparison of prevalences of complications in HHT patients from meta-analysis versus those from case-control study..... 164
Table 6.14. Methodological suggestions for future studies looking at percutaneous embolisation as a treatment for pulmonary arteriovenous malformations 169
Table 7.1. Data extraction domains for inpatient data from HES and for mortality data from ONS. 173
Table 7.2. Codes identified in the health episode statistics database considered pertinent to embolisation of pulmonary arteriovenous malformations and included in the subsequent analysis. 176
Table 7.3. Number of procedures performed stratified by admitting speciality 179
Table 7.4. Number of patients undergoing multiple procedures..... 179
Table 7.5. Mortality data citing cause of death in all patients (coded as PAVM, HHT or both) who underwent an interventional procedure..... 181

ABBREVIATIONS

ALK-1	Activin-like kinase 1
AVM	Arteriovenous malformation
BMP9	Bone morphogenic factor 9
CAVM	Cerebral arteriovenous malformation
CNS	Central nervous system
CI	Confidence interval
CT	Computerised tomography
ENG	Endoglin
GDF2	Growth differentiation factor 2
HES	Health Episodes Statistics
HHT	Hereditary haemorrhagic telangiectasia
HR	Hazard ratio
ICD	International Statistical Classification of Diseases and Health Related Problems
NIHR	National Institute for Health Research
ONS	Office for National Statistics
OPCS	Office of Population, Censuses and Surveys
PAH	Pulmonary arterial hypertension
PAVM	Pulmonary arteriovenous malformation
PCE	Percutaneous embolisation
PDGF-β	Platelet derived growth factor beta
PFO	Patent foramen ovale
PRR	Prevalence rate ratio

QOF	Quality and Outcomes Framework
SD	Standard deviation
SERM	Selective estrogen receptor modifier
TIA	Transient ischaemic attack
TGF-β	Transforming growth factor beta
THIN	The Health Improvement Network
TTCE	Transthoracic contrast echocardiography
VEGF	Vascular endothelial growth factor

CHAPTER 1: INTRODUCTION

1.1 Definitions

1.1.1 Hereditary haemorrhagic telangiectasia

Hereditary haemorrhagic telangiectasia is an autosomal dominant genetic disorder of blood vessel development characterised by epistaxis, the development of mucocutaneous telangiectases and by arteriovenous malformations in solid organs. HHT is also known as Osler-Weber-Rendu disease, named after the three physicians who characterised it at the turn of the 20th Century. Rendu first described HHT as a distinct clinical entity, reporting the case of a man with repeated attacks of epistaxis and multiple superficial angiomas on the face, neck and thorax and noticed the familial link (with affected first degree relatives)[1]. Osler also noted a familial link to epistaxis and the presence of telangiectasia and differentiated the disease from that of haemophilia as haemorrhage did not occur from sites of obvious trauma[2]. Weber was the first to describe in detail the dermatological manifestations of the disease[3]. It was Frederic Hanes, Osler's Chief resident, who in 1909 first proposed the term "hereditary hemorrhagic telangiectasia" as the definitive name for the condition[4].

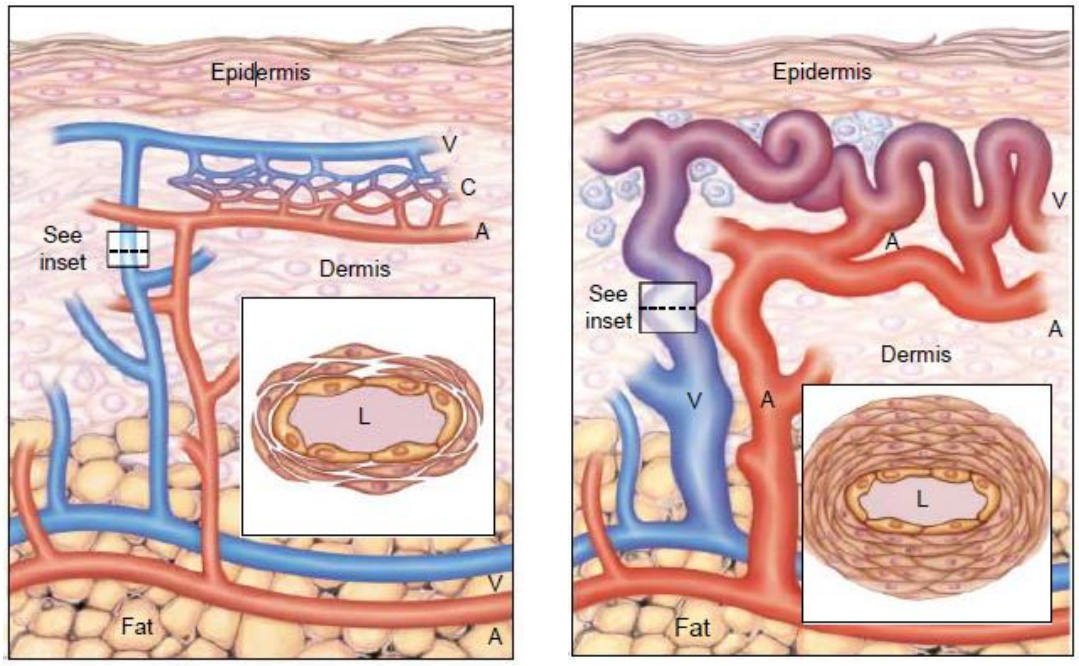
1.1.2 Arteriovenous malformations

The normal vascular structure is altered in AVMs such that an artery or arteriole connects directly to a vein or venule, bypassing the capillary bed and preventing physiological functions such as the exchange of nutrients and wastes and of oxygen and carbon dioxide[5]. AVMs are clusters of dilated feeding arteries/arterioles that collect to a nidus which then connects to a draining vein or system of veins (Figure 1.1). The lesion is termed an "arteriovenous fistula" if there is a connection between a single dilated artery and a single vein[6]. AVMs associated with HHT are found in both the pulmonary and systemic circulations. They arise most commonly in the lungs, liver and brain but have also been documented in the spine[7], kidneys[8] and pancreas[9,10]. AVMs may also be

associated with other inherited vascular disorders such as capillary malformation-AVM and can also be acquired (for example, PAVMs arising as a consequence of liver cirrhosis, thoracic surgery, cardiac surgery for congenital heart disease or infections such as actinomycosis[11]).

Figure 1.1. Diagrammatic representation of a) normal subcutaneous vascular structures and b) a mucocutaneous telangiectatic lesion

a) b)



Reproduced with permission from Guttmacher *et al* NEJM (1995) 333:918-924, Copyright Massachusetts Medical Society.
A=arteriole, C=capillary, L=lumen, V=venule

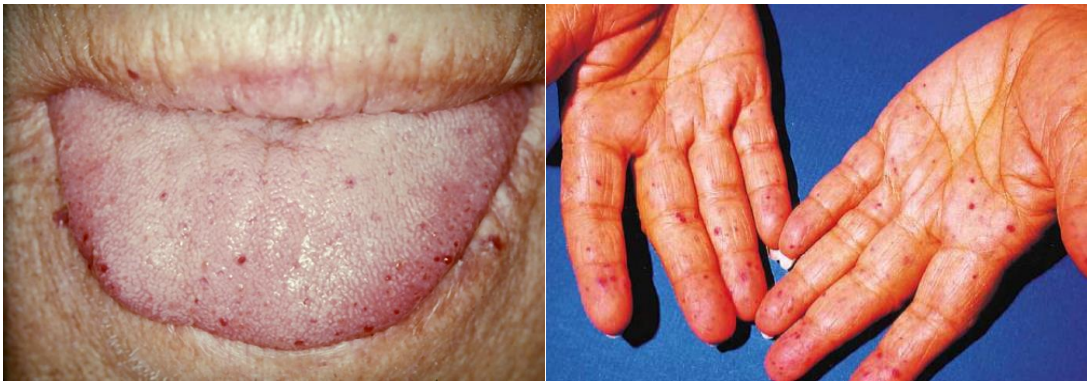
1.1.3 Telangiectasia

Telangiectases are visible dilated blood vessels of the face, lips, nose, tongue oral mucosa and fingers that may also be present in the luminal gastrointestinal system (Figure 1.2). Telangiectases are thought of as small AVMs and are at most a few millimetres in diameter whilst larger AVMs can measure up to several centimetres in size. Telangiectases appear as small pinpoint pink or red lesions which blanche on pressure and immediately refill. They are prone to bleeding

due to the friable nature of the vessel structure and bleeding is often profuse and harder to stem given their direct connection to the arterial circulation[12].

Figure 1.2. Telangiectasia of a) the tongue and lips, and b) the hands

a) b)



Copyright Herbert L. Fred, MD and Hendrik A. van Dijk. Reproduced under Creative Commons licence from Wikipedia. http://en.wikipedia.org/wiki/File:TongueTelang.JPG

Reproduced with permission from Nicoleau and Nicoleau NEJM (1999) 340:1800, Copyright Massachusetts Medical Society.

1.2 Clinical presentation and progression

The location of potential vascular malformations in HHT, together with possible ensuing complications are summarised in Table 1.1. HHT is highly penetrant with variable expressivity[13] and affected individuals are often asymptomatic in early childhood but become increasingly clinically affected throughout life. Data suggest that approximately 71% of cases will exhibit symptoms by the age of 16, with almost 90% showing signs of the disease by age 40 years[14]. The presence, severity and the age of onset of various manifestations can vary significantly even between members of the same family who have the same identified mutation[15].

Table 1.1. Complications arising in patients with Hereditary haemorrhagic telangiectasia

Clinical Manifestation	Frequency (%)	Complications
Telangiectasia	90	Nasal • Spontaneous, recurrent epistaxis • Acute anaemia or chronic iron deficiency anaemia
	80	Other mucocutaneous lesions • Cosmetic issues
Pulmonary AVMs	50	Many asymptomatic Right-to-left shunt 1.2 Dyspnoea / hypoxaemia 2.2 Stroke / TIA 3.2 Brain abscess 4.2 Migraine Haemorrhagic; • Haemoptysis • Haemothorax
Hepatic AVMs	>= 30	Many asymptomatic Hepatic AVMs • Post capillary pulmonary hypertension • High output cardiac failure Hepato-portal VMs • Portal hypertension Porto-venous VMs • Biliary ischaemia
Gastrointestinal telangiectasia	20	Chronic gastrointestinal haemorrhage Iron deficiency anaemia
Cerebral AVMs	10	Intracerebral haemorrhage Headache Seizures
Spinal AVMs	< 1	Space occupying lesion • Pain • Progressive myelopathy Haemorrhage • Spinal stroke

Adapted from Shovlin, Blood Reviews (2010) 24:203-219, Copyright with permission from Elsevier.

Telangiectases

The commonest first symptom in HHT is spontaneous recurrent epistaxis in later childhood, with 50% of individuals reporting nosebleeds before the age of 10 years, rising to 80-90% by the age of 21[12]. Telangiectases are similar in frequency to epistaxis but with an average delay of onset between 5 and 30 years after epistaxis begins (and usually developing around the third decade of

life). Gastrointestinal lesions can be seen endoscopically in 15-30% of those with HHT, but rarely bleed before the age of 30 years[16].

Arteriovenous malformations

Cerebral AVM development occurs during childhood and most lesions that will ever exist have formed early in life. It is estimated that CNS involvement occurs in between 10-23% of those with HHT[17,18]. The annual risk of CAVM rupture and haemorrhagic stroke appears to vary between as low as 0.9% in those with small superficially located lesions with no previous history of rupture, to as high as 34% in those with more deep seated lesions with a past history of rupture[19].

Pulmonary AVM development begins during puberty. The prevalence of PAVMs in a general population (in one study using thoracic CT to screen for possible lung cancer) was noted to be as high as 1 per 2,500[20]. At least 80% of PAVMs diagnosed in a general population are associated with HHT as the underlying cause[21]. The prevalence of HHT-associated PAVMs varies between studies and is related to the mutation identified, being present in between 48-75% of patients with HHT 1 mutations and 5-44% with HHT 2. Transthoracic contrast echocardiography identified right-to-left shunts in 85% and 35% of HHT 1 and HHT 2 patients respectively[22]. Major complications resulting from PAVMs include paradoxical embolic stroke, cerebral abscess, significant hypoxaemia and haemorrhagic consequences[11]. One study noted a gradual cumulative increased incidence of respiratory complications over the course of life, with median onset of cerebral abscess at 31 years and ischaemic stroke at 54[23]. There is evidence that untreated PAVMs can progress in size if left untreated[24].

Hepatic vascular abnormalities were identified in 74% of HHT-affected individuals when the liver was imaged with CT, and 41% when ultrasound was used as the modality of choice, though only a minority (8% of patients from the CT imaged group) were symptomatic[12].

1.3 Diagnosis

HHT is diagnosed clinically on the basis of a set of criteria proposed in 2000, known as the Curaçao criteria[25] (Table 1.2). A diagnosis is considered;

Definite	if 3 or 4 criteria are present,
Possible or suspected	if 2 criteria are present,
Unlikely	if fewer than 2 criteria are present

A recent study looking at the validity of these clinical criteria in first degree family members of HHT mutation carriers found a 100% positive predictive value of a 'definite' diagnosis of HHT and a 97.7% negative predictive value for an 'unlikely' diagnosis[26]. The Curaçao criteria are considered to be particularly useful in two scenarios; firstly, discriminating affected from non-affected older adults and, secondly, for ruling-in the diagnosis in younger adults and children[27].

Table 1.2. The Curaçao criteria

Criteria	Description
1. Epistaxis	Spontaneous, recurrent nosebleeds
2. Telangiectases	Multiple, at characteristic sites; • Lips • Oral cavity • Fingers • Nose
3. Visceral lesions	Such as; • Gastrointestinal telangiectasia (with or without bleeding) • Pulmonary AVM • Hepatic AVM • Cerebral AVM • Spinal AVM
4. Family history	A first degree relative with HHT according to these criteria

HHT can also be diagnosed as a result of genetic testing. Currently, in the UK, genetic testing is not universally offered but is utilised mainly to clarify the specific HHT mutation in an HHT family, allowing diagnosis among relatives

(often children and young adults) who do not meet clinical diagnostic criteria[27]. It has been suggested the addition of genetic testing to the Curaçao criteria (in those patients classified clinically as 'possible' HHT) may improve diagnostic sensitivity[28]. Likewise, the addition of pulmonary shunting (grade 2 or above) on transthoracic contrast echocardiography to the clinical criteria has been shown to slightly increase diagnostic sensitivity from 88% to 90% with no loss of specificity (74%)[29].

Irrespective of the method of diagnosis, most studies recognise that HHT is substantially under-diagnosed[30] for several reasons; it is a relatively rare disease that is little known amongst most primary care practitioners, the diagnosis may be overlooked if HHT-associated symptoms are attributed to a commoner cause, there is no active national screening programme, and some clinical genetics services do not contact-trace potentially affected relatives of a newly diagnosed index case. It is no surprise that the average time-lag between first onset of symptoms and diagnosis is 25 years[31].

1.4 Genetics

Identified mutations

To date five mutations associated with HHT have been identified. Genetic analysis involves targeted DNA sequencing and deletion/duplication analysis of coding exons of candidate genes. HHT 1 is due to a mutation in the ENG gene which codes for the protein endoglin and is present on chromosome 9[32]. HHT 2 is a mutation in the ACVRL1 gene on chromosome 12 which encodes the activin-like kinase 1 protein (ALK-1)[33]. Together, these two mutations account for approximately 80% of all known disease carriers in HHT[34] with ENG mutations (61%) being commoner than those of ACVRL (37%)[35]. Currently, over 375

different mutations have been reported for ACVRL 1 (with at least half being suspected pathogenic) and 470 variants detected in the ENG gene (with almost three-quarters thought to be pathogenic)[36]. All mutations types have been observed in both genes; deletions, insertions, missense, nonsense and splice site. The majority of mutations are unique and specific to the family tested, and most have been reported only once[37]. In addition to the common scenario of familial mutations, there are documented *de novo* mutational events that have resulted in the HHT phenotype in sporadic cases[38]. Mutations of the gene SMAD4 are identified in 1-2% of patients with HHT and are associated with Juvenile Polyposis Syndrome, a condition of multiple intestinal polyps in young people which carries a significantly increased risk of developing colonic carcinoma[39]. Two further HHT loci have been described (HHT 3 on chromosome 5 and HHT4 on chromosome 7) but remain unmapped to known defective genes[40,41]. A recently discovered mutation in BMP9 (also known as GDF2) on chromosome 10 is associated with a vascular-anomaly syndrome which has phenotypic overlap with HHT and is considered to represent HHT type 5[42].

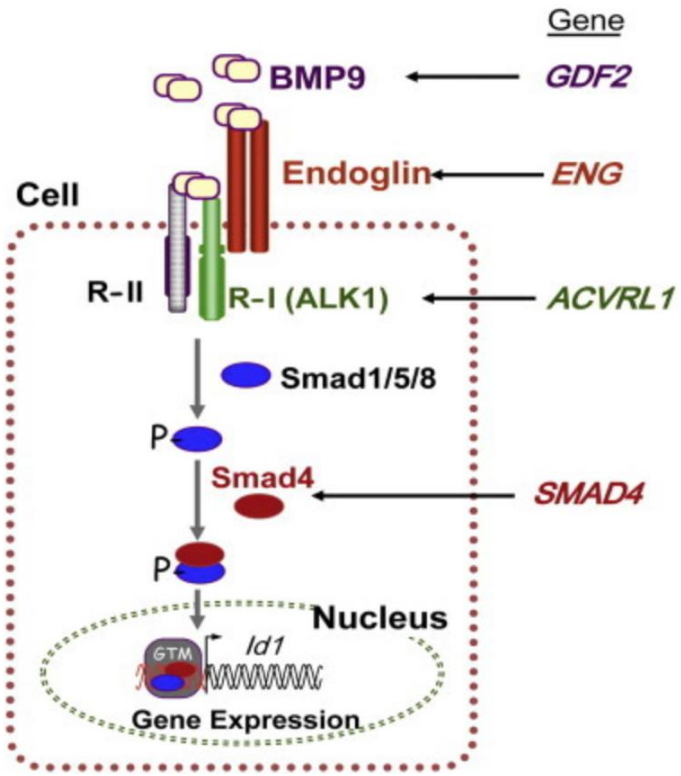
Genotype-phenotype relationship

Some studies have sought to determine whether the gene mutation has any predictive role in the likely clinical manifestations of HHT. It seems that PAVMs and CAVMs are more commonly seen in the HHT 1 phenotype whilst hepatic AVMs occurred with greater frequency in the HHT 2 phenotype[43]. Spinal AVMs were noted, in one study, only in those with HHT 2[44]. All AVM lesions are possible in both types of HHT. Work has sought to identify moderator genes that govern expression of a particular phenotype in an individual HHT patient. A recent study identified one particular gene polymorphism that, when detected, appeared to influence the prevalence of PAVMs in HHT patients[45].

Pathophysiology

The question as to how 'abnormal' genes result in abnormal blood vessel development is key and remains partly elusive. The genes so far identified encode for cell receptor bindings via the TGF-β superfamily and perturbations in this pathway have been suggested to affect the stability of angiogenesis[46]. Both ENG and ALK-1 are predominantly expressed on vascular endothelium (Figure 1.3).

Figure 1.3. Gene interactions in downstream signaling in HHT



Reproduced with permission from Wooderchak-Donohue et al Am J Hum Genet (2013) 93:530-537, Copyright Elsevier
R-I and R-II are type I and type II cell surface receptors, respectively. *Id1* is an intracellular target gene with transcriptional activity regulated by SMAD4. GTM = general transcription machinery. See abbreviations section for clarification of all other abbreviations.

Endoglin is a co-receptor for TGF-β1 and TGF-β3 isoforms, whilst ALK-1 is an alternate type 1 serine-threonine kinase receptor which signals through SMAD1/5[34]. There is a final common signaling pathway in SMAD4. Studies

measuring the functional levels of endoglin and ALK-1 proteins in HHT 1 and HHT 2 mutants respectively support haploinsufficiency as the mechanism for HHT pathology. In this model, mutations in ENG or ACVRL1 genes lead to a significant reduction of functional endoglin and ALK-1 proteins and to dysregulation of the TGF-β signaling pathways as the remaining non-mutated allele is unable to produce sufficient protein for normal function[46]. Homozygosity for either ENG or ACVRL1 is believed to result in either *in utero* or early post-natal lethality[47]. The GDF2 mutation affecting BMP9 also appears to signal though this pathway. It is thought that impaired TGF-β/BMP affects mural cell attachment and vessel stablilisation, leaving HHT vessels more sensitive to angiogenic stimuli. Thus, in addition to the genetic component which predisposes to the formation of focal vascular lesions, it is postulated that an additional vascular stressor is needed to trigger lesion development, given that most blood vessels in an HHT patient are normal in structure and function. Suggestions including local tissue inflammation and vascular endothelial injury (secondary to either hypoxia or haemodynamic changes) have been proposed[34].

Mechanism of action of potential disease modifying therapies

Certain therapies in HHT have been suggested to influence the process of angiogenesis and therefore impact on the development of aberrant blood vessels that are characteristic of the disease. These drug therapies have been used most commonly in the management of epistaxis associated with HHT. Oestrogen (either alone or in combination with progestogens) appears to reduce both epistaxis and gastrointestinal haemorrhage. One postulated mechanism is through induction of mucosal metaplasia by systemic oestrogens resulting in thickened layers of keratinizing squamous epithelium that protect against local vessel trauma[59]. Raloxifene, a SERM, appears to have in vitro effects to stimulate protein and mRNA expression of ENG and ALK1, and the promoter activity of these genes, in cultured endothelial cells. This may counteract the

haploinsufficiency of ENG and ALK1 seen in HHT[60]. Thalidomide has anti-angiogenic properties through promoting expression of PDGF-β in endothelial cells which increases mural cell coverage of HHT vasculature and appears to render the vessels less sensitive to unwanted angiogenic stimuli[67]. Bevacizumab, an anti-VEGF drug initially used in the treatment of cancer, has shown some promise both topically and intravenously in the treatment of epistaxis by blocking TGF-B stimulated VEGF production which promotes neovascularization and potentially vascular haemorrhage[66].

1.5 Screening for arteriovenous malformations

The initial work-up for any patient with suspected or presumed HHT will involve history, physical examination, full blood count (for anaemia) and possible genetic testing if clinically indicated. Given the relative frequency of PAVMs, CAVMs and hepatic AVMs in HHT, interest has developed in the role of screening for each of these lesions in patients with suspected or confirmed HHT. The usefulness of screening depends partly on the risk-benefit balance of therapeutic interventions for any identified AVM lesions, as well as the potential consequences of leaving identified AVMs 'untreated'. International guidelines, published in 2011, suggest strategies for the screening and management of various AVMs and complications arising as a result of HHT[27].

Pulmonary AVMs

A variety of investigations have been used to screen for PAVMs. Some provide anatomical detail to look for lesions suggestive of PAVMs, including chest radiography[48], thoracic CT[49], magnetic resonance imaging[50], magnetic resonance angiography[51] and pulmonary arteriography. Oxygen shunt studies, transthoracic contrast echocardiography (TTCE) and radionucleotide perfusion lung scanning[52] quantify shunt which may be associated with the presence of a PAVM. Most centres now use TTCE and/or thoracic CT as the primary screening

modality. TTCE detects right-to-left shunting of blood bypassing the effective pulmonary circulation. Saline (agitated with air) is injected into a peripheral vein whilst keeping the cardiac atria under direct visualisation with ultrasound. Contrast bubbles appear first in the right atrium and then rapidly dissipate as they are filtered by the pulmonary circulation. In patients with a right-to-left shunt these microbubbles pass through the circulation and are subsequently visualised in the left atrium. The operator counts the number of cardiac cycles that pass before bubbles appear in the left atrium, after their first appearance in the right atrium. A positive study is generally defined as one in which bubbles appear in the left atrium after three cardiac cycles. A positive right-to-left shunt may be associated with a patent foramen ovale (PFO) which must be ruled out before looking for any PAVMs. In one study the sensitivity of TTCE in detecting PAVMs was 97% (95% CI, 93.6-98.3) and negative predictive value 99% (95% CI, 96.9-99.8)[53]. CT imaging involves a radiation burden and many centres will perform TTCE first, moving on to CT if TTCE is positive. CT imaging permits sizing and localisation of any PAVMs which helps determine their suitability for treatment. It has been suggested that shunt grade on TTCE can predict the size of PAVMs subsequently seen on CT, and in those patients with grade 1 shunts (the smallest size) CT may not be necessary as any identified PAVM lesions would be too small for PCE[54]. Current guidelines suggest all patients with possible or confirmed HHT should be screened for the evidence of PAVMs, with further screening intervals determined by whether any PAVMs are identified initially and if any therapeutic intervention is undertaken. Suggested screening intervals are not currently evidence-based and derive mainly from expert recommendations from HHT specialist centres. A recent publication has suggested that in one HHT cohort studied the cumulative effective dose of radiation received (from screening, diagnostic and therapeutic procedures) was in excess of 100 millisieverts in over 10% of the cohort, and that this level of radiation exposure may be associated with significant harms[55]. This has led to

suggestions that future guidelines consider lower radiation dose screening protocols[56].

Cerebral AVMs

Screening for CAVMs is most commonly undertaken using MRI[18], although both CT and cerebral angiography have been utilised. The recent international consensus guidance suggests that patients with possible or definite HHT should undergo screening on one occasion following diagnosis[27], though this is a recommendation with low level evidence supporting it and there is no guidance as to at what age an MRI should be considered. There is no evidence for repeating an MRI scan later in life if the initial scan is negative though some centres offer regular screening with MRI (for example, every 5 years).

Hepatic AVMs

As hepatic AVMs are common, but usually asymptomatic, guidelines suggest screening only in circumstances where liver enzymes are abnormal and/or the clinical picture in a patient with HHT is suggestive of complications of liver AVMs (high output cardiac failure, portal hypertension, jaundice, portosystemic encephalopathy, steal syndrome). Both CT and doppler ultrasound have been used successfully to detect liver AVMs[57,58].

1.6 Treatments

There is currently no cure for HHT. Most treatments available are targeted towards the site of the AVMs or telangiectasia and are designed either to manage complications already arisen or to reduce risk of future significant complications occurring.

Epistaxis and anaemia

Routine therapy for acute epistaxis involves compression and packing of the nose with resorbable materials and bilateral embolisation or surgical ligation of bleeding vessels. Longer-term management is more varied. Preventative strategies involve nasal humidification or emollients in order to prevent drying and crusting of the nasal mucosa. Medical therapies include hormone treatment (with oestrogen[59,60], oestrogen-modifiers[61] and oestrogen antagonists[62,63]), tranexamic acid[64,65], sclerotherapy[66], and antiangiogenic drugs such as bevacizumab[67] and thalidomide[68]. Surgical therapies include bipolar[69] or laser photocoagulation[70,71], endovascular embolisation[72], septodermoplasty[70], or nasal closure (known as Young's procedure)[73]. Anaemia is most commonly as a result of epistaxis, though can be secondary to gastrointestinal blood loss. Iron replacement therapy in the form of oral iron supplements, intravenous iron or intermittent red cell transfusions may be necessary. If blood loss is due to gastric lesions then local endoscopic therapy with plasma argon laser or Nd:YAG laser has been shown to prevent recurrence of gastrointestinal bleeding[74,75].

Pulmonary AVMs

Pulmonary AVMs are associated with an increased risk of both neurological and haemorrhagic complications including haemoptysis, haemothorax, seizures, migraine, cerebral abscess and stroke[76-78] and are managed using an interventional radiological procedure known as percutaneous embolisation (PCE)[79]. A catheter is inserted into the femoral artery which tracks up into the lung to the afferent vessels of the AVM. The AVM is then occluded via the application of any one of the following; a detachable silicon balloon, a platinum coil, a specifically designed vascular occlusion device (the Amplatzer device) or a coagulable glue (named Onyx). In recent years the majority of patients are managed with either coils or the Amplatzer device. PCE can successfully

obliterate lesions as small as 2mm in diameter and appears to reduce the risk of neurological sequelae[80].

Cerebral AVMs

Cerebral AVMs can be detected following a complication such as intracerebral haemorrhage, seizure, headache or onset of focal neurological deficit or may be detected pre-symptomatically both incidentally or by screening. Most centres advocate intervention in eligible patients who have bled secondary to a CAVM as the subsequent rebleed rate is high. However, there is controversy surrounding the management of asymptomatic CAVMs. In addition, there are several potential therapies for CAVMs and no clear evidence for the superiority of one particular treatment. Management options include the conservative approach, microsurgery, stereotactic radiosurgery, microcatheter embolisation or mixed modality treatment. This area of the literature suffers from a lack of prospective studies. A recent systematic review of retrospective observational literature of patients with both ruptured and unruptured CAVMs noted a reduction in case fatality over time but there was no clear superior treatment modality in terms of survival[81]. A recently published randomised multicentre trial of management of unruptured CAVMs was halted early due to an excess of deaths in the intervention arm when compared to the conservatively managed arm, leading some to argue against any intervention for this patient group[82].

Hepatic AVMs

Whilst asymptomatic liver involvement is common, in the minority for whom it becomes clinically significant it can lead to considerable morbidity and mortality. Invasive therapies for liver involvement which include transarterial embolisation of liver AVMs and liver transplantation are high risk procedures and should only be considered when intensive medical management is unsuccessful[83].

1.7 Objectives

1. Determine the prevalence of HHT in the UK and its association with age, sex, socioeconomic status and region of residence.

2. Construct a case-control study using The Health Improvement Network (THIN) database to look at the relative risks of major comorbidities associated with HHT (such as stroke and anaemia) and the overall survival in this population.

3. Undertake a systematic review and meta-analysis of the observational literature for percutaneous embolization looking at the safety and efficacy of embolisation as a treatment for pulmonary arteriovenous malformations.

4. Use the Health Episodes Statistics (HES) database to investigate the mortality rate and incidence of complications associated with percutaneous embolisation in the management of pulmonary AVMs in the UK.

CHAPTER 2: DATABASES AND METHODOLOGY

The research presented in this thesis uses data from three main sources: The Health Improvement Network, Health Episodes Statistics and death certificate data from the Office for National Statistics. This chapter introduces each of these information resources.

2.1 The Health Improvement Network

Computerised records are used by all general practices in the UK, by medical, nursing and administrative staff, to record important patient data for the purposes of improving clinical care, demonstrating clinical activity and allowing financial renumeration and planning. Approximately 98% of the UK population are registered with a general practice[84]. The Heath Improvement Network (THIN) is a UK computerised, longitudinal primary care database which collects anonymised data entered by general practitioners as part of routine clinical care via a computerised software interface. THIN is a joint venture between two companies; In Practice Systems Ltd (INPS) - who developed the Vision software used by general practitioners in the UK to manage patient data - and Cegedim Strategic Data Medical Research UK (formerly known as the Epidemiology and Pharmacology Information Core, or EPIC) who provide access to the data for use in medical research. The THIN database was set up in 2002.

Data is collected on a daily basis and is entered either by physicians following patient's consultations in primary care, or is entered by administrators if derived following correspondence from secondary care. Information collected includes patient demographics, medical diagnoses, prescriptions, investigations and additional health data (such as smoking status and alcohol intake). Financial incentives exist, through the GP contract and the Quality and Outcomes Framework (QOF)[85], to ensure the data is complete and accurate. In addition, CSD Medical Research, the company which runs and administers the database, makes regular checks on practices to ensure quality coding is maintained, with

the option to remove practices from contributing to the database if data is persistently incomplete or inaccurate. Data are recorded from both primary care consultations and secondary care correspondence in the form of Read codes[86] which are specific alphanumeric codes pertaining to various medical diagnoses, investigations and medications.

2.1.1 Structure of THIN data

A THIN data extract is provided in 5 main files; the patient file, medical file, therapy file, additional health data file and the consultation file. Each patient in THIN has a unique identifier which allows data for one individual to be linked across all 5 files.

Patient file

The patient file contains information on patient characteristics and registration details, including a unique patient identifier, year of birth, year of death (if relevant), sex, marital status and registration date at practice.

Medical file

This file contains symptoms, diagnoses and interventions recorded by the GP and primary care team and information transcribed from discharge summaries following hospital stays or from letters sent by secondary care specialists. Hierarchical Read codes cover all terms relating to observations (signs and symptoms), diagnoses, procedures and investigations.

Therapy file

The therapy file records details of prescriptions issued to patients from primary care. It does not necessarily contain information on prescriptions issued from secondary care unless they are to be continued by GPs in the primary care setting. Information recorded includes formulation, strength, dose and quantity prescribed.

Additional health data (AHD)

This is a collection of lifestyle data, preventative healthcare interventions, immunisations, test results and death details. Examples include; smoking status, alcohol intake and levels of exercise frequency. Access to some laboratory investigations is also available.

Consultation data

Information on the date, time, circumstances and duration of any consultations occurring in primary care is recorded in this file.

Other data

Within THIN, categorisation of patients by socioeconomic status is accomplished by assigning a Townsend score[87]. The Townsend score is a material measure of deprivation and disadvantage based on the composite score of four variables;

- Unemployment as a percentage of those aged 16 and over who are economically active.
- Non-car ownership, as a percentage of all households.
- Non-home ownership, as a percentage of all households.
- Household overcrowding.

THIN does not collect individual data on patient address or postcode, but instead, residential areas are divided into Lower Super Output Areas (LSOAs) by postcode with approximately 1500 homes in each. Each area is then linked with a Townsend score for deprivation. We further grouped LSOAs into one of 10 UK Health Authority areas.

The higher the Townsend Index score, the more deprived and disadvantaged an area is thought to be. The overall score is expressed in quintiles with those in quintile 1 considered the most affluent and those in quintile 5 the least affluent.

The advantages of the Townsend score are its relative ease of calculation, close correlation with measures of ill health (such as standardised mortality ratios) and the fact that it can be used to look at relatively small geographical areas. The drawbacks are it appears to be a better indicator of deprivation in urban areas, rather than rural ones, and that some information on which the score relies (such as housing tenure data from the 1991 Census) is now significantly out of date.

2.1.2 Data collection

Once a practice joins THIN an initial full data collection occurs which retrieves all retrospective data from the practice. Following this, incremental data are collected automatically and unobtrusively on a daily basis. THIN processes the data and updates the research dataset every three months. Data collection under the guise of THIN commenced officially in 2003, though many practises had already been using the Vision software when THIN came into being and some have computerised patient records dating back as far as 1985. At the time of data extraction for this thesis (September 2011) THIN covered over 5% of the UK population with 3.6 million people prospectively contributing data across 532 primary care practices[88]. Data presented in this thesis span the time period of 1988 to 2010 (the last complete data year extracted).

2.1.3 Data quality in THIN

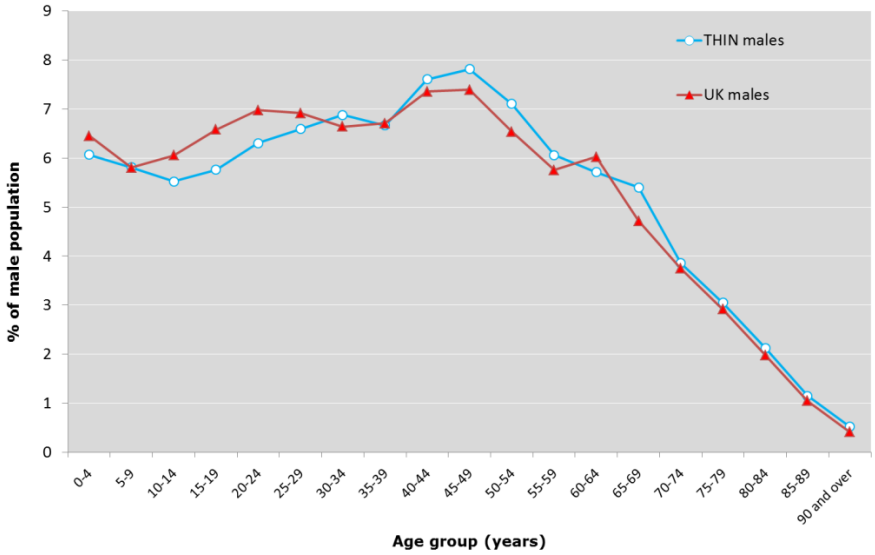
THIN provides training on the use of the Vision software and on how to achieve good quality data recording. Practices receive feedback on the quality and completeness of their coding. Practices that routinely demonstrate poorer coding efficacy and accuracy could potentially be excluded from further contributions to THIN until they can show coding practices have improved. Audit of the THIN database has shown a generally high level of completeness and accuracy of the data[89].

2.1.4 Validity and generalisability of the THIN database

Data validity is defined as the correctness and reasonableness of the data. Data generalisability refers to a broad concern that findings or insights derived from a population database sample apply to the general population. It is more or less synonymous with external validation. Studies have investigated the generalisability of the THIN population by comparing observed population demographics[90], chronic disease prevalences[90-93], prescriptions assigned[94,95] and deprivation and mortality estimates[90] with those derived from the other UK datasets.

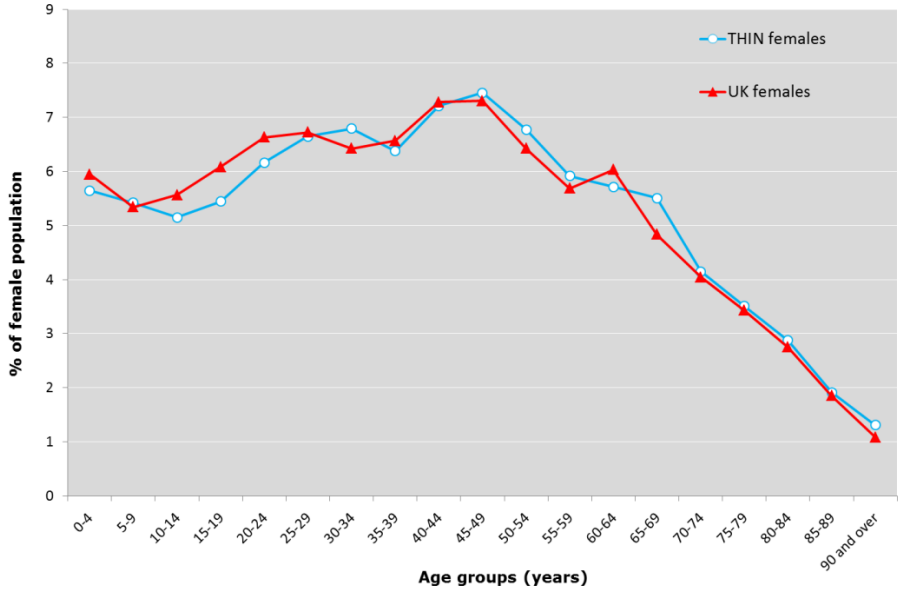
The THIN population and the UK population (derived from the UK QOF database) were similarly distributed across age groups though in THIN there is a slight underrepresentation of those under the age of 25 (of both sexes), and the match between populations slightly less good for males compared with females (Figure 2.1 and Figure 2.2).

Figure 2.1. Comparison of THIN population and UK QOF population of males in 2009 with respect to age and gender



Reproduced with permission from CSD Medical Research UK's THIN Database. CSD MR UK accepts no responsibility for any additional interpretation.

Figure 2.2. Comparison of THIN population and UK QOF population of females in 2009 with respect to age and gender



Reproduced with permission from CSD Medical Research UK's THIN Database. CSD MR UK accepts no responsibility for any additional interpretation.

Although some THIN patients do not have a Townsend score recorded, it appears that there is a slight over-representation of the least deprived quintile in the THIN database, and an under-representation of those from the most deprived quintile (Table 2.1).

Table 2.1. THIN population (2009) by Townsend quintile

Townsend quintile	2009 THIN population (%)
1 = Most affluent	21.9
2	19.8
3	19.5
4	18.3
5 = Least affluent	13.6
Missing a Townsend score	7.0

Data for table derived from[90]

THIN uses the Acceptable Mortality Reporting year (AMR) as a way of identifying practices where mortality reporting is as expected, as over- or under-reporting of mortality may bias disease rates and lead to erroneous denominators. The AMR is defined as the first year that the practice's reported number of deaths was as expected, according to national statistics and the demographic structure of the practice, and remains so until the last data collection. The AMR allows the option to restrict data analysis to the period in which the mortality reporting is considered acceptable (often leading to a loss of data from the 1990's when mortality reporting was less comprehensive).

2.1.5 Strengths and limitations of the THIN database

Strengths

The main strengths of THIN are that it includes an unselected population of patients that appears broadly representative of the UK population as a whole, meaning findings from THIN should be generalisable, less subject to selection bias and have improved validity. The size of the database is an advantage - containing data on over 10.5 million patients, with over 3.6 million actively followed - meaning it can be used to study rare diseases or outcomes such as those seen in HHT. The data are collected prospectively, minimising recall bias, and in a non-interventional way during routine practice in primary care and therefore reflect 'Real Life'. The breadth of information collected in the THIN database, including demographic data, medical diagnoses and conditions, primary care prescribing information, details of hospital admissions and outpatient consultation diagnosis and treatment, and additional health data provide a vast resource of information for academic research.

Limitations

Potential limitations of THIN include possible incompleteness of data. Although the data entered into THIN is used by the GP as the patient's medical record, and therefore information generated by the general practitioner is expected to be complete, information from specialists as well as events that occur in the hospital may not be fully captured in the electronic medical record. The database may not contain data on every patient characteristic or disease characteristic that may be required for a study (information on occupation, employment, and individual socioeconomic status is not always available electronically). Communication from specialists, discharge summaries from hospitals, and test results from pathology laboratories are often received in hard copy and must be manually entered into the computer. Since this can be a time consuming

process, some practices will only enter information that will affect the care of the patient in the future. However, current data is now more likely to be received and recorded electronically so the bias is reduced in more recent data. Minor medical events are more likely to be missed than medically significant diagnoses or events. Information on treatments that are restricted by the National Health Service to specialist care (e.g. cytotoxics or chemotherapy or biologic therapies) may be particularly problematic. Data on non-significant medical events and exposures to medications that occurred prior to enrolment in THIN and are no longer active clinical issues may also not be documented in the electronic medical record, though may be available as 'historical data' if transferred into the current electronic record. Data on important confounding variables (smoking[96], alcohol use[97], body mass index[98]) are not available for all patients, thought this is improving due to data collection initiatives driven by the Quality and Outcomes Framework[99].

2.1.6 Ethical approval

THIN data collection for use in research was approved by the NHS South-East Multi-centre Research Ethics Committee (MREC) in 2008 (See Appendix 4). Under the terms of this ethical approval, studies using pre-collected, anonymised data must undergo scientific review to help ensure appropriate analysis and interpretation of the data. This is overseen by the independent CSD Medical Research Scientific Review Committee (SRC) which provided approval for the analysis of data presented in this thesis in 2011. No data provided to me or any of the researchers involved in this thesis was individually patient identifiable.

2.2 Hospital Episode Statistics

The HES database collects information on all inpatient admissions, outpatient clinics and Accident and Emergency attendances in NHS hospitals in England. This data is collected prospectively, with over 18 million new inpatient records and 40 million new outpatient records added each year. Data is released on a monthly basis following a 6 month time delay (required for data cleaning and processing). Information is entered by trained clinical coding staff working in each hospital and all NHS hospitals are required to participate. The database is managed and administered by the Health and Social Care Information Centre and access to the data is permitted for the purposes of research. Data on hospital admissions is available for every financial year from 1989-1990 onwards and data from outpatient attendances has been collected since 2003. Inpatient data was not considered to be of a suitable standard for use in research until 1997.

Data is coded by spells and episodes. A spell is the complete period of a time a patient is admitted (i.e. from admission to discharge). An episode is the period of time a patient is under the care of a particular named consultant or is under the care of a particular hospital. If a patient is transferred to the care of a different consultant, or moved to a hospital in a different NHS trust, they would have entered a new episode, though still be in the same spell. An inpatient spell or episode ends with either discharge or a death. In the database, there is one row of data for each individual episode. Data is collected in several domains including clinical information, socioeconomic data, patient pathway, maternity data, geographical location and many others. Clinical data is coded using the International Statistical Classification of Diseases and Health Related Problems (ICD-10). Coders can enter one primary diagnosis and up to 20 secondary diagnoses per episode. Procedures undertaken during an episode are coded according to the OPCS Classification of Interventions and Procedures (Version

4.6, April 2011), and include operations, diagnostic procedures, therapeutic procedures and other non-operative treatments (for example, cognitive behavioural therapy).

2.2.1 Strengths and limitations of the HES database

The major strength of the database is its size, the largely prospective nature of data collection and the fact that all NHS trusts, including mental health and community health services are obliged to participate. Most secondary care trusts use HES data to charge for their services and, as such, there is an incentive to ensure complete data collection. It should be underlined that the reason for data collection in HES is not specifically for its value in research. Other weaknesses include the lack of detail of extracted data in certain clinical areas and the fact that data extraction from non-standardised, largely unstructured paper records may lead to under-recording or miscoding of data[100]. There are internal processes at work to ensure coding accuracy and completeness is monitored within HES[101] and the use of HES data has been validated by studies in comparison to other databases[102,103].

2.2.2 Ethical approval

Data from both the HES and ONS databases are available in the public domain and provided in an anonymised fashion. Our first HES-linked ONS extract was requested in 2011 and did not require ethical approval. A subsequent request for additional HES data in 2013, because of its use of only pseudonymised data, was also exempt from NHS REC ethics approval.

2.3 The Office for National Statistics and death certificate data

The Office for National Statistics (ONS) collects information on cause of death from the death certificate, which in the case of registered deaths (the vast majority) is completed either by a doctor or coroner. In part 1 of the death certificate the underlying cause of death is derived from the documented sequence of conditions leading directly to the death. In part 2 any other conditions or comorbidities that the patient had at the time of death, which may or may not have directly contributed to the death, are recorded.

The HES database may contain information on the circumstances under which the patient was admitted (elective, emergency etc.) or discharged (discharged with clinical consent, died etc.) but it cannot, alone, be used to identify the cause of death, nor does it capture deaths that occur outside the hospital. These limitations can be overcome by linking the ONS mortality data described above, through a unique and anonymous identifier, to the HES inpatient or outpatient episodes data[104].

2.3.1 Strengths and limitations of ONS death certificate data

The advantage of ONS mortality data is that death registration is a mandatory process to be undertaken in the UK. This means that missing data is rare. The accuracy of the data, however, cannot be quite so confidently assured. Approximately 22% of registered deaths in England undergo subsequent post-mortem[105], and in these cases, the overall sensitivity of the death certificate for predicting an individual cause of death found at post mortem was only 47% (though varied between 98% in neurological disease to 28% in diseases of the cardiovascular system)[106].

CHAPTER 3: THE PREVALENCE OF HEREDITARY HAEMORRHAGIC TELANGIECTASIA IN THE UK

3.1 Introduction

This chapter will examine the descriptive epidemiology of HHT in the UK. Worldwide, epidemiological studies estimate the prevalence of HHT to be between 1 in 5,000 and 1 in 8,000 (Table 3.1). The only UK estimate of prevalence in 1992 in the 'Northern region' of England calculated a much lower prevalence of 1 in 40,000[107], though this was acknowledged at the time to likely represent a significant underestimate. Population-based epidemiological studies in HHT are the essential first step in understanding and quantifying the burden of disease and informing healthcare planning.

The major limitations of the current literature are the relatively small sample sizes, their inherent selection bias (some studies deliberately conducted in high prevalence areas, in individuals from specific ethnic groups or from selected tertiary centre populations) and concerns over whether findings from overseas studies are generalisable to the UK population.

There are few data regarding differences in geographical prevalence of HHT in the UK or associations with sex, age and socioeconomic status, and this is important as understanding these relations may increase knowledge of factors that modify both development and diagnosis of the disease.

Hence, the aim of this chapter is to determine, using a representative sample of the UK population obtained via an electronic general practice database, a contemporary prevalence of diagnosed HHT and its association with age, sex, geographical location and deprivation status.

Table 3.1. Summary of prevalence studies of HHT (including data from this thesis)

Year of study	Year of estimate	Authors	Study setting and methodology	Study size	Prevalence rate (per 10,000)	Prevalence rate
2014	2010	Donaldson *et al*[108]	UK primary care database	365	1.06	1 per 9,400
2013	2005-2010	Grosse *et al*[109]	US health insurance database	1203	0.3	1 per 33,000
2003	1998	Westermann *et al* [110]	Screening extended pedigree of previously identified cases in Antilles, Netherlands	112	7.51	1 per 1,300
2002	2002	Dakeishi *et al*[111]	Screening extended pedigree of cases referred to tertiary centre in Akita prefecture, Northern Japan	23	1.25	1 per 8,000
1999	1995	Kjeldsen *et al*[112]	Regional patient database, Fyne county, Denmark	73	1.56	1 per 6,400
1995	1994	Guttmacher *et al*[113]	Postal questionnaire of identified cases in Vermont, USA	34	0.61	1 per 16,400
1992	1991	Jessurun *et al*[114]	Study of cases hospitalised to one centre in Leeward Islands, Antilles, Netherlands	32	1.94	1 per 5,200
1992	1990	Porteous *et al*[107]	Postal questionnaire study of cases in Newcastle, "Northern Region", UK	79	0.25	1 per 40,000
1989	1989	Bideau *et al*[115]	Postal questionnaire study of cases identified by physicians in France (52 departments)	406	1.20	1 per 8,300
1984	1983	Plauchu *et al*[116]	Postal questionnaire study of cases identified by physicians in Ain department, France	150	4.25	1 per 2,400

3.2 Methods

3.2.1 Study population

This study utilised an anonymised, computerised, longitudinal general practice database known as The Heath Improvement Network (THIN).

3.2.2 Definition of disease

We identified all recorded diagnoses (by medical Read codes) between the years 2000 and 2010 of Hereditary Haemorrhagic Telangiectasia (G770.00) and Rendu- Osler-Weber Disease (G770.11) available in the THIN database. Given the high prevalence of HHT in individuals with pulmonary AVMs[117] we also searched for Read codes pertinent to pulmonary AVMs (we excluded any individuals previously identified as having Read codes for HHT or Rendu-Osler-Weber disease to prevent double-counting) (see Appendix 1). Population denominator values were derived from the annual mid-year populations contributing to THIN. The results presented in this chapter are for patients coded as Hereditary Haemorrhagic Telangiectasia (G770.00) or Rendu- Osler-Weber Disease (G770.11) only. A repeat analysis of a wider population was conducted which included all the Read codes listed in Table 3.2.

3.2.3 Statistical methods

Data for 2010 (the most recent complete data year) were used to calculate a point prevalence for HHT. We stratified our results by sex, age group (<15 years, 15-49 years and 50+ years), geographical location and socioeconomic status. Geographical location was defined by UK Health Authority areas and socioeconomic status was based on the Townsend index score in quintiles[87]. Given the relatively small numbers available for analysis by health authority in 2010, we used combined data from 2000-2010 to calculate prevalence estimates for HHT between different health authorities in the UK adjusting for the use of repeated measures (see below). We were able to look for any significant

changes in the prevalence of HHT over the 10 year period between 2000 and 2010. Prevalence estimates taken over multiple years were adjusted by direct standardisation to the 2010 THIN population. Random effects modelling (Huber's Method) allowed for the non-independent nature of the cases contributing each year to the overall disease prevalence estimate, adjusting the standard errors of the final model. We used Poisson regression to compare prevalence rate ratios, controlling for year, age, sex, Townsend score and health authority. Statistical tests of significance were performed using the likelihood ratio method unless otherwise stated. All analyses were carried out in Stata SE12 (Stata Statistical Software: Stata/SE12.0 for Windows; Stata Corporation, College Station, Texas, USA).

3.3 Results

We identified a total of 563 individuals diagnosed with HHT/Rendu-Osler-Weber disease in the THIN database from the years 2000–2010 with 365 cases contributing to the calculated point prevalence in 2010. Table 3.2 presents the total number of diagnosed cases identified in 2010 stratified by Read code.

Table 3.2. Prevalent cases of HHT identified between 2000-2010 from the THIN database summarised by Read code

Disease	Read Code	Year (2010)		Years (2000-2010)	
		N	%	N	%
Hereditary haemorrhagic telangiectasia	G770.00	342	86.4	513	83.3
Rendu-Osler-Weber disease	G770.11	23	5.8	50	8.1
Sub total		**365**		**563**	
Arteriovenous fistula of pulmonary vessels	G420.00	17	4.3	34	5.5
Pulmonary arterio-venous malformation	P736.12	5	1.3	9	1.5
Pulmonary arterio-venous fistula	P736.11	6	1.5	6	1.0
Pulmonary arterio-venous aneurysm	P736.00	3	0.8	4	0.7
Total		**396**		**616**	

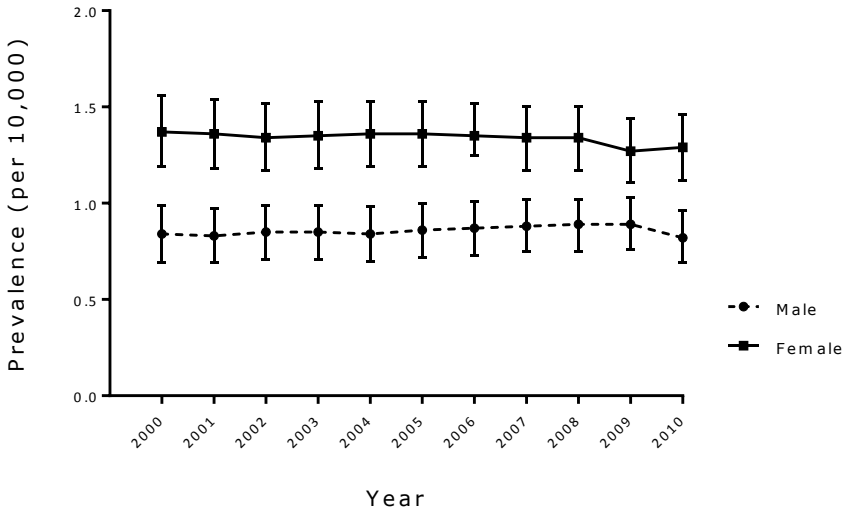
3.3.1 Overall prevalence of HHT

The point prevalence of HHT in 2010 was 1.06 per 10,000 (95% CI: 0.95-1.17) or 1 per 9,400. In the sensitivity analysis using broader diagnostic criteria (combining all Read codes from Table 3.2) the point prevalence in 2010 increased to 1.15 per 10,000 (95% CI: 1.04-1.26) or 1 per 8,700.

3.3.2 Prevalence by sex and year

The prevalence of a diagnosis of HHT was strongly related to sex, with a higher prevalence rate in females compared to males for all years between 2000 and 2010 (Figure 3.1 and Table 3.3). In 2010 the point prevalence in women was 1.29 per 10,000 person years (95% CI: 1.12-1.46) and for men was 0.82 per 10,000 person years (95% CI: 0.69-96). After adjusting for age, deprivation status and geographical location, the prevalence rate ratio (PRR) in 2010 for HHT was higher in women compared with men (PRR 1.59, 95% CI: 1.30-1.94, $p<0.0001$). The prevalence rate for both men and women has remained relatively constant over the last 10 years.

Figure 3.1. Standardised UK prevalence of HHT by year and sex (2000-2010)



Error bars represent 95% CI

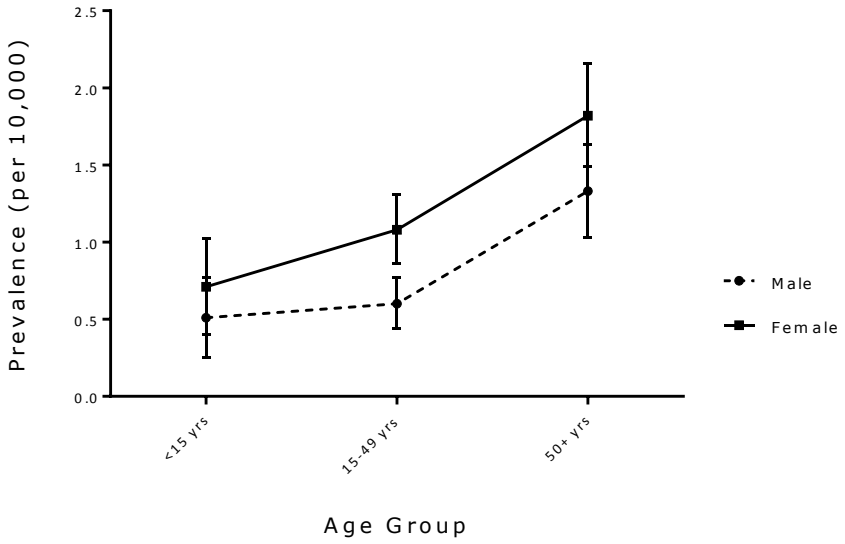
Table 3.3. Total prevalent cases of HHT by year (2000-2010)

Year	Total prevalent cases
2000	336
2001	351
2002	364
2003	374
2004	383
2005	397
2006	399
2007	405
2008	405
2009	394
2010	365

3.3.3 Prevalence by sex and age group

Prevalent cases from 2010 were grouped into 3 different age categories (<15 years, 15-49 years and 50 years and over) and stratified by sex (Figure 3.2 and Table 3.4). The unadjusted prevalence rate in both sexes was lowest in those aged <15 years and highest in the 50+ age group and the adjusted prevalence rate ratios across the age groups differed significantly (p test for trend <0.0001) (Table 3.5).

Figure 3.2. UK prevalence of HHT by age group in 2010



Error bars represent 95% CI

Table 3.4. Prevalent HHT cases by age group and sex in 2010

Age group	Male cases	Female cases
<15	15	20
15-49	51	90
50+	75	114
Total	141	224

Table 3.5. Crude prevalence rates and prevalence rate ratios of HHT derived from Poisson regression modelling using The Health Improvement Network dataset in 2010

	Crude prevalence rates (95% CI) per 10,000 person-years	**Crude prevalence rate ratios (95% CI)**	**Mutually adjusted prevalence rate ratios (95% CI)[a]**
Sex			
Male	0.84 (0.70-0.98)	1.00	1.00
Female	1.28 (1.11-1.44)	1.56 (1.25-1.95)	1.53 (1.24-1.88)
			p=0.0001
Age group (years)			
<15 years	0.61 (1.15-1.77)	1.00	1.00
15-50 years	0.84 (0.71-0.98)	1.39 (0.88-2.19)	1.39 (0.96-2.02)
>50 years	1.58 (1.35-1.81)	2.62 (1.69-4.07)	2.53 (1.76-3.63)
			p<0.0001 p=<0.0001[b]
Townsend Score			
1 (Least deprived)	1.31 (1.07-1.55)	1.93 (1.29-2.89)	1.74 (1.14-2.64)
2	1.05 (0.81-1.29)	1.55 (1.701-2.38)	1.36 (0.88-2.11)
3	1.10 (0.85-1.35)	1.62 (1.03-2.55)	1.50 (0.97-2.31)
4	0.87 (0.63-1.10)	1.28 (0.79-2.08)	1.23 (0.78-1.94)
5 (Most deprived)	0.68 (0.43-0.93)	1.00	1.00
9 (Missing values)	1.34 (0.77-1.91)	1.98 (1.12-3.52)	2.20 (1.25-3.88)
			p=0.026 p=0.60[b]

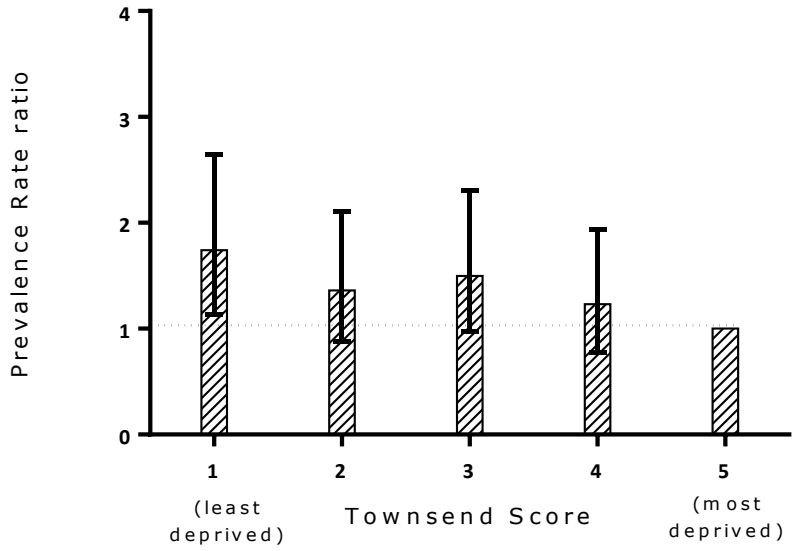
[a]Adjusted for sex, age group, Townsend score and UK health authority

[b]p-trend across categories

3.3.4 Prevalence by deprivation status

The prevalence of HHT was inversely associated with socioeconomic deprivation (Figure 3.3). The crude prevalence rate in the most deprived group (Townsend score: quintile 5) was 0.68 per 10,000 (95% CI: 0.43-0.93) and was 1.31 per 10,000 in the least deprived quintile (95% CI: 1.07-1.55). After adjusting for the effects of age, gender and geographical location, the prevalence rate ratio was higher in those in least deprived socioeconomic group when compared to those in the most deprived group (PRR 1.74, 95% CI: 1.14-2.64, p<0.0001).

Figure 3.3. Standardised UK prevalence of HHT by Townsend score (2000-2010)*



*Adjusted for age and sex

Error bars represent 95% CI

3.3.5 Prevalence by health authority

There was substantial variation in estimates of HHT prevalence across the UK when stratified by health authority over the 10 year period 2000-2010 (Figure 3.4 and Table 3.6). The adjusted prevalence rate ratio varied almost twofold across the different UK health authority boundaries with the lowest adjusted prevalence in the West Midlands and the highest prevalence in the South West (PRR 1.86, 95% CI: 1.61-2.15, p<0.0001, comparing West Midlands and South West regions).

Figure 3.4. The crude prevalence of hereditary haemorrhagic telangiectasia (per 10,000) by UK health authority area (2000-2010)

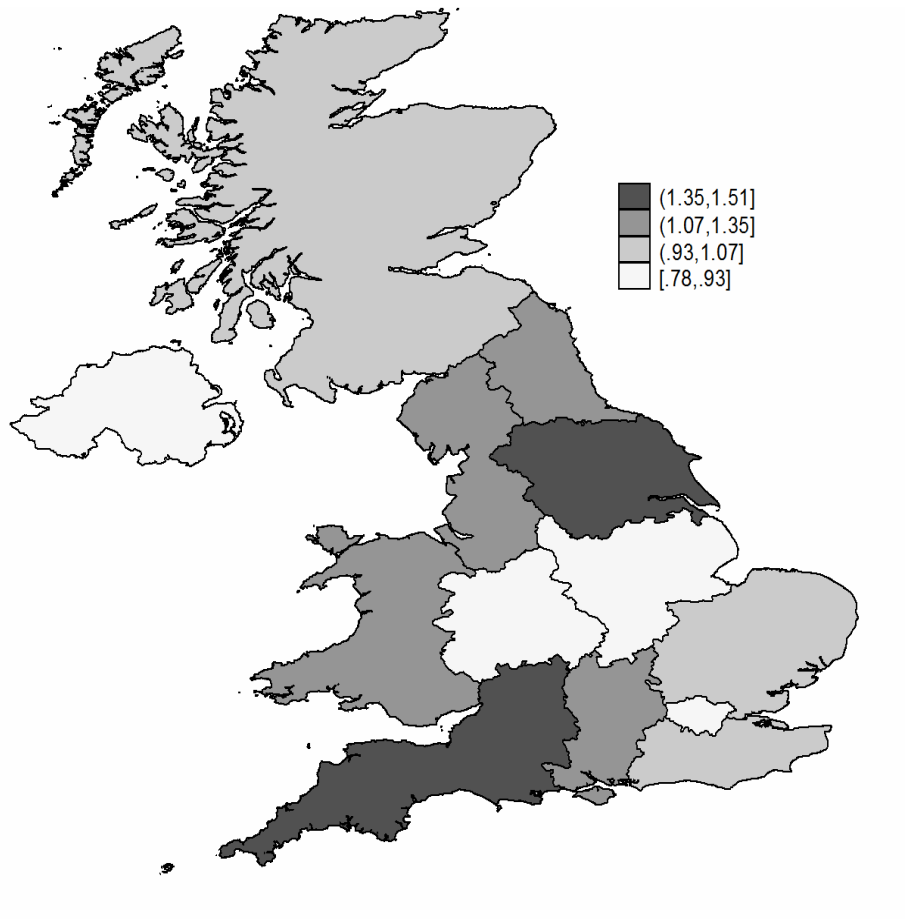


Table 3.6. Standardised prevalence of hereditary haemorrhagic telangiectasia by UK health authority area (2000-2010)

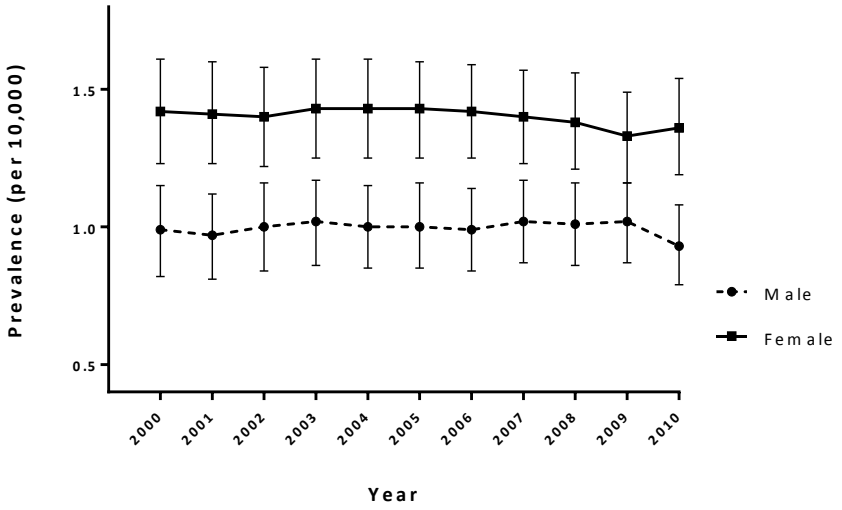
Health Authority	Crude prevalence rates (95% CI) per 10,000 person-years	Crude prevalence rate ratios (95% CI)	Mutually adjusted prevalence rate ratios (95% CI)*
West Midlands	0.78 (0.69-0.88)	1.00	1.00
East Midlands	0.85 (0.71-1.00)	2.08 (1.11-3.90)	1.08 (0.88-1.33)
London	0.78 (0.69-0.87)	0.93 (0.54-1.62)	1.13 (0.95-1.34)
South East Coast	1.02 (0.92-1.13)	1.09 (0.64-1.87)	1.30 (1.11-1.52)
Northern Ireland	0.93 (0.77-1.09)	1.10 (0.53-2.29)	1.30 (1.05-1.61)
East of England	1.07 (0.95-1.18)	1.45 (0.83-2.50)	1.35 (1.15-1.59)
Scotland	1.07 (0.97-1.17)	1.50 (0.92-2.43)	1.45 (1.25-1.69)
North West	1.14 (1.03-1.25)	1.29 (0.77-2.16)	1.48 (1.27-1.72)
South Central	1.23 (1.13-1.33)	1.34 (0.82-2.18)	1.54 (1.33-1.77)
Yorkshire & Humber	1.37 (1.18-1.55)	2.19 (1.15-4.15)	1.76 (1.46-2.11)
Wales	1.35 (1.20-1.51)	1.46 (0.83-2.55)	1.77 (1.50-2.09)
North East	1.35 (1.14-1.55)	1.74 (0.91-3.36)	1.80 (1.48-2.19)
South West	1.51 (1.39-1.63)	2.09 (1.31-3.36)	1.86 (1.61-2.15)
			p<0.0001

*Adjusted for age group, sex and Townsend score

3.3.6 Sensitivity analysis

The above analyses were repeated to include all Read codes listed in Table 3.2, rather than those for HHT and Rendu-Osler-Weber disease alone and revealed no significant differences in the qualitative trends of our results nor significance values for these trends (Figure 3.5, Figure 3.6 and Figure 3.7; Table 3.7, Table 3.8 and Table 3.9). There was a slight change in the prevalence rate ratios calculated for the different health authority areas in the sensitivity analysis, with HHT or PAVMs diagnosed least commonly in London rather than the West Midlands (Table 3.10).

Figure 3.5. Standardised UK prevalence of HHT/PAVMs by year and sex (2000-2010)

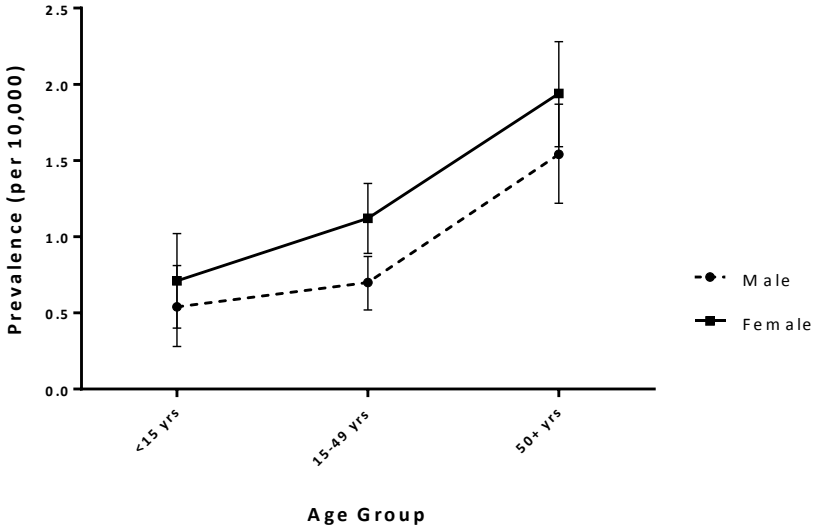


Error bars represent 95% CI

Table 3.7. Total prevalent cases of HHT/PAVMs by year (2000-2010)

Year	Total prevalent cases
2000	363
2001	380
2002	401
2003	418
2004	427
2005	438
2006	436
2007	441
2008	440
2009	429
2010	396

Figure 3.6. UK prevalence of HHT/PAVMs by age group in 2010



Error bars represent 95% CI

Table 3.8. HHT/PAVM cases by age group and sex (2010)

Age group	Male cases	Female cases
<15	16	20
15-49	59	93
50+	87	121
Total	162	234

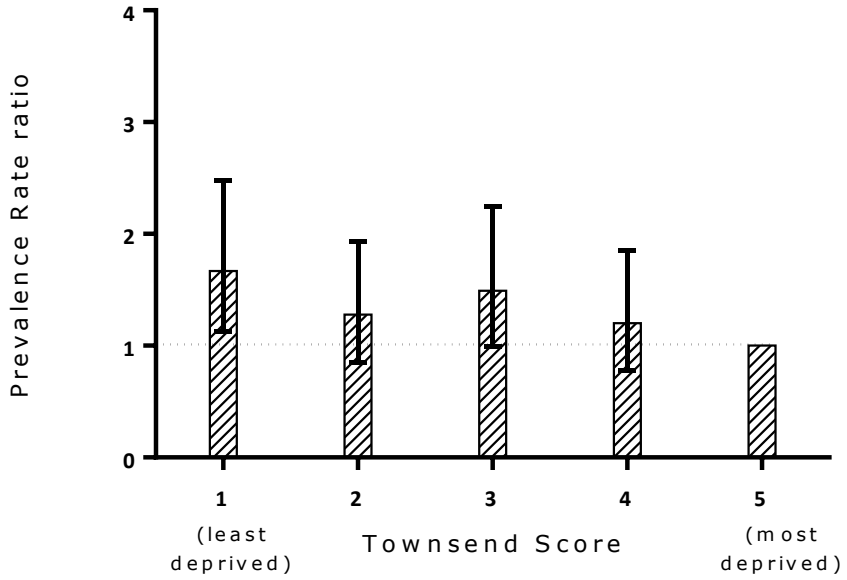
Table 3.9. Crude prevalence rates and prevalence rate ratios of HHT/PAVMs derived from Poisson regression modelling using The Health Improvement Network dataset in 2010

	Crude prevalence rates (95% CI) per 10,000 person-years	**Crude prevalence rate ratios (95% CI)**	**Mutually adjusted prevalence rate ratios (95% CI)[a]**
Sex			
Male	0.96 (0.81-1.11)	1.00	1.00
Female	1.33 (1.16-1.50)	1.42 (1.15-1.76)	1.39 (1.13-1.69)
			p=0.001
Age group (years)			
<15 years	0.63 (0.42-0.83)	1.00	1.00
15-50 years	0.91 (0.76-1.05)	1.45 (0.93-2.27)	1.46 (1.02-2.10)
>50 years	1.74 (1.50-1.98)	2.81 (1.83-4.32)	2.72 (1.91-3.88)
			p<0.0001 p<0.0001[b]
Townsend Score			
1 (Least deprived)	1.41 (1.34-1.49)	1.83 (1.26-2.66)	1.67 (1.13-2.48)
2	1.09 (1.02-1.16)	1.43 (0.96-2.14)	1.28 (0.85-1.93)
3	1.27 (1.18-1.35)	1.59 (1.05-2.42)	1.49 (0.99-2.24)
4	1.23 (1.15-1.32)	1.23 (0.78-1.95)	1.20 (0.78-1.85)
5 (Most deprived)	0.94 (0.85-1.04)	1.00	1.00
9 (Missing values)	1.18 (1.01-1.34)	1.74 (1.00-3.03)	1.94 (1.12-3.36)
			p=0.037 p=0.40[b]

[a]Adjusted for sex, age group, Townsend score and health authority

[b]p-trend across age categories

Figure 3.7. Standardised UK prevalence of HHT/PAVMs by Townsend score (2000-2010)



Prevalence rate ratios adjusted for age and sex

Error bars represent 95% CI

Table 3.10. Standardised prevalence of HHT/PAVMs by UK health authority area (2000-2010)

Health Authority	Crude prevalence rates (95% CI) per 10,000 person-years	Crude prevalence rate ratios (95% CI)	Mutually adjusted prevalence rate ratios (95% CI)*
London	0.89 (0.79-0.98)	1.02 (0.87-1.19)	1.00
West Midlands	0.87 (0.77-0.97)	1.00	1.06 (0.90-1.24)
East Midlands	0.92 (0.77-1.07)	1.06 (0.87-1.29)	1.14 (0.93-1.38)
South East Coast	1.12 (1.01-1.23)	1.30 (1.12-1.50)	1.35 (1.17-1.57)
South Central	1.26 (1.16-1.37)	1.45 (1.27-1.67)	1.46 (1.27-1.68)
East of England	1.21 (1.09-1.34)	1.40 (1.20-1.63)	1.46 (1.25-1.70)
Scotland	1.05 (1.15-1.26)	1.33 (1.15-1.43)	1.52 (1.32-1.75)
North West	1.23 (1.12-1.34)	1.42 (1.23-1.64)	1.53 (1.33-1.77)
Wales	1.43 (1.27-1.59)	1.64 (1.40-1.93)	1.69 (1.44-1.98)
Northern Ireland	1.42 (1.22-1.62)	1.64 (1.37-1.97)	1.76 (1.47-2.10)
North East	1.35 (1.14-1.55)	1.55 (1.28-1.88)	1.87 (1.54-2.26)
Yorkshire & Humber	1.38 (1.58-1.79)	1.82 (1.54-2.16)	2.08 (1.75-2.46)
South West	1.61 (1.48-1.73)	1.85 (1.61-2.12)	2.09 (1.83-2.40)
			p<0.0001

*Adjusted for age, sex and Townsend score

3.4 Discussion

3.4.1 Summary of results

This chapter describes the use of a national primary care population-based database to estimate national prevalence figures for HHT in the UK and to explore age, sex, socioeconomic and regional differences in the diagnosed prevalence of the disease. The 2010 point prevalence for HHT in the UK is 1.06 per 10,000 (or 1 per 9,400) which has remained relatively stable between 2000

and 2010. The prevalence estimate is higher when additional Read codes likely to be associated with HHT are included (1 per 8,700) and is higher still if the prevalence in females is considered to be more representative of the population as a whole (1 per 7,800). The prevalence increases with age. The diagnosed prevalence ratio of HHT was 59% higher in women than in men and 74% higher in those from the least deprived socioeconomic group when compared to those in the most deprived group. There is a substantial geographical variation in the diagnosed prevalence of HHT across the UK.

3.4.2 Strengths and limitations

This is the first population-based study of HHT using a primary care database in the UK. With a total of 365 HHT prevalent cases identified in 2010 our study is almost four times the sample size of the last UK estimate undertaken in 1992[107], is nationally representative and comparable in size with epidemiological studies conducted in other countries[110-112]. We have been able to stratify our prevalence estimates by sex, age group, deprivation status and geographical location without the risk of bias that may occur either from low response rates (as have been observed in previous surveys of HHT prevalence in the UK[107]) or from case-series in specialist centres which may lack a denominator population or represent cases referred for specialist care with potentially more severe disease.

There are potential limitations to the study which should be addressed. The first is that of the validity of the HHT diagnoses, which are recorded by general practitioners in the THIN database whilst the clinical diagnosis is generally made in secondary care. In practice, we are reasonably confident that the vast majority of these diagnoses will be valid with the increasing involvement of clinical geneticists in the screening and diagnosis of HHT which should result in more reliable information being conveyed to the primary care practitioner, and hence entered into the database. It seems very unlikely that a primary care practitioner would enter a diagnosis of HHT into the database unless it was

supported by correspondence from secondary care. That our HHT prevalence estimate is consistent with other estimates from previous studies also supports the reliability of our findings. One further limitation that complicates all studies of HHT prevalence at present is the possibility of undiagnosed asymptomatic or symptomatic cases at large in the community. This may explain the higher prevalence of PAVMs as defined by radiological criteria (and by inference, HHT) in patients who were participating in a recent Japanese CT screening program for lung cancer[20] than we observed in our dataset which did not use this radiological definition of the disease. Diagnosis is often confounded by the heterogeneous clinical presentation of HHT due to its variable genetic penetrance and expressivity[118]. Hence, our prevalence estimates represent those with diagnosed HHT, and are likely to be lower than the true prevalence defined as all individuals with a mutation compatible with the disease. Other studies have also recognised the issue of under-diagnosis in HHT[30]. The fact that our data show the prevalence of the disease has been stable in both sexes over the last decade would suggest that the consistency in coding practice over this period has been maintained.

We used the Townsend score which is a deprivation index based on geographical area as it was not possible to access individual-level deprivation data. This score presumes that individuals within a geographical area have a similar deprivation status which may not be the case. However, there is evidence to suggest that the Townsend scores calculated at a district level are good proxy measures for individual levels of deprivation[119].

3.4.3 Interpretation of results

Reasons for the marked sex difference between the diagnosed prevalence of HHT require careful consideration. One study from the Dutch Antilles showed a 33% increased prevalence ratio of a 'definite' diagnosis of HHT in females compared with males (using the Curacao criteria)[110], and a recent US paper

found a female:male ratio of 1.54, with HHT being diagnosed more commonly in females[109]. Other studies have reported a more balanced distribution between sexes[111,118]. Given HHT is an autosomal dominant disorder, the offspring of affected individuals will have a 50% chance of inheriting a mutation and this should not *per se* be associated with a sex bias. Our data show a significant difference in diagnosis of HHT in women compared with men which appears to be greatest between the ages of 15 and 49. One possible explanation for this observation is that the higher diagnosed prevalence of HHT in females we observed is due to a difference in access to healthcare resources. Women have significantly higher rates of consultation with primary care providers during the ages of 15 to 70 years with many consultations due to issues surrounding contraception, pregnancy and childcare, and this may explain an increased ascertainment of symptomatic females with HHT[120,121]. A possible alternative explanation for the disparity between sexes may be that the expression of the HHT phenotype is more common in females with the gene mutation. Little is known about the role of other genetic factors (such as moderator genes) or environmental factors that may modify the HHT phenotype but there is limited evidence that symptoms such as epistaxis may be amenable to treatment via manipulation of oestrogen and progesterone levels[62]. During pregnancy there is an increased risk of developing complications of HHT[122,123] and it has been suggested that this may represent a modification of the HHT vasculature by female hormones or be secondary to the haemodynamic changes of pregnancy.

An interesting parallel can be drawn with a different disease of the pulmonary vasculature – pulmonary arterial hypertension (PAH). PAH encompasses both idiopathic and heritable forms, and can develop secondary to other systemic diseases or drug/toxin exposure. Nearly all subtypes of PAH show a significant sex bias, being more commonly diagnosed in females, with a female to male ratio of between 1.7:1 and 2.3:1 depending on the disease registry studied[124-

[127].

Though females develop PAH more commonly than males, they have a better survival – this has been termed the 'oestrogen paradox' following investigation into the potential cellular/hormonal mechanisms underpinning this observation[128]. Whilst acutely elevated levels of oestrogen have a protective vasodilatory effect on the pulmonary vasculature, murine models of PAH suggest that more chronic oestrogen exposure activates pulmonary artery smooth muscle proliferation and ultimately increases pulmonary arterial pressure. 17β-oestradiol has been shown to upregulate serotonin signalling which has direct effects on pulmonary vasoconstriction and remodelling, leading to PAH[129]. The paradoxical improvement in survival may to be due to direct protective effects of higher circulating oestrogen levels which appear to improve systolic function of the right ventricle[130]. Whilst the exact role of oestrogens in the pathophysiology of PAH has yet to be conclusively determined, it is interesting to speculate that observations from this PAH cohort may be applicable to development of PAVMs in the HHT population and thus contribute to the sex bias also observed in HHT. Clarifying the relative contribution of behavioural factors (influencing disease ascertainment) versus biological/hormonal influences in the presentation and diagnosis of HHT is an important area for further research.

The reduced prevalence of diagnosed HHT in those from lower socioeconomic groups has multiple potential explanations which encompass controversial issues such as the proximity and quality of healthcare services provided in more deprived areas, as well as differences in individuals' thresholds for accessing these services across different socioeconomic groups. It is internationally recognised that health and healthcare access inequities vary along social gradients[131] and one study looking at health-seeking behaviour in those from more deprived areas with asthma found that these populations reported a higher prevalence of respiratory symptoms but had lower consultation rates for those

symptoms[132]. Explanations such as varying access to health care, differing perceptions of symptom severity or less positive views of health care services were postulated to explain this disparity[132,133]. These issues may also be relevant to patients with HHT and their healthcare-seeking behaviours.

Finally, we observed an almost two-fold difference in diagnosed prevalence throughout the UK; least common in the West Midlands and most common in the South West. A pattern of geographical variability has been seen in in other studies, most notably in the landmark French paper which first identified a particularly high concentration of affected individuals in the Ain, Jura and Deux-Sevres regions of the country[115]. They attributed their findings to a local founder effect where an initial new mutation had given rise to a cluster of affected individuals that then gradually moved by diffusion to involve other nearby regions[134]. It is not possible to say whether our findings could represent genetic clusters of the disease in the UK or if they are the result of variations in local primary or secondary care recording practice or access to healthcare resources. Further work should try to address this as there may be regions of the UK with a disproportionate under-diagnosis of HHT, thus exposing individuals to the avoidable risk of the complications of this disease.

3.4.4 Comparison with existing literature

Table 3.1 provides a summary of the HHT prevalence estimates of different studies conducted worldwide over the last 25 years. Each study has investigated different populations using different methodologies which, in part, explains the differing results. Certain areas such as the Dutch Antilles and the Ain department of France have shown particularly high prevalence of the disease. Elsewhere, most studies indicate a prevalence between 1 and 1.6 per 10,000 (or between 1 per 6,000 and 1 per 10,000) and our study estimate falls within this range, although data from individuals with health insurance in the USA provide estimates as low as 1 per 33,000[109]. Our findings with respect to age are

consistent with previous work with the prevalence of HHT being higher in older age groups, suggesting that the disease has an age-related penetrance[118] or alternatively that the likelihood of diagnosis is related to longevity. No other studies have looked at the prevalence of diagnosis by deprivation status and most studies have been restricted to a small geographical area excepting the epidemiological data from France which also shows a wide variation in prevalence depending on geographical location[115,116,135]. Further research should consider the influence of disease severity on the diagnosed prevalence rate and its potentially confounding effect on our observations with respect to sex, socioeconomic status and geographical location.

3.4.5 Implications

This is the first contemporary study in a representative UK population to estimate the prevalence of HHT and suggests that it is much more common than the previously thought, and similar to the prevalence seen in other countries. Assuming that the prevalence of HHT in males is the same as for females, the "true" estimate of total prevalence would be closer to 1.28 per 10,000 or 1 per 7800 (the figure calculated for females alone). A similar approach extrapolating the "true" prevalence from females living in the South West of the UK (the health authority with the highest crude prevalence of HHT) estimates a prevalence of 1.9 per 10,000 and would equate to at least 11,800 cases of HHT in a population of 62.3 million in 2010[136]. The lower diagnostic rate of HHT in males and those from less affluent social backgrounds suggests a sociological (or alternatively a biological role) in the presentation of HHT, while the previously unreported regional differences is an observation that requires validation in other datasets. Future research would ideally draw on a national rare disease database with integrated clinical information and genetic samples allowing greater understanding of the presentation of the disease, the genotype-

phenotype relationship in HHT and the influences upon it of moderator genes and external environmental factors.

CHAPTER 4: COMPLICATIONS AND COMORBIDITIES ASSOCIATED WITH HHT: A POPULATION-BASED STUDY

4.1 Introduction

Several studies have attempted to quantify the risk of complications associated with HHT. Most complications of the disease are due to the development of AVMs, particularly those in the cerebral and pulmonary circulations. It is estimated that between 1-10% of patients with HHT have cerebral AVMs[17,43,137], and between 15-45% develop pulmonary AVMs[117,138]. Neurological complications of HHT include embolic stroke, cerebral abscess, migraine, haemorrhagic stroke and seizures[17,23,80,139,140]. Haemorrhagic sequelae include epistaxis, haemoptysis, gastrointestinal bleeding and anaemia[23,107,110,141,142].

HHT complications causally related to AVMs are important because if the AVMs can be identified in high risk patients and treated in a safe and timely fashion then significant morbidity and mortality may be avoided. For example, embolization of pulmonary AVMs may be associated with a reduced risk of neurological sequelae[80]. No consensus currently exists as to the optimal management of cerebral AVMs[81,82].

Many studies of HHT-related complications are published from specialist centre cohorts and are potentially susceptible to selection bias as more severe cases may be more likely to be referred for specialist care, possibly leading to an overestimate of the frequency and severity of complications identified. Using a population-based UK primary care database (THIN) we undertook a matched case-control analysis to investigate the association of various complications with a diagnosis of HHT.

In addition to complications directly related to HHT, very few studies have considered the association of common cardiovascular comorbidities and malignancy[143] with the disease. The prevalence of comorbidities associated with HHT should be recognised in this patient group to allow a better understanding of the real burden of HHT and to encourage clinicians to identify potentially

treatable causes of additional morbidity and mortality in this patient group. Thus, in addition to looking at complications directly related to HHT as detailed above, we also looked for associations with common cardiovascular comorbidities and solid organ cancers.

4.2 Methods

The THIN primary care database was used as the data source for analysis (see Chapter 2). Whilst THIN was officially launched in 2003 many practices in the UK were already using computerised software to collect clinical information with some providing prospective data to THIN dating back as far as 1985. At the time of data extraction (September 2011), THIN covered 5% of the UK population with 3.5 million people contributing data across 550 primary care practices[88].

4.2.1 Case-control set

Cases were defined as those with a diagnosis of hereditary haemorrhagic telangiectasia or Rendu-Osler-Weber disease coded in their THIN computerised records between January 1, 1985 and September 1, 2011. THIN collects most data contemporaneously, though in some cases historical data (from consultations prior to the start of a practice contributing prospectively to THIN) are available having been retrospectively added to the database. For the majority of patients an index date was set as the first recorded diagnosis of HHT appearing in their existing records and they were categorised as 'contemporaneous' cases. If a diagnosis of HHT was made prior to a patients' practice contributing to THIN, then the date the practice joined THIN and started to provide longitudinal data was set as the index date (these individuals were categorised as 'historical' cases). Each case had a stop date defined as either the last date of data collection within THIN or the date of death. Up to 10 control

subjects who were alive and contributing data on each case's index date were matched to cases by age, sex and primary care practice.

4.2.2 Data extraction and processing

At the point of each case's index date, data were extracted on age (grouped in 3 categories: less than 15 years, 15-49 years and 50 years and over), sex, socioeconomic status (as defined by Townsend score in quintiles[87], including a category for missing data), geographical location (defined by UK Health Authority), and smoking status (never smoker, ex-smoker, current smoker or unknown status). At any point during the time period that the case contributed data to THIN, we searched for any complications potentially related to HHT (anaemia, cerebral abscess, dyspnoea, epistaxis, gastrointestinal bleeding, haemoptysis, intracerebral haemorrhage, migraine, seizure, stroke and transient ischaemic attack), common cardiovascular comorbidities (ischaemic heart disease, myocardial infarction, cardiac failure and venous thromboembolism) and common solid organ cancers (breast, lung, prostate and bowel). The occurrence of any complication was counted only once for each HHT case or matched control. Tables of Read codes used to identify complications in the THIN database are included in Appendix 2.

4.2.3 Data analysis

Conditional logistic regression was used to quantify the association between a diagnosis of HHT and potential complications in HHT-affected cases compared to control subjects. THIN provided information on smoking status, diabetes and hypertension which were considered as possible confounding variables for some complications. Only smoking status differed significantly between the cases and control groups and as such we adjusted all crude odds ratios solely for smoking status. A sensitivity analysis compared complication rates in the contemporaneous HHT cases versus those from the historical HHT cohort to explore whether this variable had any significant impact on recorded

complications of the disease. Data analysis was carried out using Stata statistical software version 12.0 (Stata Corp, College Station, TX, USA).

4.3 Results

Six hundred and seventy five individuals with a diagnosis of HHT or Rendu-Osler-Weber disease were identified, together with a total of 6696 controls. The mean age of cases was 53.8 years (SD 23.0 years) and 63% were female. Cases had a similar socioeconomic distribution and a lower proportion of never smokers (38.5% vs. 42.4%) when compared with controls (Table 4.1).

Univariate analysis determined that odds ratios for several complications were significantly higher in cases with HHT than in matched controls, including bleeding complications (anaemia: OR 4.42, 95%CI 3.51-5.55; epistaxis: OR 11.6, CI 9.10-14.7; haemoptysis: 2.13, 95%CI 1.23-3.70 and gastrointestinal haemorrhage: OR 6.08, 95%CI 2.75-13.4) and neurological sequelae (cerebral abscess: 30.0, 95%CI 3.12-288; migraine: OR 1.68, 95%CI 1.28-2.20 and ischaemic/embolic stroke: 1.81, 95%CI 1.25-2.66) (Table 4.2). We did not detect a significantly increased odds of seizures, intracerebral haemorrhage, transient ischaemic attack or venous thromboembolism in individuals with HHT. After adjustment for smoking as a confounder, most odds ratios did not change appreciably. The adjusted odds ratio for cardiac failure was higher in those with HHT (OR 2.36, 95%CI 1.52-3.67), though not that of ischaemic heart disease or myocardial infarction. The odds of colon cancer in HHT cases was higher than controls (OR 2.76, 95%CI 1.11-6.85) but there was no detectable difference in rates of other solid organ tumours (Table 4.2).

Table 4.1. Characteristics of cases and controls

	Cases (N=675)		Controls (N=6696)		Odds ratio* (95% CI)
	n	(%)	n	(%)	
Age					
Mean age (years)	53.8 (SD 23.0)		53.9 (SD 22.8)		
Age group					
<15	29	4.3	269	4.0	Matching
15-50	256	38.0	2547	38.0	variable
50+	390	58.0	3880	58.0	
Gender					
Males	249	36.9	2469	36.9	Matching
Females	426	63.1	4227	63.1	variable
Socioeconomic status					
1 (Least deprived)	182	27.0	1899	28.4	Reference
2	134	19.9	1423	21.3	1.00 (0.79-1.28)
3	133	19.7	1250	18.7	1.14 (0.89-1.46)
4	111	16.4	1068	16.0	1.13 (0.86-1.48)
5 (Most deprived)	67	9.9	671	10.0	1.10 (0.79-1.53)
Missing	48	7.1	385	5.75	1.62 (1.03-2.55)
Smoking Status					
Never smoker	260	38.5	2841	42.4	Reference
Ex-smoker	161	23.9	1231	18.4	1.47 (1.19-1.83)
Current smoker	114	16.9	1078	16.1	1.17 (0.92-1.48)
Unknown/Missing	140	20.7	1546	23.1	0.93 (0.72-1.19)
Diabetes					
Never coded as diabetic	619	91.7	6233	93.1	Reference
Ever coded as diabetic	56	8.3	463	6.9	1.24 (0.92-1.67)
Hypertension					
Never coded as hypertensive	531	78.7	5258	78.5	Reference
Ever coded as hypertensive	144	21.3	1438	21.5	0.98 (0.78-1.23)

SD = Standard deviation
*Statistical analysis using conditional logistic regression

Table 4.2. Crude and adjusted odds ratios of complications in HHT cases versus controls

Complications	Cases (N=675) n (%)	Controls (N=6696) n (%)	Crude Odds ratio (95% CI)	P value	Adjusted odds ratios* (95% CI)	P value
Neurological						
Stroke	37 (5.5)	212 (3.2)	1.81 (1.25-2.66)	0.002	1.76 (1.20-2.58)	0.004
TIA	14 (2.1)	92 (1.4)	1.56 (0.87-2.82)	0.146	1.52 (0.84-2.76)	0.167
Intracerebral Haemorrhage	4 (0.6)	20 (0.3)	2.00 (0.68-5.85)	0.21	1.99 (0.68-5.84)	0.21
Cerebral Abscess	3 (0.4)	1 (0.01)	30.0 (3.12-288.4)	0.003	29.3 (3.03-282.8)	0.004
Migraine	71 (10.5)	448 (6.7)	1.68 (1.28-2.20)	<0.001	1.67 (1.29-2.20)	<0.001
Seizure	8 (1.2)	62 (0.9)	1.29 (0.61-2.71)	0.50	1.26 (0.60-2.66)	0.54
Haemorrhagic						
Anaemia	135 (20.0)	401 (6.0)	4.42 (3.51-5.55)	<0.001	4.41 (3.50-5.56)	<0.001
Epistaxis	177 (26.2)	230 (3.4)	11.6 (9.10-14.7)	<0.001	11.4 (8.99-14.5)	<0.001
Gastrointestinal haemorrhage	10 (1.5)	16 (0.2)	6.08 (2.75-13.4)	<0.001	6.13 (2.76-13.6)	<0.001
Haemoptysis	16 (2.4)	77 (1.2)	2.13 (1.23-3.70)	0.007	1.99 (1.14-3.46)	0.015
Cardiovascular comorbidities						
Cardiac Failure	30 (4.4)	141 (2.1)	2.39 (1.53-3.71)	<0.001	2.37 (1.53-3.70)	<0.001
Ischaemic Heart Disease	53 (7.9)	429 (6.4)	1.25 (0.90-1.72)	0.184	1.19 (0.86-1.65)	0.289
Myocardial Infarction	33 (4.9)	217 (3.2)	1.53 (1.03-2.27)	0.034	1.46 (0.98-2.17)	0.06
Venous thromboembolism	18 (2.7)	154 (2.3)	1.18 (0.71-1.94)	0.527	1.12 (0.68-1.86)	0.643
Malignancies						
Lung cancer	5 (0.7)	37 (0.6)	1.36 (0.53-3.49)	0.524	1.20 (0.46-3.08)	0.712
Breast cancer	10 (1.5)	117 (1.8)	0.85 (0.44-1.63)	0.623	0.86 (0.45-1.65)	0.647
Prostate cancer	3 (0.4)	56 (0.8)	0.50 (0.15-1.63)	0.25	0.49 (0.15-1.60)	0.235
Colon cancer	6 (0.9)	22 (0.3)	2.76 (1.11-6.85)	0.029	2.76 (1.10-6.90)	0.03

*Adjusted for smoking status using conditional logistic regression

4.3.1 Sensitivity Analysis

373 cases of HHT had a contemporaneous diagnosis within THIN, with the remaining 302 coded as 'historical' HHT cases. Demographic breakdown of contemporaneous cases (Table 4.3) and historically diagnosed cases (Table 4.4) are presented and show that these two cohorts were similar in age, sex, socioeconomic status and prevalence of smoking, diabetes and hypertension. Odds ratios for complications in HHT were similar between contemporaneously (Table 4.5) and historically diagnosed patients (Table 4.6).

Table 4.3. Characteristics of cases and controls with contemporaneously diagnosed HHT

	Cases (N=373)		Controls (N=3712)		Odds ratio (95% CI)
	n	(%)	n	(%)	
Age					
Mean age (years)	54.8 (SD 23.7)		54.8 (SD 23.6)		
Age group					
<15	22	5.9	220	5.9	Matching
15-50	123	32.7	1220	32.7	variable
50+	230	61.3	2292	61.4	
Gender					
Males	133	35.7	1324	35.7	Matching
Females	240	64.3	2388	64.3	variable
Socioeconomic status					
1 (Least deprived)	106	28.4	1052	28.3	Reference
2	72	19.3	791	21.3	0.92 (0.67-1.27)
3	75	20.1	715	19.3	1.05 (0.76-1.46)
4	75	20.1	605	16.3	1.23 (0.88-1.74)
5 (Most deprived)	25	6.7	367	9.9	0.66 (0.40-1.09)
Missing	20	5.4	182	4.9	1.12 (0.57-2.22)
Smoking Status					
Never smoker	155	41.6	1577	42.5	Reference
Ex-smoker	78	20.9	669	18.0	1.21 (0.90-1.63)
Current smoker	64	17.2	568	15.3	1.15 (0.84-1.58)
Unknown/Missing	76	20.4	898	24.2	0.75 (0.53-1.06)
Diabetes					
Never coded as diabetic	343	92.0	3427	92.3	Reference
Ever coded as diabetic	30	8.0	285	7.7	1.05 (0.70-1.57)
Hypertension					
Never coded as hypertensive	288	77.2	2839	76.5	Reference
Ever coded as hypertensive	85	22.8	873	23.5	0.94 (0.70-1.26)

SD = Standard deviation

Table 4.4. Characteristics of cases and controls with historically diagnosed HHT

	Cases (N=302)		Controls (N=2984)		Odds ratio (95% CI)
	n	(%)	n	(%)	
Age					
Mean age (years)	52.6 (SD 22.0)		52.9 (SD 21.6)		
Age group					
<15	7	2.3	49	1.6	Matching
15-50	135	44.7	1347	45.1	variable
50+	160	53.2	1588	53.0	
Gender					
Males	116	38.4	1145	38.4	Matching
Females	186	61.6	1839	61.6	variable
Socioeconomic status					
1 (Least deprived)	76	25.2	847	28.4	Reference
2	62	20.5	632	21.2	1.11 (0.77-1.60)
3	58	19.2	535	17.9	1.25 (0.86-1.83)
4	36	11.9	463	15.5	0.93 (0.59-1.46)
5 (Most deprived)	42	13.9	304	10.2	1.76 (1.10-2.80)
Missing	28	9.3	203	6.8	2.24 (1.21-4.14)
Smoking Status					
Never smoker	105	34.8	1264	42.4	Reference
Ex-smoker	83	27.5	562	18.8	1.88 (1.37-2.59)
Current smoker	50	16.7	510	17.1	1.20 (0.84-1.73)
Unknown/Missing	64	21.2	648	21.7	1.20 (0.83-1.73)
Diabetes					
Never coded as diabetic	276	91.4	2806	94.0	Reference
Ever coded as diabetic	26	8.6	178	6.0	1.55 (0.99-2.44)
Hypertension					
Never coded as hypertensive	243	80.5	2419	81.1	Reference
Ever coded as hypertensive	59	19.5	565	18.9p	1.05 (0.74-1.48)

SD = Standard deviation

Table 4.5. Crude and adjusted odds ratios of complications in HHT cases with contemporaneously diagnosed HHT versus controls

Complications	Cases (N=675) n (%)	Controls (N=6696) n (%)	Crude Odds ratio (95% CI)	P value	Adjusted odds ratios* (95% CI)	P value
Neurological						
Stroke	21 (5.6)	130 (3.5)	1.69 (1.03-2.77)	0.037	1.70 (1.03-2.80)	0.037
TIA	7 (1.9)	55 (1.5)	1.26 (0.55-2.89)	0.588	1.25 (0.54-2.88)	0.601
Intracerebral haemorrhage	2 (0.5)	11 (0.3)	1.82 (0.4-8.20)	0.437	1.87 (0.41-8.49)	0.417
Cerebral Abscess	1 (0.3)	1 (0.03)	10 (0.63-159.9)	0.103	10.5 (0.65-167.9)	0.097
Migraine	35 (9.4)	236 (6.4)	1.56 (1.06-2.28)	0.022	1.56 (1.07-2.29)	0.022
Seizure	8 (2.1)	33 (0.9)	2.45 (1.12-5.36)	0.025	2.45 (1.12-5.37)	0.025
Haemorrhagic						
Anaemia	82 (22.0)	236 (6.4)	4.71 (3.49-6.35)	<0.001		
Epistaxis	103 (27.6)	128 (3.5)	12.4 (9.0-17.0)	<0.001		
Gastrointestinal haemorrhage	4 (1.1)	9 (0.2)	4.19 (1.28-13.7)	0.02		
Haemoptysis	9 (2.4)	46 (1.2)	2.01 (0.96-4.20)	0.063	1.88 (0.90-3.96)	0.092
Cardiovascular comorbidities						
Cardiac Failure	13 (3.5)	82 (2.2)	1.64 (0.87-3.10)	0.129	1.64 (0.86-3.10)	0.130
Ischaemic Heart Disease	27 (7.2)	264 (7.1)	1.01 (0.65-1.58)	0.953	0.99 (0.63-1.55)	0.967
Myocardial Infarction	18 (4.8)	125 (3.4)	1.49 (0.88-2.52)	0.136	1.44 (0.85-2.46)	0.175
Venous thromboembolism	9 (2.4)	101 (2.7)	0.88 (0.744-1.78)	0.729	0.85 (0.42-1.71)	0.656
Malignancies						
Lung cancer	4 (1.1)	21 (0.6)	1.92 (0.65-5.63)	0.236	1.74 (0.59-5.12)	0.316
Breast cancer	4 (1.1)	75 (2.0)	0.52 (0.19-1.44)	0.211	0.53 (0.19-1.45)	0.647
Prostate cancer	1 (0.3)	31 (0.8)	0.30 (0.04-2.27)	0.246	0.30 (0.04-2.23)	0.239
Colon cancer	4 (1.1)	14 (0.4)	2.91 (0.94-8.97)	0.063	2.88 (0.93-8.96)	0.067

*Adjusted for smoking status

Table 4.6. Crude and adjusted odds ratios of complications in HHT cases with historically diagnosed HHT versus controls

Complications	Cases (N=302) n (%)	Controls (N=2984) n (%)	Crude Odds ratio (95% CI)	P value	Adjusted odds ratios* (95% CI)	P value
Neurological						
Stroke	16 (5.3)	82 (2.6)	2.03 (1.12-3.65)	0.019	1.89 (1.04-3.44)	0.037
TIA	7 (2.3)	37 (1.2)	2.01 (0.85-4.75)	0.110	1.89 (0.79-4.50)	0.151
Intracerebral haemorrhage	2 (0.7)	9 (0.3)	2.22 (0.48-10.3)	0.31	2.22 (0.48-10.3)	0.307
Cerebral Abscess	2 (0.7)	0 (0)	-			
Migraine	36 (12.0)	212 (7.1)	1.82 (1.24-2.67)	0.002	1.82 (1.24-2.67)	0.002
Seizure	0 (0)	29 (1.0)	-			
Haemorrhagic						
Anaemia	53 (17.6)	165 (5.5)	4.04 (2.82-5.77)	<0.001		
Epistaxis	74 (24.5)	102 (3.4)	10.7 (7.44-15.3)	<0.001		
Gastrointestinal haemorrhage	6 (2.0)	7 (0.2)	8.57 (2.88-25.5)	<0.001		
Haemoptysis	7 (2.3)	31 (1.0)	2.30 (1.00-5.29)	0.05	2.20 (0.96-5.07)	0.064
Cardiovascular comorbidities						
Cardiac Failure	17 (5.7)	59 (2.0)	3.66 (1.95-6.88)	<0.001	3.60 (1.90-6.82)	<0.001
Ischaemic Heart Disease	26 (8.6)	165 (5.5)	1.64 (1.01-2.66)	0.044	1.48 (0.90-2.41)	0.120
Myocardial Infarction	15 (5.0)	92 (3.1)	1.59 (0.87-2.88)	0.130	1.45 (0.79-2.66)	0.230
Venous thromboembolism	9 (3.0)	53 (1.8)	1.73 (0.84-3.55)	0.527	1.62 (0.78-3.34)	0.194
Malignancies						
Lung cancer	1 (0.3)	16 (0.5)	0.62 (0.08-4.74)	0.645	0.53 (0.07-4.06)	0.539
Breast cancer	6 (2.0)	42 (1.4)	1.45 (0.60-3.51)	0.404	1.48 (0.61-3.59)	0.381
Prostate cancer	2 (0.7)	25 (0.8)	0.74 (0.16-3.35)	0.699	0.69 (0.15-3.07)	0.622
Colon cancer	2 (0.7)	8 (0.3)	2.50 (0.53-11.8)	0.246	2.45 (0.51-11.7)	0.260

*Adjusted for smoking status
-Unable to calculate OR

4.4 Discussion

4.4.1 Summary

Using a representative primary care dataset comparing HHT cases with matched controls we have quantified the risk of developing HHT-related complications. We have identified several bleeding complications (anaemia, epistaxis, gastrointestinal bleeding) and neurological sequelae (migraine, cerebral abscess and stroke) that are more common in patients with HHT. Cardiac failure is commoner in patients with HHT, as is development of colon cancer.

4.4.2 Complications

We found a higher risk of bleeding (anaemia, epistaxis, haemoptysis and gastrointestinal haemorrhage) and neurological complications (cerebral abscess, stroke and migraine) in HHT cases. A recent study using US health insurance data for surveillance of HHT and its complications found the disease to be under-recognised in this database[109]. We suggest this is partly due to the relatively high costs of US health insurance, meaning individuals unable to afford health insurance are likely to be under-represented in the dataset. The UK National Health Service has a much wider coverage, with close to 98% of the population registered with a general practitioner[84]. Most published work looking at complications in the disease are descriptive analyses in cohorts often recruited from specialist HHT centres. On comparing the prevalences of clinical complications, most of our estimates are lower than those cited in the existing literature (Table 4.7). This may be a consequence of the ascertainment of complications being lower in a primary care database than in a clinical study with access to detailed clinical data that is collected in secondary and tertiary medical care centres. Alternatively, previous studies may have overestimated the prevalences of complications due to a referral and selection bias if more complicated or severe cases are seen in the specialist centres from which the cohort is derived. It is widely acknowledged that many cases of HHT in the

general population remain undiagnosed. Whilst some symptomatic patients presenting to healthcare services elude diagnosis because clinicians do not have a sufficiently high index of suspicion for HHT, there are likely to be other HHT gene carriers who remain undiagnosed simply because they display a milder phenotype of the disease.

We noted a higher odds of colonic carcinoma in our HHT cases (in approximately 1%) which may be a true association or alternatively be the consequence of mis-classification with juvenile polyposis syndrome (JPS), a disease known to be associated with the HHT phenotype via a shared mutation in the SMAD4 gene[35,144]. JPS is associated with up to a 40% increased risk of colon cancer[145], and this may explain the increase in bowel cancer risk we observed.

Overall, our data from a population-based sample of HHT patients suggest that the risks of complications of HHT may not be as high as have been suggested by previous studies. Future work could help validate our findings further by accessing the primary and secondary care records of the individuals in the THIN database included in this study, although previous audit has shown a relatively high level of completeness of clinical diagnostic data[89].

Table 4.7. Comparison of our prevalence estimates for complications of HHT with those made in other studies (excluding any that confirmed the presence of pulmonary arteriovenous malformations)

Complications	Our prevalence estimate (%)	Range of prevalence estimates from other literature (%)	References
Anaemia	20	29	[141]
Cerebral Abscess	0.4	0.03-9.1	[80,139,146-148]
Epistaxis	26.2	90-99	[107,141,142]
Gastrointestinal bleeding	1.5	13-30	[107,149]
Intracerebral bleed	0.6	2.1	[17]
Migraine	10.5	33-40	[150,151]
Stroke	5.5	7.2-9	[80,140,152]
TIA	2.1	4.1	[152]

4.4.3 Strengths and limitations

The strengths of this study are the combination of a relatively large number of participants (containing data from almost 700 patients with HHT) and the long period of follow up - in excess of 20 years for some - which would be more difficult to achieve in a prospectively designed clinical study. Our findings are population-based and hence provide representative estimates for complications, minimising certain biases that can arise as a consequence of case-series analysis from specialist centres. The case-control design allows comparative estimates of relative risk to be made against a matched control group providing new data in addition to that generated by previous studies which used mainly descriptive analyses of complication frequencies in HHT-only cohorts.

The potential limitations of this study require consideration. We were only able to study individuals clinically diagnosed with HHT. However, we expect a diagnosis of HHT recorded in THIN to have a relatively high specificity as most diagnoses are made in secondary care and we consider it unlikely that a primary care physician would code a patient as having HHT unless supported by evidence

from a specialist centre. We did not detect an increased risk of certain complications (such as intracerebral haemorrhage) which are well documented possible sequelae of HHT[17]. This may reflect issues of ascertainment inherent in primary care databases resulting from the miscoding of complications (for example coding intracerebral haemorrhage as stroke).

4.5 Conclusion

In conclusion, we present evidence from a large, representative primary care database providing quantitative estimates of complication risks in HHT compared to matched controls. Whilst some patients undoubtedly suffer significant morbidity due to HHT, our study suggests complication rates amongst the diagnosed population may not be as high as previously thought. This may impact on the information given in the counselling of newly diagnosed patients when discussing the natural history of the disease. As many of these complications are amenable to intervention, early diagnosis and treatment should remain the priority for responsible clinicians.

CHAPTER 5: MORTALITY IN PATIENTS WITH HHT: A CASE-CONTROL STUDY

5.1 Introduction

There are relatively few published studies that have looked at survival in patients with HHT[112,153-155]. The largest published epidemiological study includes 113 individuals and thus provides survival estimates limited by sample size[155]. The limited published literature suggests a diagnosis of HHT is associated with a reduction in life expectancy, and some of this reduced life expectancy may be as a result of complications related to the disease itself. Studies have not so far considered the association between age at diagnosis, sex, geographical area of residence nor socioeconomic status on survival of patients recorded with a diagnosis of HHT. This data may potentially be of use in identifying patients, via their demographic characteristics, who may be at a higher risk of death, either from the complications of HHT or related medical disease. Using the THIN database (see Chapter 2) we undertook a matched case-control analysis to provide a population-based estimate of survival in 675 HHT individuals compared to age, sex and general practice-matched controls.

5.2 Methods

Data were extracted from the THIN database in September 2011. The methodology used was similar to that detailed in Chapter 4, with the same definition of contemporaneous and historical cases, and of index and stop dates. Up to 10 control subjects who were alive and contributing data on each case's index date were matched to cases by age, sex and primary care practice. This study used a later data extract (obtained in September 2012) from that presented in chapter 3 (extract from September 2011) and as such includes a slightly different number of HHT cases within its analysis.

5.2.1 Data extraction and processing

Data were extracted on age (grouped in 3 categories: less than 15 years, 15-49 years and 50 years and over), sex, socioeconomic status (as defined by Townsend score in quintiles[87], including a category for missing data), geographical location (defined by UK Health Authority) and smoking status (never smoker, ex-smoker, current smoker or unknown status). Date of death was extracted for any case or control that died whilst contributing data to THIN.

5.2.2 Data analysis

Survival analysis was performed using Kaplan-Meier methods, comparing HHT cases with controls. Start date was set as the index date (see definition in chapter 4) and end date was date of death or loss to follow-up. Cox regression analysis was used to compare mortality rates between the two groups adjusting for smoking status. Rates of ischaemic heart disease, diabetes and hypertension did not differ substantially between the cases and the control group and thus were not adjusted for in the mortality analyses (see Table 4.1, Chapter 4). We looked at survival differences stratified by sex and socioeconomic group amongst the HHT cases and also explored survival of cases diagnosed at age under 60 years versus those 60+ years at the time of inclusion to the database as a previous study had reported a survival paradox with a subset of younger HHT patients having a higher mortality[112]. The Cox proportional hazards assumption was tested using log-minus-log plots of survival and Schoenfeld residuals (Appendix 5). A sensitivity analysis was undertaken to look at survival outcomes in the contemporaneous HHT cases and the historical HHT cases. Data analysis was carried out using Stata statistical software version 12.0 (Stata Corp, College Station, TX, USA).

5.3 Results

Six hundred and seventy five individuals with a diagnosis of HHT or Rendu-Osler-Weber disease were identified, together with a total of 6696 controls, matched by age, sex and general practice. The demographic details of cases and controls are the same as those listed in Table 4.1, Chapter 4.

5.3.1 Survival analysis

The median follow up time was 6.9 years for cases, 10.1 years for controls, 6.5 years for 'historical cases' and 8.2 years for 'contemporaneous cases'. A total of 73 cases with HHT (10.8%) and 486 controls (7.3%) died. The overall crude mortality rate in HHT cases was 11.0 per 1000 patient-years (95% CI 8.8-13.9) and in their matched controls was 6.1 per 1000 patient-years (95% CI 5.5-6.6). We found a worse survival in patients with HHT compared to their age, sex and practice-matched controls with a hazard ratio for death of 2.03 (CI 1.59-2.60, $p<0.0001$) (**Error! Reference source not found.**). The proportional hazards assumption did not hold true for these data (Figure 5.2) and thus the adjusted hazard ratios were split into three time periods of follow-up demonstrating a higher hazard ratio for mortality in the time period closest to a recorded diagnosis of HHT which persisted, but tailed off, at all time periods; 0-3 years (HR 4.57, CI 2.56-8.18, $p<0.001$), 3-10 years (HR 2.07, CI 1.42-2.99, $p<0.001$) and 10 or more years (HR 1.45, CI 0.95-2.21, $p<0.001$).

Figure 5.1. Survival in HHT cases versus controls

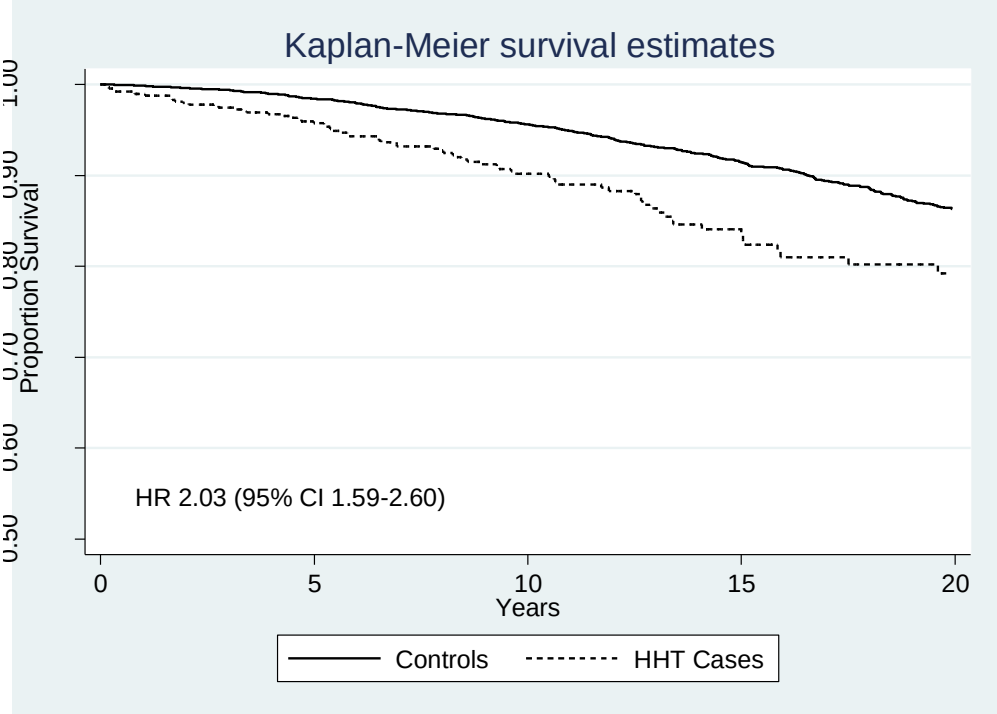
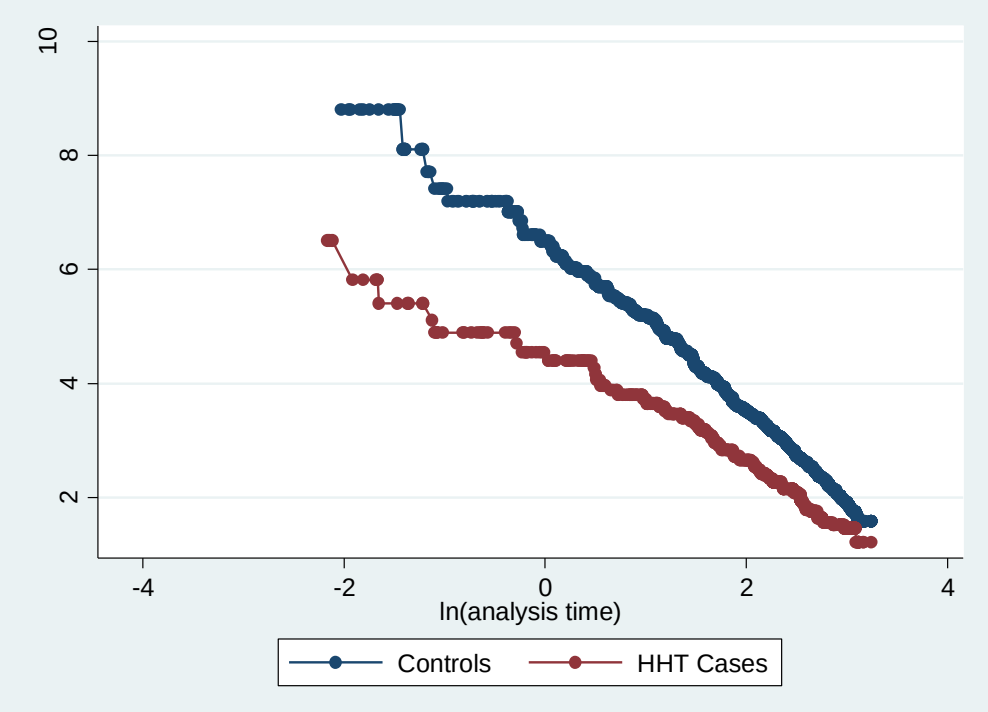


Figure 5.2 Log-minus-Log plot of survival in HHT cases compared to matched controls



Age at death was plotted using a histogram for cases with HHT (Figure 5.3) and their matched controls (Figure 5.4) and both showed a negatively skewed distribution. Median age at death was 77 years for HHT cases (Interquartile range (IQR) 67-85 years) and 80 years for controls (IQR 74-87 years). Survival in HHT cases did not differ between males and females (HR 1.06, CI 0.66-1.70, p=0.825) (Figure 5.5) but was higher in those from the most affluent socioeconomic group when compared to the least (HR 1.15, CI 1.04-1.27, p=0.007) (Figure 5.6). After stratification by age, mortality was increased for both those aged 60+ years on entry to the study (i.e. at the index date) (HR 1.60, CI 1.17-2.21, p=0.004) and for those under 60 years compared to matched controls (HR 6.74, CI 4.2-10.8, p<0.0001). Survival differed between cases aged <60 years at diagnosis when compared to cases aged 60+ years on diagnosis (HR 2.93, CI 1.80-4.75, p<0.0001) and was higher in the latter group (Figure 5.7). Cases diagnosed between the years 1990-1999 (labelled pre-2000) did not have a significantly different survival to those cases diagnosed between 2000-2010 (labelled post-2000) (HR 1.28, CI 0.72-2.28, p=0.41) (Figure 5.8).

Figure 5.3. Histogram detailing age of death in cases with HHT

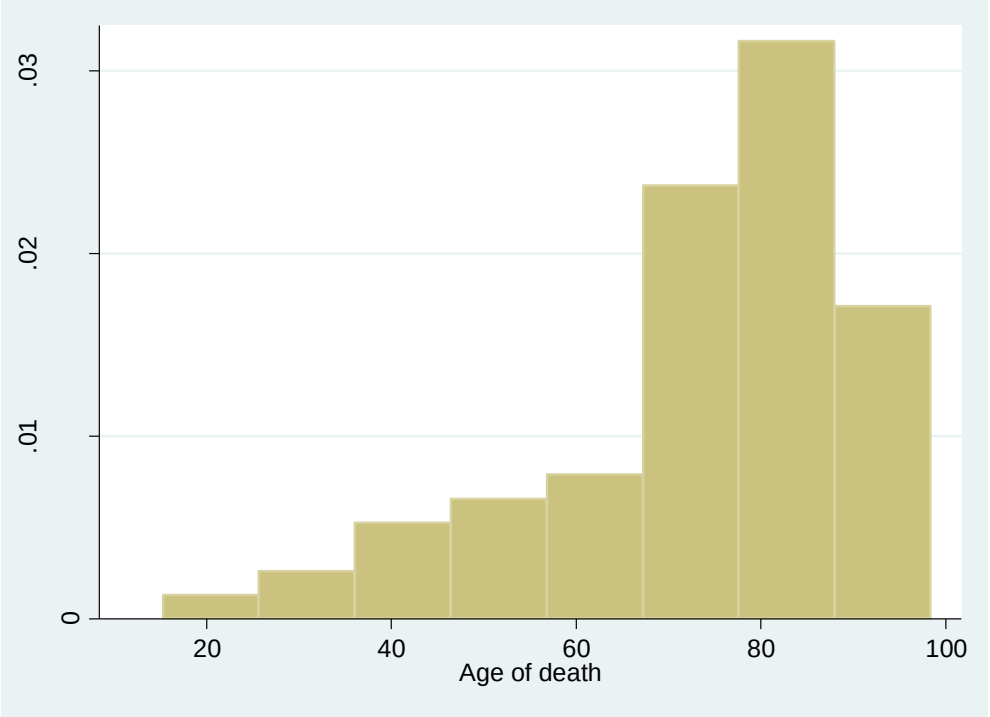


Figure 5.4. Histogram detailing age of death in matched controls without HHT

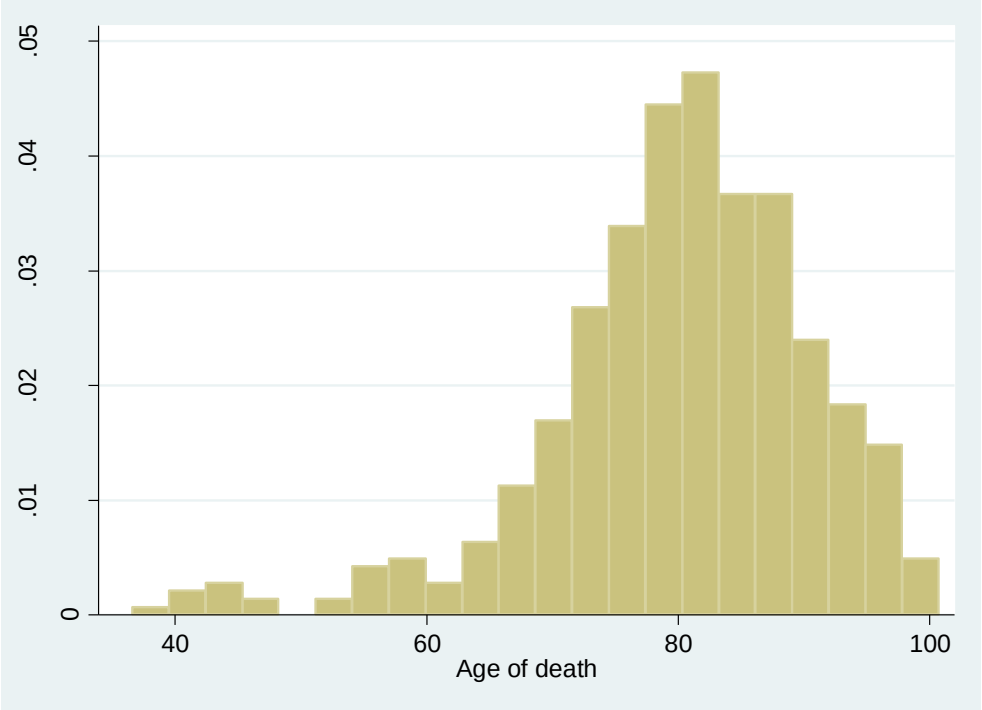


Figure 5.5. Kaplan-Meier plot of survival amongst HHT cases stratified by sex

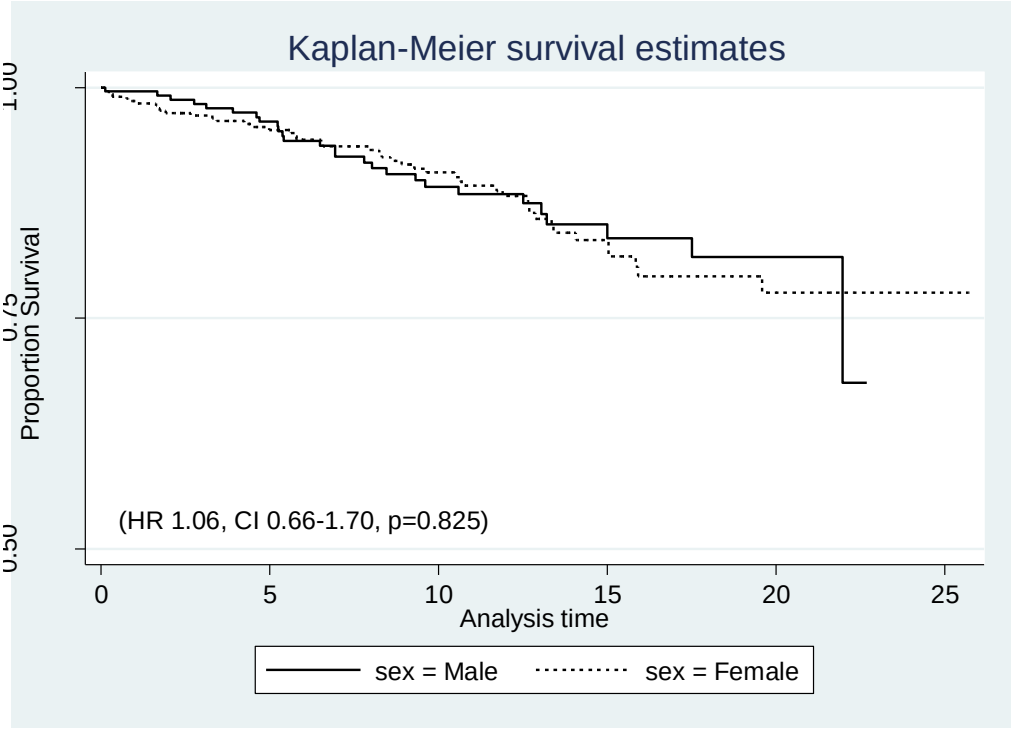
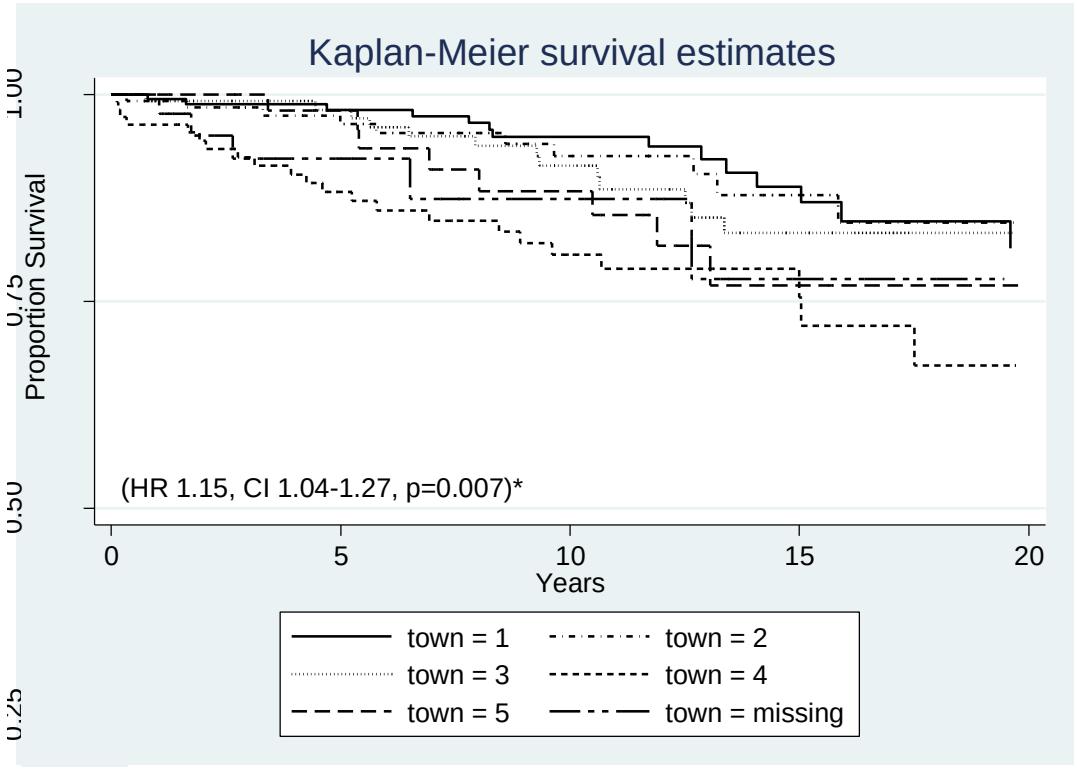


Figure 5.6. Kaplan-Meier plot of overall survival amongst all HHT cases stratified by Townsend score



*HR comparing survival between highest and lowest socioeconomic groups (Townsend 1 versus 5)

Figure 5.7. Kaplan-Meier plot of survival amongst HHT cases aged under 60 years at date of diagnosis versus those over 60 years at date of diagnosis.

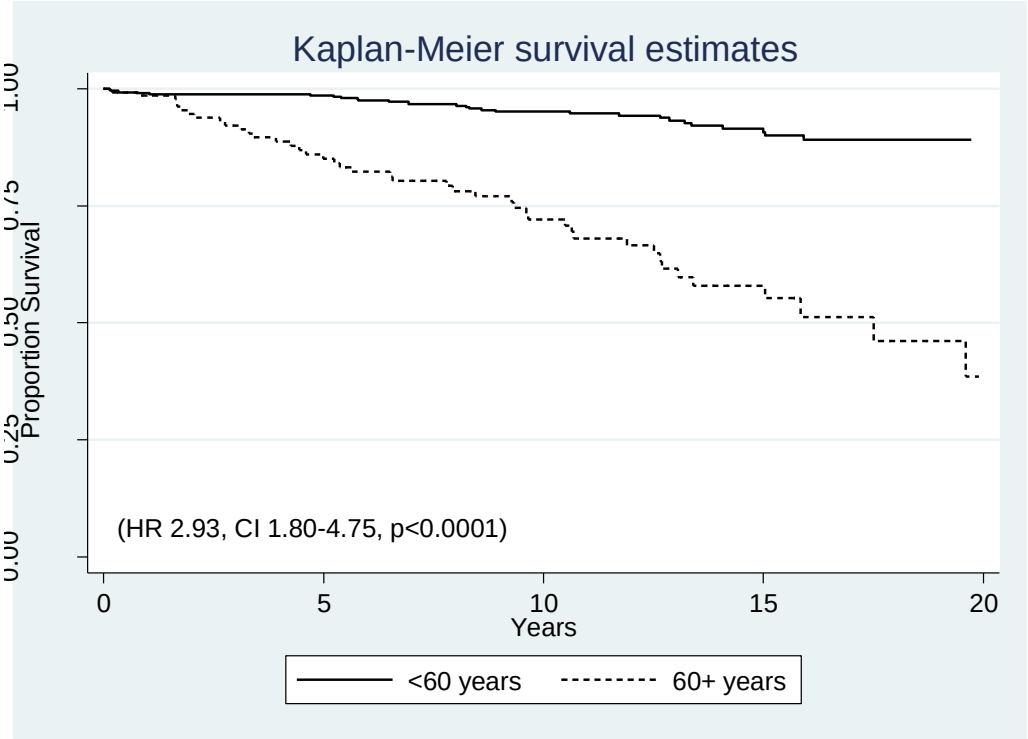
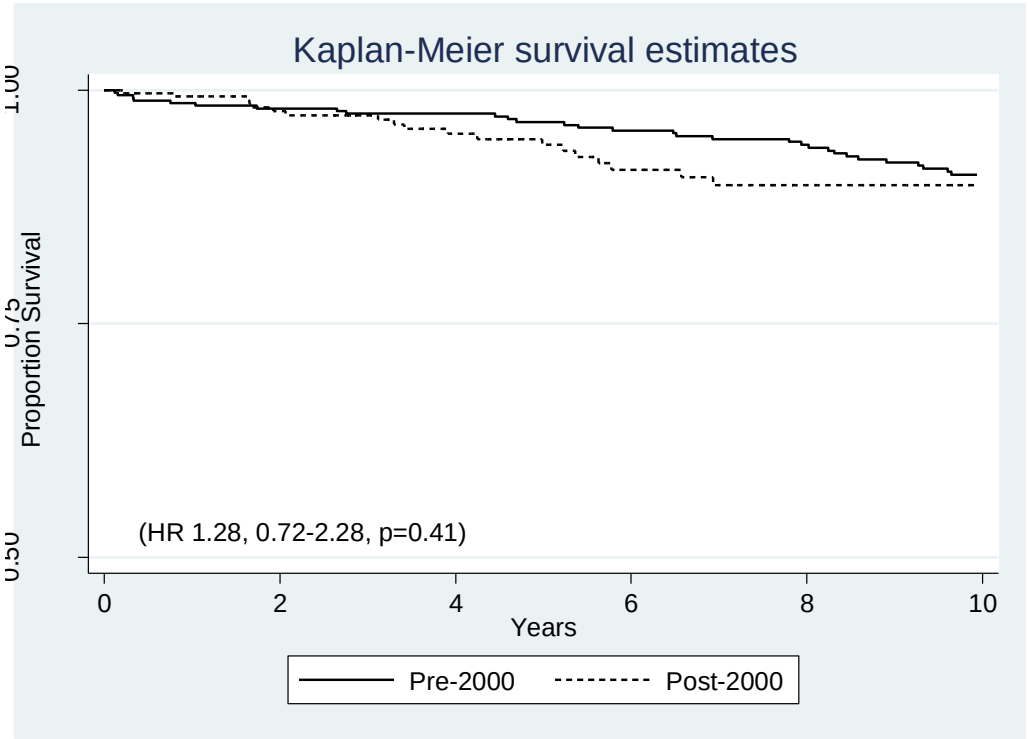


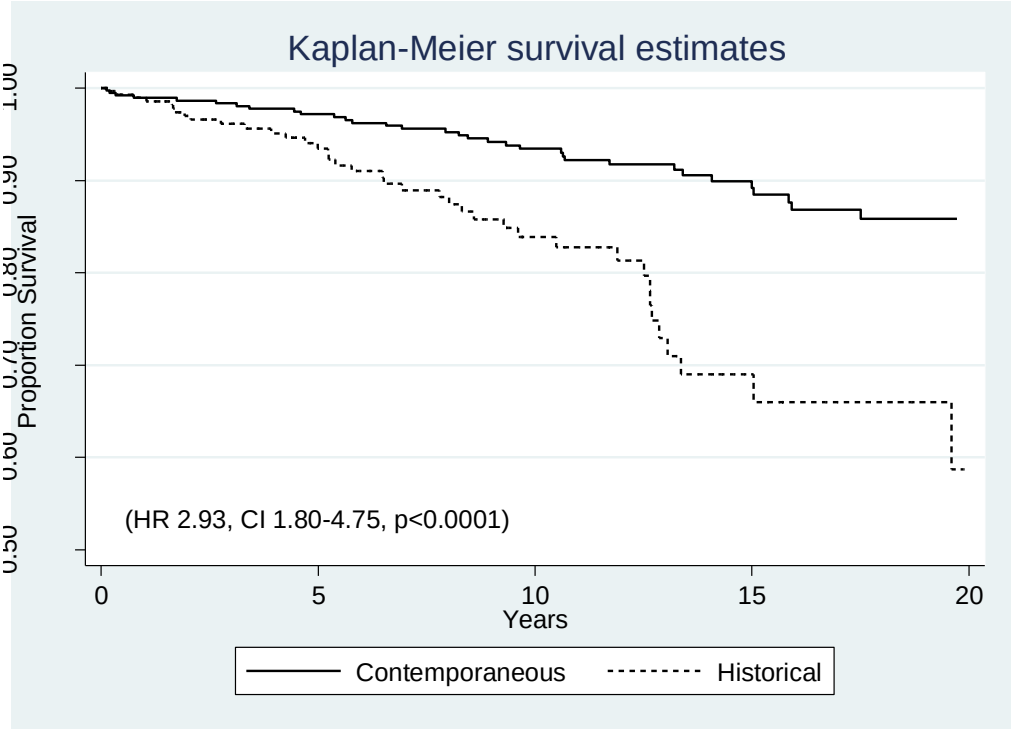
Figure 5.8. Kaplan-Meier plot of survival amongst HHT cases diagnosed pre-2000 versus those diagnosed post-2000.



5.3.2 Sensitivity analysis

373 (55%) cases of HHT had a contemporaneous diagnosis within THIN, with the remaining 302 (45%) coded as 'historical' HHT cases. Survival in contemporaneous cases was worse than in their matched controls (HR 1.61, CI 1.13-2.30, p=0.008) and the same pattern was evident when looking at the survival of historical cases compared with controls (HR 2.57, CI 1.81-3.66, p<0.0001). Age-adjusted survival in historically diagnosed HHT cases was worse than that in those diagnosed contemporaneously (HR 2.93, CI 1.80-4.75, p<0.0001) (Figure 5.9).

Figure 5.9. Kaplan-Meier plot of survival amongst contemporaneous cases of HHT versus historically diagnosed cases.



5.4 Discussion

5.4.1 Summary

Using a representative primary care dataset comparing HHT cases with matched controls we observed a two-fold increase in hazard ratio for death in patients with HHT and a median age of death 3 years earlier than in those without the disease. There was no discernable difference in survival in HHT cases with respect to sex or whether the diagnosis was made before or after the year 2000. HHT cases in the higher socioeconomic group, adjusted for smoking status, had a better survival than those from the lowest socioeconomic group.

5.4.2 Data interpretation

Our data demonstrate that HHT patients have a poorer survival compared to controls. Median age at death was 77 years in HHT cases compared with 80 years in controls. The published literature of survival in HHT is relatively small consisting of three papers[112,153,154] and an abstract[155] studying a total of 283 cases, compared to our analysis of 675 individuals with the disease. These studies have either compared survival in HHT cases compared to matched controls[112,154] or have looked at the parents of HHT-affected offspring and compared the age of death of parents with HHT to that of parents without the disease[153,155] (Table 5.1). Where studies have identified a younger mean/median age of death in HHT cases, their estimates have been of a similar size to our own. The hazard ratios for death were highest in the three years following initial diagnosis and tail off later which may reflect the nature in which some HHT patients are diagnosed, for example, after a potentially life-limiting complication such as stroke.

Table 5.1. A summary of studies of survival in HHT

Year Publi -shed	Authors	Study size (cases)	Methodology	Cases vs controls	Mean Follow-up (years)	Mean difference in age at death in cases vs controls (reduction in years)
2015	Donaldson *et al*	675	Prospective epidemiological study	HHT cases vs age, sex and location-matched controls	11.8[a]	3[b]
2010	Edwards *et al*[155]	113	Cross-sectional questionnaire study of HHT offspring	HHT-affected parents vs unaffected parents	n/a	8.3
2006	Sabba *et al*[153]	40	Retrospective clinical study	HHT-affected parents vs unaffected parents	n/a	6.8[b]
2005	Kjeldsen *et al*[154]	73	Prospective clinical/epidemiological study	HHT cases vs age, gender and location-matched controls	7.5	0
1999	Kjeldsen *et al*[112]	57	Prospective clinical/epidemiological study	HHT cases vs 'expected mortality' calculated from life table analysis	21	n/a

[a]median follow-up
[b]median age at death
n/a = not available

Whilst HHT appears to be more commonly diagnosed in females (see chapter 3) it is interesting that the mortality associated with a diagnosis does not differ between the sexes. In contrast, those in a higher socioeconomic group have a better survival than those in lower socioeconomic groups when adjusted for smoking. The disparities in survival across different socioeconomic groups is an area that has been extensively researched. Papers suggest a variety of reasons why individuals from lower socioeconomic groups may have a higher mortality when compared to their more affluent peers[156,157]. Contributing factors may include; persons of lower socioeconomic status knowing less about healthy life styles, health problems, and when and where to seek medical care; more limited

ability to purchase health-promoting and life-prolonging goods and services such as medical care; a greater likelihood of working in contact with hazardous and unhealthy working conditions and the propensity of individuals to invest in their own health (by smoking cessation, healthy diet, regular exercise, avoiding excessive alcohol or drug use). Some, or all of these factors may influence the survival disparity between HHT patients from differing socioeconomic strata.
It is interesting to note that the survival in those HHT cases diagnosed in the last decade (2000-2010) was not significantly different from those diagnosed in the decade prior (1990-2000). This perhaps suggests that our current interventions, though beneficial in reducing morbidity from HHT, are not having the same impact with regards to improving survival. Understanding in greater detail the cause of the higher mortality, whether it be due to complications of the disease itself, or an interaction with commoner comorbidities such as cardiovascular or respiratory disease is an important step in trying to improve mortality outcomes.

Whilst one study appeared to identify a survival paradox within a subset of HHT patients, such that those that were younger at diagnosis had a higher mortality than those whom were older at diagnosis, we did not replicate this finding in our study. We found, perhaps more in line with expectations, that those diagnosed with HHT at an older age had a higher mortality, than those diagnosed when younger - their life expectancy being shorter as a result of their more advanced age. It is important to recognise that these groups of older HHT cases will partly have 'self-selected' in order to appear in the THIN database at the time of data collection and thus in general this older group of patients may represent the less severe end of the disease spectrum.

A substantial number of the HHT cases included in THIN had a historical rather than contemporaneous date of diagnosis. Whilst both groups had worse survival than their matched controls, the hazard ratio for death was almost three times

as high in the historically diagnosed group of HHT cases compared to the contemporaneous cases. This may be explained by more severe or symptomatic disease in the historical cases as a consequence of presentation earlier in life compared to those who were diagnosed as incident cases during the course of our period of data collection. This is consistent with our clinical experience that developments such as the formulation of the diagnostic Curaçao criteria[25], the publication of international guidelines for the diagnosis and management of HHT[27], the increasing use of genetic testing and, perhaps, an increased awareness of the disease[56], have contributed to diagnosis of more patients before they are severely symptomatic.

5.4.3 Strengths and limitations

The strengths of this study are its size and the relatively long period of follow-up in which the ascertainment of deaths is likely to be higher than in a study conducted over a shorter timescale. Our survival analysis compares mortality between HHT cases and matched controls from the general population rather than relying on estimated life expectancies from life tables[112] and includes a population over 10 times larger than the previous largest case-control study estimating survival[154].

The potential limitations of this study are partly addressed in chapter 4 (with the study on HHT complications that utilises the same data extract) and include the fact that we were only studying individuals with a clinical diagnosis of HHT and, whilst we expect a diagnosis of HHT recorded in THIN to have a relatively high specificity, there are likely to be a substantial minority of patients with undiagnosed HHT whose mortality would not be recorded in the THIN database in a way that could be linked to their disease. Furthermore, though our data show a higher mortality in HHT patients compared with controls, we are not able to comment on whether this poorer survival is related directly to complications

of HHT as we could not access patients' clinical notes or death certification in order to confirm the cause of death. A previous study found that just over a third of deaths in HHT patients could be attributed directly to complications of the disease[112].

5.4.4 Conclusion

In conclusion, we present evidence from a large, representative primary care database confirming that on average a diagnosis of HHT is associated with a 3 year reduction in median age at death compared to matched controls. The reduction in median age of death in this patient cohort suggests that clinicians should strive harder to achieve early diagnosis in HHT and to offer timely and appropriate intervention in those with potentially life limiting disease if survival in HHT is to improve.

CHAPTER 6: THE SAFETY AND SUCCESS RATES OF PERCUTANEOUS EMBOLISATION FOR PULMONARY ARTERIOVENOUS MALFORMATIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS

6.1 Introduction

A recent study suggests that PAVMs in the general population are more common than previously appreciated[20]. Approximately 70% of individuals with PAVMs have the autosomal dominant genetic disorder hereditary haemorrhagic telangiectasia (HHT)[117]. PAVMs may also arise secondary to other conditions including chest trauma, thoracic surgery, longstanding hepatic cirrhosis and mitral stenosis[11]. Untreated PAVMs may be associated with increased morbidity from complications including stroke, cerebral abscess, and haemoptysis and may contribute to the reduced life expectancy noted in some patients with HHT[153,154]. There is some evidence that treatment of PAVMs is associated with a reduced rate of serious complications[80,158].

Initially, surgical resection was the only curative treatment available, though interventional radiological therapy has now superseded it. Percutaneous embolisation (PCE) involves catheterisation and embolisation of the PAVM lesions with metal coils, specifically designed devices (such as the Amplatzer device) and detachable balloons (now rarely used). The aim of PCE is threefold; reduce the risk of paradoxical emboli passing through the PAVM, reduce the size of any shunt (and thus improve hypoxia) and reduce the risk of PAVM haemorrhage. A recent Cochrane review was unable to identify any randomised controlled studies comparing PCE to conservative management[159], and for ethical reasons such studies are unlikely to be conducted now. Thus, current evidence for the safety and effectiveness of PCE is derived solely from observational studies. We carried out a systematic review and meta-analysis of the literature to provide summary statistics of the procedural safety and effectiveness to allow better understanding of the risks and benefits of the procedure. We investigated several areas;

1) the clinical characteristics of patients considered for PCE,
2) the frequency of peri-procedural complications associated with PCE,
3) long-term complications following PCE (occurring after 30 days),
4) the overall effectiveness of PCE as a treatment for PAVMs,
5) reasons for failed PCE (mechanisms of reperfusion in treated lesions)

6.2 Materials and Methods

6.2.1 Data sources and searches

We searched Medline from 1946 and EMBASE from 1974, both up until 1st February 2014 using electronic search terms for pulmonary arteriovenous malformations and for percutaneous embolisation. We included search terms for thoracic surgery in order to include studies where patients may have received mixed-modality therapy (i.e. surgery and embolisation). Our search was restricted to English language articles. The search strategy is reproduced below (Figure 6.1).

Figure 6.1. Literature search strategy

1. exp Arteriovenous Malformations/
2. arteriovenous malformation$.mp.
3. exp Arteriovenous Fistula/
4. arteriovenous fistula.mp.
5. avm.mp.
6. a-v malformation.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. pulmonary.mp.
9. 7 and 8
10. PAVM.mp.
11. 9 or 10
12. Embolisation, Therapeutic/
13. emboli#ation.mp.
14. 12 or 13
15. 11 and 14
16. Thoracic Surgery/
17. surgery.mp.
18. surgical.mp.
19. 16 or 17 or 18
20. 11 and 19

6.2.2 Study selection

We included papers on patients with PAVMs with any of the following information; details of the clinical characteristics of those considered for PCE, information regarding the peri-procedural and long-term complications associated with PCE, data regarding the procedural success rate in studies with documented follow-up and, finally, details of the mechanism of reperfusion in studies where recurrent PAVMs were detected after PCE had been undertaken. We arbitrarily defined peri-procedural complications as those occurring within 30 days of embolisation (as this was how they were defined in some of the studies we identified), but also included any later complications where there was a clear causal link with the procedure (for example, delayed sepsis following a pulmonary infarct). Procedural success rate was calculated as the percentage of patients (or of PAVMs) successfully treated by an initial course of embolisation as defined by the absence of reperfusion of treated lesions on subsequent radiological imaging. The denominator used was the total number of patients/PAVMs who underwent embolisation, except in the case of the

procedural success rate and reperfusion meta-analyses, when the denominator was the total number of patients/PAVMs who underwent embolisation *and had radiological follow-up available*. The concept of a 'course of treatment' was necessary as some patients required staged embolisation procedures, usually as a result of the number of PAVMs needing treatment or perceived detriment to undergoing a prolonged procedure. Papers contributing to the reperfusion meta-analysis used the classification system for mechanisms of PAVM reperfusion described by Pollak et al[160], namely; a) recanalisation of the embolised vessel, b) growth of a missed or previously small accessory artery (also described as a previously untreated feeder), c) bronchial or other systemic artery collateral flow (systemic-to-pulmonary reperfusion), d) pulmonary artery to pulmonary artery collateral flow around the occlusion (pulmonary-to-pulmonary reperfusion). We excluded case series reporting on fewer than 15 patients on the basis that these may derive from centres with limited experience of the procedure and may skew our estimates of risk and effectiveness. Also excluded were review articles, editorials, published letters and any studies looking specifically at embolisation of PAVMs developing as a consequence of treatment for congenital heart disease.

6.2.3 Data extraction and quality assessment

Two authors independently reviewed the literature in 3 rounds; first titles, then abstracts and finally full text of papers, excluding in each round studies not fitting our inclusion criteria. References of all full text papers were hand searched to identify any additional pertinent papers. Disagreements were resolved by face-to-face meetings between the two authors, with any unresolved issues referred to an independent third reviewer. Data extraction was performed by two authors using a structured extraction form collecting information on study design and location; year of publication; numbers recruited, treated or lost to follow-up; mean age of study population; sex ratio of participants and

proportion with diagnosed HHT. Study methodological quality was rated using a modified score based on a published checklist for assessment of case series [161] (Table 6.1) with the mean quality score for all studies used as a threshold for defining higher or lower methodological quality. Data on clinical characteristics, peri-procedural and longer-term complications, procedural success rate (expressed both by numbers of successfully treated patients and PAVMs) and reasons for persistent PAVMs post-treatment were collected. Where possible, we defined a successful procedure as one in which subsequent radiological imaging did not identify persistence/reperfusion of previously treated lesions. We documented the mean follow-up periods for each study post-embolisation and the imaging protocol used. When multiple publications arose from the same cohort (as determined by overlapping recruitment time periods), we included the largest cohort only. When analysing papers that looked at reasons for the reperfusion of previously embolised PAVMs we did exclude one paper[162], not on the basis of its sample size, but because it looked mainly at the use of detachable silicon balloons which are now rarely used in clinical practice by interventional radiologists. For the meta-analysis considering the causes of PAVM reperfusion we included, in preference, those papers that had treated the largest number of PAVM lesions rather than those that had treated the most patients (though often, as expected, the larger studies by patient number would also be the largest by PAVM number).

Table 6.1. Methodological quality assessment scale for case series

Category	Questions	Response			Score
		Yes	No	Unsure or N/A	
1.Diagnosis	Are diagnostic criteria for pulmonary arteriovenous malformations clearly identified and met by patients?	☐	☐	☐	**1**
2.Informed Consent	a) Has patient consent been documented? b) For prospective studies: is IRB/Ethics committee approval documented?	☐ ☐	☐ ☐	☐ ☐	**1** **1**
3.Treatment	Is the treatment modality clearly stated? (e.g. coils vs balloons)?	☐	☐	☐	**1**
4.Follow-up	Were patients followed up over time post-embolisation?	☐	☐	☐	**1**
5.Outcome Measures	Are outcomes well defined and clinically relevant? Are they subjective, objective or standardised?	☐	☐	☐	**1**
6.Patient Perception	Is there any documentation of the patient's perception of outcome and of the intervention?	☐	☐	☐	**1**
7.Safety	Do the authors describe known risks associated with the intervention (i.e. their own complication rate)?	☐	☐	☐	**1**
8.Author's Conclusions	Do the authors abstain from unfounded claims about safety or efficacy?	☐	☐	☐	**1**
9.Inclusion/ Exclusion Criteria	Are inclusion and exclusion criteria clearly stated?	☐	☐	☐	**1**
10. Consecutive Cases	Are all treated patients; Consecutive? Treated by one physician or at one institution?	 ☐ ☐	 ☐ ☐	 ☐ ☐	 **1** **1**
					TOTAL 12

6.2.4 Data synthesis and analysis

With respect to the meta-analysis of clinical characteristics of patients undergoing embolisation, we deliberately excluded any paper from the particular meta-analysis that did not document at least one patient with PAVMs who had described said clinical characteristic. For example, if a paper did not include mention of at least one patient describing a reduced exercise tolerance prior to consideration for PCE, then this paper would not be included in the clinical characteristics meta-analysis for that particular symptom. The rationale was to reduce underestimation of symptom prevalences by excluding studies that might have a calculated 0% prevalence of a particular clinical characteristic by virtue of the fact that said study did not ask specifically about it or measure it as part of the protocol.

We grouped peri-procedural complications into 'major' and 'minor' based on criteria in the quality improvement guideline published by the Society of Interventional Radiology[79]. In practice, major clinical complications included death, stroke, haemopericardium secondary to myocardial puncture and venous thromboembolic events. Separate proportions meta-analyses were conducted to look at the weighted frequency of certain clinical characteristics, peri-procedural and longer-term complications and to look at estimates of procedural success rate and mechanisms of reperfusion. All prevalence estimates are presented, weighted by study size. Confidence intervals at the 95% level were determined with a random effects model using the DerSimonian and Laird method to calculate weights[163]. Study heterogeneity was assessed using I^2 scores. If substantial heterogeneity was detected (defined as I^2 value > 50%) subgroup analysis was undertaken, stratified for study methodological quality and whether or not the study pertained to a select patient group. Select patient groups were defined as those in the following categories; diffuse PAVMs only, large PAVMs only (defined as diameter >=8mm) and idiopathic PAVMs only (PAVMs lesions

not associated with a confirmed diagnosis of HHT). Funnel plots were assessed visually for asymmetry to look for evidence of publication bias. The study protocol is listed on the website of the International Prospective Register of Systematic Reviews (PROSPERO)[164]. The presentation of the meta-analyses adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[165]. All analyses were performed using the StatsDirect statistical software package version 2.7.9.

6.3 Results

The literature search identified 2,104 articles by title, from which 96 full text papers were obtained (Figure 6.2). A further 9 full text papers were included after manually searching the references of the aforementioned 96 papers. A total of 27 papers contributed to the meta-analyses[23,160,166-190], though not all papers contributed data to each meta-analysis (Table 6.2). Papers excluded due to potential recruitment overlap are listed (Table 6.3). One study was prospective in design[160] whilst all other studies were retrospective case series. No randomised controlled trials were identified. The mean age of study participants across all included papers ranged from 34-56 years and there was a 60% female preponderance (95% CI 55-64%, I^2 56.1%). The mean value for quality score was 8 (range 5-12, from a possible total score of 12), with 10 of the 23 studies (44%) ranked in the higher methodological quality group (quality score >8). Lower quality scores were due to unclear inclusion/exclusion criteria, absence of well-defined objectives/standardised outcome measures, absence of documented consent/ethical approval and a lack of clarity over whether embolised patients represented a consecutive series treated consistently by one operator or at one institution. Four of 27 studies (15%) were in selected patient groups: 2 studies including only diffuse PAVMs[191,192], one including large PAVMs

only[193], one looking solely at idiopathic PAVMs[189]. Visual analysis of funnel plots for publication bias did not display noticeable asymmetry (see Appendix 3).

Figure 6.2. PRISMA flowchart for identifying studies included in meta-analysis

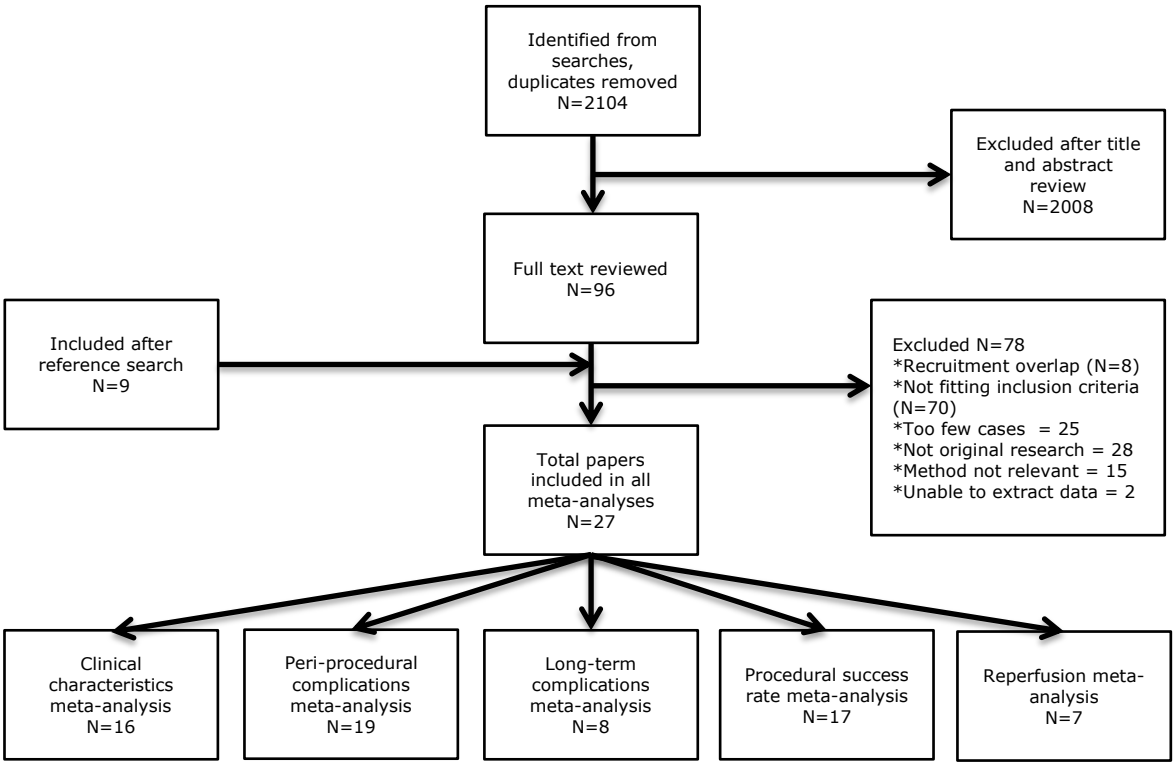


Table 6.2. Study characteristics of all papers included in the separate meta-analyses

Ref*	Author	Year	Recruiting Institutions	Study size	Mean	Female	Quality	Selected	Meta-analyses				
				Patients / PAVMs	Age (years)	(%)	score	patient group?**	Clinical features	Peri-procedural	Long-term	Success rate	Reperfusion
[166]	Allison	1990	Hammersmith Hospital, UK	19 / -			†		√				
[167]	Andersen	2006	Odense Hospital, Denmark	35 / 106	49	60	9		√	√	√	√	
[23]	Cottin	2007	Multicentre (6 French hospitals)	126 / -	43.1	62.7	†		√				
[168]	Dutton	1995	Hammersmith Hospital, UK	53 / 102	41	57.1	7			√	√	√	
[169]	Grosso	2008	S.Croce e Carle Hospital, Cuneo, Italy	30 / 60	47.8	53.3	5		√	√		√	
[170]	Gupta	2002	Hammersmith Hospital, UK	66 / 225	44.4	31.8	9		√	√	√	√	
[171]	Haitjema	1995	St Antonius Hospital, Netherlands	32 / 92	36	71.9	6			√			
[172]	Hart	2010	Hammersmith Hospital, UK	69 / 161	44.6	59.4	8		√	√		√	
[173]	Hayashi	2012	Kagoshima University, Japan	21 / 37	43	81	10			√		√	√
[174]	Lacombe	2009	Hopital Ambroise Pare, France	39 / 681	35	79.5	12	a	√	√	√	√	
[175]	Lee	1997	New Haven Hospital, Yale, USA Johns Hopkins Hospital	45 / 45	41.6	48.9	8	b					√
[176]	Letourneau-Guillon	2010	St Michael's, Toronto, Canada St Justine, Montreal, Quebec, Canada	24 / 35	50	70.8	10		√	√	√	√	√
[177]	Liu	2010	Chinese People's Liberation Army General Hospital, Beijing, China	23 / -	-	52.2	7		√	√	√	√	
[178]	Mager	2004	St Antonius, Nieuwegein UMC, Utrecht, Netherlands	112 / 349	45	60.7	9		√	√	√	√	
[179]	Pierucci	2008	Yale University, USA	36 / -	35.4	58.3	9	a		√			
[180]	Pollak	1994	New Haven Hospital, Yale, USA	35 / 96	-	-	8			√	√		
[160]	Pollak	2006	New Haven Hospital, Yale, USA	155 / 415	45	58.1	10		√	√		√	√
[181]	Prasad	2004	St Michaels' Hospital, Toronto, Canada	54 / 306	39.2	-	10			√		√	√
[182]	Puskas	1993	Massachusetts General Hospital, USA	21 / -	37.5	61.9	†		√				
[183]	Remy-Jardin	2006	Calmette Hospital, Lille, France	38 / 64	34.3	55.3	7					√	√
[184]	Saluja	1999	Yale University, USA	82 / 238	40	62.2	8					√	
[185]	Swanson	1999	Mayo Clinic, USA	48 / 200	40	52.7	7		√	√		√	
[186]	Tapping	2011	Hull Royal Infirmary, UK	15 / 19	56	73	8		√	√		√	

187	Trerotola	2009	University of Pennsylvania, USA	51 / 154	44	72.5	9		√	√			
180	White	1988	Johns Hopkins, USA	76 / 276	36	59.2	7		√	√			
189	Wong	2011	St Michaels Hospital, Toronto, Canada	17 / 28	47	65	9	c				√	
190	Woodward	2013	University of Pennsylvania, USA	23 / 162	44	56.5	10						√

*Reference numbers in table refer to those listed in the main manuscript

**a) diffuse PAVMs only, b) large PAVMs only, c) idiopathic PAVMs only

†Quality score not applicable, as not all patients studied underwent embolisation thus could not reasonably have fulfilled some of the criteria of the quality score

Table 6.3. Papers excluded from the meta-analyses due to potential overlap in patient recruitment

Ref	Author	Publication Year	Institution Location(s)
[194]	Andersen	1999	Odense Hospital, Denmark
[195]	Brillet	2006	Calmette Hospital, Lille, France
[196]	Chilvers	1990	Hammersmith Hospital, UK
[197]	Faughnan	2004	St Michael's Hospital, Toronto, Canada Hospital for Sick Children, Toronto, Canada Sunnybrook and Women's Centre, Toronto, Canada Yale Medical School, New Haven, USA Good Samaritan Medical Centre, Phoenix, Arizona, USA
[198]	Jackson	1990	Hammersmith Hospital, UK
[49]	Remy	1992	Lille Hospital, France
[199]	White	1983	Johns Hopkins, USA

6.3.1 Results: meta-analysis of clinical characteristics

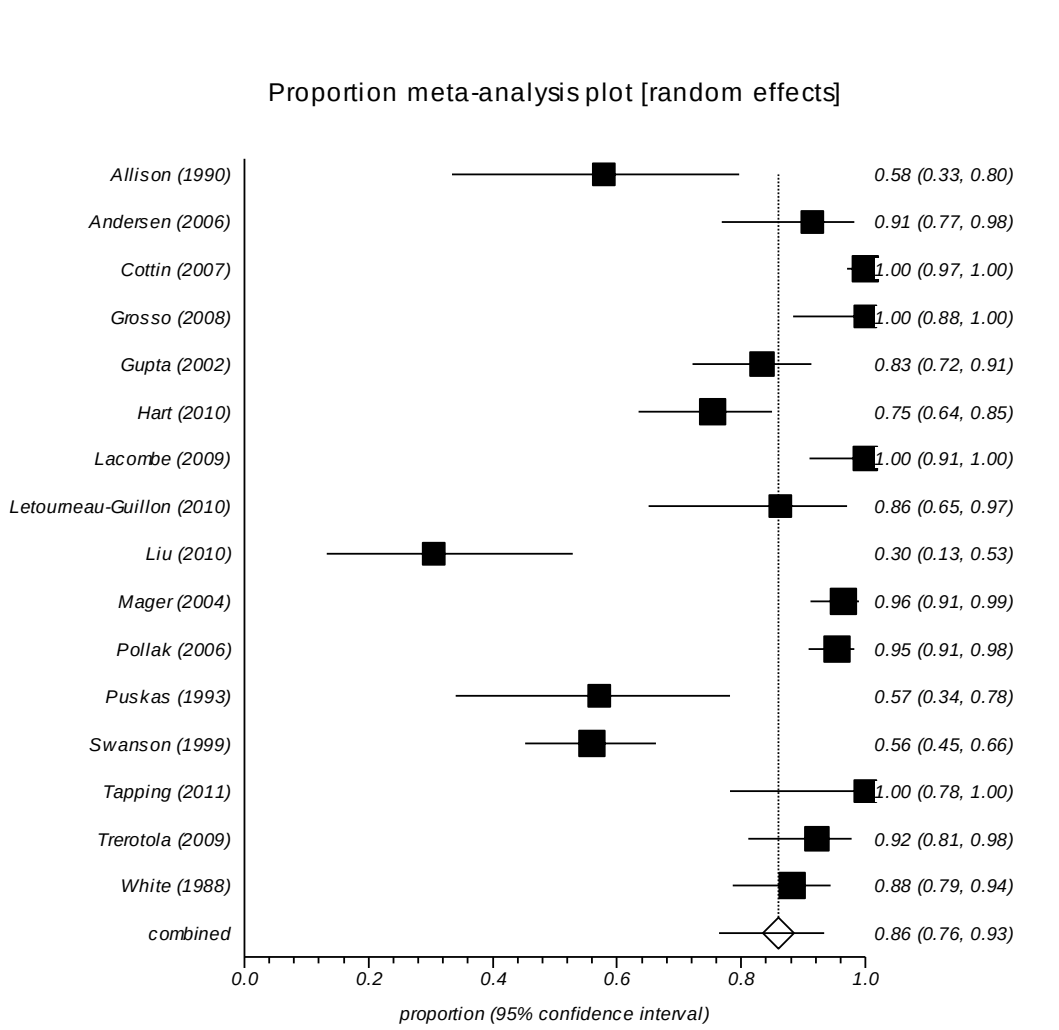
The prevalence of a diagnosis of HHT in patients with PAVMs considered for treatment was 86% (95% CI 76-93, I^2 93%, estimates from 16 studies including 1122 patients) (Figure 6.3). The commonest prior symptoms were a reduction in exercise tolerance in 68% (95% CI 49-84%, I^2 86.7%), epistaxis in 63% (95% CI 45-79%, I^2 90.4%) and dyspnoea in 58% (95% CI 49-67%, I^2 80.7%). Neurological complications occurred in over 40% of patients, with a previous stroke or TIA in 26.3% (95% CI 17.4-36.4%, I^2 92.1%) and previous cerebral abscess in 12.6% (95% CI 9-16.8%, I^2 67.6%) (Table 6.4, Figure 6.3 to Figure 6.9). For all clinical characteristics except haemothorax and seizure there were high levels of heterogeneity between studies. Additional clinical characteristics were reported in studies but not included in the meta-analysis calculations due to a limited quantitative data – they include; fatigue, anaemia, undefined chest pain, cardiac murmur, cardiac dysfunction, cerebral AVM, non-cerebral abscess, hepatic AVM and gastrointestinal bleeding.

Table 6.4. Meta-analysis of clinical characteristics of patients with pulmonary arteriovenous malformations considered for embolisation

Clinical Characteristic	Prevalence (%)	95% CI	Heterogeneity (I^2) (%)	Contributing population Studies / Patients	Figure
Hypoxaemia*	98.2	95.7-100	**	1 / 112	
Epistaxis	61	39-81	92	6 / 291	6.4
Telangiectasia	60	26-89	93.7	3 / 177	6.5
Reduced exercise tolerance*	58.7	50.9-66.5	**	1 / 155	
Dyspnoea	54	42-66	89.4	12 / 628	6.6
Cyanosis	36	18-55	83.5	4 / 205	6.7
Migraine	33	21-47	86.4	5 / 387	6.8
Clubbing	30	15-47	80.9	3 / 211	6.9
Stroke or TIA	27	17-39	92.7	16 / 952	6.10
Transient ischaemic attack	18	12-24	79.2	13 / 787	6.11
Stroke	12.7	10-15.7	28.3	13 / 795	6.12
Haemoptysis	11	7-15.8	75	13 / 860	6.13
Cerebral abscess	10.8	7.2-15	66.2	13 / 798	6.14
Seizure	6.9	3.8-10.9	0	3 / 190	6.15
Haemothorax	4.4	2.6-6.7	8.1	5 / 415	6.16
Intracranial haemorrhage*	2.4	0.3-5.0	**	1 / 126	

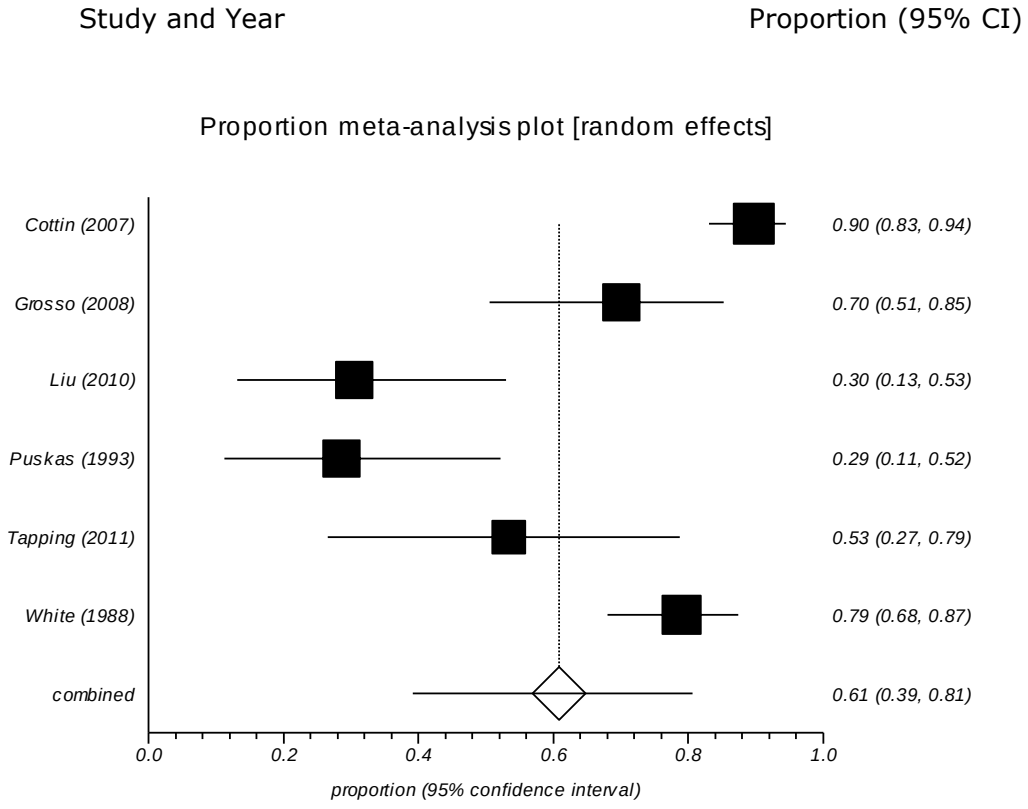
*Confidence intervals calculated manually around the prevalence in one paper
**No heterogeneity value calculated as <3 studies contribute to estimate

Figure 6.3. Proportion of patients evaluated for embolisation diagnosed with HHT



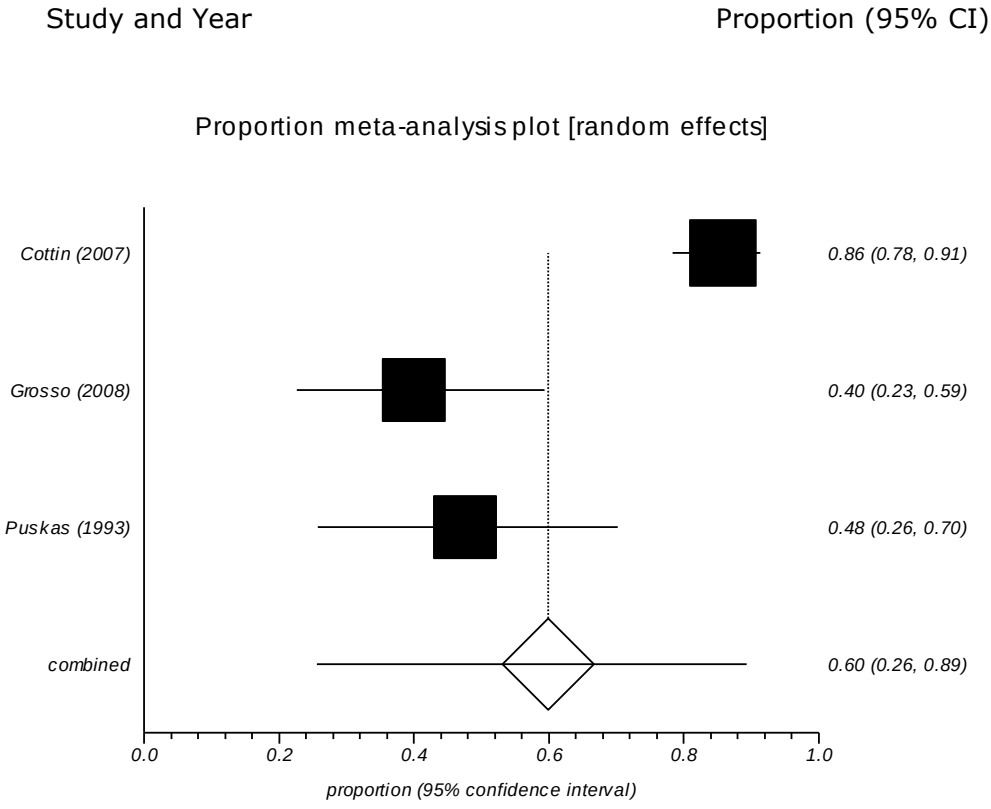
Heterogeneity (I^2) = 77.2%

Figure 6.4. Proportion of patients evaluated for embolisation with a history of epistaxis



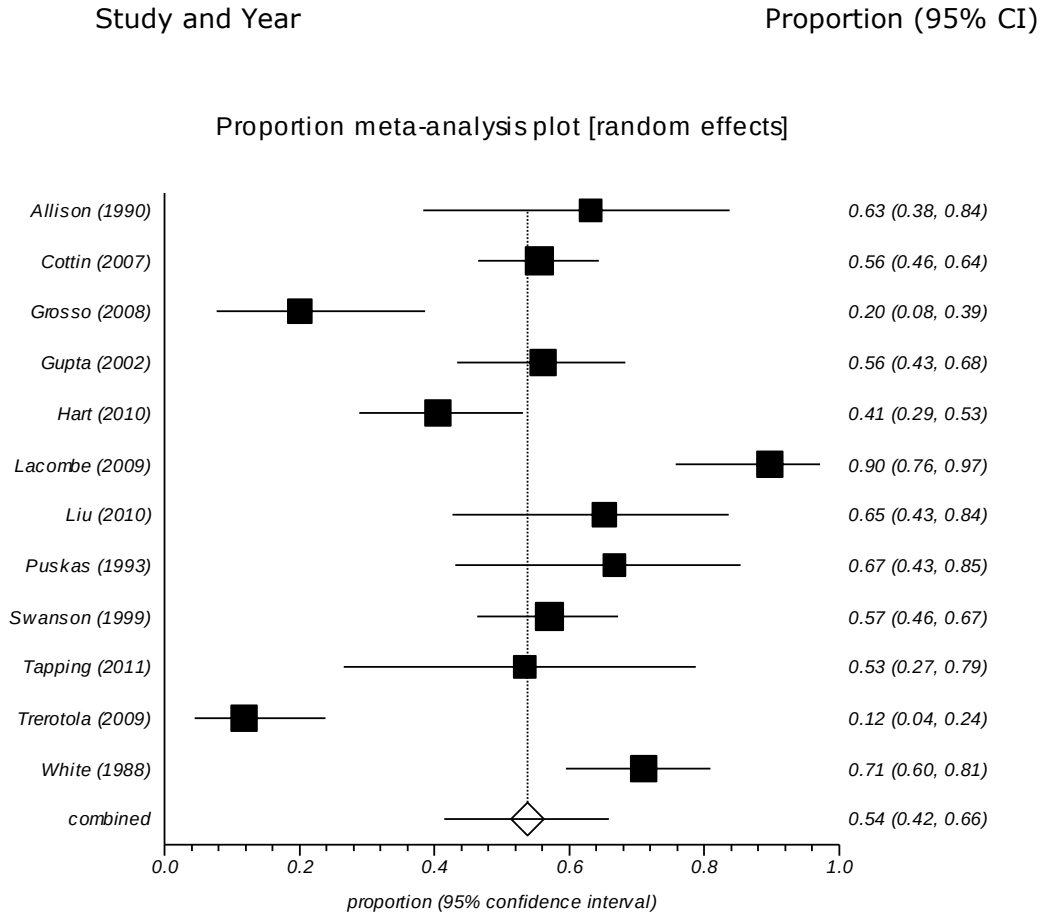
Heterogeneity (I^2) = 92%

Figure 6.5. Proportion of patients evaluated for embolisation with a history of telangiectasia



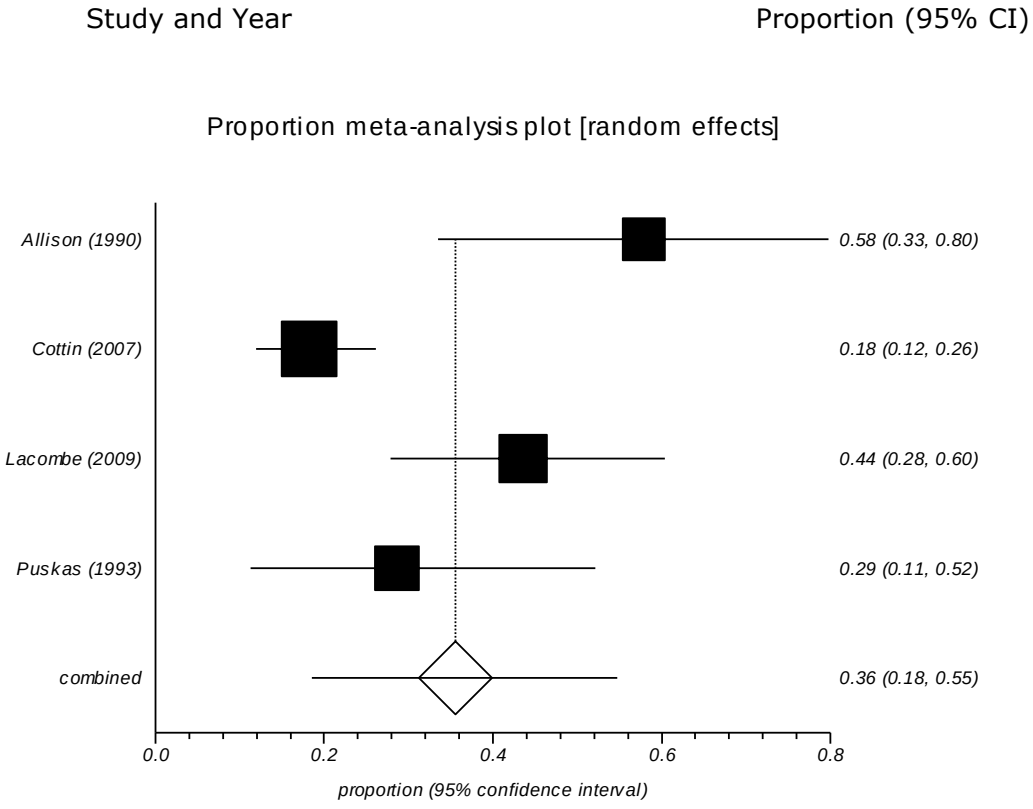
Heterogeneity (I^2) = 93.7%

Figure 6.6. Proportion of patients evaluated for embolization with a history of dyspnoea



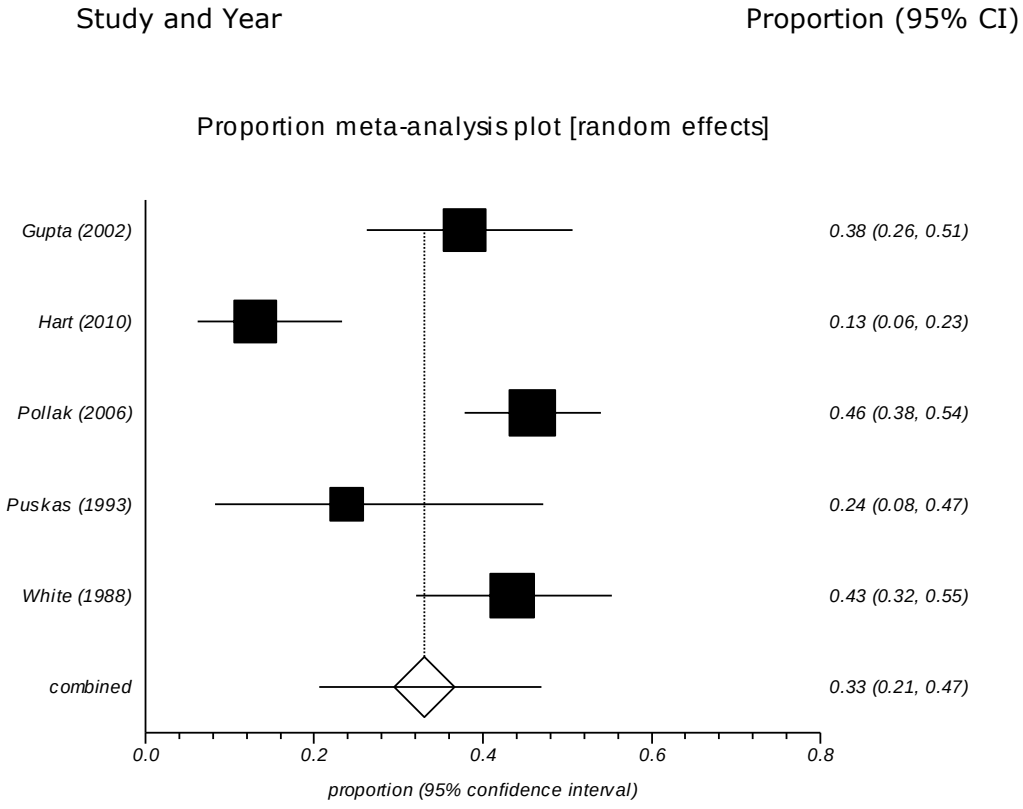
Heterogeneity (I^2) = 89.4%

Figure 6.7. Proportion of patients evaluated for embolisation with a history of cyanosis



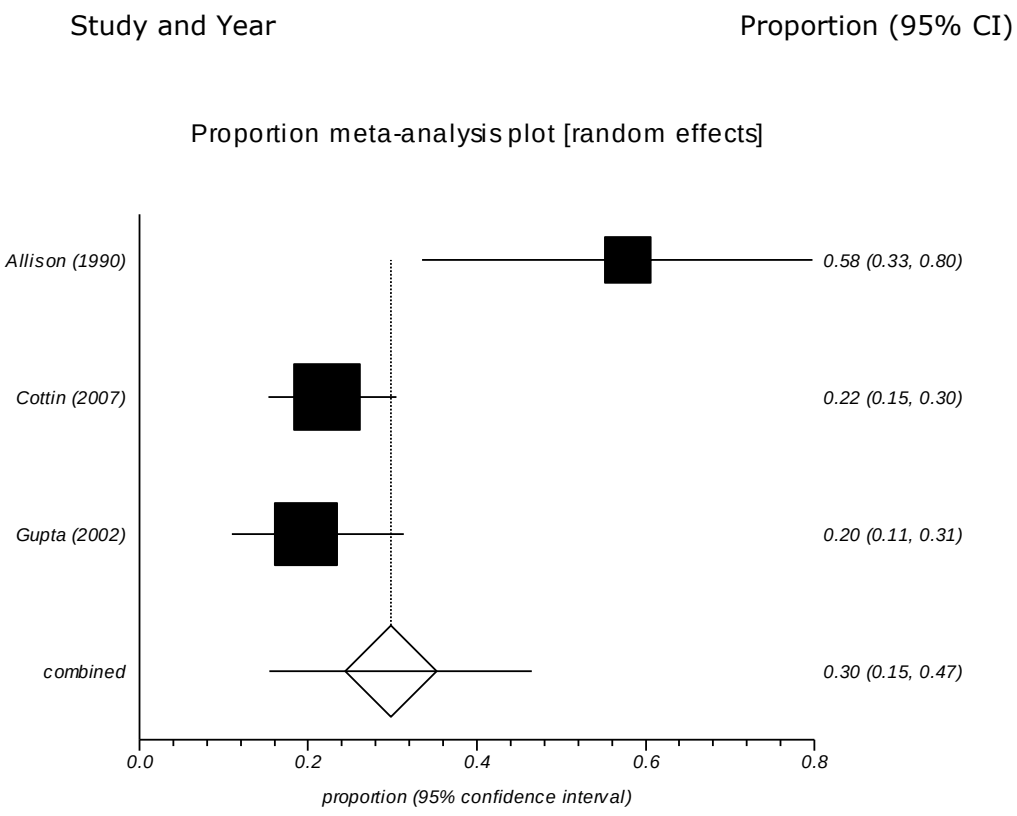
Heterogeneity (I^2) = 83.5%

Figure 6.8. Proportion of patients evaluated for 106mbolization with a history of migraine



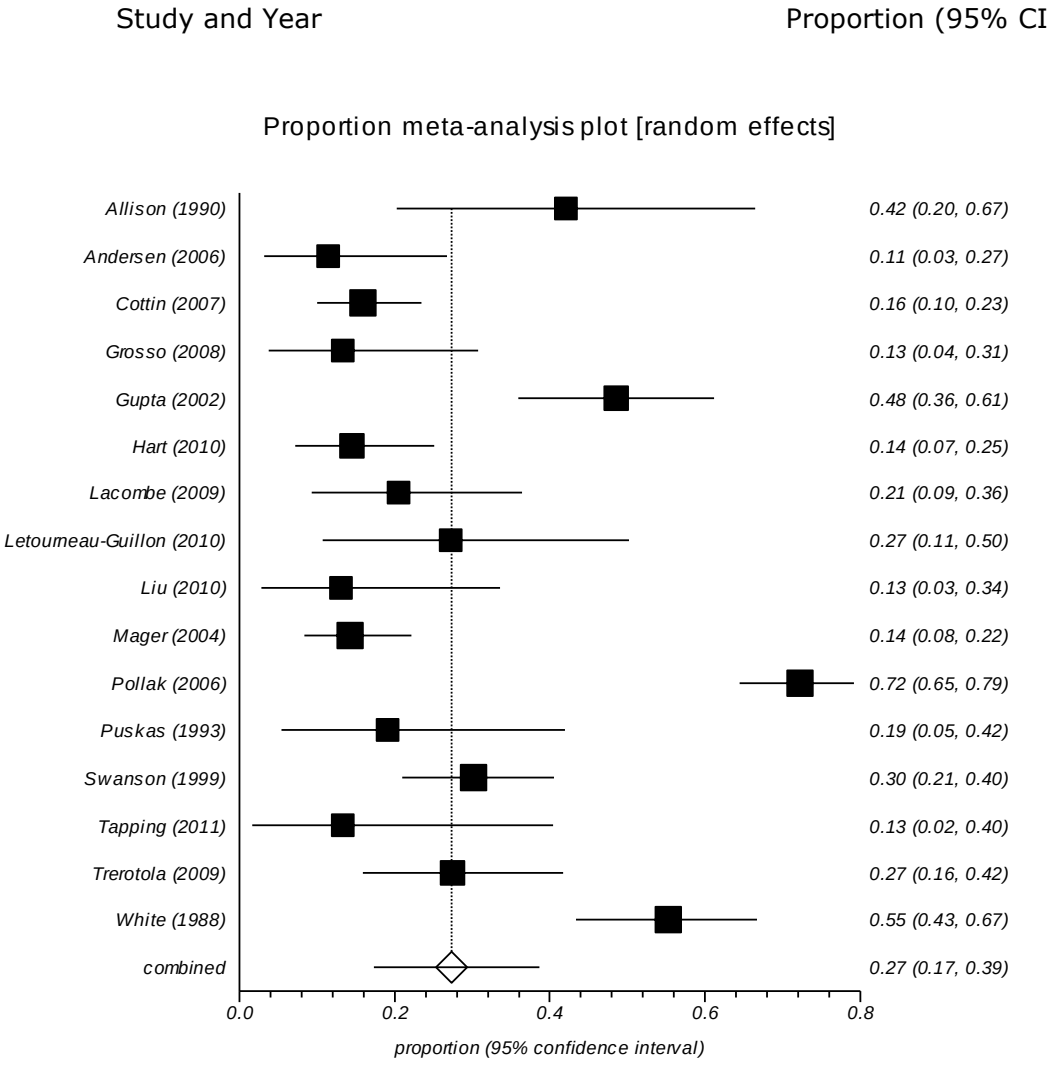
Heterogeneity (I^2) = 86.1%

Figure 6.9. Proportion of patients evaluated for embolisation with a history of clubbing



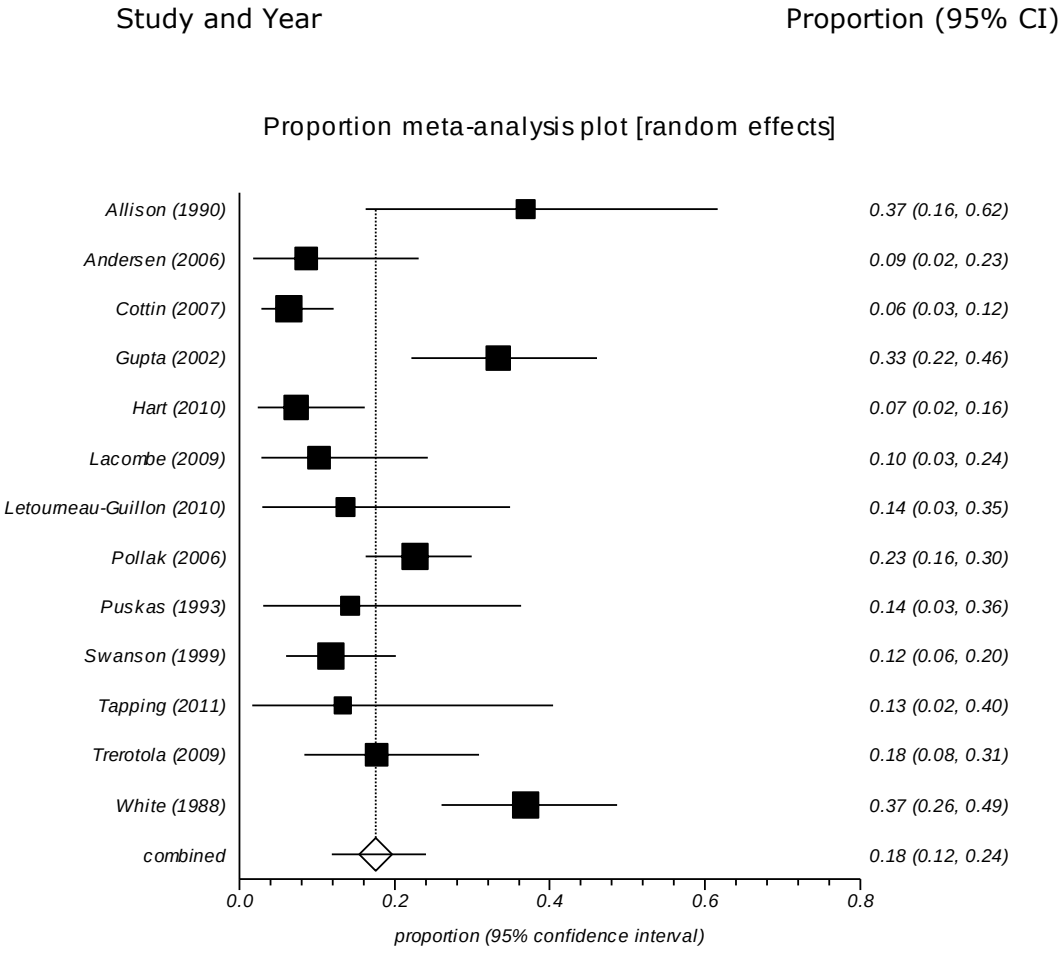
Heterogeneity (I^2) = 80.9%

Figure 6.10. Proportion of patients evaluated for embolisation with a history of stroke or transient ischaemic attack



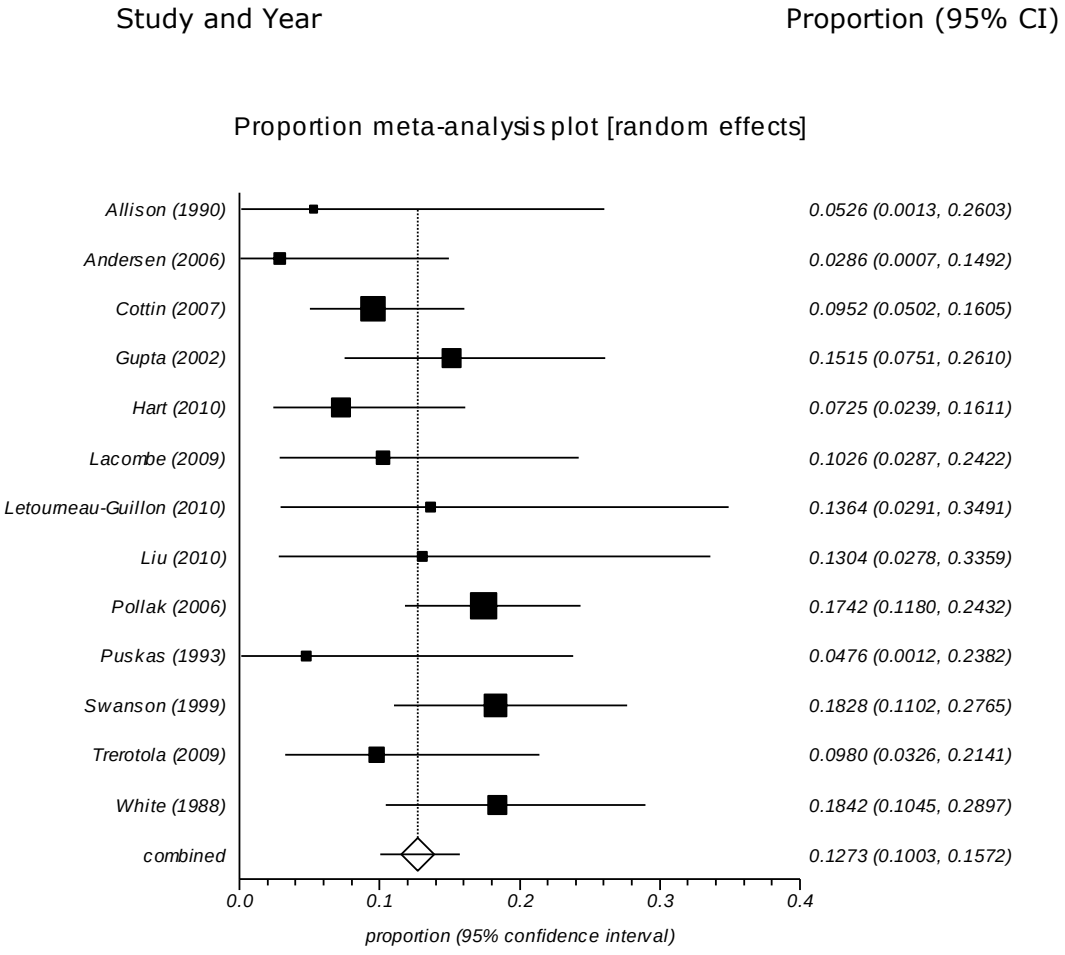
Heterogeneity (I^2) = 92.7%

Figure 6.11. Proportion of patients evaluated for embolisation with a history of transient ischaemic attack



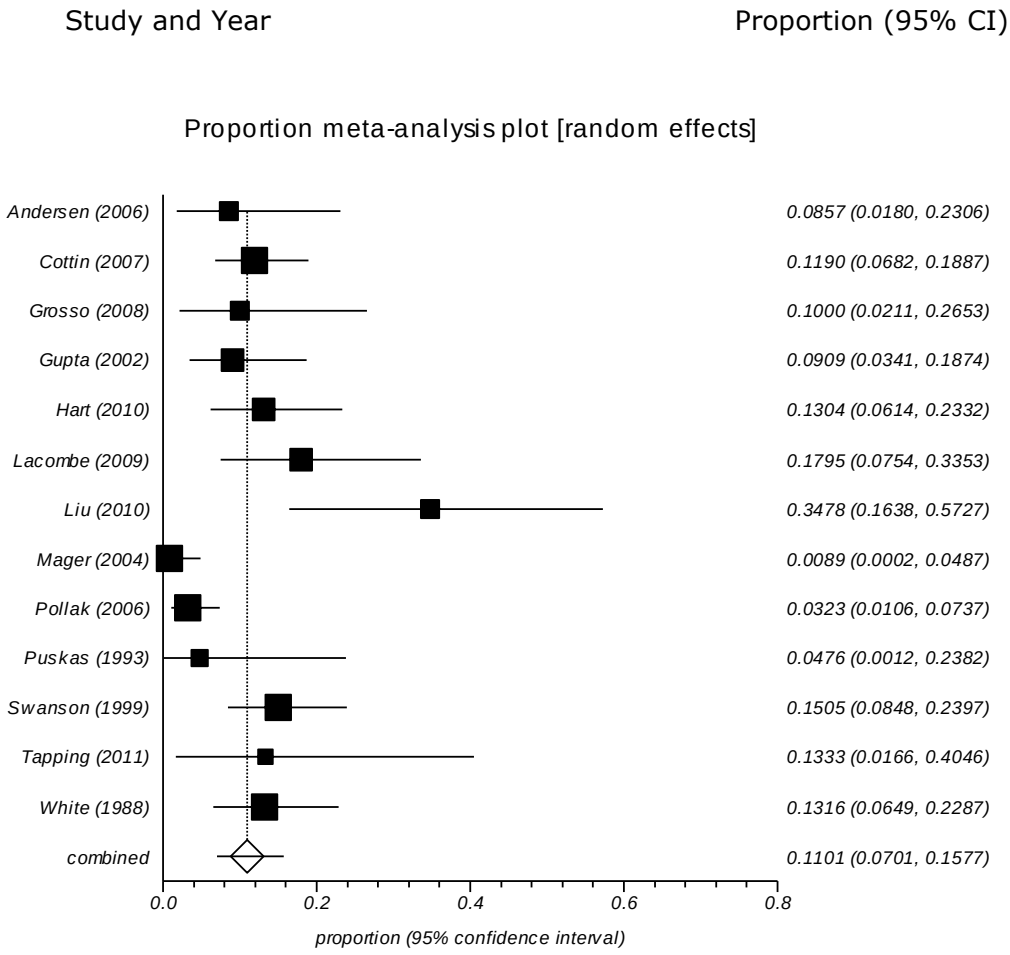
Heterogeneity (I^2) = 79.2%

Figure 6.12. Proportion of patients evaluated for embolisation with a history of stroke



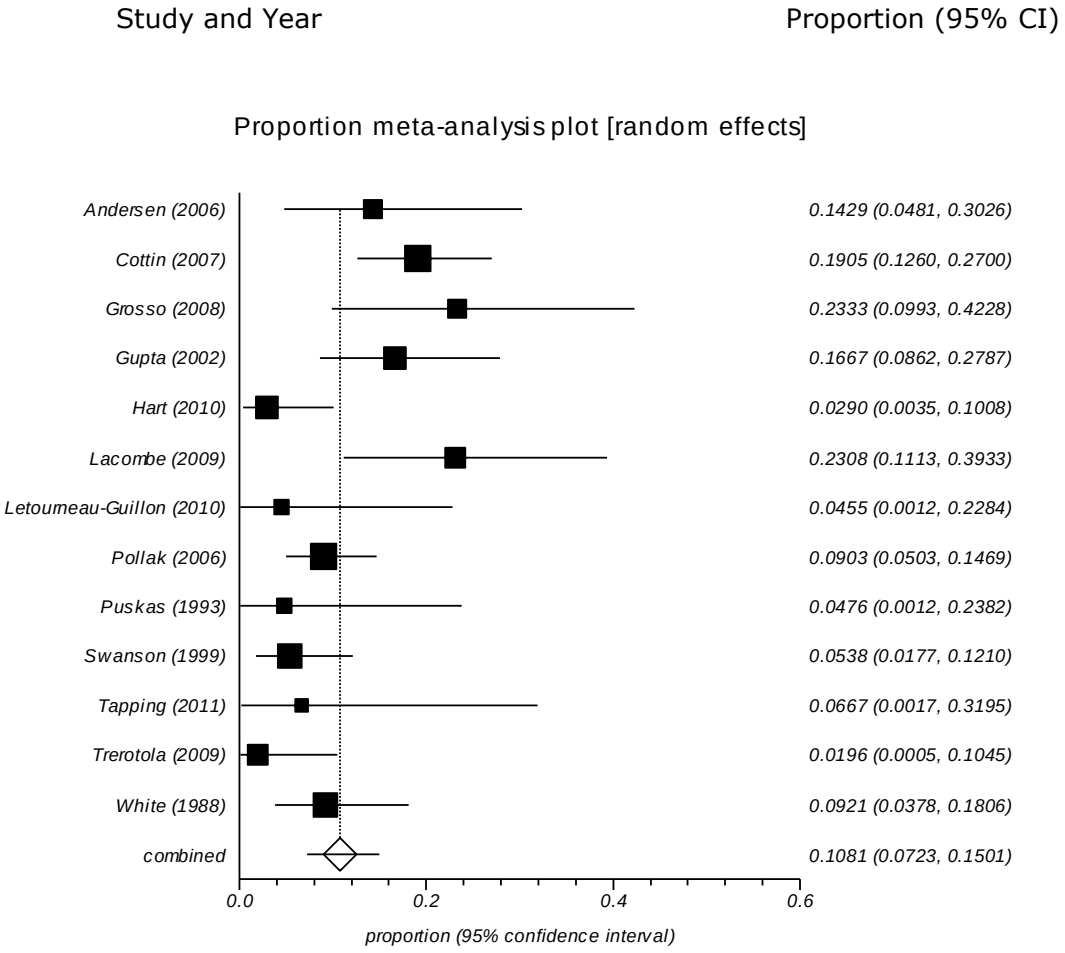
Heterogeneity (I^2) = 28.3%

Figure 6.13. Proportion of patients evaluated for embolisation with a history of haemoptysis



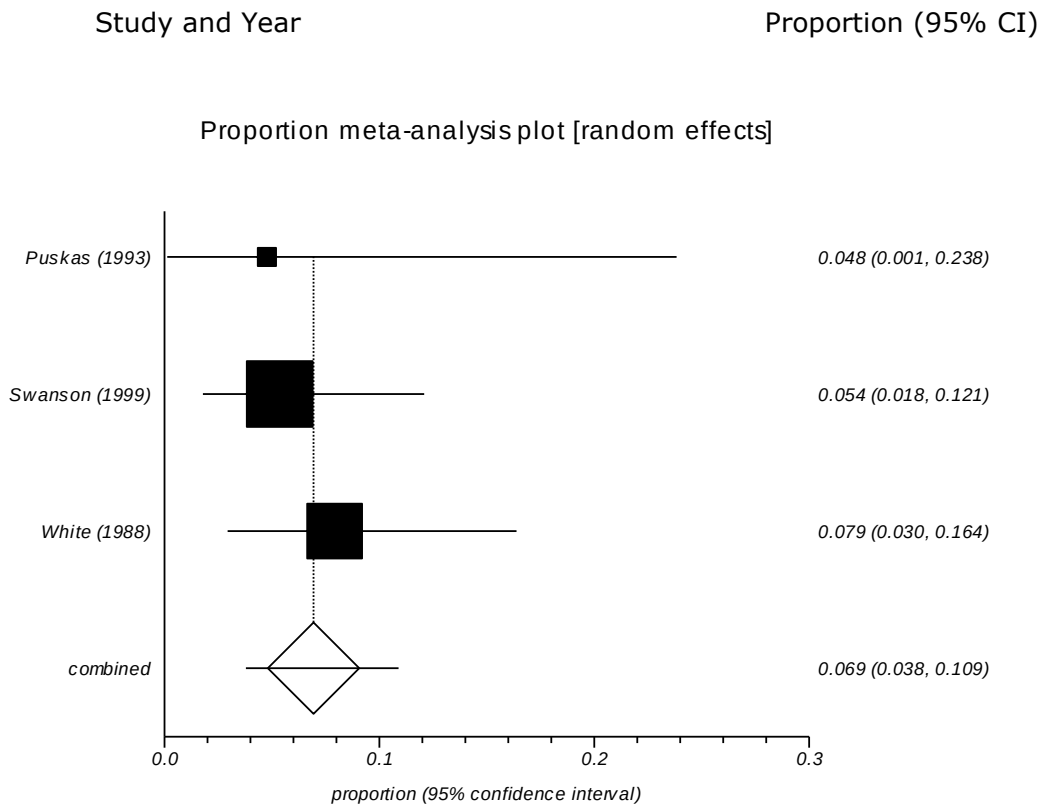
Heterogeneity (I^2) = 75%

Figure 6.14. Proportion of patients evaluated for embolisation with a history of cerebral abscess



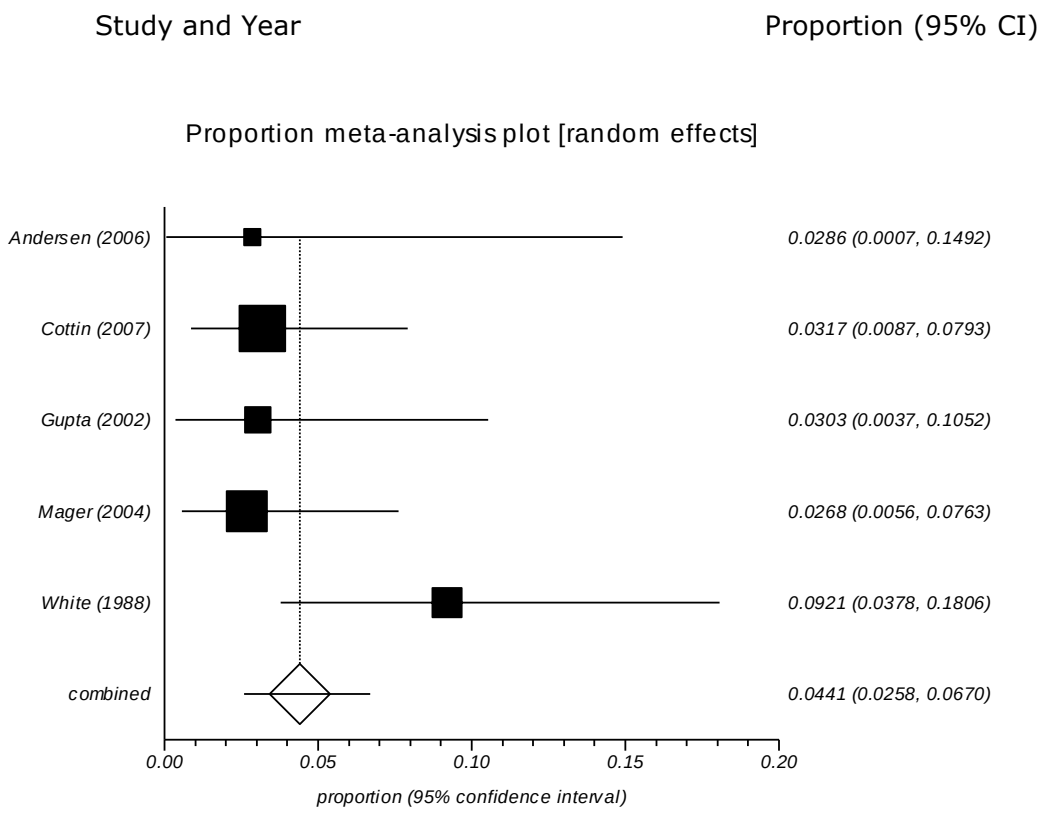
Heterogeneity (I^2) = 66.2%

Figure 6.15. Proportion of patients evaluated for embolisation with a history of seizure



Heterogeneity (I^2) = 0%

Figure 6.16. Proportion of patients evaluated for embolisation with a history of haemothorax



Heterogeneity (I^2) = 8.1%

6.3.2 Results: meta-analysis of peri-procedural complications

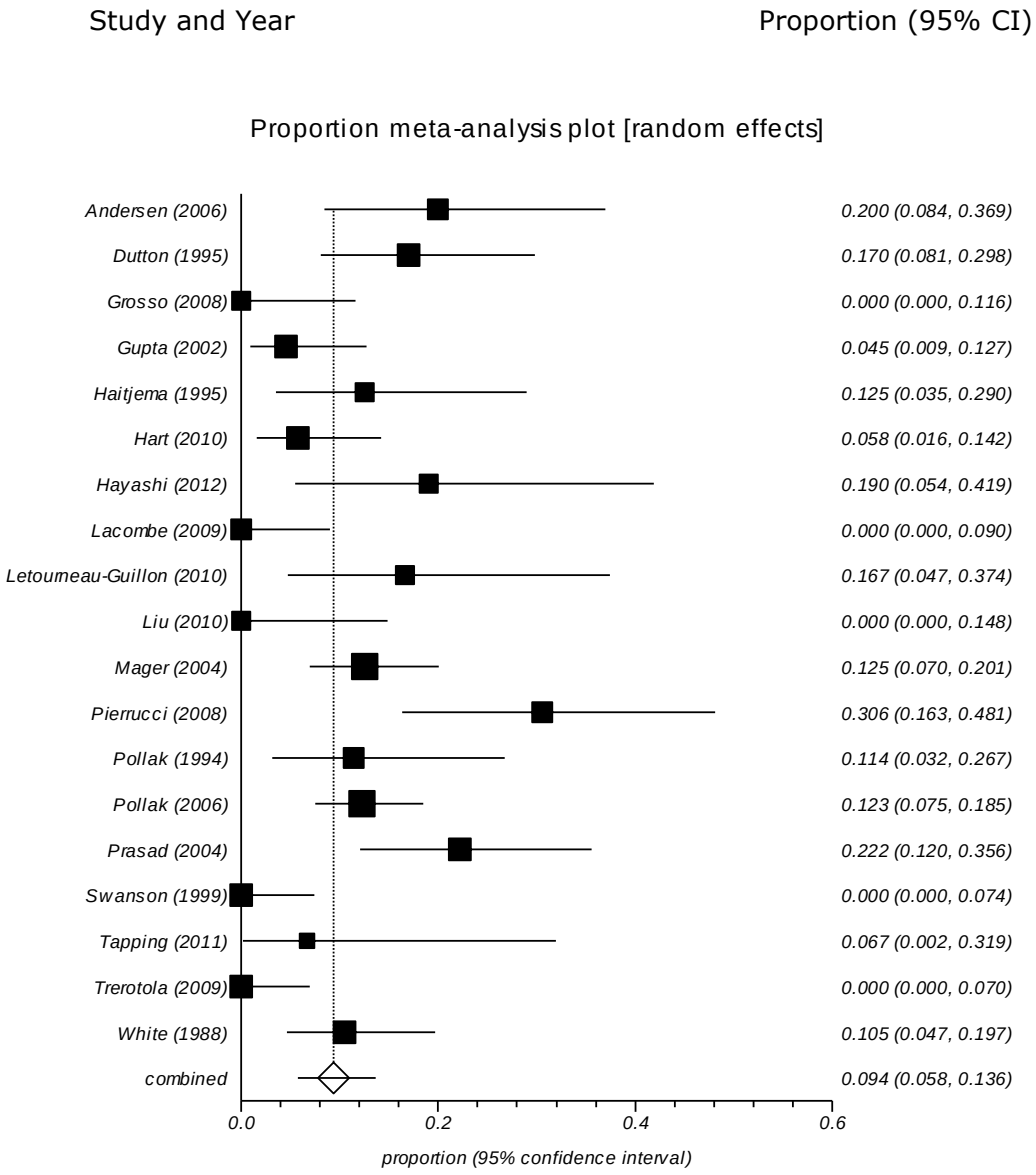
A total of 1,111 patients had embolotherapy across all the studies included in the meta-analyses of peri-procedural complications and of success rate (with at least 3644 PAVMs treated). Amongst 974 patients (3314 treated lesions) in the peri-procedural complications meta-analysis, major complications included one death (due to pyogenic infection secondary to pulmonary infarction) (prevalence 0.5%, 95% CI 0.2-1.0, I^2 0%), 6 strokes (prevalence 1.0%, 95% CI 0.5-1.7%, I^2 0%), 2 venous thromboembolic events (prevalence 0.7%, 95% CI 0.2-1.2%, I^2 0%), and one patient with a haemopericardium secondary to probable cardiac perforation following attempted retrieval of a dislocated coil from the left ventricle (prevalence 0.6%, 95% CI 0.2-1.2%, I^2 0%) (Table 6.5). We calculated a procedural rate of 1.0% for major clinical complications (10/974). Commoner complications included pleuritic chest pain/pleurisy in 9.4% (95% CI 5.8-13.6, I^2 77.2%) and ischaemic chest pain in 2.2% (95% CI 1.2-3.4, I^2 25.8%). There were no documented episodes of myocardial infarction. Box plots for each complication are available (Figure 6.17 - Figure 6.33). Heterogeneity between studies existed in prevalence estimates for some complications (for example, pleuritic chest pain/pleurisy) but this was not explained methodological quality nor whether included studies contained or omitted selected populations (as defined above) (Table 6.6).

Table 6.5. Meta-analysis of peri-procedural complications of percutaneous embolisation for pulmonary arteriovenous malformations in 19 studies with 974 patients

Complications	Prevalence (%)	95% CI	Heterogeneity (I^2) (%)	Figure
Pleuritic chest pain/Pleurisy	9.4	5.8-13.6	77.2	6.17
Ischaemic chest pain	2.2	1.2-3.4	25.8	6.18
Other*	1.8	0.6-3.6	67.4	6.19
Haemoptysis	1.7	0.8-3.0	41.1	6.20
Pulmonary infarct	1.4	0.6-2.6	44.8	6.21
Uncatheterisable/ Unoccludable PAVM	1.4	0.5-2.7	51.8	6.22
Device embolism	1.1	0.6-1.9	0	6.23
Device migration	1.0	0.5-1.8	0	6.24
Stroke	1.0	0.5-1.7	0	6.25
Arrhythmia**	0.9	0.4-1.6	0	6.26
Transient ischaemic attack	0.8	0.4-1.5	0	6.27
Groin haematoma	0.8	0.4-1.5	0	6.28
Air embolism	0.8	0.3-1.4	0	6.29
Venous thromboembolism†	0.7	0.2-1.2	0	6.30
Haemopericardium	0.6	0.2-1.2	0	6.31
Ectopic device deposition	0.5	0.2-1.1	0	6.32
Death	0.5	0.2-1	0	6.33
Myocardial infarction	0	0	0	

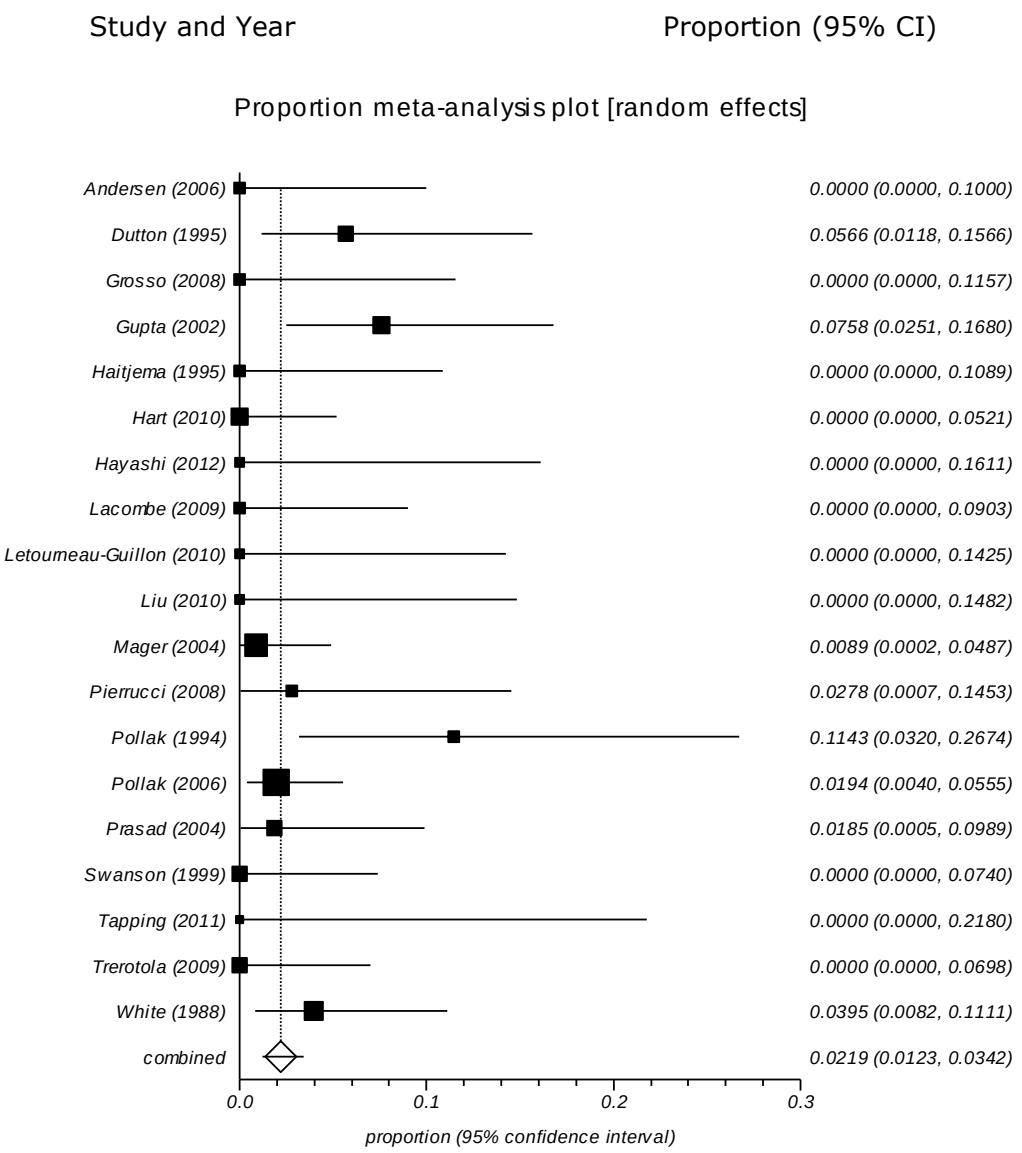
* These include; transient confusion (n=1), perioral pain (n=1), intra-procedure leg pain (n=1), transient brachial plexus injury (n=1), episode of transient deafness (n=1), delayed lung abscess (n=1), pleural effusion (n=9) and mild contrast reaction (n=1)
**Bradycardia or atrial fibrillation
† Deep venous thrombosis or pulmonary embolus

Figure 6.17. Proportion of embolised patients experiencing pleuritic chest pain/pleurisy



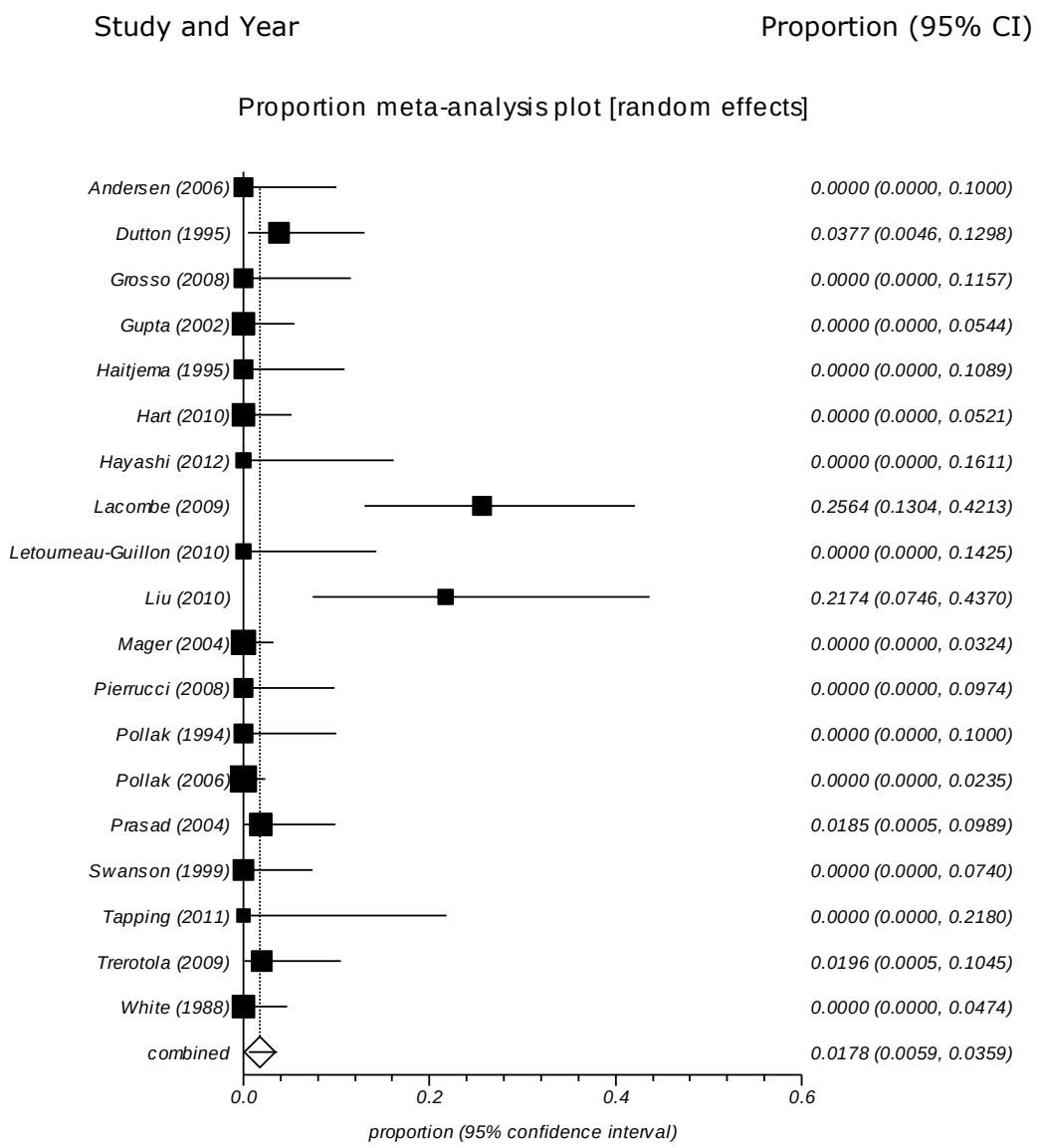
Heterogeneity (I^2) = 77.2%

Figure 6.18. Proportion of embolised patients experiencing ischaemic chest pain



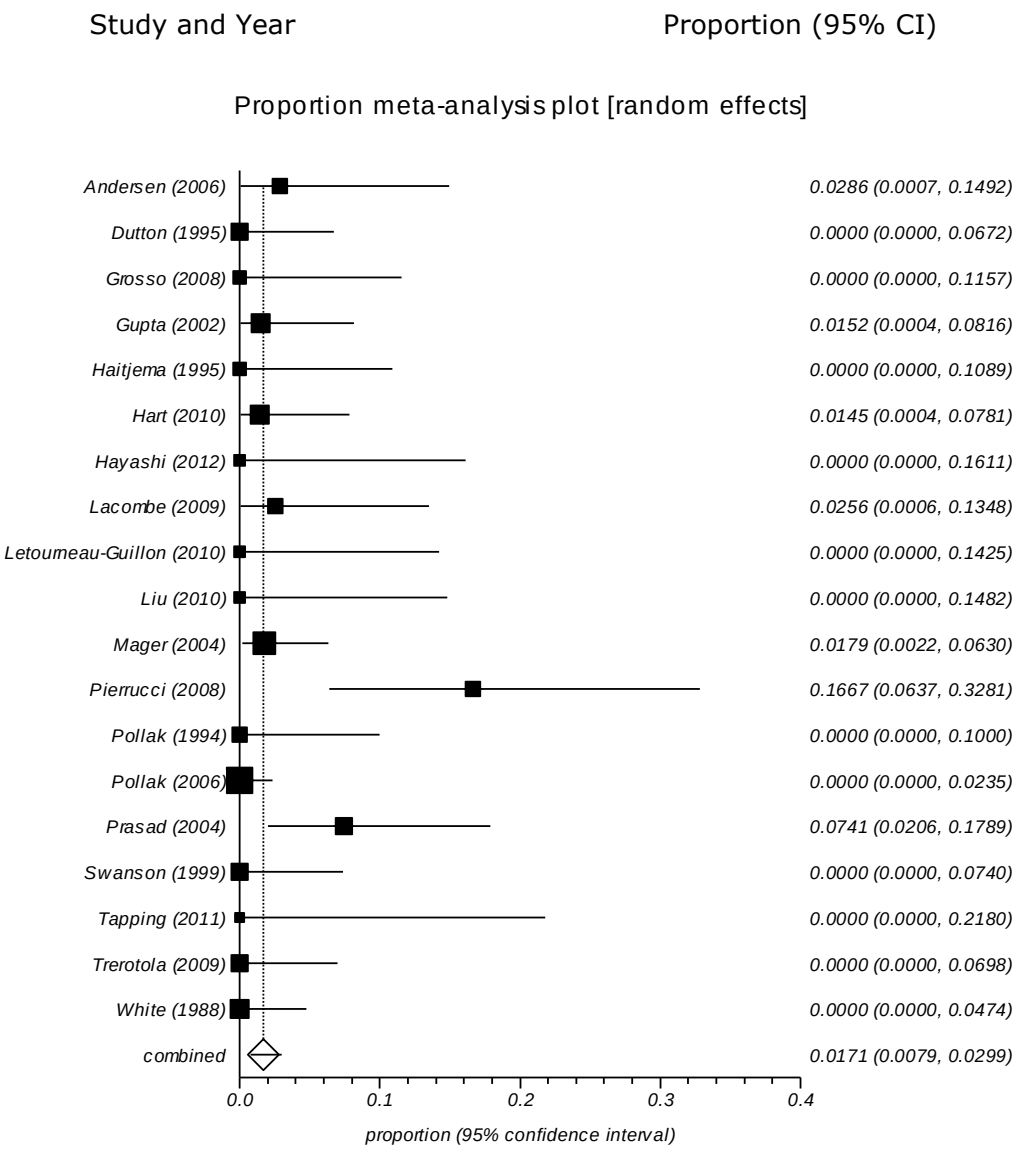
Heterogeneity (I^2) = 25.8%

Figure 6.19. Proportion of embolised patients with 'other' complications



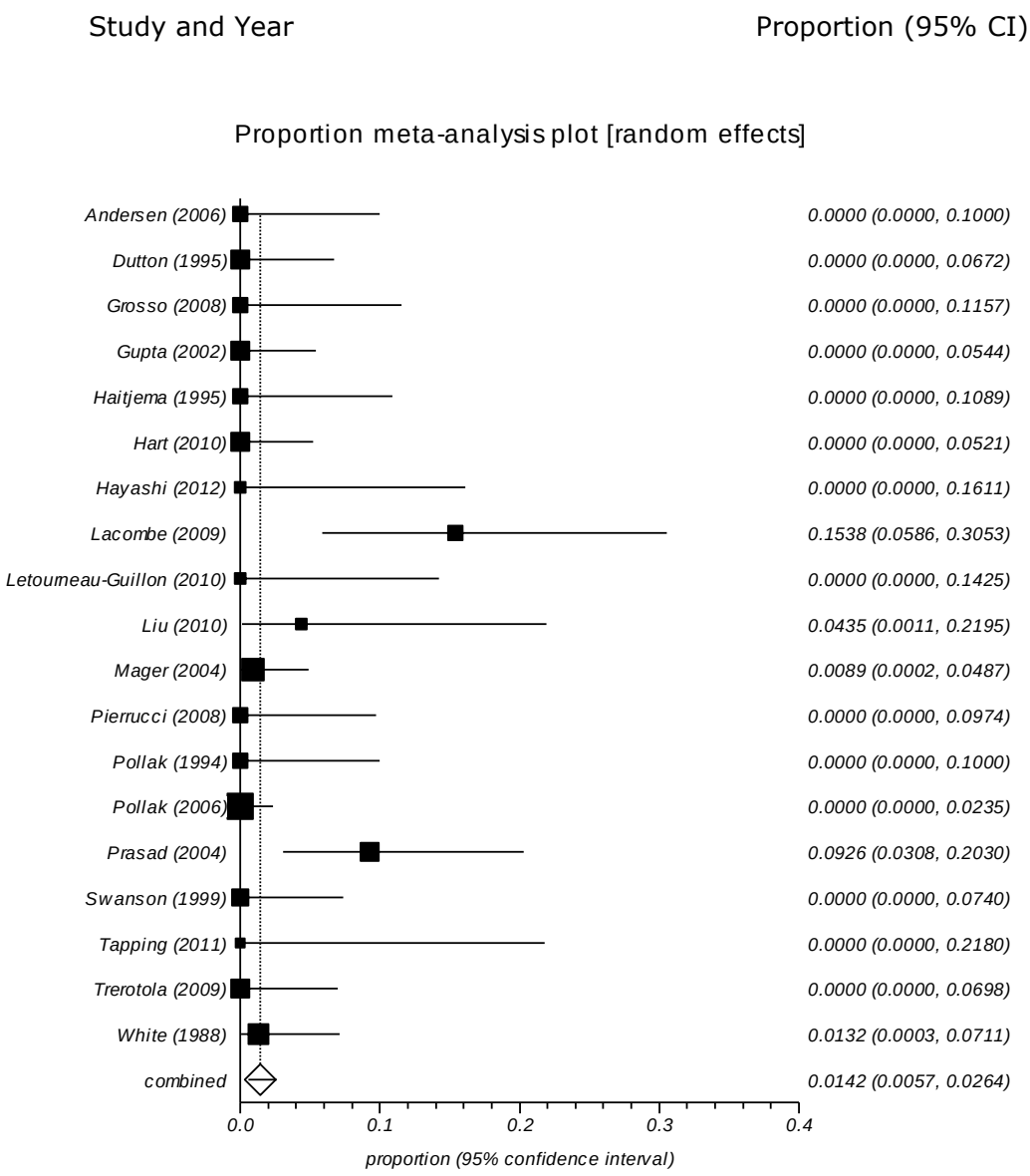
Heterogeneity (I^2) = 67.4%

Figure 6.20. Proportion of embolised patients developing haemoptysis



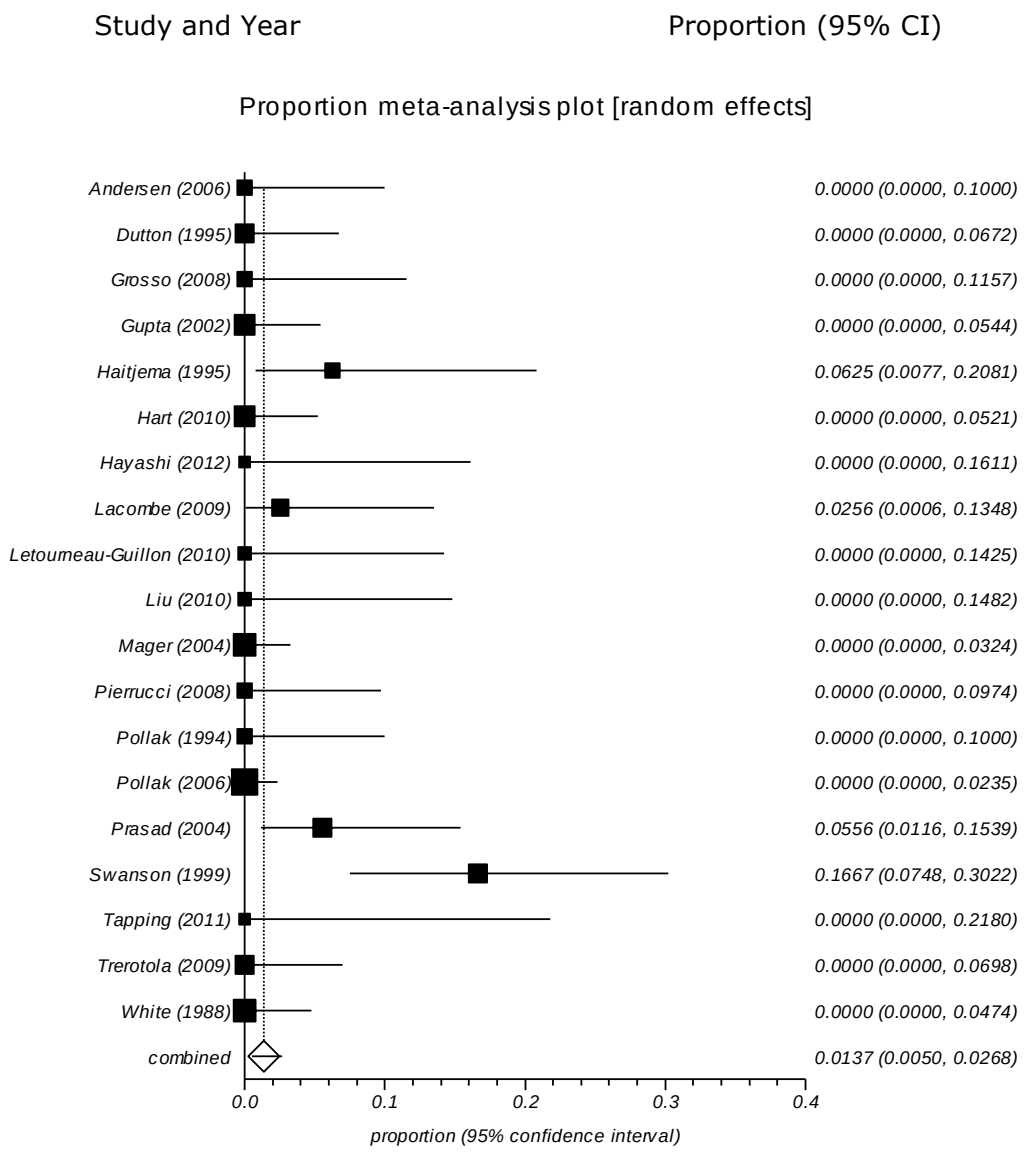
Heterogeneity (I^2) = 41.1%

Figure 6.21. Proportion of embolised patients developing pulmonary infarcts



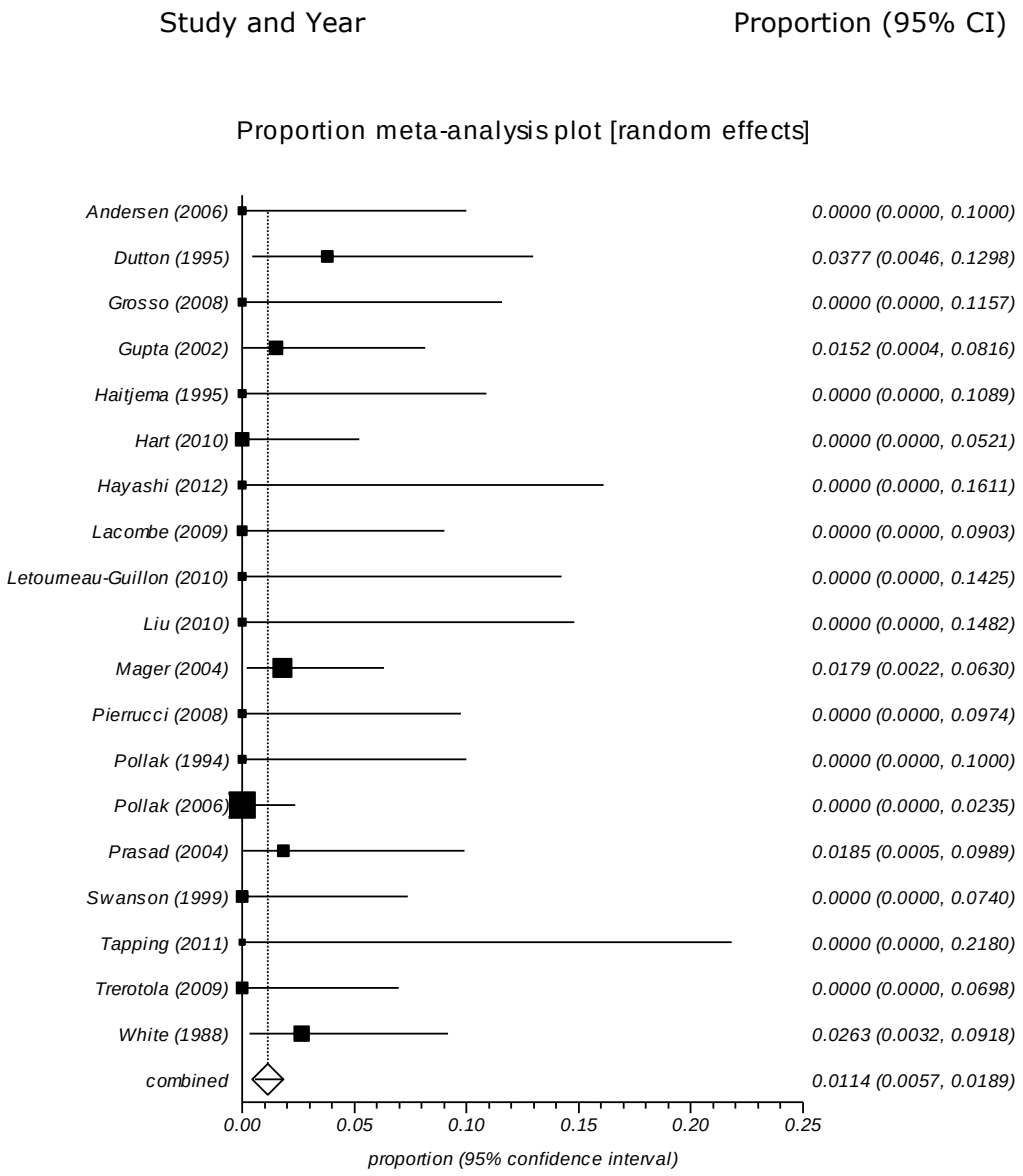
Heterogeneity (I^2) = 44.8%

Figure 6.22. Proportion of embolised patients with uncatheterisable/unoccludable pulmonary arteriovenous malformations



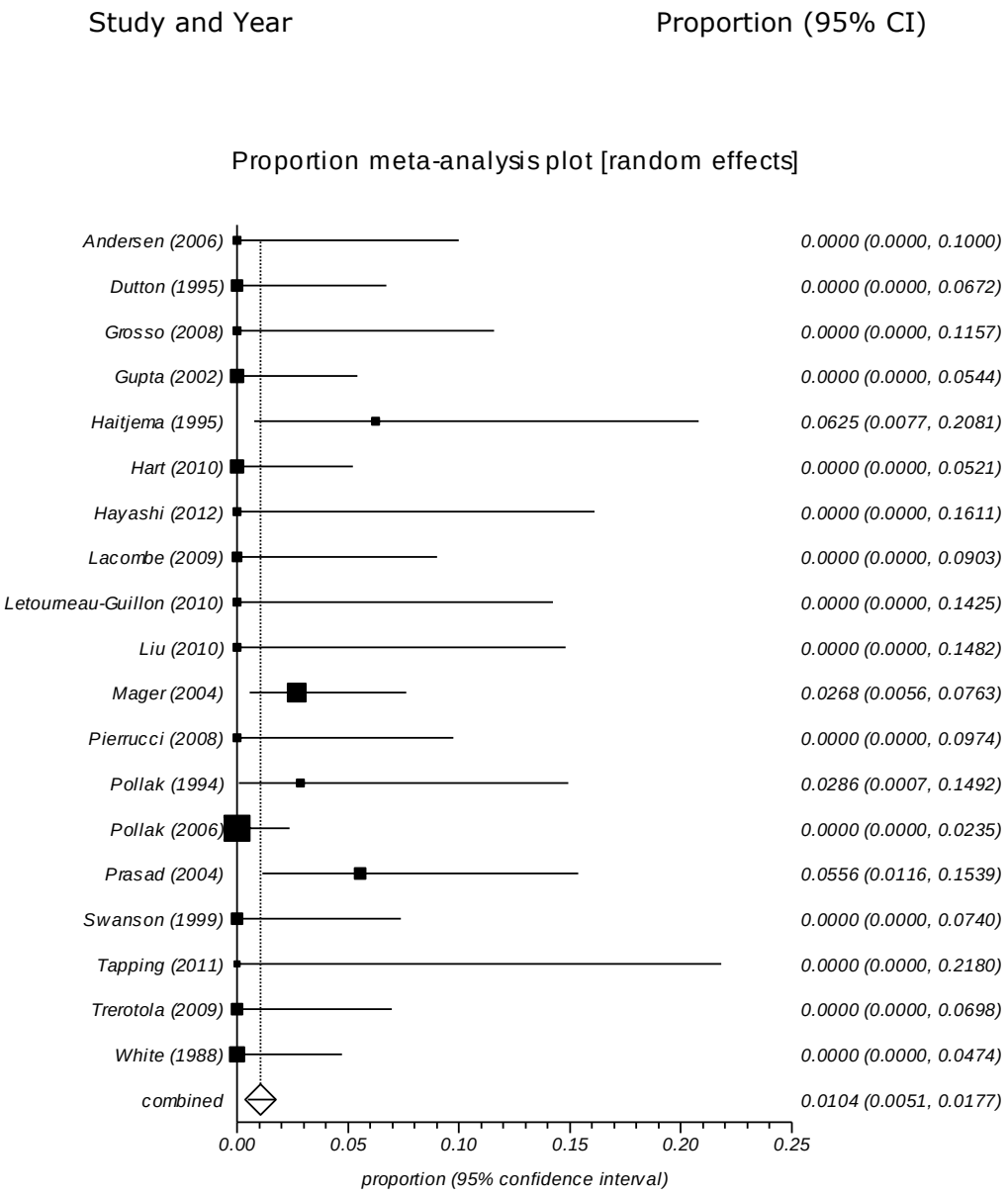
Heterogeneity (I^2) = 51.9%

Figure 6.23. Proportion of embolised patients with device embolism



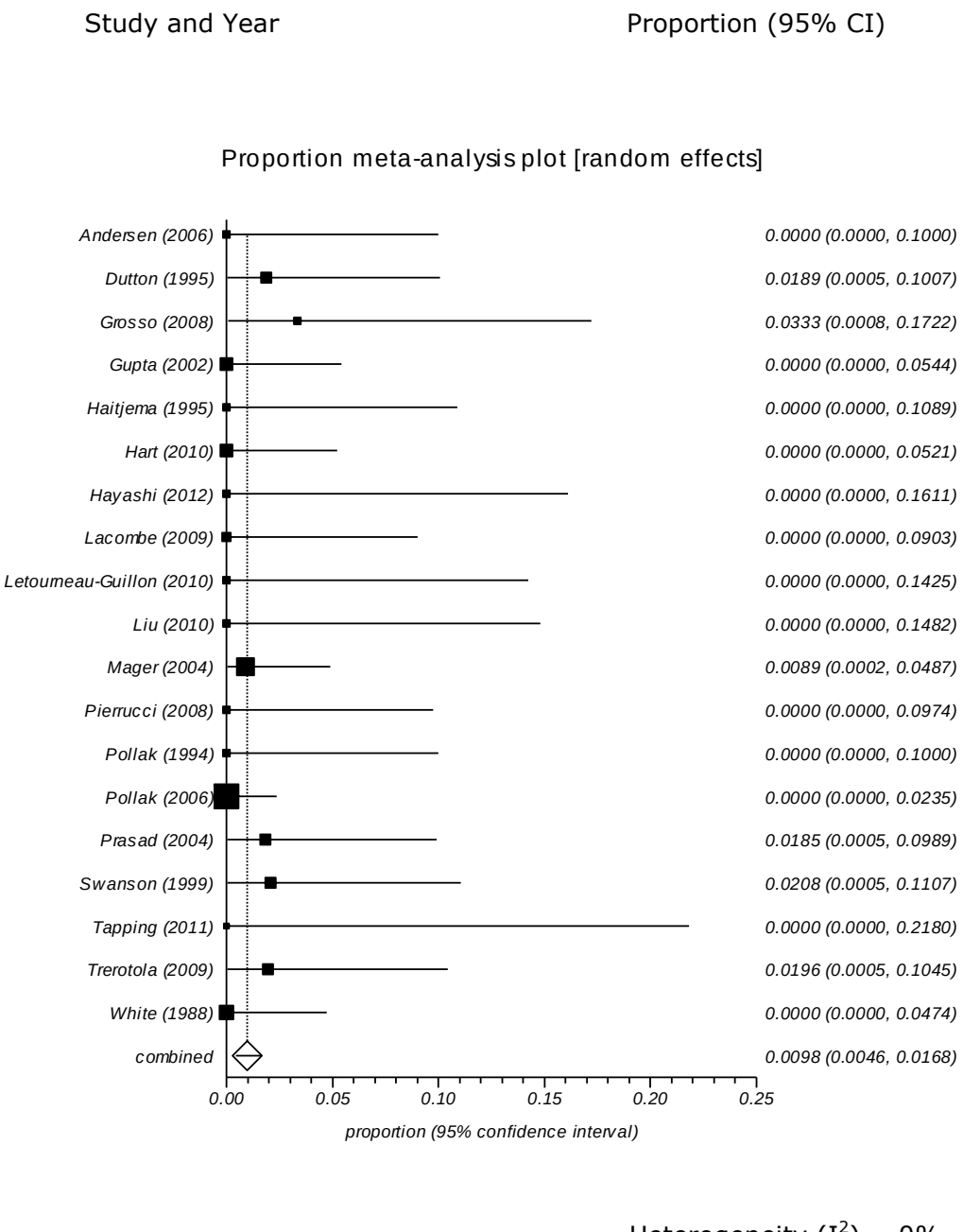
Heterogeneity (I^2) = 0%

Figure 6.24. Proportion of embolised patients with device migration



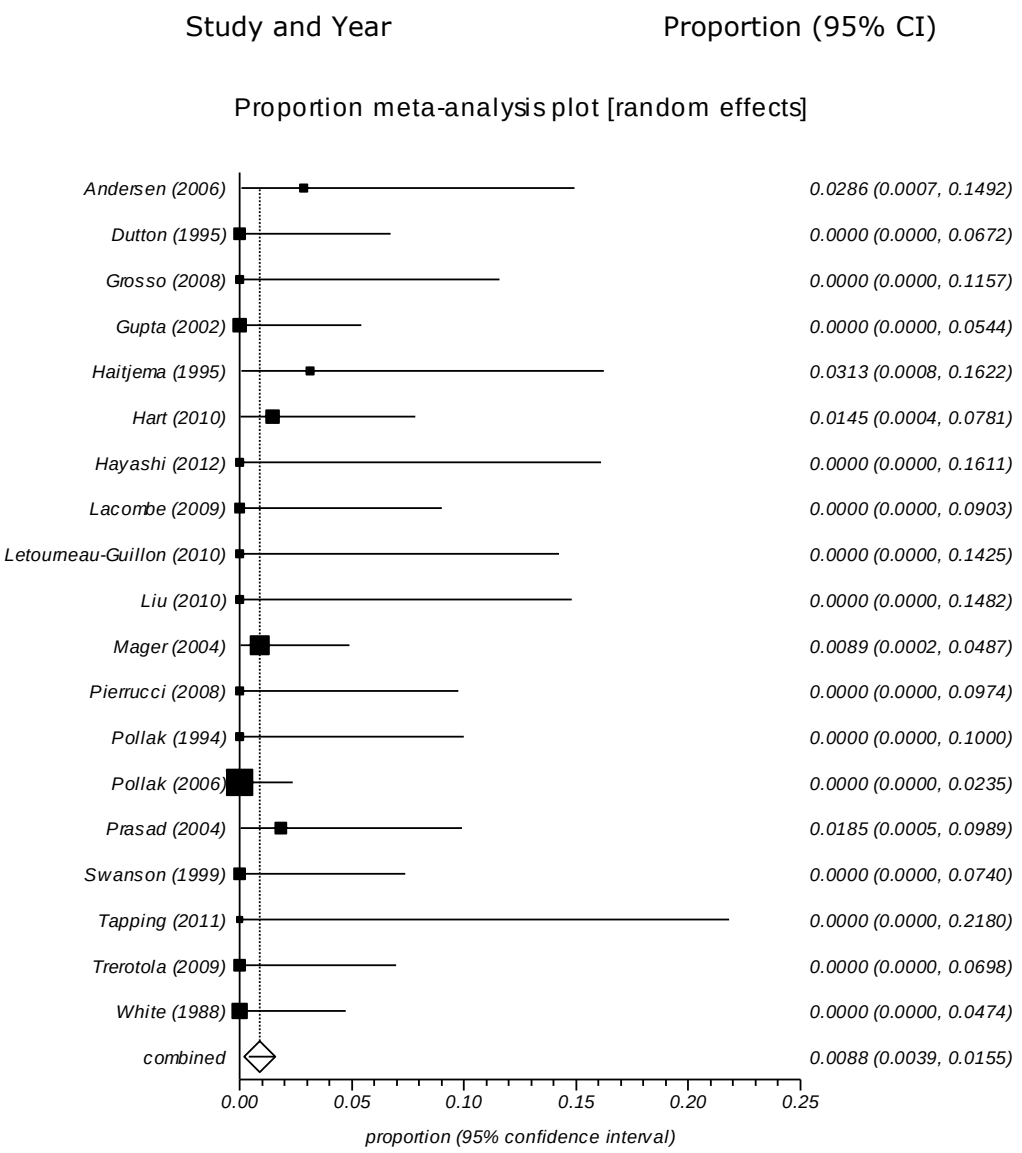
Heterogeneity (I^2) = 0%

Figure 6.25. Proportion of embolised patients developing stroke



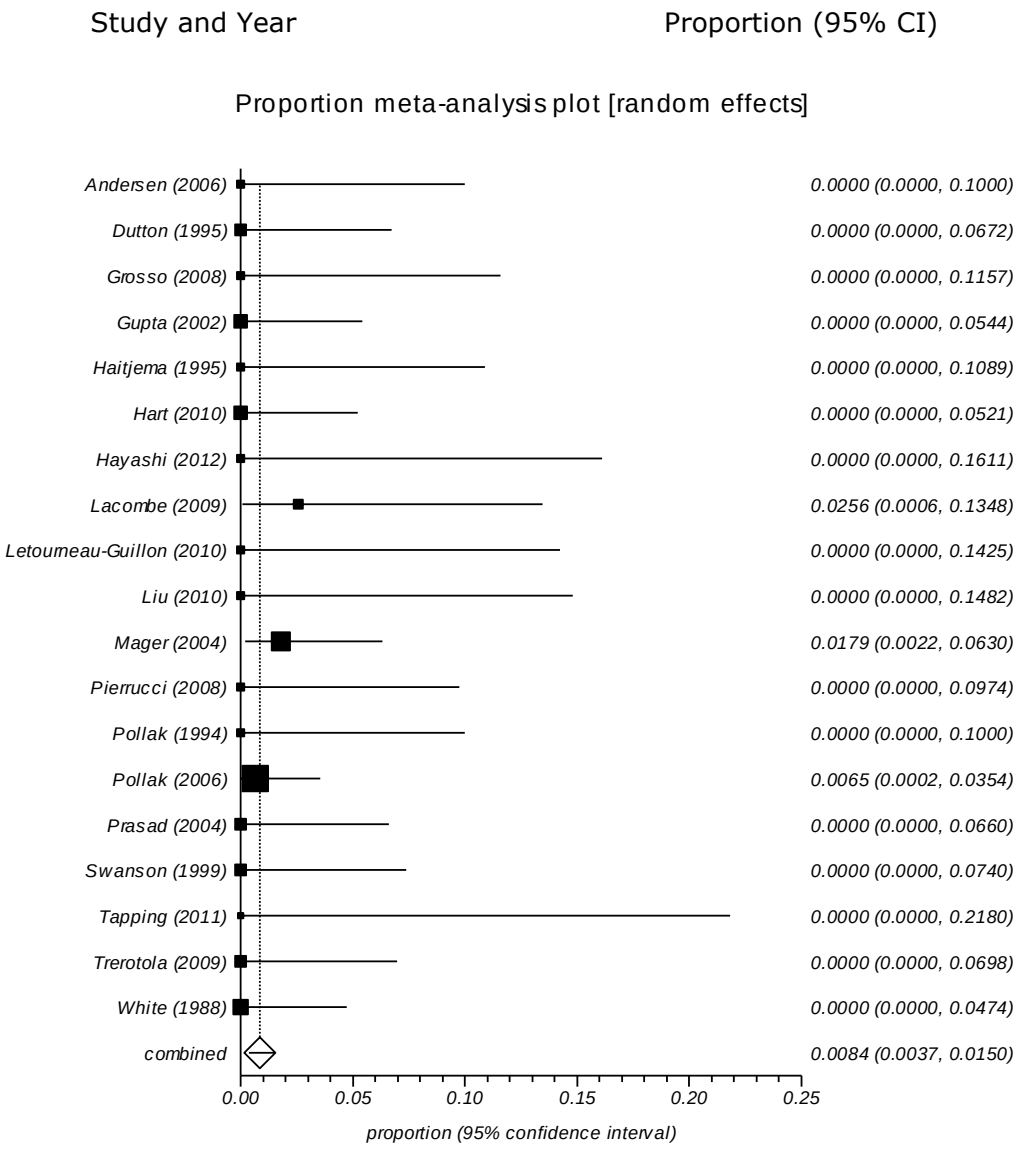
Heterogeneity (I^2) = 0%

Figure 6.26. Proportion of embolised patients developing arrhythmia



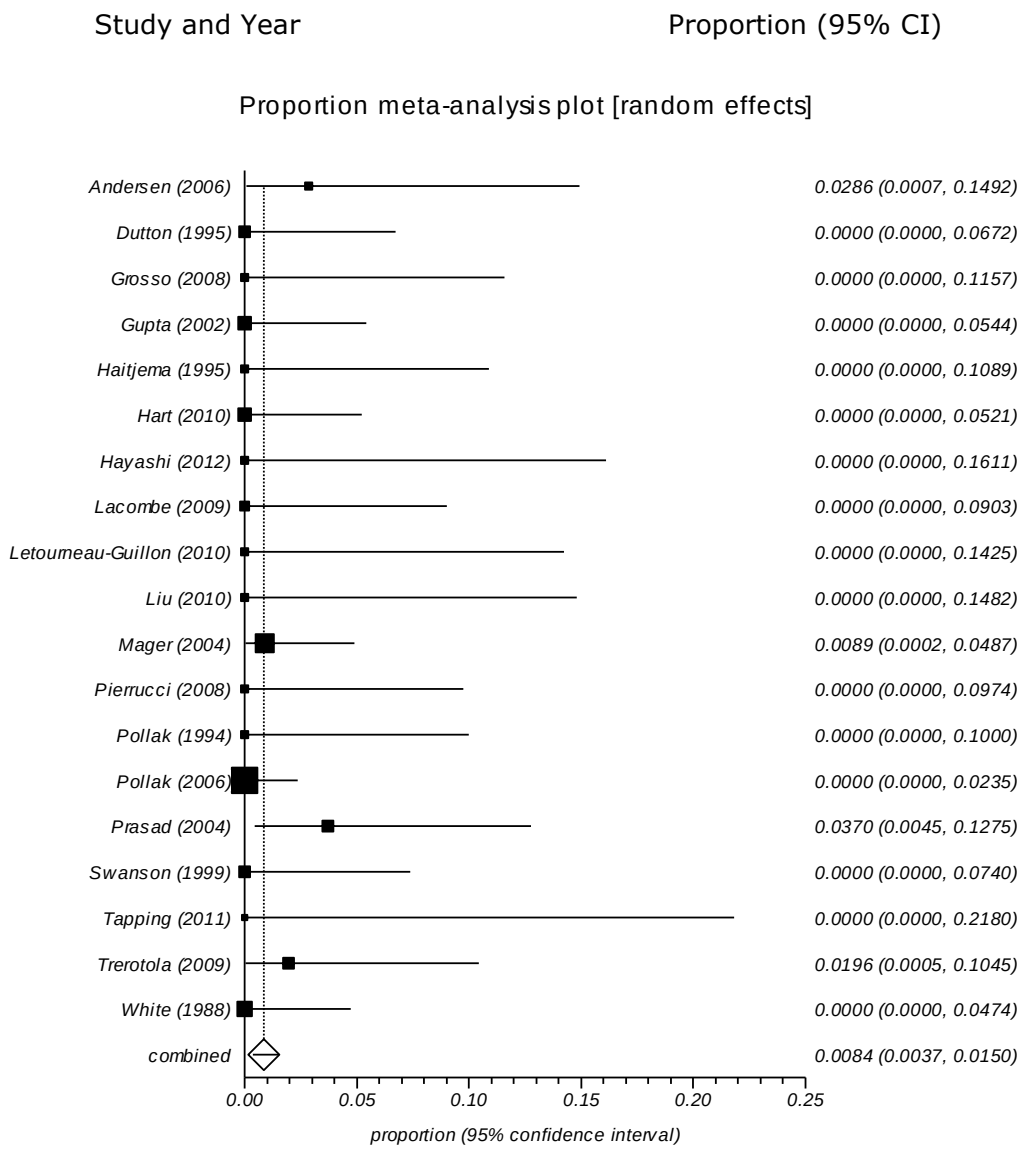
Heterogeneity (I^2) = 0%

Figure 6.27. Proportion of embolised patients developing transient ischaemic attack



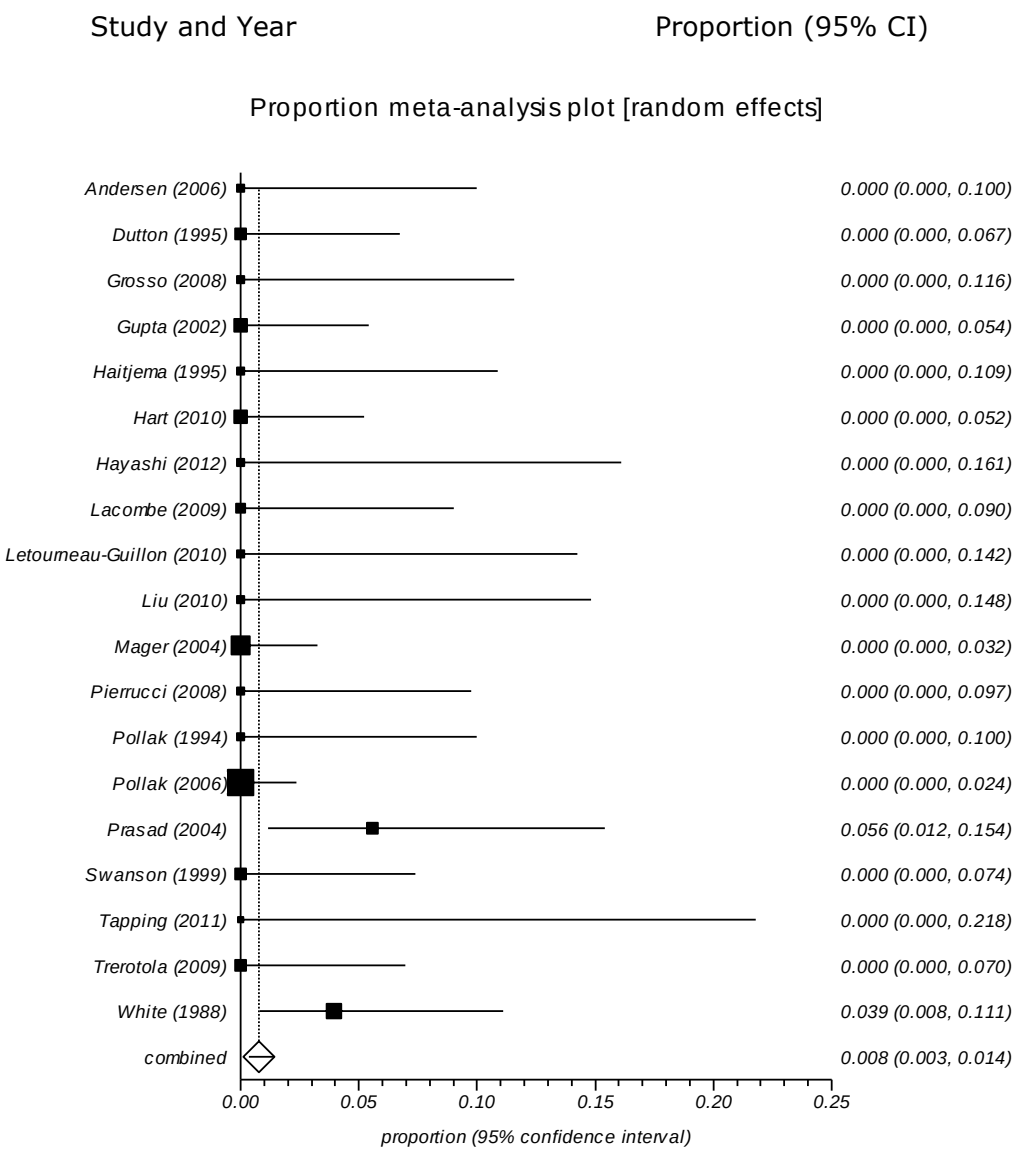
Heterogeneity (I^2) = 0%

Figure 6.28. Proportion of embolised patients developing a groin haematoma



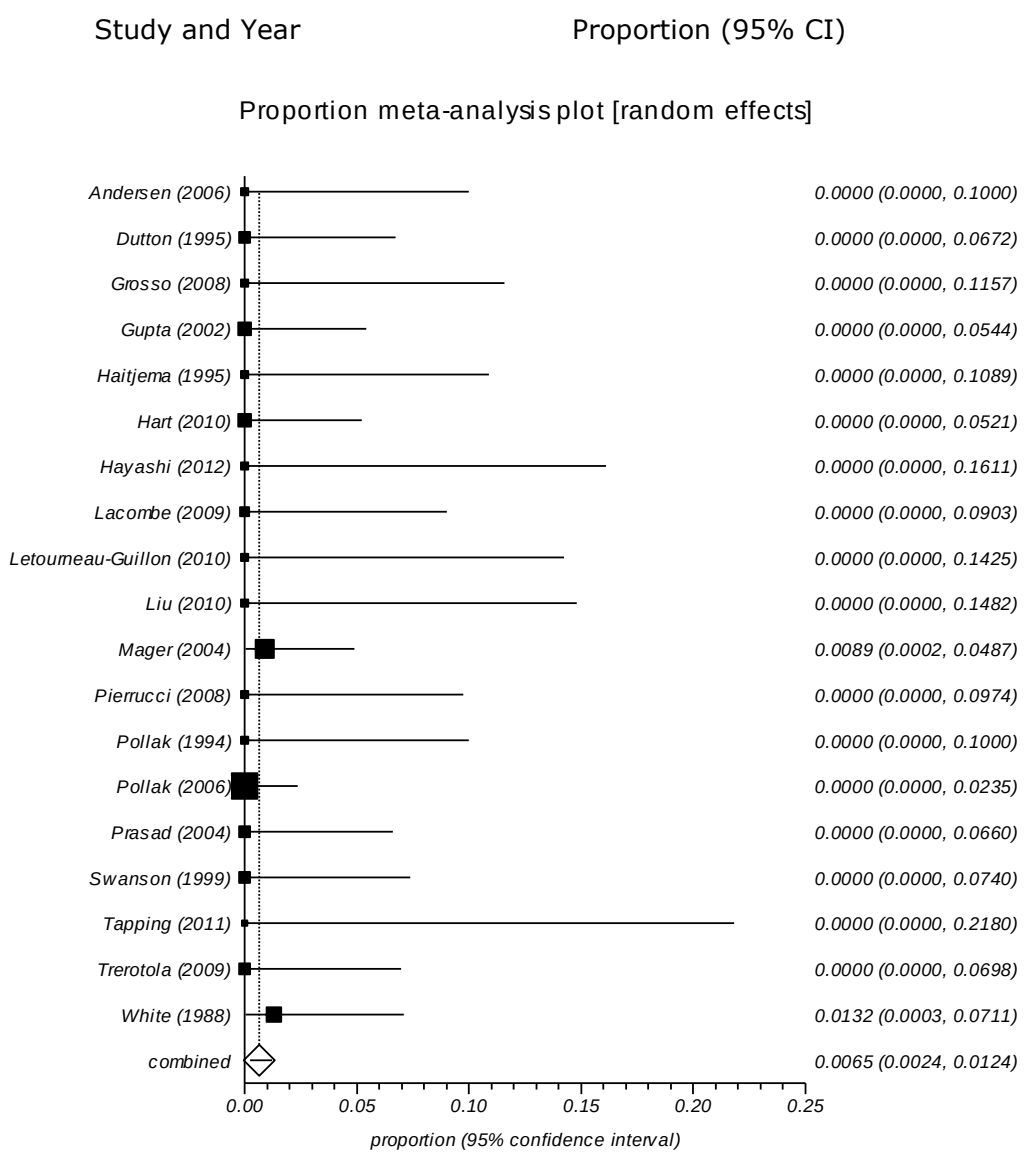
Heterogeneity (I^2) = 0%

Figure 6.29. Proportion of embolised patients developing symptoms of air embolism



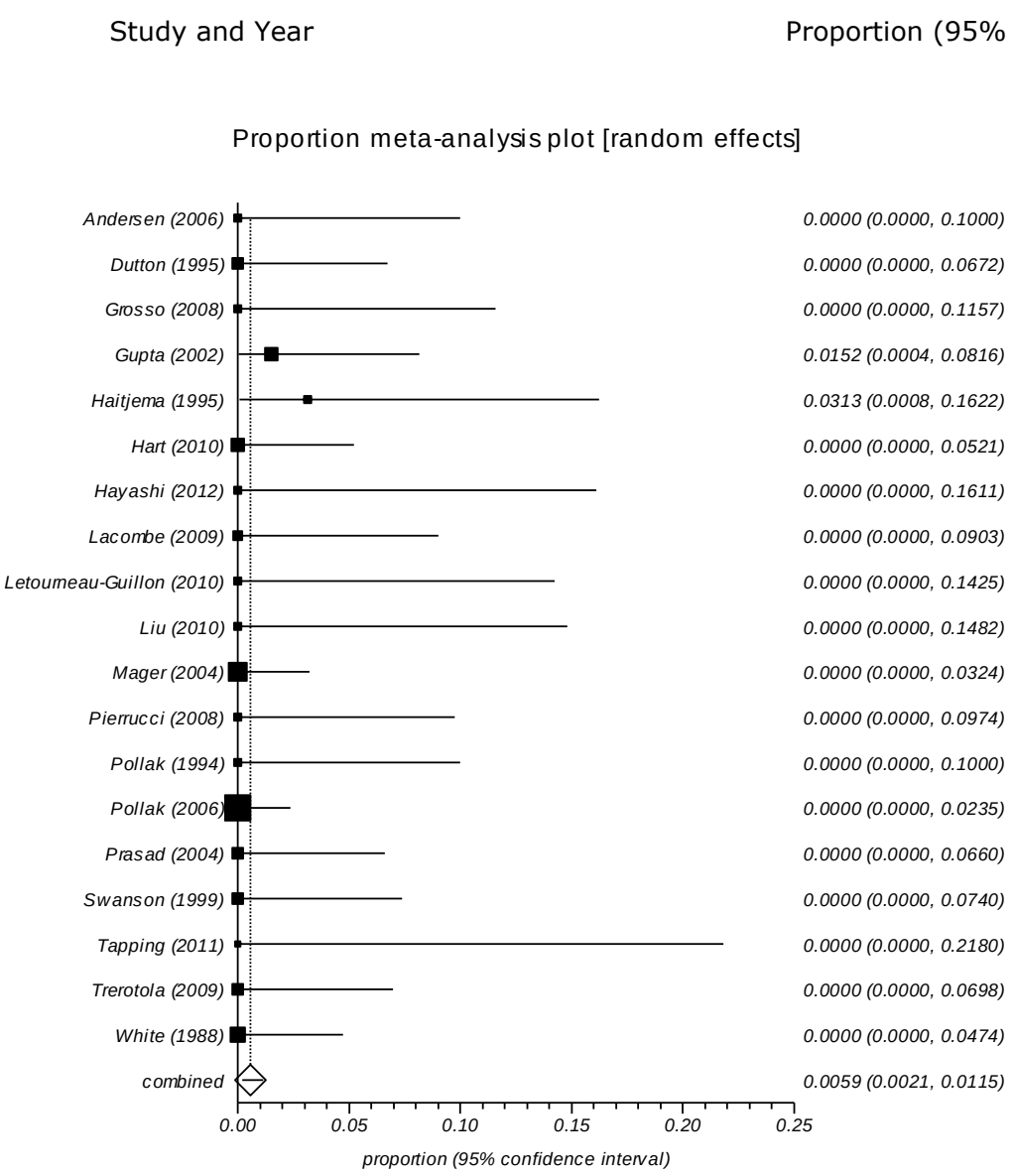
Heterogeneity (I^2) = 41.4%

Figure 6.30. Proportion of embolised patients developing a venous thromboembolic event



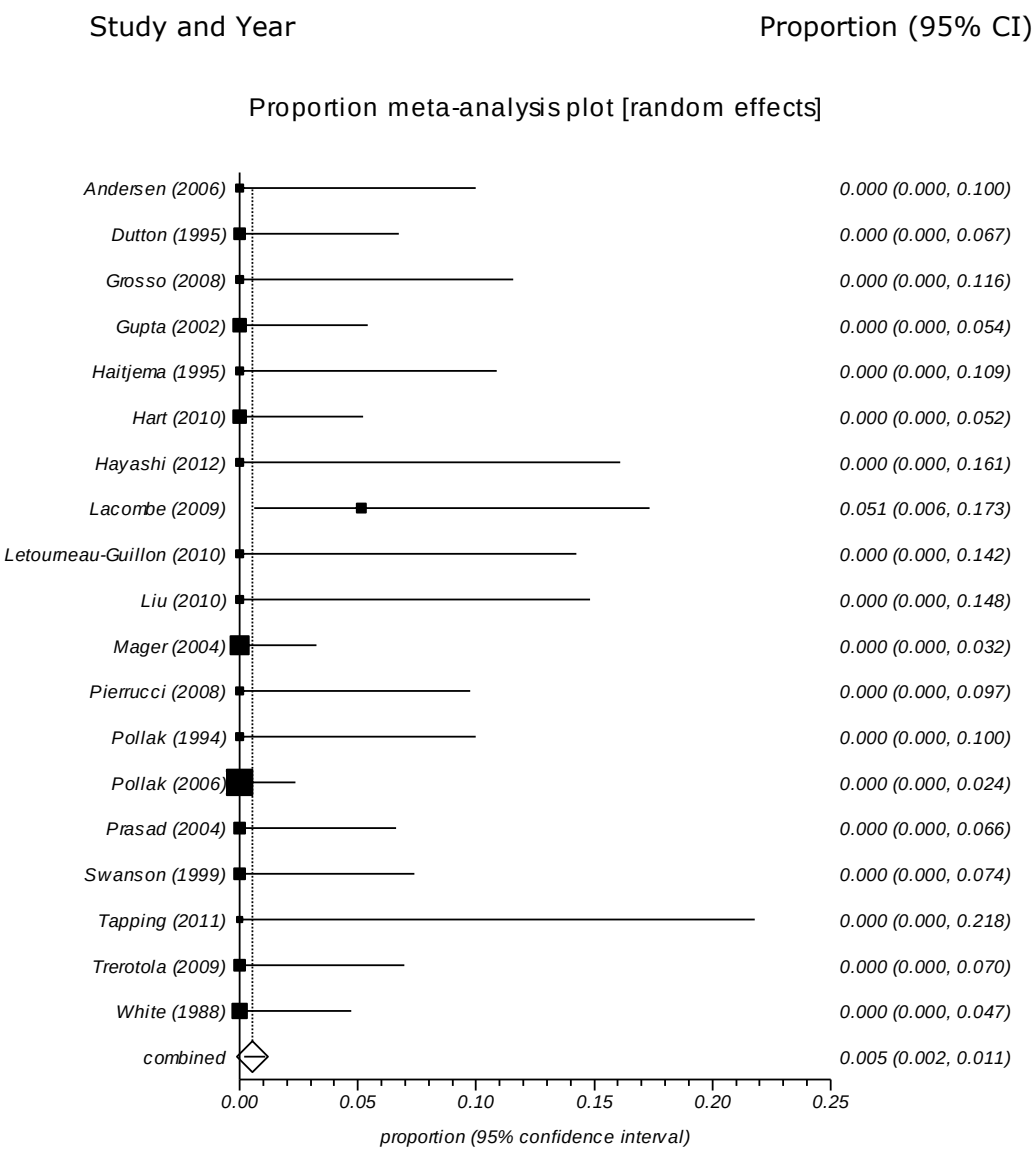
Heterogeneity (I^2) = 0%

Figure 6.31. Proportion of embolised patients developing haemopericardium



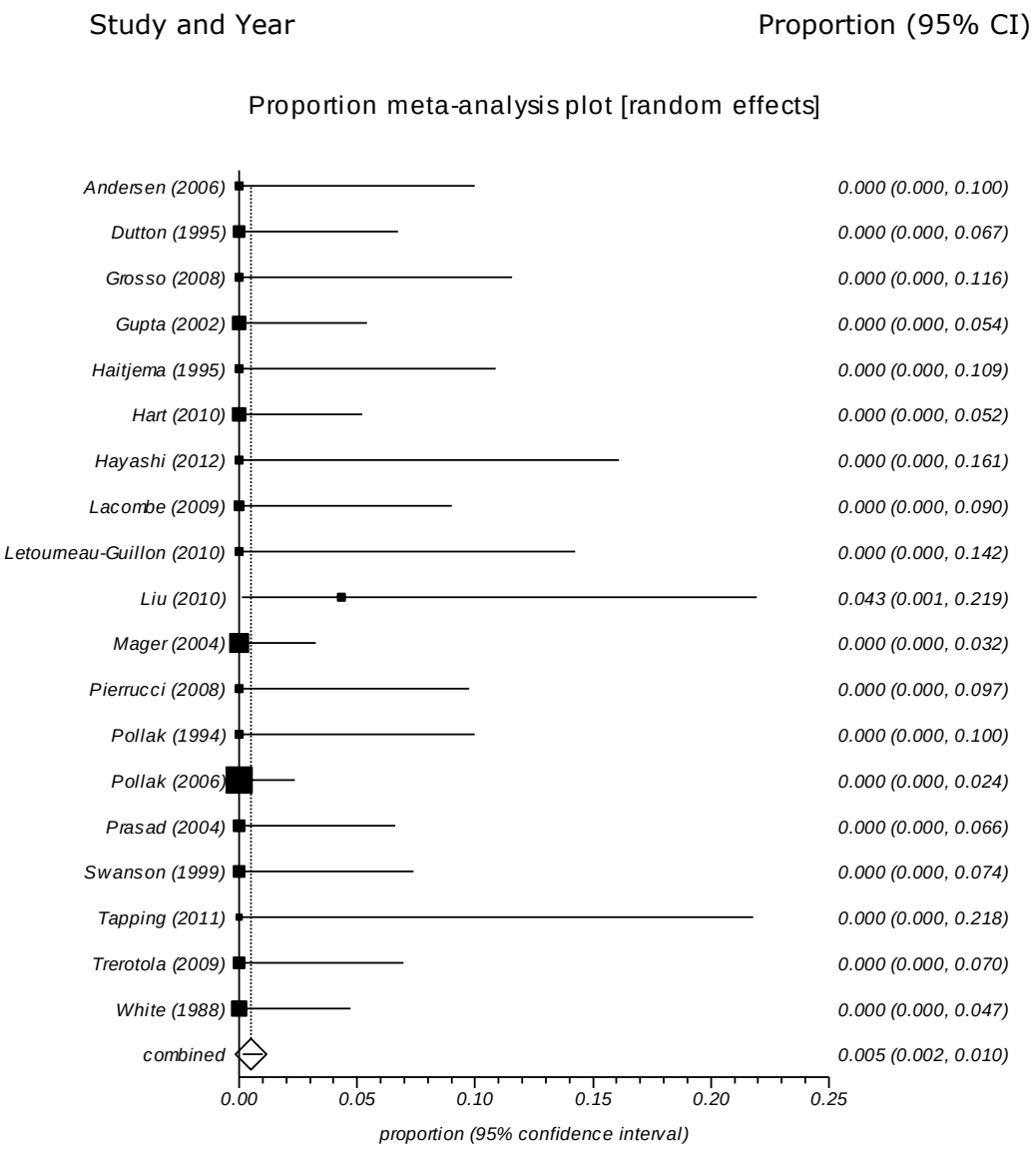
Heterogeneity (I^2) = 0%

Figure 6.32. Proportion of embolised patients with ectopic device deposition



Heterogeneity (I^2) = 0%

Figure 6.33. Proportion of deaths in embolised patients



Heterogeneity (I^2) = 0%

Table 6.6. Sensitivity analysis: peri-procedural complications

	ALL PAPERS			HIGHER QUALITY SCORE[a]			LOWER QUALITY SCORE[b]			NON-SELECTED PATIENT GROUPS ONLY[c]		
Complications	Prevalence	95% CI	Heterogeneity (I^2)	Prevalence	95% CI	Heterogeneity (I^2)	Prevalence	95% CI	Heterogeneity (I^2)	Prevalence	95% CI	Heterogeneity (I^2)
Pleuritic pain/Pleurisy	9.4	5.3-13.6	77.2	11.9	6.3-19.0	81.9	6.8	3.0-12	67.2	9.2	5.8-13.3	72.7
Ischaemic chest pain	2.2	1.2-3.4	25.8	2.1	1.1-3.4	3.9	2.4	0.7-5.0	45.7	2.2	1.2-3.6	30.8
Other†	1.8	0.6-3.6	67.4	1.8	0.3-4.7	75.2	1.7	0.3-4.4	57.6	1.1	0.4-2.2	36.5
Haemoptysis	1.7	0.8-3.0	41.1	2.8	0.9-5.7	65.4	0.8	0.2-1.9	0	1.2	0.6-2.0	0
Pulmonary Infarct	1.4	0.6-2.6	44.8	1.9	0.4-4.4	68.7	1.0	0.3-2.2	0	1.0	0.4-1.8	7.4
Uncatheterisable/ Unoccludable PAVM	1.4	0.5-2.7	51.8	0.8	0.2-1.8	12.8	2.0	0.3-5.3	67.8	1.3	0.4-2.8	55.7
Device Embolism	1.2	0.6-1.9	0	1.0	0.4-1.9	0	1.4	0.5-2.8	0	1.2	0.6-2.0	0
Device Migration	0.8	0.5-1.8	0	1.1	0.4-2.2	17.1	1.0	0.3-2.3	0	1.1	0.5-2.0	10.3
Stroke	0.9	0.5-1.7	0	0.8	0.3-1.7	0	1.2	0.4-2.6	0	1.0	0.5-1.8	0
Arrhythmia	0.9	0.4-1.6	0	0.8	0.3-1.7	0	1.0	0.3-2.2	0	0.9	0.4-1.6	0
Transient Ischaemic Attack	0.8	0.4-1.5	0	1.1	0.4-2.0	0	0	0	0	0.8	0.3-1.4	0
Groin Hematoma	0.8	0.4-1.5	0	1.1	0.4-2.0	0	0	0	0	0.9	0.4-1.6	0
Air Embolism	0.8	0.3-1.4	0	0.6	0.1-1.4	0	1.1	0.3-2.4	0	0.8	0.3-1.5	0
Venous Thromboembolism	0.6	0.2-1.2	0	0.6	0.1-1.3	0	0.8	0.2-1.9	0	0.7	0.2-1.3	0
Haemopericardium	0.6	0.2-1.2	0	0	0	0	0.7	0.1-1.8	0	0.6	0.2-1.2	0
Ectopic Device Deposition	0.6	0.2-1.1	0	0.5	0.1-1.3	0	0	0	0	0	0	0
Death	0.5	0.2-1.0	0	0	0	0	0.7	0.1-1.8	0	0.5	0.1-1.0	0

Prevalence estimates, Confidence intervals (CI) and heterogeneity estimates are all expressed as percentages
*See Table 1 (main manuscript) for a list of 'other' complications
[a]Quality score >8
[b]Quality score <=8
[c]Papers considering diffuse, large or idiopathic PAVMs excluded from analysis

6.3.3 Results: meta-analysis of long-term complications

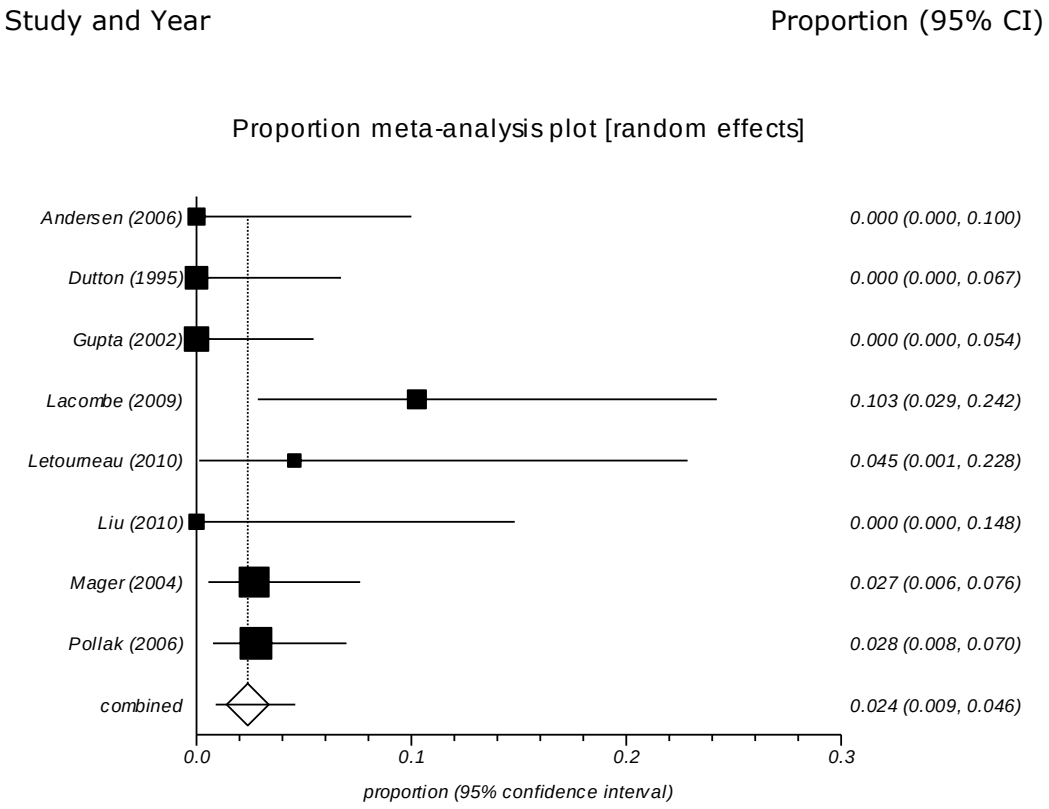
Over a median period of follow-up of 39 months in 8 studies including 494 patients there were a total of 2 deaths, neither of which were attributed by the original authors to the complications of HHT or its treatment. One patient had a cardiorespiratory arrest after appendix surgery the second patient was found, at post-mortem examination, to have died of pneumonia. One death was a complication of intrahepatic shunt insertion for liver telangiectases. The commonest long-term complications in patients embolised for PAVMs were TIA (prevalence 2.5%, 95% CI 0.9-4.9%, I^2 54.4%), cerebral abscess (prevalence 2.1%, 95% CI 1.1-3.3%, I^2 0%) and haemoptysis (prevalence 1.1%, 95% CI 0.3-2.6%, I^2 41.5%). (Table 6.7, Figure 6.34 - Figure 6.38). There was no evidence of significant heterogeneity between prevalence estimates of long-term complications and thus a sensitivity analysis was not undertaken for this variable.

Table 6.7. Meta-analysis of long-term complications occurring in patients with pulmonary arteriovenous malformations post-embolisation

Long-term Complications	Prevalence (%)	95% CI	Heterogeneity (I^2) (%)	Figure
Transient ischaemic attack	2.4	0.9-4.6	41.4	6.34
Cerebral abscess	2.1	1.1-3.3	0	6.35
Haemoptysis	1.1	0.3-2.5	35.9	6.36
Stroke	0.5	0.06-1.3	0	6.37
Total deaths	0.6	0.1-1.5	0	6.38
Total deaths attributable to HHT*	0	0	0	
Death directly due to HHT disease*	0	0	0	
Death due to intervention for PAVM*	0	0	0	
Haemothorax*	0	0	0	
Venous thromboembolism*	0	0	0	
Pulmonary Hypertension*	0	0	0	

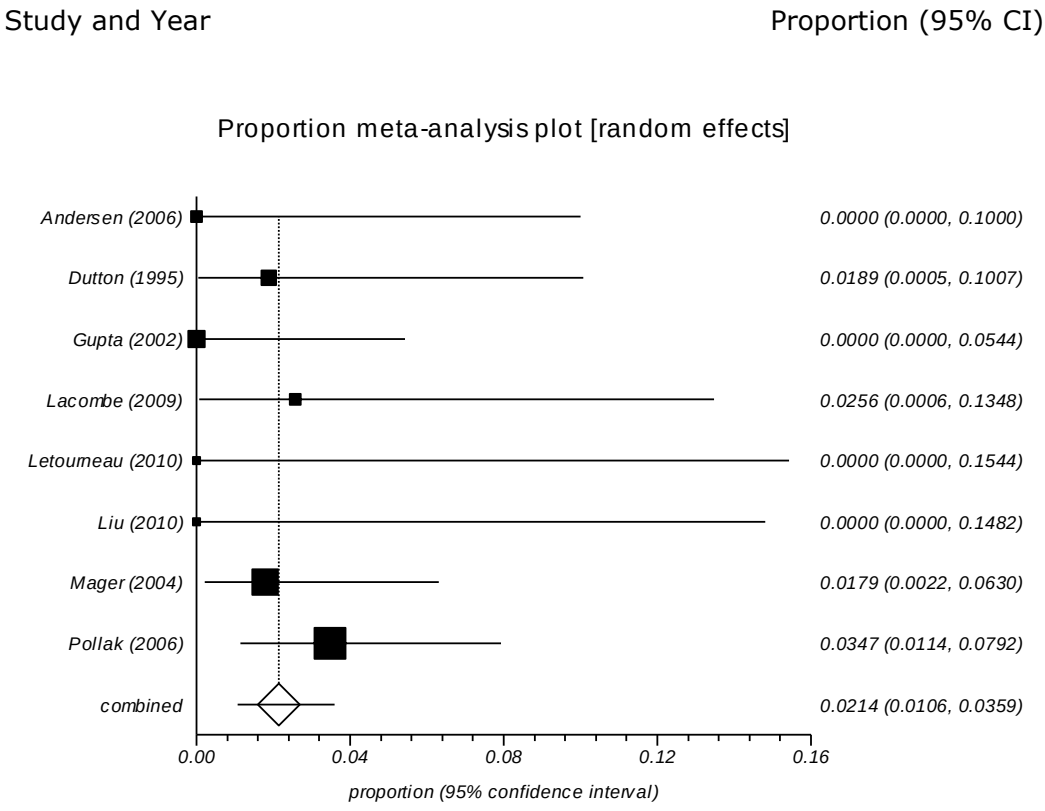
*No cases recorded in the examined literature and thus box plots of prevalence not reproduced below

Figure 6.34. Proportion of patients experiencing a transient ischaemic attack over long-term follow-up post-embolisation



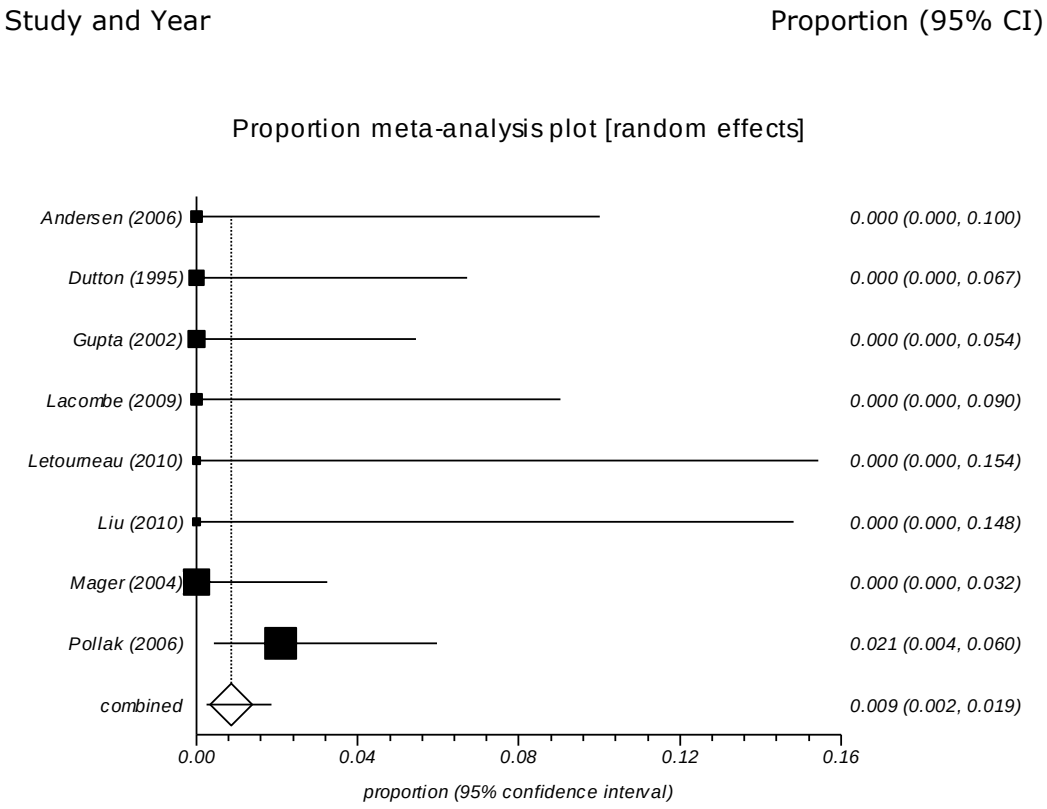
Heterogeneity (I^2) = 41.4%

Figure 6.35. Proportion of patients with cerebral abscess diagnosed over long-term follow-up post-embolisation



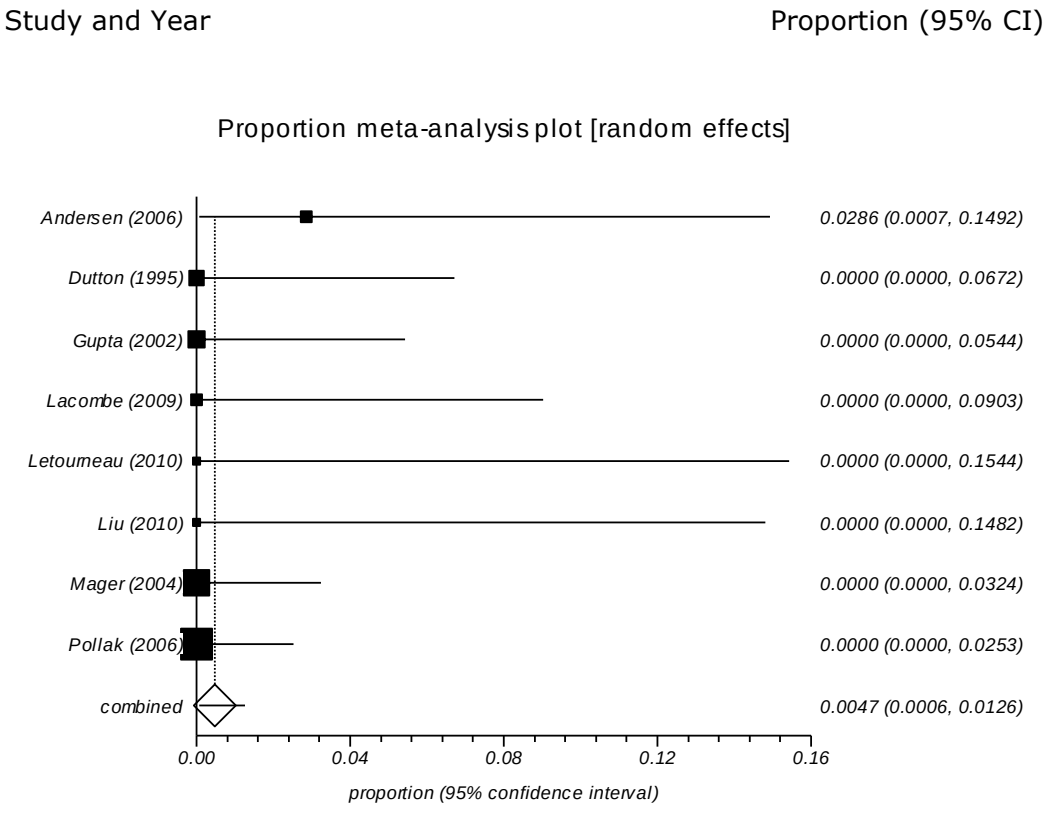
Heterogeneity (I^2) = 0%

Figure 6.36. Proportion of patients experiencing haemoptysis over long-term follow-up post-embolisation



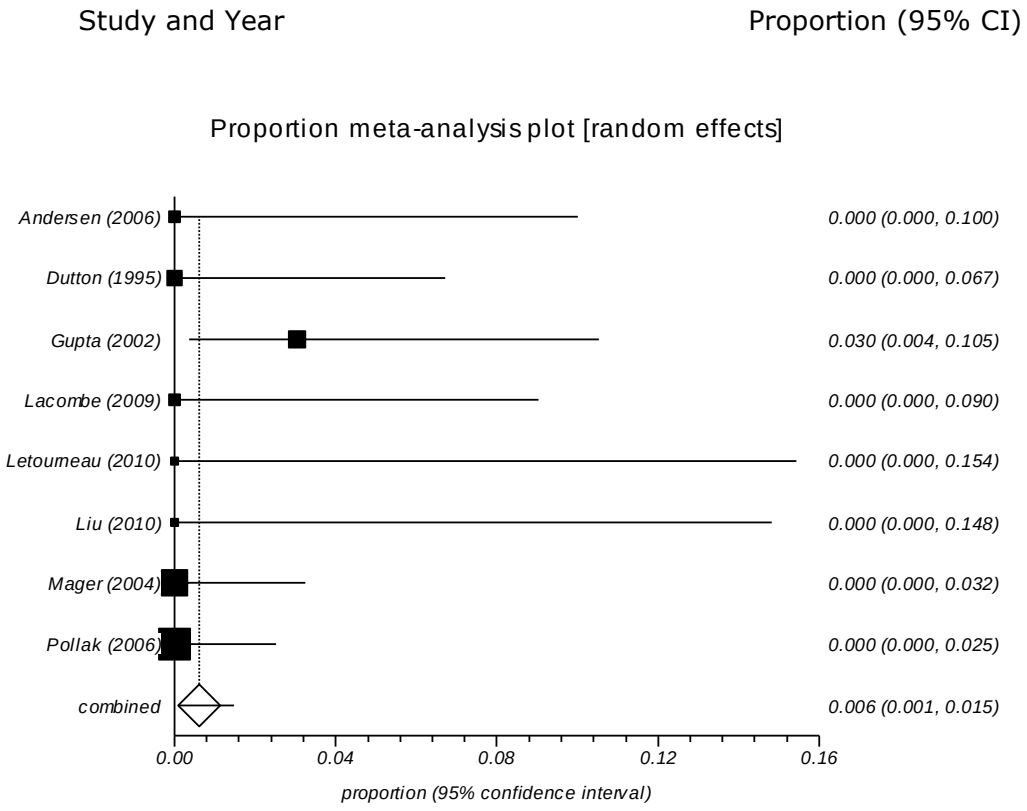
Heterogeneity (I^2) = 0%

Figure 6.37. Proportion of patients developing stroke over long-term follow-up post-embolisation



Heterogeneity (I^2) = 0%

Figure 6.38. Proportion of total deaths over long-term follow-up post-embolisation



Heterogeneity (I^2) = 0%

6.3.4 Results: meta-analysis of embolisation success rate

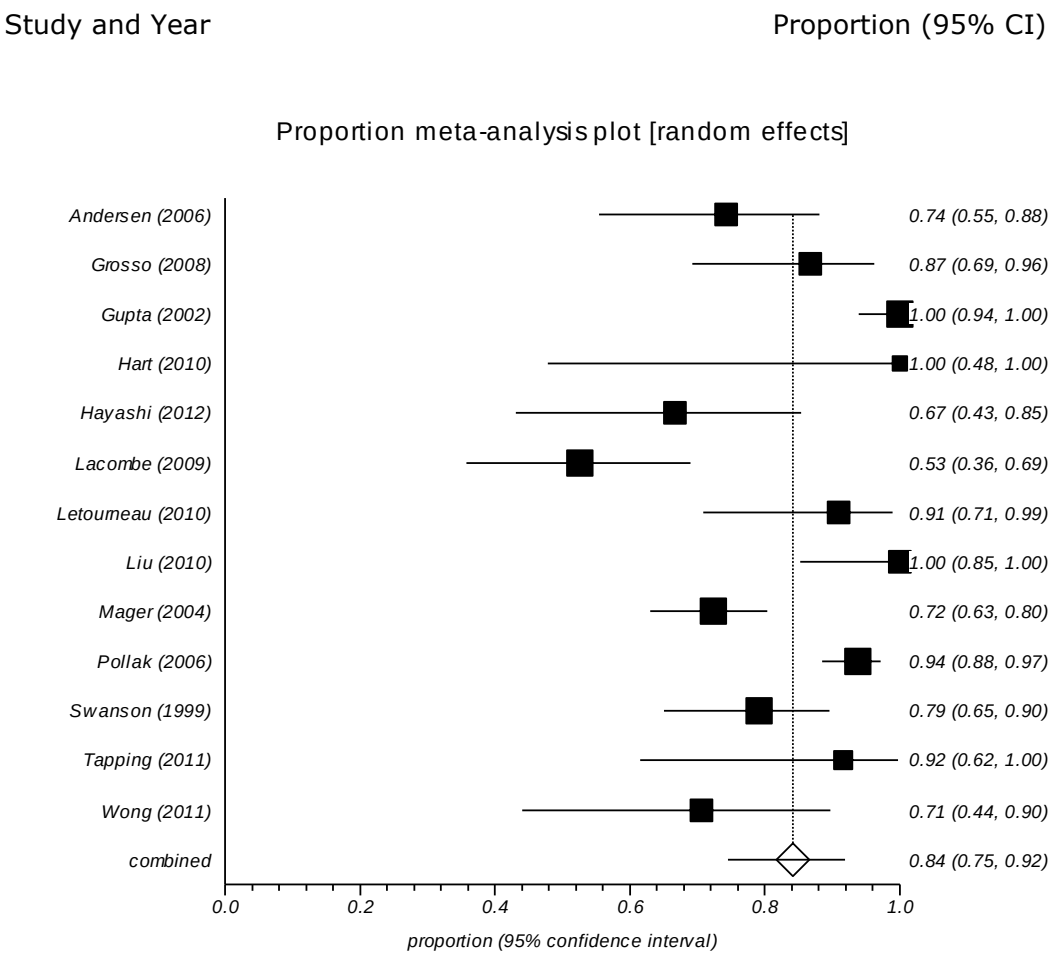
The overall procedural success rate for individual patients was 84% (95% CI 75-92%, I^2 87%, 13 studies, 561 patients) over a median follow-up period of 41 months. The overall success rate of embolisation for individual PAVMs was 90% (95% CI 83-95%, I^2 93%, 10 studies, 1444 PAVMs) (Table 6.8 and Figure 6.39 - Figure 6.43). When only studies with at least 12 months follow-up using either thoracic CT or pulmonary angiography, and with < 20% loss to follow-up, were analysed the success rate by patient was 82% (95% CI 67-93%, I^2 87%, 7 studies, 294 patients) and by PAVM was 88% (95% CI 79-95%, I^2 95%, 6 studies, 825 PAVMs) (Figure 6.42). Studies where coils alone (steel, platinum, or both) were used had a success rate of 80% by patient (95% CI 58-95%, I^2 91%, 5 studies, 243 patients). Studies using coils in combination with the Amplatzer device had a success rate of 86% by patient (95% CI 74-95%, I^2 86%, 7 studies, 251 patients). It was not possible to calculate success rates for balloon embolisation alone or use of the Amplatzer device alone. Heterogeneity existed but was not attributable to study methodological quality nor whether included studies focussed solely on non-selected populations (see definition above) (Table 6.9). We calculate a post-embolisation recanalisation rate of 5.9% (across all embolised PAVMs, not solely those reperfused) (95% CI 3.3-9.4, I^2 80, from 9 studies and 1394 PAVMs embolised).

Table 6.8. Meta-analysis of procedural success rate of percutaneous embolisation for pulmonary arteriovenous malformations (by patient and by PAVM)

	Patients			Population	Figure	Pulmonary AVMs			Population	Figure
	Prevalence (%)	95% CI	Heterogeneity (I^2) (%)	Studies / Patients		Prevalence (%)	95% CI	Heterogeneity (I^2) (%)	Studies / PAVMs	
Overall success rate	84	75-92	87	13 / 561	6.39	0	83-95	93	10 / 1444	6.40
By Device used*										
Coils alone	80	58-95	91	5 / 243		87	70-97	97	5 / 880	6.41
Mixed (Coils and Amplatzer)	86	74-95	86	7 / 251		-**	-	-	-	
Follow-up										
CT or angiography follow-up for > 12 months **and** < 20% loss to follow-up	82	67-93	87	7 / 294		88	79-95	90	6 / 825	6.42
Recanalisation rate	5.1	1.2-11.4	83	10 / 493		5.9	3.3-9.4	80	9 / 1394	6.43

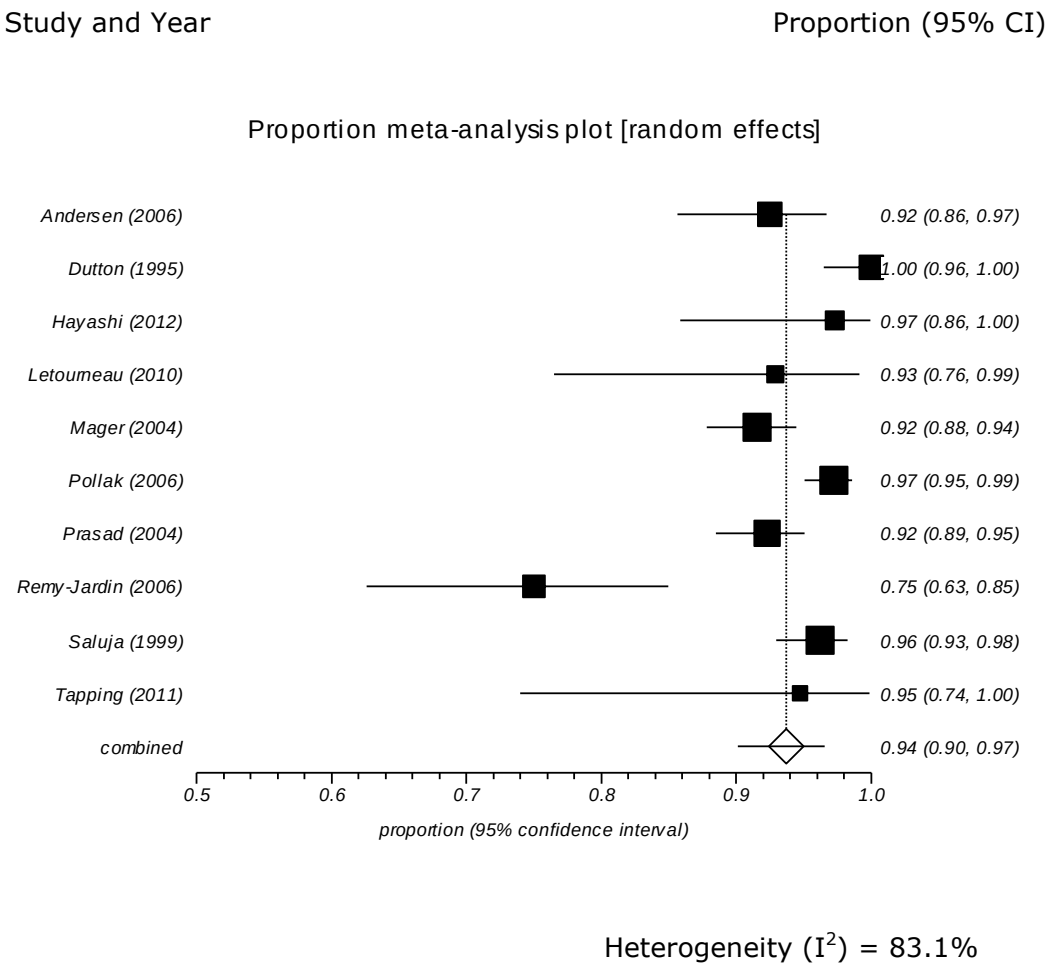
*Insufficient studies published to look at success rate for either balloon embolisation alone or Amplatzer alone
** only one study using a combination of coils and Amplatzer devices

Figure 6.39. Overall embolisation success rate (by patient)



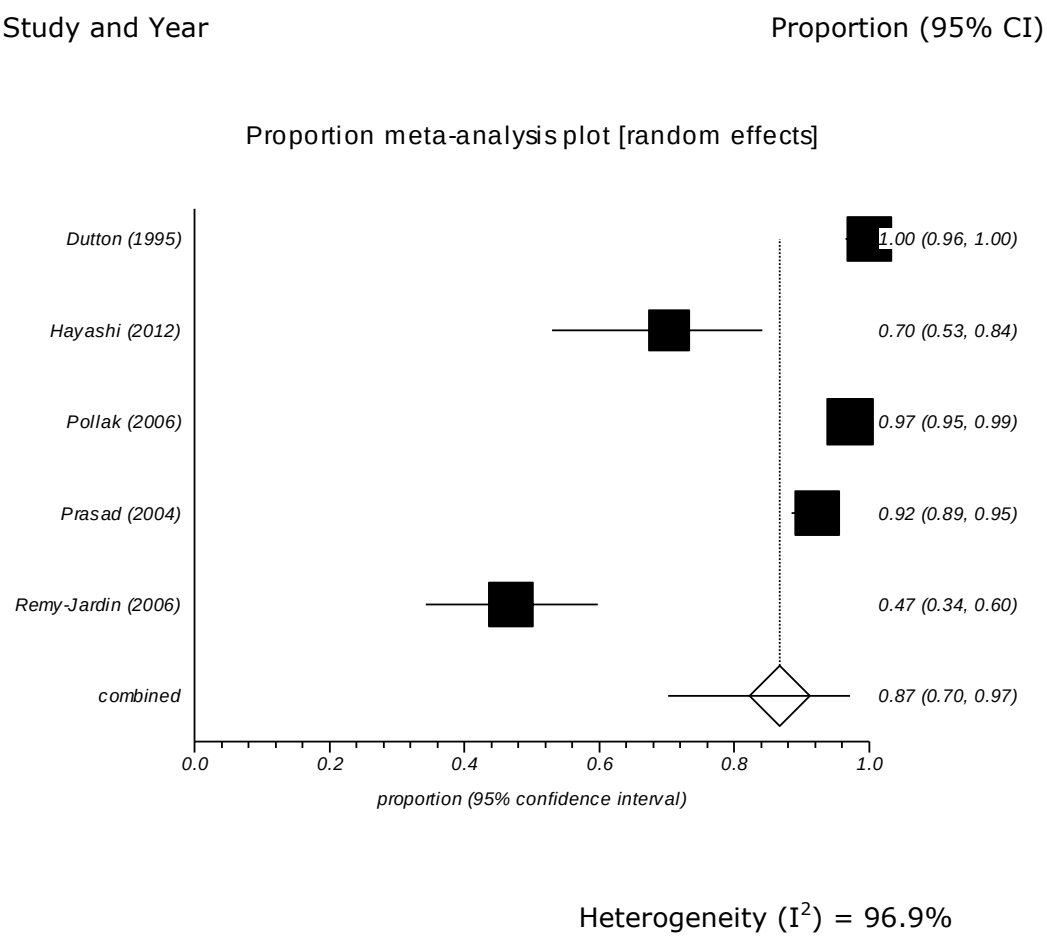
Heterogeneity (I^2) = 86.6%

Figure 6.40. Overall embolisation success rate (by PAVM)



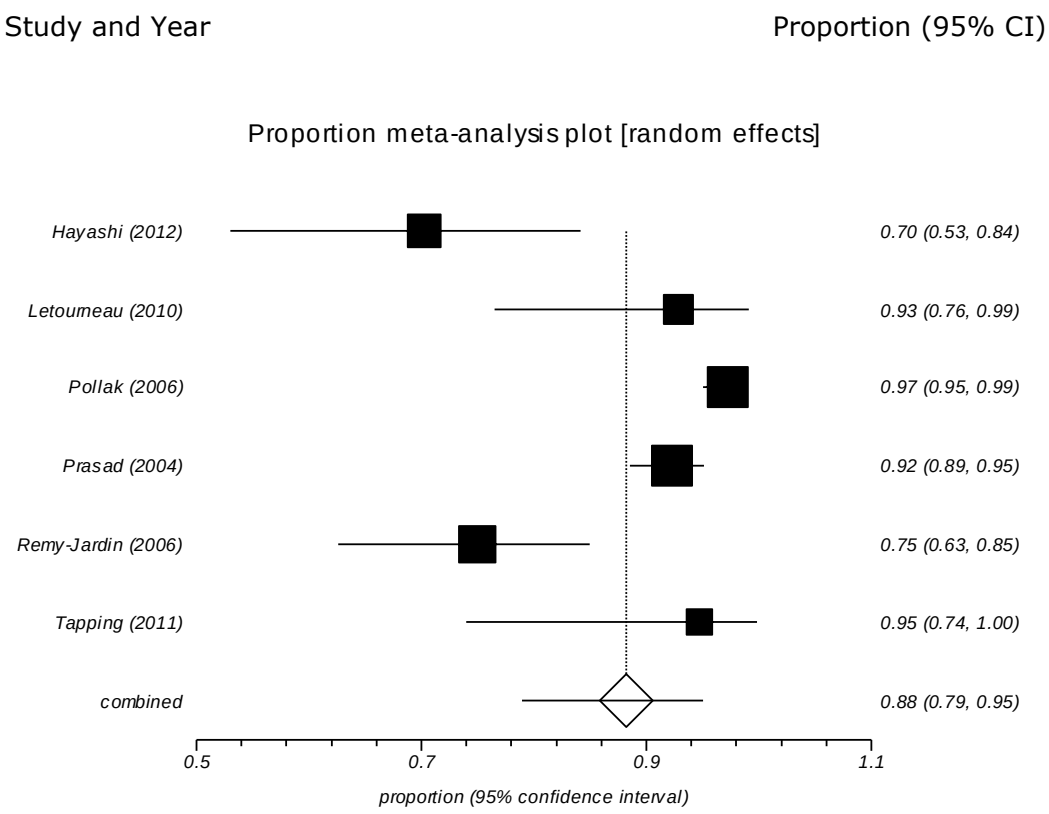
Heterogeneity (I^2) = 83.1%

Figure 6.41. Embolisation success rate (by PAVM) when coils alone were used



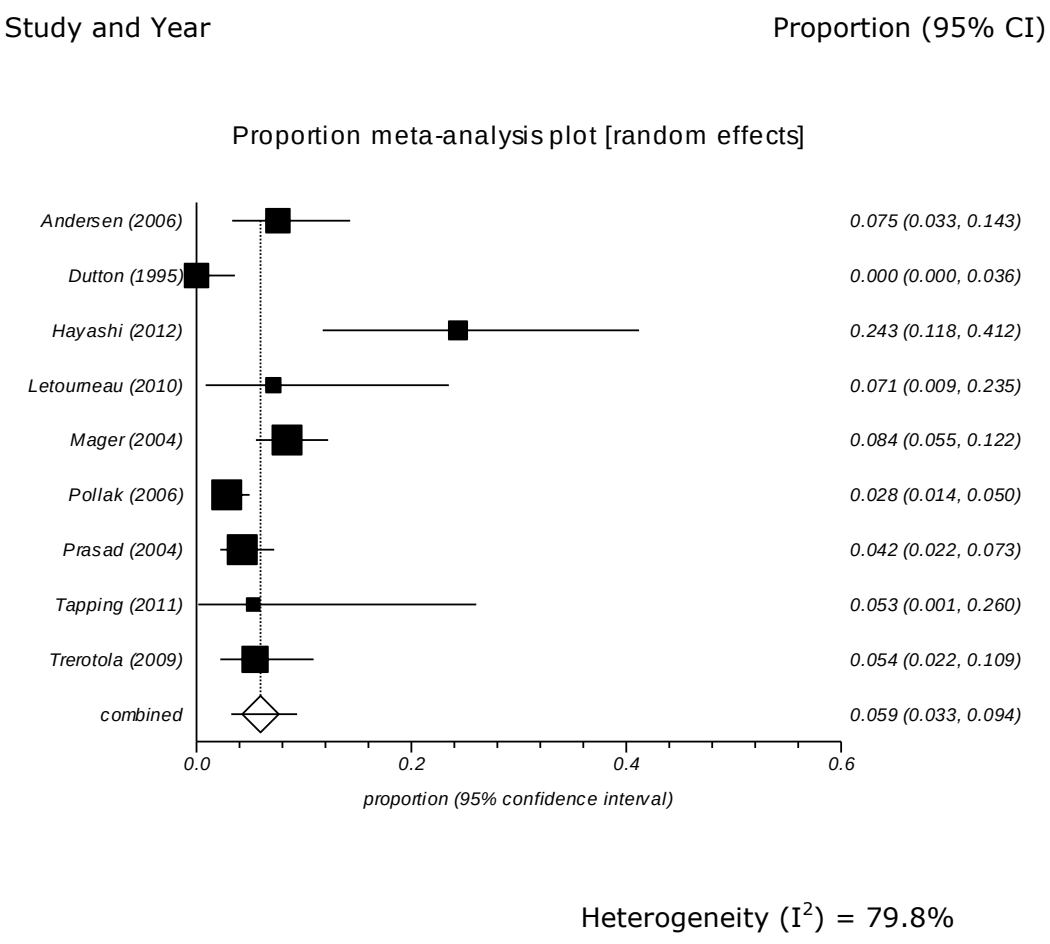
Heterogeneity (I^2) = 96.9%

Figure 6.42. Embolisation success rate (by PAVM) when follow-up protocol included CT thorax or pulmonary angiography, follow-up exceeded 12 months, and < 20% of patients were lost to follow-up



Heterogeneity (I^2) = 89.5%

Figure 6.43. Overall recanalisation rate (by PAVM)



Heterogeneity (I^2) = 79.8%

Table 6.9. Sensitivity analysis: procedural success rate

	ALL PAPERS			HIGHER QUALITY SCORE[a]			LOWER QUALITY SCORE[b]			NON-SELECTED PATIENT GROUPS ONLY[c]		
Success rates	Prevalence	95% CI	Heterogeneity (I^2)	Prevalence	95% CI	Heterogeneity (I^2)	Prevalence	95% CI	Heterogeneity (I^2)	Prevalence	95% CI	Heterogeneity (I^2)
Success expressed by pulmonary AVMs embolised												
Overall success rate	90	84-94	83	91	86-95	84.1	91	86-95	84.1	87	73-96	80.5
By device used												
Coils alone	87	70-97	97	90	79-97	92.7	90	79-97	92.7	90	79-97	92.7
Mixed (Coils and Amplatzer)	91	79-99	*	91	79-99	*	91	79-99	*	91	79-99	*
By follow-up												
CT or angiography follow-up for > 12 months **and** < 20% loss to follow-up	88	79-95	90	90	81-97	89.2	90	81-97	89.2	90	81-97	89.2
Recanalisation rate	5.9	3.3-9.4	80	7.4	4-11.8	80.6	7.4	4-11.8	80.6	7.4	4-11.8	80.6

Table 6.10 (continued). Sensitivity analysis: procedural success rate

	ALL PAPERS			HIGHER QUALITY SCORE[a]			LOWER QUALITY SCORE[b]			NON-SELECTED PATIENT GROUPS ONLY[c]		
Success rates	Prevalence	95% CI	Heterogeneity (I^2)	Prevalence	95% CI	Heterogeneity (I^2)	Prevalence	95% CI	Heterogeneity (I^2)	Prevalence	95% CI	Heterogeneity (I^2)
Success expressed by patients embolised												
Overall success rate	83	75-91	88	91	81-98	89.6	95	90-98	0	29	85-97	85
By device used												
Coils alone	80	58-95	91	93	77-100	90.3	99	91-99	*	94	70-99	92.3
Mixed (Coils and Amplatzer)	86	74-95	86	88	70-98	*	93	82-99	*	91	83-97	0
By follow-up												
CT or angiography follow-up for > 12 months **and** < 20% loss to follow-up	82	67-93	87	90	72-99	90.9	86	72-95	68.6	92	82-98	83.1
Recanalisation rate	5.1	1.2-11.4	83	5.4	0.5-15.2	90.2	4.3	1.2-9.4	0	94	87-99	84.6

Prevalence estimates, Confidence intervals (CI) and heterogeneity estimates are all expressed as percentages
*No heterogeneity estimate as <3 studies contribute to the meta-analysis
†See Table 1 (main manuscript) for a list of 'other' complications
[a]Quality score >8, [b]Quality score <=8
[c]Papers considering diffuse, large or idiopathic PAVMs excluded from analysis

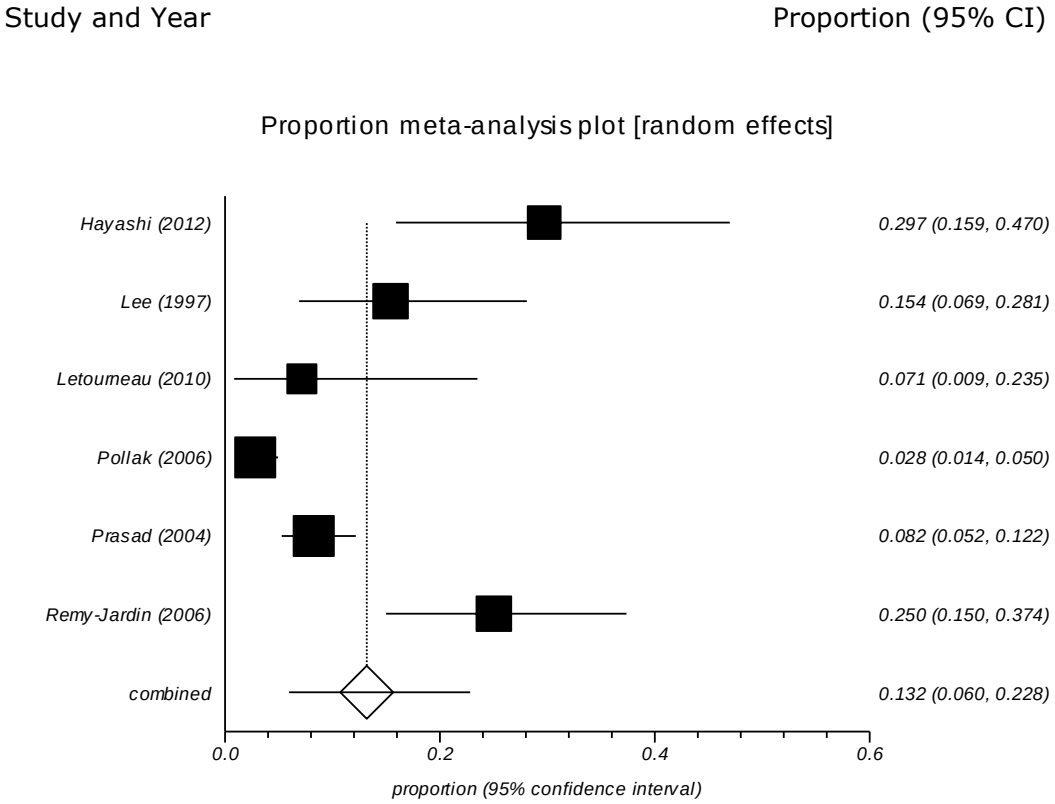
6.3.5 Results: meta-analysis of reperfusion mechanism

Of the studies that considered the reasons for the reperfusion/persistence of previously embolised PAVMs we present the following data. The overall rate of reperfusion (by PAVM) was 13.2% (95% CI 6-22.8, I^2 90.4%, from 6 studies and 841 PAVMs embolised). Analysis of mechanisms of reperfusion is presented in Table 6.11 and Table 6.12 with the prevalences in Table 6.11 presented with a denominator of all PAVMs embolised, and the prevalences in Table 6.12 presented with a denominator of all reperfused PAVMs. The commonest cause of a persistent PAVM was recanalisation of a previously embolised lesion (prevalence 9.7%, 95% CI 4.1-17.3, I^2 88%, from 6 studies and 841 PAVMs embolised) (Table 6.11, Figure 6.44 - Figure 6.48). If studies that only included reperfused PAVMs (rather than all PAVMs embolised) are considered, recanalisation remains the dominant mechanism of persistent PAVM lesions (prevalence 75%, 95% CI 61-86, I^2 54%, from 7 studies and 123 reperfused PAVMs included) (Table 6.12, Figure 6.49 - Figure 6.52).

Table 6.11. Meta-analysis of causes for reperfusion of previously embolised pulmonary arteriovenous malformations (denominator as total number of embolised PAVMs).

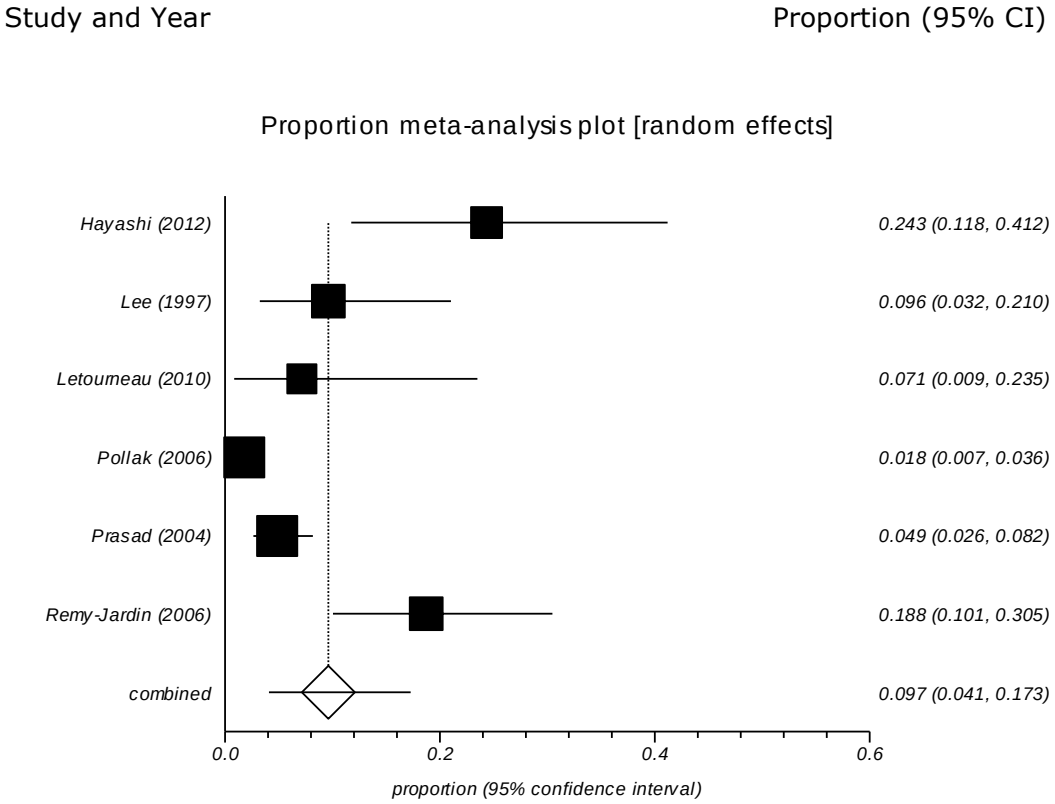
Recurrence marker	Prevalence (%)	95% CI	Heterogeneity (I^2) (%)	Number of PAVMs/studies	Figure
Reperfusion	13.2	6-22.8	90.4	841 / 6	6.44
Recanalisation	9.7	4.1-17.3	88	841 / 6	6.45
Previously untreated feeder	1.9	0.5-4.2	65.7	841 / 6	6.46
Systemic-to-pulmonary reperfusion	1.6	0.3-3.8	66.7	841 / 6	6.47
Pulmonary-to-pulmonary reperfusion	0.3	0.04-0.8	0	841 / 6	6.48

Figure 6.44. Reperfusion rate (by PAVM)



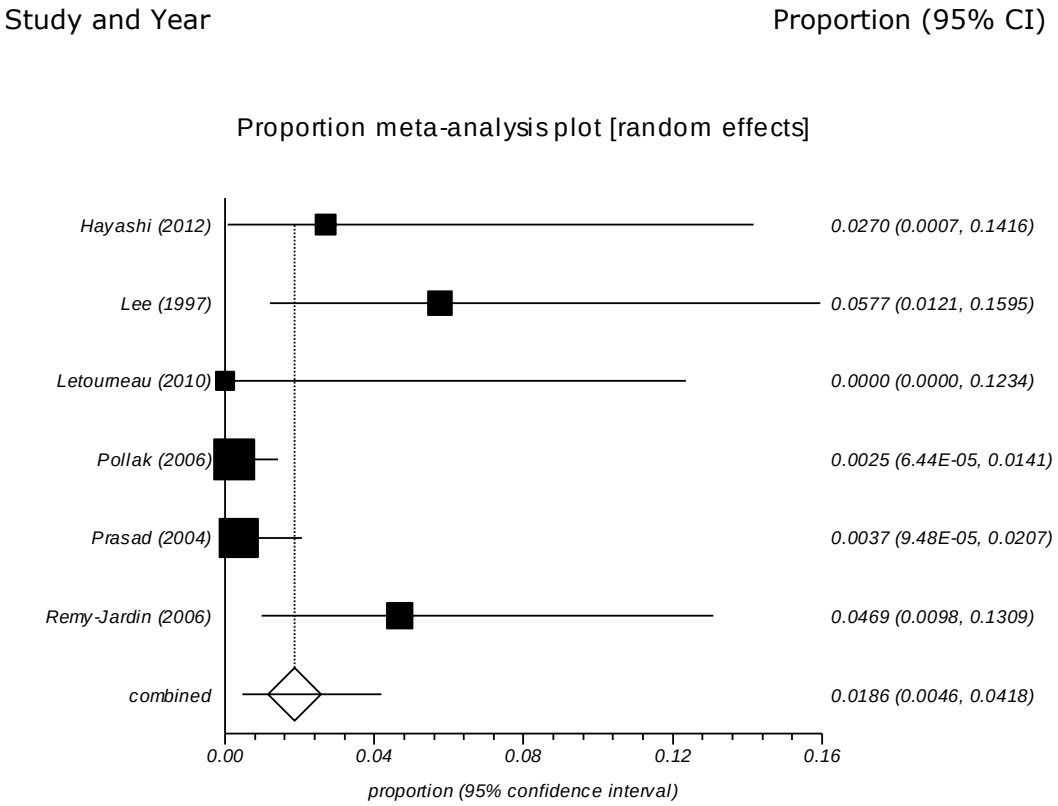
Heterogeneity (I^2) = 90.4%

Figure 6.45. Recanalisation rate (by PAVM)



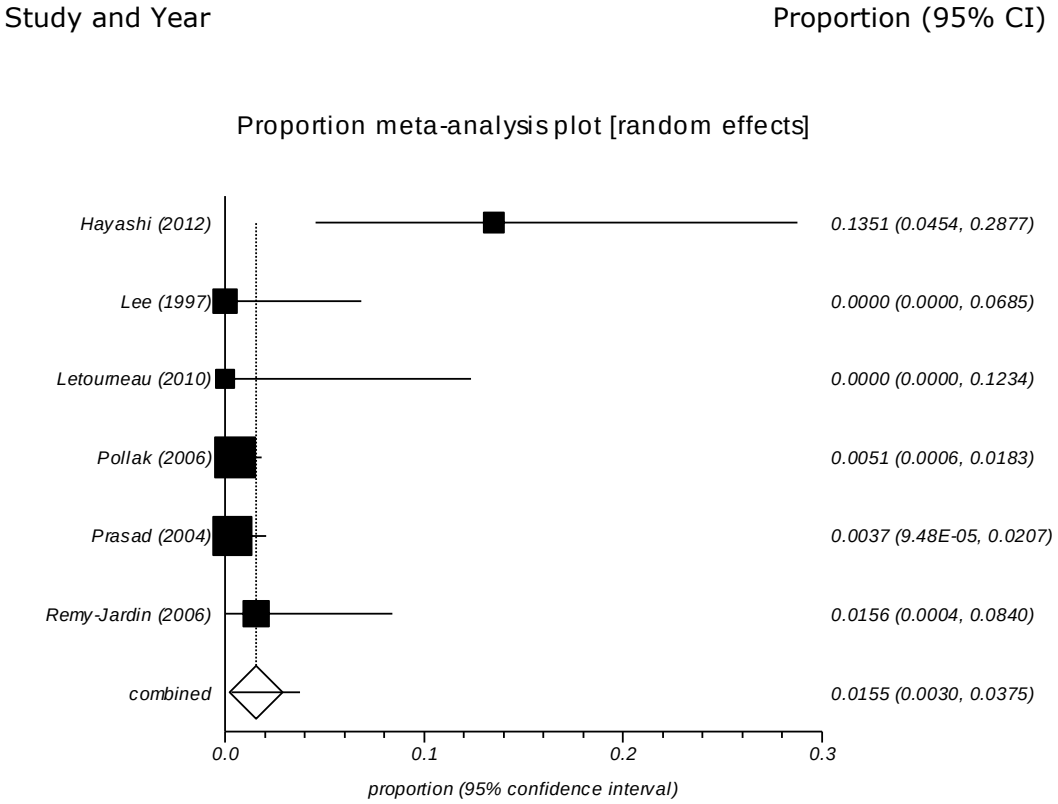
Heterogeneity (I^2) = 88%

Figure 6.46. Untreated feeder vessel (by PAVM)



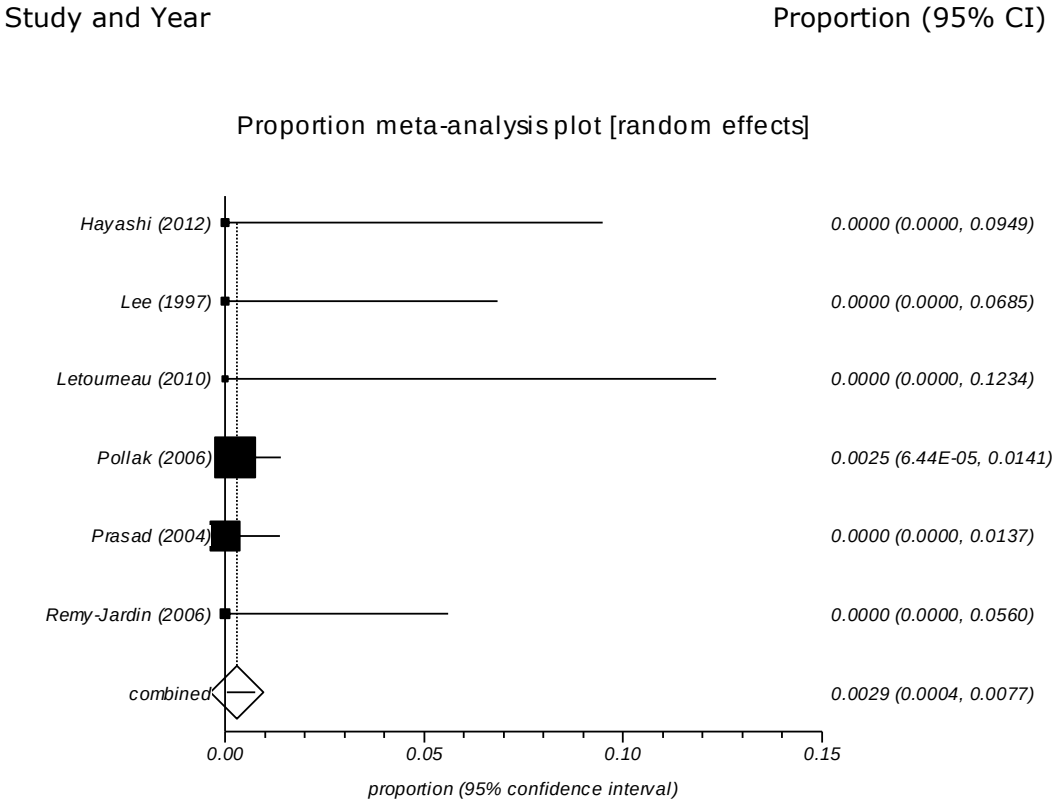
Heterogeneity (I^2) = 65.7%

Figure 6.47. Systemic-to-pulmonary reperfusion (by PAVM)



Heterogeneity (I^2) = 66.7%

Figure 6.48. Pulmonary-to-pulmonary reperfusion (by PAVM)

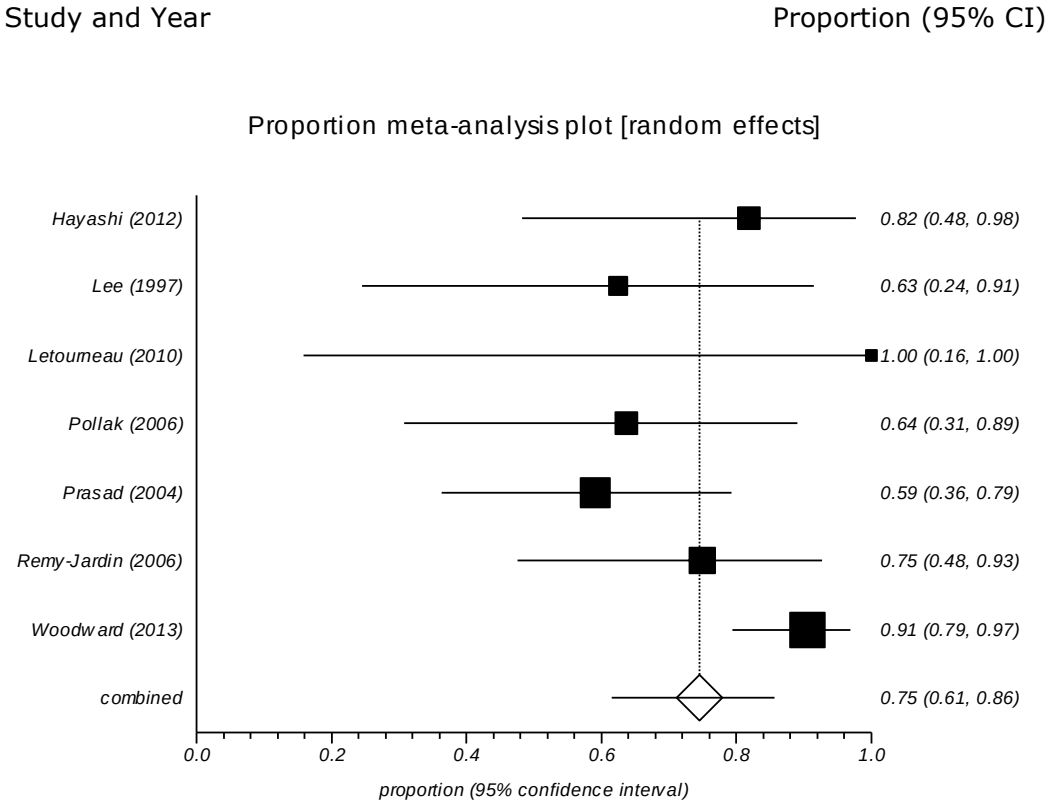


Heterogeneity (I^2) = 0%

Table 6.12. Meta-analysis of causes for reperfusion of previously embolised pulmonary arteriovenous malformations (denominator as total number of reperfused PAVMs).

Recurrence marker	Prevalence (%)	95% CI	Heterogeneity (I^2) (%)	Number of AVMs/studies	Figure
Recanalisation	75	61-86	54	933 / 7	6.49
Previously untreated feeder	14.8	9.3-21.4	0	933 / 7	6.50
Systemic-to-pulmonary reperfusion	8.0	1.9-17.8	58.8	933 / 7	6.51
Pulmonary-to-pulmonary reperfusion	6.3	0.8-16.7	67	933 / 7	6.52

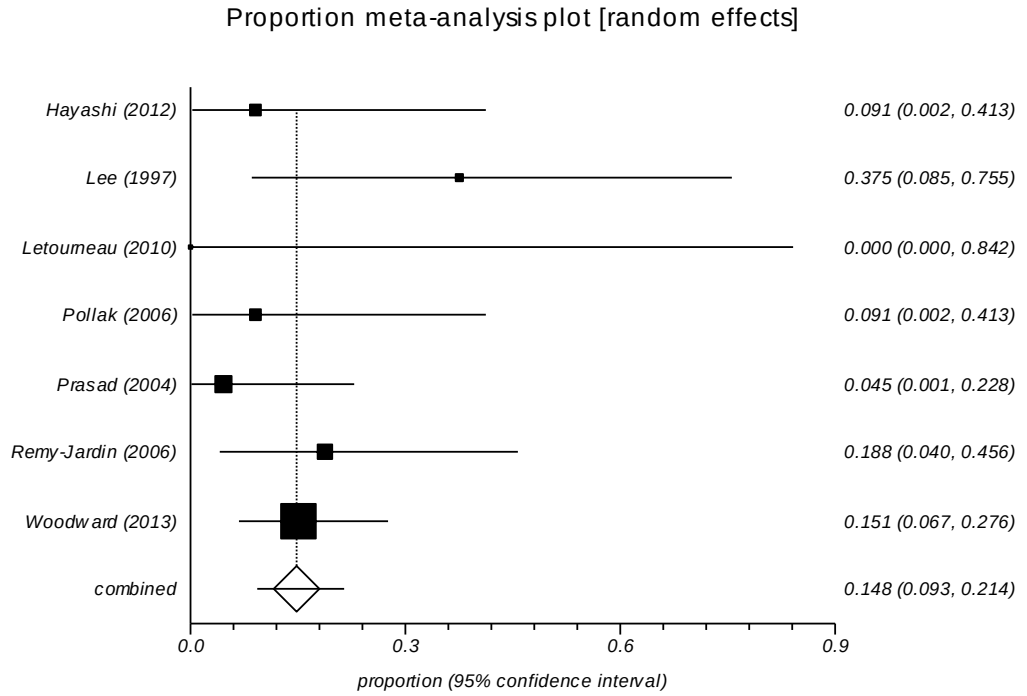
Figure 6.49. Recanalisation (by PAVM)



Heterogeneity (I^2) = 54%

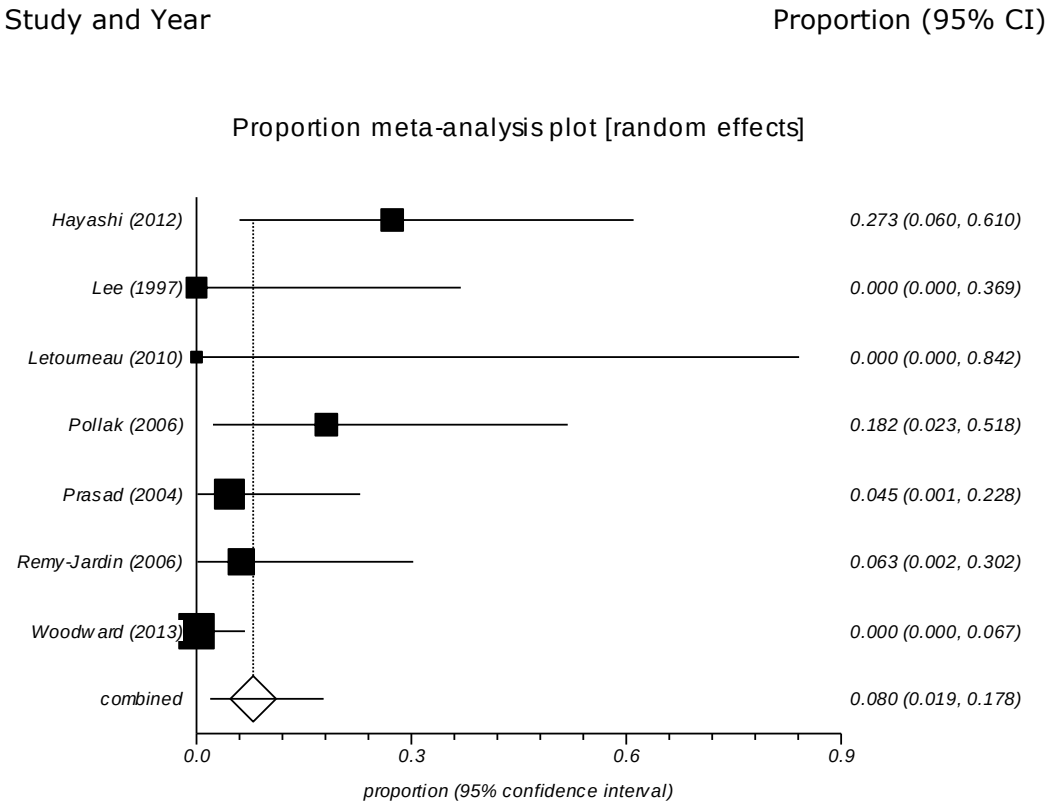
Figure 6.50. Untreated feeder vessel (by PAVM)

Study and Year | Proportion (95% CI)



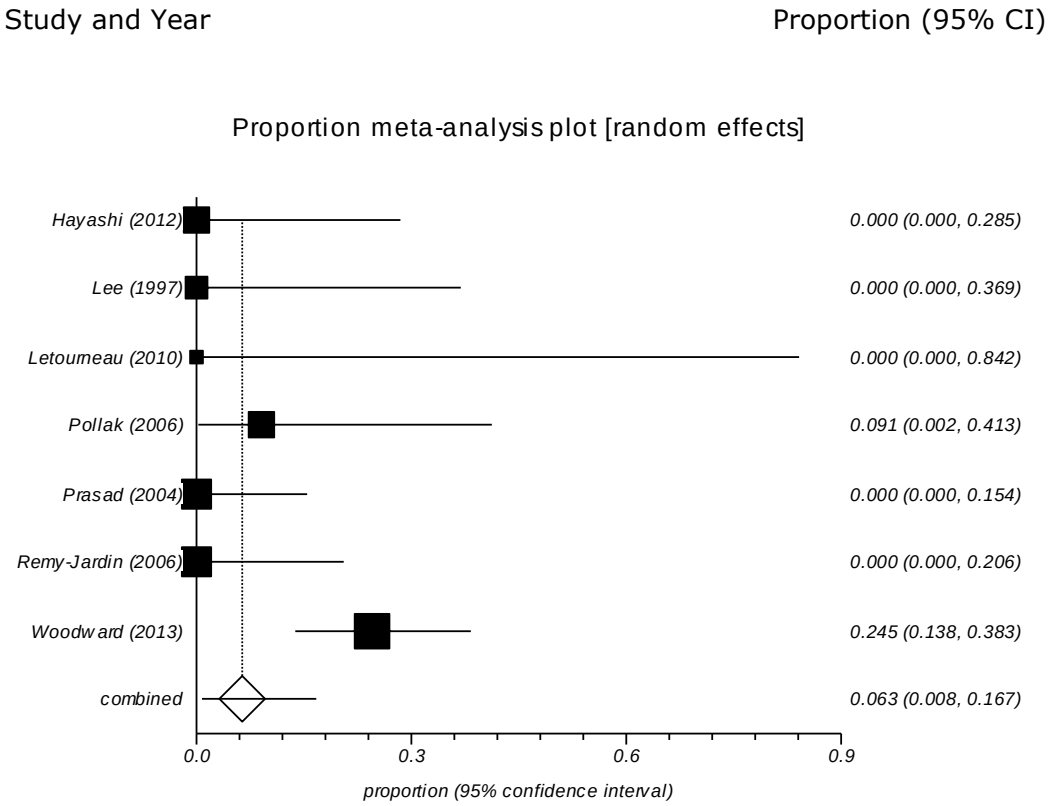
Heterogeneity (I^2) = 0%

Figure 6.51. Systemic-to-pulmonary reperfusion (by PAVM)



Heterogeneity (I^2) = 58.8%

Figure 6.52. Pulmonary-to-pulmonary reperfusion (by PAVM)



Heterogeneity (I^2) = 67%

6.4 Discussion

6.4.1 Summary

This is the first meta-analysis undertaken of the observational literature concerning percutaneous embolisation as a treatment for pulmonary arteriovenous malformations and provides summary estimates of procedural safety and procedural success rate. A major clinical complication occurred in 1% of PCE procedures undertaken. Our calculated procedural success rate is 84% per patient, or 90% per PAVM over a median follow-up period of 41 months. We conclude, on the basis of the current published literature, that PCE is effective for obliterating PAVMs in the majority of patients and that it is associated with a low rate of clinically significant complications.

6.4.2 Interpretation of results

Clinical characteristics of patients considered for embolisation

Patients considered for embolisation showed a high prevalence of complications related to HHT and when these prevalences are compared directly with those derived from the case-control study described in chapter 4 the former group had a higher burden of complications (Table 6.13). This is due to the fact that the former group is highly selected and includes patients with known pulmonary AVMs, whilst the latter patient population is a more representative sample of those with diagnosed HHT, not all of whom will have evidence of PAVMs. In addition, there is the issue of recall bias in the patient group included in the meta-analysis as most studies relied on patients answering questions from memory regarding whether they had experienced particular complications that could have been attributable to PAVMs in HHT. In addition, the way we analysed our meta-analysis data may have contributed to skewing the prevalence estimates. We deliberately omitted any papers that failed to mention a certain complication from being counted as a denominator to prevalence for that specific

complication. In other words, a paper would have to specifically mention in the text or table what the prevalence of a specific complication was for that complication to be included in the meta-analysis – i.e. no assumptions were made. Thus, studies in which no patients had developed haemoptysis, for example, would only be included if they specifically mentioned haemoptysis was asked about and documented that its prevalence was zero.

Table 6.13. Comparison of prevalences of complications in HHT patients from meta-analysis versus those from case-control study

Clinical Characteristic	Prevalence from meta-analysis (%)	Prevalence from case-control study (%)
Epistaxis	61	26.2
Migraine	33	10.5
Stroke or TIA	27	7.6
Transient ischaemic attack	18	2.1
Stroke	12.7	5.5
Haemoptysis	11	2.4
Cerebral abscess	10.8	0.4
Seizure	6.9	1.2
Intracranial haemorrhage	2.4	0.6

Peri-procedural complications associated with embolisation

Percutaneous embolisation is now the procedure of choice in patients with PAVMs of a size amenable to intervention and is graded as a strong recommendation in the international guidelines on the management of patients

with PAVMs and HHT[27]. According to our data, major complications associated with PCE are rare, and this should be of reassurance to patients undergoing this intervention. Counselling patients in advance of the likelihood of developing the commoner symptoms (such as pleuritic chest pain) should be undertaken so that patient expectations prior to the procedure are appropriate and timely management is achievable in the event of symptoms.

Longer-term complications following embolisation

Over the longer term, there is little data collected in patients following PCE, but the commonest recorded complications are neurological (TIA, stroke and cerebral abscess). These complications could have occurred due to a failed initial procedure, a reperfusion following an initially successful procedure, or could be unrelated to PAVMs, being as they are also complications that are common in the general population and can arise due to, for example, atherosclerotic cardiovascular disease. Studies did not investigate these patients in sufficient detail over the longer term to allow us to discern the reason for any complications that occurred.

Effectiveness of embolisation in managing pulmonary AVMs

Initial technical success rates for PCE approach 100% [160,170,178,181,188,193,196,197,200], but after follow-up with appropriate imaging embolisation fails to treat PAVM lesions in around 15% of individuals. These patients are at risk of significant embolic complications via their reperfused lesions and must be screened on a regular basis post-treatment to ensure recurrent lesions are identified. Whilst the evidence base for a consequent reduction in PAVM-related complications post-embolisation is not extensive, there are studies suggesting a reduction in shunt and breathlessness [201] and a decreased ischaemic stroke rate [80]. Current guidelines recommend screening follow-up at 6-12 months post procedure (with multidetector CT) and thereafter, every 3-5 years [27]. A recent study suggests that the radiation burden inherent in screening and treating PAVMs in some patients may be unacceptably high[55] and has prompted calls for a rethink about safer screening and follow-up strategies post-embolisation[56].

Mechanisms of reperfusion in treated lesions (failed embolisation)

Recanalisation is by far the commonest method of reperfusion. It occurs when the nest of coils or the Amplatzer device blocking the feeding vessels to the PAVM fails to stem the flow completely through the PAVM. This may be due to a technical failure early on or during device deployment or may reflect a more chronic process of organisation and recanalisation of clot established in the PAVM that allows subsequent reperfusion. Few studies a have looked at the methods of reperfusion but given that recanalisation is so common, better strategies to treat PAVMs, better embolisation materials and devices, and more experienced operators will be required to bring reperfusion rates down further.

6.4.3 Strengths and limitations

The major strength of this review is its ability to provide summary estimates of the literature, based on a sample of patients undergoing PCE that is over six

times larger than that of individual studies. This permits a more representative estimate of peri-procedural complication rates which will inform clinicians and interventional radiologists, allowing them to counsel patients with more accurate information on the risks and benefits of the procedure. We are able to present figures for overall success rate, stratified by method of embolisation and method of follow-up. There are several potential limitations in this meta-analysis. First is the level of observational evidence available for inclusion (mainly retrospective case series). This partly reflects the ethical problems inherent in designing a study with a conservatively managed comparator group of patients with PAVMs who would be deprived of a procedure perceived to be effective in preventing significant complications, including stroke.

A second limitation is the possibility of bias in the included studies. Language bias may exist as we included only studies published in English. Asymmetry was not detected on visual analysis of funnel plots which reduces the likelihood of significant publication bias though does not rule it out completely. Selection bias could exist as we excluded case reports and small case series from our analysis in a bid to limit skewing of our effectiveness estimates. We accept that small published studies may describe mortality or a rare complication of PCE that would not be included in our meta-analysis. One example of this is the suggestion that PAVM sacs that persist post-embolisation and acquire a systemic arterial collateral blood supply could pose a risk of subsequent massive haemoptysis[202]. This particular paper was not identified in our literature search for the meta-analysis and therefore there could be other evidence that remains unidentified or has been specifically excluded from our study that would, in fact, offer useful insight into complications post embolisation for PAVMs.

Third, heterogeneity was relatively high in estimates of success rates, as would be expected from a synthesis of procedures from different centres. Much heterogeneity arose as a result of the differing methodology employed in each

study and, as a result of this, and to aid reporting, we suggest that future studies included certain important information about the study design (Table 6.14).

.

Table 6.14. Methodological suggestions for future studies looking at percutaneous embolisation as a treatment for pulmonary arteriovenous malformations

Study Design
Consecutive patients should be included – with reasons explained if this did not occur
Clearly state when studies contain overlapping patient populations
Clear inclusion and exclusion criteria stated
Record details of all patients with PAVMs a) initially evaluated, b) subsequently embolised and c) any lost during follow-up.
Clearly state the definition of a peri-procedural complication. We arbitrarily suggest 30 days, with any complications occurring later able to be defined as peri-procedural if there is a clear causal link with the procedure
Follow-up both embolisation patients and if possible any patients ineligible for embolisation or refusing the procedure in order to better define the history of untreated PAVMs.
Be specific about follow-up criteria; • Aim for follow-up of at least 36 months • Follow-up protocol should preferably include either CT or angiography as oximetry, shunt studies, chest radiograph and cardiac bubble echo are less sensitive means of detecting recurrent PAVMs • State the details of the follow-up protocol used • State, if different, the time periods of clinical and radiological follow-up obtained.
Use a clear definition of a 'successful procedure'. One example from a recent study(36); • *Success* – marked reduction (>30%) or disappearance of aneurysmal sac, with no pulmonary or systemic perfusion • *Partial success* - <30% reduction in the size of the aneurysmal sac with persistent pulmonary perfusion and patent feeding artery beyond the level of the embolisation device too small for a re-embolisation (<2-3mm) • *Partial failure* – Substantial reduction in the size of the aneurysmal sac, persistent pulmonary perfusion and a patent feeding artery/arteries beyond the level of the embolisation device larger than 2-3mm which was an indication for re-embolisation • *Failure* – An unchanged or enlarged aneurysmal sac with persistent pulmonary perfusion
In patients with reperfused PAVMs, where possible, specify the mechanism according to these criteria(9); • recanalisation of an embolised vessel, • growth of a missed or previously small accessory artery (previously untreated feeder), • bronchial or other systemic artery collateral flow (systemic-to-pulmonary reperfusion), • pulmonary artery to pulmonary artery collateral flow around the occlusion (pulmonary-to-pulmonary reperfusion).
Consider documenting any symptomatic improvements post embolisation with use of structured patient questionnaires/symptom scales

*Reference numbers in table refer to those listed in the main manuscript

Fourth, we acknowledge that the evidence base reflects publications from a limited number of specialist centres who likely perform a relatively high number of PCEs annually in comparison with smaller centres. PCE is an operator-dependent procedure and, whilst most studies published consecutive cases from one or two centres where the operator remained the same over time, we were not able to adjust our results for operator experience. For this reason it is important that all interventional radiologists undertaking PCE are aware of their own local safety estimates and success rates.

Despite its limitations, our study provides pooled estimates from a population over six-fold larger than previously published studies, and allows more representative estimates of procedural risk and success rate. These estimates may guide clinicians in providing more informed consent to patients with PAVMs when discussing the risks and benefits of undergoing PCE as well as providing a benchmark for less experienced centres offering the procedure. We emphasize the need for all centres to have a structured approach to screening patients for the recurrence of lesions post-treatment. The summary of published evidence from observational studies suggests that serious complications of PCE are infrequent and that embolisation is an effective intervention for PAVMs.

CHAPTER 7: EMBOLISATION FOR PULMONARY ARTERIOVENOUS MALFORMATIONS ACROSS ENGLAND OVER THE LAST DECADE: AN OBSERVATIONAL EPIDEMIOLOGICAL STUDY USING HOSPITAL EPISODES STATISTICS DATA

7.1 Introduction

Percutaneous embolisation (PCE) as a treatment for pulmonary AVMs is now the 'gold standard' management for identified lesions in which the procedure is technically feasible[160,170,178]. In this thesis we have previously shown (see chapter 6), based on published evidence, that PCE is associated with a relatively low risk of mortality or major complications. However, the published evidence derives mainly from specialist centres with a declared interest in the procedure that may have a relatively high volume of activity and hence may not be representative of the safety profile of the procedure nationally. Likewise, local audit of the procedure from individual hospital trusts, presuming it is even regularly undertaken, would miss mortality or complications associated with PCE which had occurred in other geographical regions. We used a national database collecting inpatient data from all hospitals in England over a 15 year period to describe geographic and temporal trends and mortality associated with embolisation of pulmonary arteriovenous malformations.

7.2 Methods

7.2.1 Study design, setting and source of data

We conducted a retrospective national study using data obtained from the Health Episodes Statistics (HES) database (see chapter 2). We were provided with a pseudonymised extract of data between years 1997/98 and 2010/11. The domains under which data were requested are listed in Table 7.1. 2011 data was considered provisional as it was supplied before the end of the calendar year, but these data were included where appropriate for completeness. Filters were applied to search for relevant patients by both procedural code and diagnostic code. A procedure filter was applied using OPCS-4[203] codes (version 4.6, April 2011) to identify procedures likely to correspond to embolisation therapy for

pulmonary AVMs. The diagnosis filter was then applied by searching for both the ICD-9 and ICD-10[204] codes for "arteriovenous fistulae of pulmonary vessels" (417.0 and I28.0, respectively) and hereditary haemorrhagic telangiectasia

Table 7.1. Data extraction domains for inpatient data from HES and for mortality data from ONS.

Inpatient data	ONS mortality data
Demographic data	**All data**
Month and year of birth	Date of death
Sex	Date of registration of death
Ethnic category	Sex
Postcode district of residence	Date of death
Lower Super Output Area	Original underlying cause of death
Middle Super Output Area	Death record used (HES or ONS)
Rural/Urban indicator	
Admission data	
Date of admission	
Date of decision to admit	
Method of admission	
Waiting time	
Date of discharge	
Method of discharge	
Duration of spell	
Duration of episode	
Clinical data	
Diagnosis codes	
Operative procedure codes	
Main admitting speciality	
Treatment speciality	
Socioeconomic status	
Lower Super Output Area	
Middle Super Output Area	
Rural/Urban indicator	

(448.0 and I78.0 in ICD-9 and ICD-10, respectively) as over 70% of patients with pulmonary AVMs have underlying HHT[117]. Thus three extracts were provided for patients who had undergone embolisation; those coded with an "arteriovenous fistulae of pulmonary vessels" only, those coded as HHT only and those coded as both. These data were linked to ONS mortality records to detect any patients that subsequently died.

7.2.2 Data management and analysis

We combined the three extracts described above to produce the final dataset for analysis. A unique HES-assigned identification number is provided to identify individuals (generated by an algorithm that may combine information including sex, date of birth, NHS number, postcode of residence and provider code)[205] and thus allows distinction between multiple procedures undertaken in the same patient or the appearance of the same patient in different extracts and prevents inadvertent double counting.

The data extract provided contained records on 540 procedures. 12 records were dropped from analysis as they were coded as having been admitted under the specialties of neurology or neurosurgery (likely to be treatment of cerebral AVMs). 55 records were excluded from analysis as the procedure code did not specify embolisation in the *lung* and the diagnosis code contained only HHT (with no code specifying pulmonary AVMs) thus, again, we could not safely assume the procedure was specific to the pulmonary circulation.

We undertook a descriptive analysis looking at the age and sex distribution of procedures undertaken, numbers of procedures by year, by admitting speciality and by geographical location (postcode area of patient residence). We calculated the median length of stay (by looking at the surrogate of 'duration of episode' which is the difference between date of admission and date of discharge) and analysed any deaths occurring in patients after the procedure (looking at cause

of death and time of death relative to admission date for the procedure) to help determine whether they could have been as a result of the intervention.

7.3 Results

7.3.1 Procedure demographics

Data were available on a total of 473 procedures undertaken in 340 individuals over the period between 1997–2011. Of those 340 individuals, 62% were female. Table 7.2 shows the procedure codes searched for, with by far the majority coded as "Percutaneous transluminal embolisation of pulmonary artery". The annual number of procedures (Figure 7.1) shows a gradual increase in the number of embolisations undertaken up to a peak in 2003 and then for following years the numbers vary between 23 to 44 per year. There was a wide age range of individuals undergoing embolisation (from 2 to 78 years) with the most procedures undertaken in the age group 40 to 49 years (Figure 7.2). A geographical map of the postcode area of residence of patients undergoing the procedure (Figure 7.3) showed variation across the UK, with the most embolised patients residing in postcode areas of; Portsmouth, Bristol, Newcastle and Northwest London. The median length of stay was 2 nights (interquartile range (IQR) 2-2) and 6% of embolisations had an episode duration of zero days suggesting they were day case procedures. Respiratory medicine is the admitting specialty for the vast majority of embolisations undertaken with many fewer admissions coded under cardiology, general medicine and radiology (Table 7.3). The median number of procedures undertaken per patient was one (range 1-7) with 25% needing at least one repeat procedure (Table 7.4).

Table 7.2. Codes identified in the health episode statistics database considered pertinent to embolisation of pulmonary arteriovenous malformations and included in the subsequent analysis.

Procedure type	Procedure code	Number of procedures	%
Percutaneous transluminal embolisation of pulmonary artery	L132	443	93.7
Embolisation of arteriovenous abnormality not elsewhere classified (NEC)	L753	24	5.1
Percutaneous transluminal embolisation of arteriovenous malformation (NEC)	L754	5	1.1
Percutaneous transluminal venous embolisation of arteriovenous malformation	L755	1	0.2
Total		**473**	

Figure 7.1. Annual number of percutaneous embolisation procedures performed between 1997 and 2010 in England

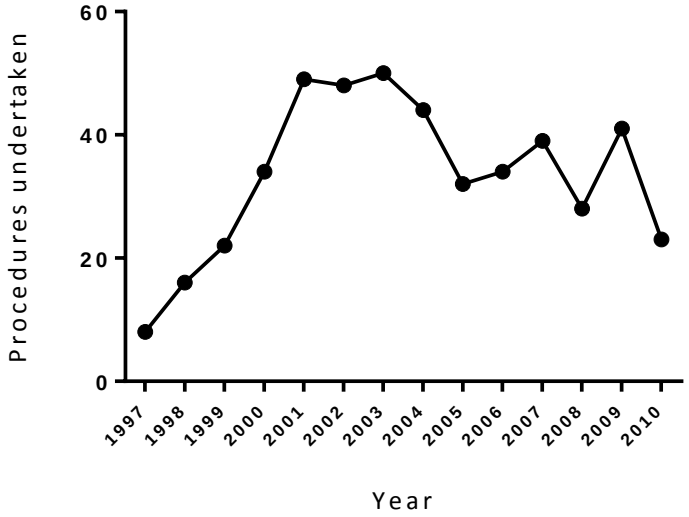


Figure 7.2. Patient age at first embolisation procedure

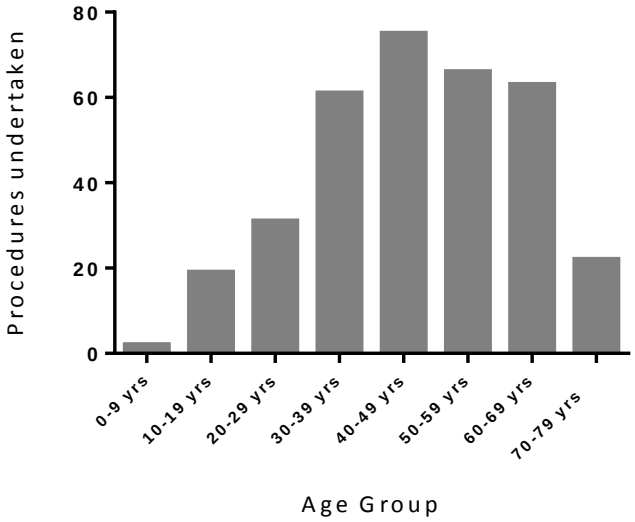


Figure 7.3. Geographical map by postcode area of patient residence of those undergoing percutaneous embolisation (by number of patients).

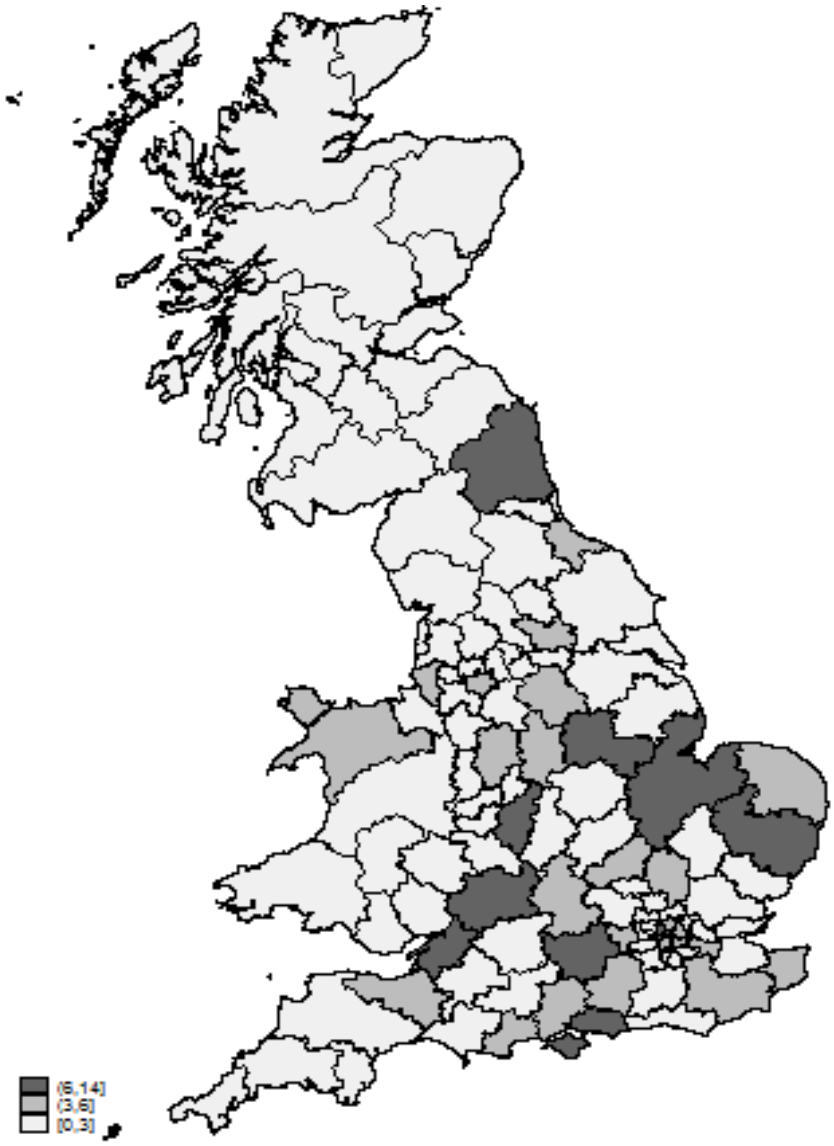


Table 7.3. Number of procedures performed stratified by admitting speciality

Specialty	Procedure number	%
Respiratory Medicine	417	88.2
General Medicine	15	3.2
Cardiology	15	3.2
Radiology	15	3.2
Cardiothoracic surgery	4	0.9
A+E	2	0.4
Other*	5	1.1
Total	**473**	

*General surgery, ENT, Gastroenterology, Infectious Diseases, Paediatrics

Table 7.4. Number of patients undergoing multiple procedures.

Procedure number	Number of patients	%
1	253	74.4
2	61	17.9
3	16	4.7
4	5	1.5
5	2	0.6
6	1	0.3
7	2	0.6
Total	**340**	

7.3.2 Mortality

No patients died within 7 days of any individual procedure, though two died within 30 days. Of those two deaths, one was due to bronchiectasis and the second was attributed to a pulmonary AVM. 35 patients were recorded as having died at some time point following their embolisation. In those patients that subsequently died, most did so several years after their admission for embolisation (median time interval 3.3 years (IQR = 1.8-5.9). The commonest causes of subsequent death were malignancy (N=11) or HHT itself (N=5) (Table 7.5).

Table 7.5. Mortality data citing cause of death in all patients (coded as PAVM, HHT or both) who underwent an interventional procedure.

Extract filter (HHT, PAVM, Both)	Cause of death	Procedure code	n	Death within 7 days of admission	Death within 30 days of admission	Comments
HHT	Acute MI	410	1	N	N	
PAVM	Intracerebral haemorrhage	431	1	N	N	
HHT	Acute anaemia due to blood loss	4480	1	N	N	
PAVM	Progressive spinal ataxia	7473	1	N	N	
PAVM	Malignant neoplasm of stomach, unspecified	C169	1	N	N	
PAVM	Malignant neoplasm of unspecified part of	C349	2	N	N	
PAVM	bronchus or lung					
PAVM	Malignant neoplasm of breast of unspecified site	C509	1	N	N	
PAVM	Malignant neoplasm of kidney, except renal pelvis	C64	1	N	N	
PAVM	Malignant neoplasm without specified site	C80	1	N	N	
PAVM	Acute myeloblastic leukaemia	C920	1	N	N	
HHT	Acute promyelocytic leukaemia	C924	1	N	N	
PAVM	Chronic ischaemic heart disease, unspecified	I259	1	N	N	
Both	Primary pulmonary hypertension	I270	1	N	N	
PAVM	Hereditary haemorrhagic telangiectasia	I780	4	N	N	
HHT				N	N	
HHT				N	N	
Both				N	N	
Both	Bronchopneumonia, unspecified organism	J180	1	N	N	
PAVM	Pneumonia, unspecified organism	J189	1	N	N	
HHT	COPD with acute LRTI	J440	1	Y	N	Died day 7
HHT	COPD	J449	1	N	N	
PAVM	Bronchiectasis	J47	1	N	Y	Death within 10d

HHT	Pneumonitis due to inhalation of food and vomit	J690	1	N	N
Both	Biliary cirrhosis, unspecified	K745	1	N	N
HHT	Other and unspecified cirrhosis of liver	K746	1	N	N
PAVM	Car driver injured in collision with car, pick-up truck or van in traffic accident	V435	1	N	N
PAVM	Unspecified fall	W190	1	N	N
	Total		**29**		

7.4 Discussion

7.4.1 Summary

This is the first nationally representative study in England to investigate the geographical and temporal trends and mortality after radiological embolisation of pulmonary arteriovenous malformations. The annual number of procedures increased until 2003 and then plateaued while the mortality associated with pulmonary embolisation is low.

7.4.2 Strengths and limitations

One particular strength of our analysis is that the HES data allows us to consider a relatively large number of procedures undertaken over a long time period, with linkage to ONS cause of death statistics. These data are representative of all eligible procedures undertaken in England over this time period, and this approach provides a national audit of the mortality after this procedure.

This study has a number of limitations to consider. Firstly, the majority of procedures included were coded as "percutaneous transluminal embolisation of pulmonary artery" rather than a code that was specific for embolisation of a pulmonary arteriovenous malformation. Given that the second data filter searched specifically for individuals with codes for pulmonary AVMs and/or HHT, we believe that we are identifying relevant embolisation procedures in the correct patient group. Secondly, though we were provided with data related to procedural mortality, we did not have any reliable data concerning complication rates associated with the procedure. Thirdly, we did not have information related to the centre where the patient was treated so we are unable to map procedure activity across England stratified by treating centre. Finally, while there were two deaths within 30 days of a procedure (due to bronchiectasis and a pulmonary AVM), the relation of these events to the intervention is not clear, and hence we

are unable to distinguish between mortality as result of emergency interventions to prevent haemoptysis as opposed to direct complications of the procedure in previously stable patients with these diseases. As a consequence, a mortality rate of 0.4% per procedure can be considered the upper limit of mortality rate attributable to the intervention, with a lower limit of 0%.

7.4.3 Interpretation of results

The number of procedures undertaken for those patients coded with PAVMs or HHT increased over the time period from 1997 to 2003 which may reflect an increased ascertainment of PAVMs considered treatable by vascular embolisation or a move away from surgical intervention as an alternative treatment option. Since 2004 there have been approximately 25 to 40 procedures annually. Most procedures are undertaken in those aged 40 to 49 years which corresponds with the mean age of diagnosis of PAVMs at 43 years[23]. Two-thirds of treated patients were female, which is consistent with observations that there is a higher diagnostic rate of both HHT and PAVMs in women[108,206]. The wide variation across England in embolisation rates when stratified by geographical area may partly be due to differences in the diagnosed prevalence of HHT across England[108] as it may exist in clusters of affected family members given its autosomal dominant pattern of inheritance. That the vast majority of patients are under the care of respiratory medicine is unsurprising as most patients with HHT are referred to the speciality for screening to detect potential PAVMs. Just over a quarter (26%) of patients had multiple episodes associated with embolisation on different dates which we assumed to be due to multiple interventions. There are several possible explanations as to why patient may have undergone repeated procedures; some patients may have required 'staged' embolisation procedures, usually as a result of the number of PAVMs needing treatment; some patients may have experienced a reperfusion of previously

treated lesions, development of a new lesion or growth of previously small untreatable lesions that became sizeable enough to require a further embolisation. Our data did not allow us to distinguish between these different indications for a repeat intervention.

7.4.4 Conclusion

Our analysis of a representative database of embolisation procedures for pulmonary AVMs undertaken across England suggests the procedure is associated with a low mortality (0.4% at most). Establishing a national database of patients undergoing the procedure, would allow the identification of any significant mortality or morbidity related to embolisation. These data are of importance for both physicians and radiologists when counselling patients with pulmonary AVMs who are considered potentially suitable for embolotherapy.

CHAPTER 8: CONCLUSIONS AND FUTURE RESEARCH

8.1 Summary

During my period of research as demonstrated by this thesis I have been able to more clearly describe the epidemiology of hereditary haemorrhagic telangiectasia in the UK, including its complications and associated mortality and have demonstrated the relative safety and effectiveness of percutaneous embolisation as a treatment for pulmonary arteriovenous malformations (a common complication of the disease). This work has culminated in the publication of two papers in peer-reviewed journals, with a further two currently under consideration by editors, and several abstracts presented at international conferences.

The main findings are;

1. Trends in prevalence of HHT across the UK

The diagnosed prevalence of HHT within the UK is at least 1.06 per 10,000 (95% CI: 0.95-1.17) (or 1 per 9,400 individuals), has been stable over the decade 2000-2010 and is in line with estimates from other countries worldwide. The true UK prevalence is likely to be higher than our diagnosed prevalence as many cases remain clinically undetected. A diagnosis of HHT is more commonly made in females (PRR 1.59, 95% CI: 1.30-1.94), and those from higher socioeconomic groups (PRR 1.74, 95% CI: 1.14-2.64). This pattern may partly reflect an ascertainment bias associated with an increased attendance of females to primary care (due, for example, to consultation for contraception and child health issues) though may also be a reflection of the role of oestrogens (and/or genetic influences) on the manifestation of disease complications. Differences in usage of primary care services across socioeconomic groups may partly explain the different prevalences of the disease when stratified for markers of social deprivation. HHT prevalence varies twofold throughout different geographical

regions as defined by UK health authority, which may be as a result of ascertainment bias or clustering of affected cases due to the pattern of inheritance of HHT.

2. Complications associated with HHT.

We characterised the risk of developing certain complications of HHT in a representative population of patients from the UK when compared with unaffected controls. Bleeding complications, including anaemia, epistaxis, haemoptysis and gastrointestinal haemorrhage were commoner in those with HHT, as were several significant neurological sequelae including ischaemic/embolic stroke, cerebral abscess and migraine. Of the cardiovascular comorbidities analysed, only cardiac failure was found to more common in those with HHT, though not the prevalence of ischaemic heart disease or myocardial infarction. Bowel cancer was commoner in HHT cases (OR 2.76, 95%CI 1.11-6.85) likely as a consequence of the overlap between HHT and juvenile polyposis syndrome (with the latters' association with increased risk of gastrointestinal malignancy) linked to the gene SMAD 4, common to both. There was no discernable difference in rates of other solid organ tumours.

3. Mortality associated with HHT.

Mortality in patients with HHT compared to their age, sex and general practice-matched controls was significantly higher with a hazard ratio for death of 2.03 (95% CI 1.59-2.60). Median age at death was decreased by 3 years in those with HHT compared to controls. Whilst our data do not allow us to investigate the cause of death for these patients, it is likely that the disease itself confers some of the increased mortality by virtue of the significant complications that

are associated with it such as stroke, cerebral abscess and significant haemorrhage[112]. Survival in HHT did not differ by sex but was higher in those from the most affluent socioeconomic group when compared to the least (HR 1.15, CI 1.04-1.27, p=0.007). The survival advantage associated with higher socioeconomic status has been demonstrated in a variety of other diseases[207-209].

4. Evidence for safety and effectiveness of embolotherapy for pulmonary arteriovenous malformations.

The commonest minor complications associated with percutaneous embolisation were pleuritic and ischaemic chest pain. There was a major complication rate of 1% associated with procedures (these were due to a death (sepsis following pulmonary infarct), stroke, venous thromboembolism and haemopericardium due to cardiac perforation). Overall, there is a very low mortality associated with embolisation in the published literature.

Our calculated procedural success rate is 84% per patient, or 90% per PAVM over a median follow-up period of 41 months. Thus, approximately 15% of patients potentially require a repeat embolisation procedure for persistent lesions at follow-up. Recanalisation is the commonest mechanism for persistence of a previously embolised PAVM lesion (occurring in 75% of persistent lesions identified). It is suggested that improved embolisation strategies, better operator experience and updated embolisation materials and devices will be required to reduce recanalisation, and persistence rates further.

Overall we conclude that embolisation is a safe and effective procedure for the management of pulmonary AVMs, though caution that smaller, less experienced centres should be aware of their own success and complication rates when counselling patients undergoing embolisation.

5. Mortality of embolisation undertaken for pulmonary arteriovenous malformations in England.

Since 2004 there have been approximately 25 to 40 embolisation procedures annually within England. A quarter of all those embolised require a subsequent procedure. There is a geographical variation in the region of residence of those undergoing the procedure which may be related to genetic clustering of the disease HHT. Mortality associated with the procedure is, at most, 0.4% but may be as low as zero. It should be of reassurance to patients and interventional radiologists that our representative sample of embolisations has a low procedural mortality that is comparable to that suggested by the worldwide literature included in our meta-analysis study described above.

8.2 Ongoing work

In parallel with the epidemiological research undertaken we have also been collecting samples for a genetic study into HHT. The aim of this part of research is to obtain a cross sectional sample of salivary DNA from both HHT patients and unaffected related controls to allow analysis using novel high throughput genetic sequencing techniques to better characterise the genetic basis of HHT.

Our specific objectives are;

- Identify new polymorphisms associated with disease causing mutations in patients with HHT.
- Discover new gene loci potentially associated with the disease and in particular with the development of the pulmonary arterio-venous malformation phenotype
- Attempt to more closely correlate disease-causing genetic mutations with specific complications of the disease (analysis of the genotype-phenotype interaction).

- Discover moderator genes that may influence the expression of disease causing genes in hereditary haemorrhagic telangiectasia.

A significant minority of patients with clinically suspected or confirmed HHT do not test positive for known mutations. This has implications for screening in their families. Given the significant clinical variability between sufferers of HHT it remains possible that rare, low frequency alleles, so far unrecognised, may have major roles to play in the phenotype of this variable disease.

To search for new polymorphisms associated with known HHT genes involves sequencing the exomes of HHT patients and identifying sequences of interest that appear in multiple HHT patients in the region of known HHT loci. These sequences can then be compared to a database of already discovered polymorphisms[210]. If the polymorphisms have not been previously identified they are then compared to the 1000 Genome project database (a database of the complete genetic sequence of 1000 'healthy' individuals) to see if they are 'normal variants' in the human population[211]. If not, they could represent candidate polymorphisms involved in the HHT phenotype.

To search for novel gene loci associated with the disease requires a case-control design. Patients with HHT (cases) are subject to whole exome sequencing alongside their unaffected first-degree relatives (controls). We will use a combination of the most relevant sequencing approaches including targeted sequencing, whole exome sequencing and the recently developed whole exome chip. Targeted sequencing, as the name implies, relies on sequencing a pre-selected area of the genome thought to be relevant to the disease. When looking for novel mutations this approach can lead to investigators 'missing' an area of importance in the genome. The advantage of whole exome sequencing is that it allows all the exons of an individual to be sequenced thus covering significantly

larger areas of potential interest without the selection bias[212]. However, this comes at a substantially increased cost, so complimentary sequencing approaches will be employed.

We have currently collected a total of 67 salivary DNA samples, 37 from possible HHT cases and 30 from their relatives (presumed to be unaffected based on a questionnaire sent to all participants in the study asking about specific symptoms of the disease and whether they had ever received a formal diagnosis of HHT or were followed-up by a specialist clinic). We looked to see whether any of the cases or controls had undergone specific genetic testing for HHT mutations and if so whether any common mutations were identified (ENG, ACVRL 1 and SMAD 4). After excluding patients with known mutations or without comparable samples from first-degree relatives, we identified a total of 7 paired samples in for further testing. These salivary DNA samples are currently stored awaiting initially to be tested first for the three common mutations, and if negative for all, will proceed to high throughput gene sequencing. Further research publications from this data will depend on any pertinent findings as a result of this genetic sequencing.

8.3 Recommendations for future research

Suggestions for potential further research projects are divided into those that arise as an extension of the epidemiological findings in this thesis, and those that may be explored in the context of UK-wide advances in genetics and genomics research.

Some of the limitations of the research described in this thesis could form the basis for further study.

Validation study of HHT diagnoses

Whilst several studies have attempted to validate the diagnoses coded within THIN in patients with commoner pathologies such as chronic kidney disease or cardiovascular disease, none has been published in HHT. Such a validation study would require a sample of patient notes to be reviewed to confirm that a diagnosis of HHT in the notes was accurately coded in THIN by practice administrators. This may strengthen the validity of our prevalence estimates for HHT within THIN. In addition, it was not possible to determine by what criteria patients within THIN were diagnosed as having HHT. We do not know what proportion of patients were diagnosed based on clinical criteria alone compared with those that had a positive gene test. This information may be available from patient notes/genetic databases and could further strengthen the validity of a diagnosis coded in THIN, particularly if the proportion of diagnoses made using gene testing (the current 'gold standard' in those patients with mutations amenable to detection) was relatively high. This data may also provide insight into UK trends in the use of gene testing as part of the diagnostic pathway.

Investigation into the sex bias in diagnosed rates of HHT

We identified a significantly larger proportion of females diagnosed with HHT which may be as a result of ascertainment bias due to females consulting behaviours in primary care but could also potentially be due to biological or genetic factors that influence the presentation of the HHT phenotype. Published literature offers conflicting observations on the existence of a bias in sex. A study in a larger patient cohort, derived, for example, from the USA may provide more statistical power to confirm a difference. In addition, a larger patient cohort may also allow exploration of the relationship between pregnancy and the use of hormonal treatments, including the oral contraceptive, on diagnosed rates of HHT which may support a role for biological factors in the disease phenotype.

We were unable to look at this specifically in our THIN cohort due to low statistical power from small numbers and missing data.

Complications associated with HHT

Our recorded complication rates for patients with diagnosed HHT appeared to be lower than those in the published literature worldwide, mainly derived from non-epidemiological studies. This may be due to lower ascertainment of complications from an epidemiological database or may actually be more accurate as a result of discerning a more representative sample. We do not know what proportion of our patients coded in THIN were diagnosed as 'possible' or 'definite' HHT clinically by use of the Curacao criteria which has variable sensitivity and specificity for the diagnosis of HHT depending on the number of criteria fulfilled. It may be that we had a higher rate of 'possible' HHT diagnoses within our cohort and that lower complication rates reflected a proportion of patients included in the cohort who had a milder phenotype of disease or did not, in fact, have HHT. A prospective study recruiting a large number of patients from a representative sample and collecting regular data on complications would be the ideal way to study the natural history of the HHT phenotype and complication rates in both treated and untreated individuals.

Mortality associated with HHT

Whilst we demonstrate a two-fold increase in the hazard ratio for death in patients with HHT compared to age and sex matched control subjects we were not able to attribute this mortality directly to complications associated with HHT. Linkage to ONS data regarding death certification or direct review of a sample of patients' clinical records would allow us to be more explicit about whether HHT

or its complications confer a higher mortality in this patient population or whether death was attributable to other factors not directly linked to the disease itself. This is important, as if the former, it would strengthen the argument for more proactive approaches to patient screening/diagnosis and the offering of evidence-based therapeutic interventions (such as treatment for PAVMs and possibly CAVMs) in this population.

Validation study of codes for embolisation of PAVMs

The majority of the patients in our study described in chapter 7 were coded as having undergone "Percutaneous transluminal embolisation of pulmonary artery " with the assumption made that, in the context of HHT, this meant a therapeutic intervention specifically for PAVMs. This assumption could be tested, again by a review of a sample of patient notes to ensure that the validity of coding of the procedure.

Complication rates for embolisation and performing centres in England.

It would be informative to use the HES data to characterise the complication rates associated with embolisation of PAVMs in England (given that we had access only to mortality data). We could further identify the centres where the procedures were actually undertaken, rather than the geographical areas from which the patients undergoing embolisation were referred from. This would allow us to look at procedural activity throughout England, and identify areas where the population were not served by a 'local' centre undertaking embolisation. This would offer an important insight into areas of the country where patients may have to travel significant distances for appropriate treatment. With these data, we may also be able to comment on which performing centres had lower

complication rates for embolisation, both compared to published complication rates from 'HHT Centres of Excellence' and with other centres in England. Whilst these findings may be contentious, they could potentially be used facilitate the linking of more experienced centres with those who perform fewer procedures, or have less good outcomes in a bid to improve standards of patient care.

We did submit a request for these data from the Health and Social Care Information Centre (the guardians of HES data) but experienced significant delays in the response to our data extract request and had to complete this thesis in the absence of this additional data.

Follow-up screening protocols for patients with diagnosed and/or treated pulmonary AVMs

Current guidelines recommend screening follow-up at 6-12 months post embolisation (with multi-detector CT) in patients with treated pulmonary AVMs and thereafter, every 3 years [27]. These guidelines are based on expert opinion rather than evidence. Recently concerns have been raised that patients screened and treated for pulmonary AVMs may be exposed to an unacceptably high risk of radiation[213]. Radiation exposure is greatest in those undergoing interventional therapy for PAVMs but is also associated with repeated thoracic CT screening protocols. This is especially pertinent in those patients who are relatively young and may need long-term follow-up, or are female or pregnant, given the radiation exposure risk to the breast or foetus. In the cited study, 11% (26 patients) received a cumulative effective dose of in excess of 100 millisieverts (mSv) which is the level at which there is considered to be good evidence for a significant risk of harm and an excess lifetime cancer risk of 1%. Whilst TTCE can be used as a repeat screening tool in those previously negative for PAVMs, given that it can remain positive[214] (due to collateral microcirculation) in patients

following treatment for PAVMs it is not considered a useful follow-up imaging method in this patient cohort, and as such, 'radiation heavy' screening methods such as thoracic CT are more commonly considered. Future studies should look at cumulative radiation exposure stratified by number and type of PAVMs (embolised or unembolised) and may suggest safer, more effective or at least more evidence-based screening protocols for these patients.

Future research using clinical databases and genetic techniques

The UK government published, in 2012, its strategy for rare diseases[215] which places research high on the agenda and recognises specifically that using genetic databases and next generation sequencing techniques is key to advancing our knowledge base. Many outstanding questions regarding HHT, its clinical presentation, diagnosis, complications and appropriate management could usefully be addressed by the development of a UK-wide or indeed worldwide registry of HHT patients with data collected on patient demographics, disease phenotype and genetic mutations. Such a comprehensive database does not currently exist. Genetic mutations are collected worldwide and are available online at the HHT mutation database[36], but this does not link directly with individual patient demographics or clinical data. Several recent UK-based initiatives, described below, may provide useful data in the medium to long-term.

A) RD-Connect

This initiative led by the University of Newcastle Upon Tyne, is developing a unique global infrastructure that links up databases, registries, biobanks and clinical bioinformatics data used in rare disease[216].

B) UK Biobank

UK Biobank aims to investigate the respective contributions of genetic predisposition and environmental exposure (including nutrition, lifestyle, medications etc.) to the development of certain diseases[217]. Though the focus is predominantly on common and chronic diseases such as cancer, heart disease, stroke and diabetes, there may be useful data gleaned on those patients who develop rarer inherited diseases such as HHT. Between 2006-2010 UK Biobank recruited 500,000 people aged between 40-69 from across the UK to provide demographic and clinical data, blood/urine/saliva samples for future analysis, and who agreed to have their health followed over the long-term. This has the potential to be a powerful resource for looking at the genotype-phenotype correlation in any patients included who are diagnosed with HHT and also for investigating rare genetic variants associated with HHT in patients who do not test positive for an identifiable mutation (currently 15% of cases). However, given the size of the database and the prevalence of HHT we would not expect to have significant numbers of HHT cases included in UK Biobank archives until the database expands to recruit more of the UK population (for example, in a database of 500,000 and a minimum prevalence of HHT of 1 per 9,400, we would expect just over 50 patients to be included). Most of the larger genetic studies in HHT worldwide report on cohorts of between 150-200 patients.

C) 100,000 Genomes project

Launched in late 2012 with the aim to sequence 100,000 genomes by 2017, the main focus of this research project is on patients with rare disease and their families as well as patients with cancer[211]. A total of 3 million people in the UK are affected by a rare disease, which is 1 in 17 or 6-7% of the whole population. Samples will be obtained from 75,000 people, with 40,000 being patients with disease. About 15,000 patients in total will be included from those with a rare disease. This data, which will be obtained using cutting edge high throughput

gene sequencing techniques may help us to understand in more detail the role of genetics in moderating the phenotypic presentation of HHT cases.

Ultimately, these genetic databases will take time to recruit and none are specifically focussed upon HHT. The priority should be to establish a national or international register of suspected or confirmed cases of HHT with the aim to facilitate further clinical studies in larger patient cohorts and encourage a collaboration between the relatively few specialist centres worldwide with a research interest in HHT.

REFERENCES

1. Rendu H. Epistaxis repetees cuez un sujet porteur de petits angiomes cutanes et muqueux. *Gaz de Hop.* 1896;49:1322.
2. Osler W. On a family form of recurring epistaxis, associated with multiple telangiectases of the skin and mucous membranes. *Bull Johns Hopkins Hospital.* 1901;12:333-337.
3. Weber F. Multiple hereditary developmental angiomata (telangiectases) of the skin and mucous membranes associated with recurring haemorrhages. *Lancet.* 1907;1:160-162.
4. Hanes F. Multiple hereditary telangiectases causing hemorrhage (hereditary hemorrhagic telangiectasia). *Bull Johns Hopkins Hospital.* 1909;20:63-73.
5. Whitehead KJ, Smith MCP, Li DY. Arteriovenous malformations and other vascular malformation syndromes. *Cold Spring Harb Perspect Med.* 2013;3(2):a006635.
6. Al-Shahi R, Warlow C. A systematic review of the frequency and prognosis of arteriovenous malformations of the brain in adults. *Brain.* 2001;124(Pt 10):1900-1926.
7. Calhoun ARUL, Bollo RJ, Garber ST, et al. Spinal arteriovenous fistulas in children with hereditary hemorrhagic telangiectasia. *J Neurosurg Pediatrics.* 2012;9(6):654-659.
8. Cooke DA. Renal arteriovenous malformation demonstrated angiographically in hereditary haemorrhagic telangiectasia (Rendu-Osler-Weber disease). *J R Soc Med.* 1986;79(12):744-746.
9. Lacout A, Pelage JP, Lesur G, et al. Pancreatic involvement in hereditary hemorrhagic telangiectasia: assessment with multidetector helical CT. *Radiology.* 2010;254(2):479-484.

10. Lim K, Tam W, Worthley C, Nguyen NQ. Hepatobiliary and Pancreatic: Pancreatic vascular malformations in hereditary hemorrhagic telangiectasia. *Journal of Gastroenterology and Hepatology.* 2012;27(5):989.

11. Khurshid I, Downie GH. Pulmonary arteriovenous malformation. *Postgrad Med J.* 2002;78(918):191-197.

12. McDonald J, Bayrak-Toydemir P, Pyeritz RE. Hereditary hemorrhagic telangiectasia: An overview of diagnosis, management, and pathogenesis. *Genet Med.* 2011;13 (7):607-616.

13. Letteboer TGW, Mager JJ, Snijder RJ, et al. Genotype-phenotype relationship in hereditary haemorrhagic telangiectasia. *J Med Genet.* 2006;43(4):371-377.

14. Begbie ME, Wallace GMF, Shovlin CL. Hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu syndrome): a view from the 21st century. *Postgrad Med J.* 2003;79(927):18-24.

15. Sabba C. A rare and misdiagnosed bleeding disorder: hereditary hemorrhagic telangiectasia. *J Thromb Haemost.* 2005;3(10):2201-2210.

16. Grand'Maison A. Hereditary hemorrhagic telangiectasia. *CMAJ.* 2009;180 (8):833-835.

17. Maher CO, Piepgras DG, Brown RD, Jr., Friedman JA, Pollock BE. Cerebrovascular manifestations in 321 cases of hereditary hemorrhagic telangiectasia. *Stroke.* 2001;32(4):877-882.

18. Fulbright RK, Chaloupka JC, Putman CM, et al. MR of hereditary hemorrhagic telangiectasia: prevalence and spectrum of cerebrovascular malformations. *Am J Neuroradiology.* 1998;19(3):477-484.

19. Stapf C, Mast H, Sciacca RR, et al. Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. *Neurology.* 2006;66(9):1350-1355.

20. Nakayama M, Nawa T, Chonan T, et al. Prevalence of Pulmonary arteriovenous malformations as estimated by low-dose thoracic CT screening. *Internal Medicine.* 2012;51(13):1677-1681.

21. Faughnan ME, Granton JT, Young LH. The pulmonary vascular complications of hereditary haemorrhagic telangiectasia. *Eur Respir J.* 2009;33(5):1186-1194.

22. van Gent MWF, Post MC, Snijder RJ, Westermann CJJ, Plokker HWM, Mager JJ. Real prevalence of pulmonary right-to-left shunt according to genotype in patients with hereditary hemorrhagic telangiectasia: a transthoracic contrast echocardiography study. *Chest.* 2010;138(4):833-839.

23. Cottin V, Chinet T, Lavole A, et al. Pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia: A series of 126 patients. *Medicine.* 2007;86 (1):1-17.

24. Sluiter-Eringa H, Orie NG, Sluiter HJ. Pulmonary arteriovenous fistula. Diagnosis and prognosis in noncomplainant patients. *Am Rev Respir Dis.* 1969;100(2):177-188.

25. Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet.* 2000;91(1):66-67.

26. van Gent MWF, Velthuis S, Post MC, et al. Hereditary hemorrhagic telangiectasia: How accurate are the clinical criteria? *Am J Med Genet Part A.* 2013;161(3):461-466.

27. Faughnan ME, Palda VA, Garcia-Tsao G, et al. International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. *J Med Genet.* 2011;48(2):73-87.

28. Torring PM, Brusgaard K, Ousager LB, Andersen PE, Kjeldsen AD. National mutation study among Danish patients with hereditary haemorrhagic telangiectasia. *Clin Genet.* 2014;86(2):123-133.

29. Velthuis S, Vorselaars VM, van Gent MW, et al. Role of transthoracic contrast echocardiography in the clinical diagnosis of hereditary hemorrhagic telangiectasia. *Chest.* 2013;144(6):1876-1882.

30. Latino GA, Brown D, Glazier RH, Weyman JT, Faughnan ME. Targeting under-diagnosis in hereditary hemorrhagic telangiectasia: a model approach for rare diseases? *Orphanet J Rare Dis.* Vol 9. England2014:115.

31. Pierruci P, Lenato GM, Suppressa P, et al. A long diagnostic delay in patients with Hereditary Haemorrhagic Telangiectasia: a questionnaire-based retrospective study. *Orphanet J Rare Dis.* 2012;7(7).

32. McAllister KA, Grogg KM, Johnson DW, et al. Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. *Nat Genet.* 1994;8(4):345-351.

33. Johnson DW, Berg JN, Baldwin MA, et al. Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. *Nat Genet.* 1996;13(2):189-195.

34. Abdalla SA, Letarte M. Hereditary haemorrhagic telangiectasia: current views on genetics and mechanisms of disease. *J Med Genet.* 2006;43(2):97-110.

35. Gallione CJ, Richards JA, Letteboer TGW, et al. SMAD4 mutations found in unselected HHT patients. *J Med Genet.* 2006;43(10):793-797.

36. HHT Mutation Database. The University of Utah Department of Pathology and ARUP Laboratories; 2013. http://arup.utah.edu/database/HHT/. Accessed 01-06-2015

37. Govani FS, Shovlin CL. Hereditary haemorrhagic telangiectasia: a clinical and scientific review. *Eur J Hum Genet.* 2009;17(7):860-871.

38. Lastella P, Sabba C, Lenato GM, et al. Endoglin gene mutations and polymorphisms in Italian patients with hereditary haemorrhagic telangiectasia. *Clin Genet.* 2003;63(6):536-540.

39. Gallione C, Aylsworth AS, Beis J, et al. Overlapping spectra of SMAD4 mutations in juvenile polyposis (JP) and JP-HHT syndrome. *Am J Med Genet Part A.* 2010;152A(2):333-339.

40. Cole SG, Begbie ME, Wallace GMF, Shovlin CL. A new locus for hereditary haemorrhagic telangiectasia (HHT3) maps to chromosome 5. *J Med Genet.* 2005;42(7):577-582.

41. Bayrak-Toydemir P, McDonald J, Akarsu N, et al. A fourth locus for hereditary hemorrhagic telangiectasia maps to chromosome 7. *Am J Med Genet Part A.* 2006;140(20):2155-2162.

42. Wooderchak-Donahue W L, McDonald J, O'Fallon B, et al. BMP9 Mutations Cause a Vascular-Anomaly Syndrome with Phenotypic Overlap with Hereditary Hemorrhagic Telangiectasia. *Am J Hum Genet.* 2013;93(3):530-537.

43. Sabba C, Pasculli G, Lenato GM, et al. Hereditary hemorrhagic telangiectasia: clinical features in ENG and ALK1 mutation carriers. *J Thromb Haemost.* 2007;5(6):1149-1157.

44. Bayrak-Toydemir P, McDonald J, Markewitz B, et al. Genotype-phenotype correlation in hereditary hemorrhagic telangiectasia: mutations and manifestations. *Am J Med Genet Part A.* 2006;140(5):463-470.

45. Benzinou M, Clermont FF, Letteboer TGW, et al. Mouse and human strategies identify PTPN14 as a modifier of angiogenesis and Hereditary Hemorrhagic Telangiectasia. *Nat Comms.* 2012;3:616-616.

46. Shovlin CL. Hereditary haemorrhagic telangiectasia: pathophysiology, diagnosis and treatment. *Blood Rev.* 2010;24(6):203-219.

47. Karabegovic A, Shinawi M, Cymerman U, et al. No live individual homozygous for a novel endoglin mutation was found in a consanguineous Arab family with hereditary haemorrhagic telangiectasia. *J Med Genet.* 2004;41(11):e119.

48. Dines DE, Arms RA, Bernatz PE, et al. Pulmonary arteriovenous fistulas. *Mayo Clin Proc.* 1974;49(7):460-465.

49. Remy J, Remy-Jardin M, Wattinne L, et al. Pulmonary arteriovenous malformations: evaluation with CT of the chest before and after treatment. *Radiology.* 1992;182(3):809-816.

50. Silverman JM, Julien PJ, Herfkens RJ, et al. Magnetic resonance imaging evaluation of pulmonary vascular malformations. *Chest.* 1994;106(5):1333-1338.

51. Khalil A, Farres MT, Mangiapan G, et al. Pulmonary arteriovenous malformations: Diagnosis by contrast-enhanced magnetic resonance angiography. *Chest.* 2000;117 (5):1399-1403.

52. Whyte MKB, Peters AM, Hughes JMB, et al. Quantification of right to left shunt at rest and during exercise in patients with pulmonary arteriovenous malformations. *Thorax.* 1992;47 (10):790-796.

53. van Gent MWF, Post MC, Luermans JGLM, et al. Screening for pulmonary arteriovenous malformations using transthoracic contrast echocardiography: a prospective study. *Eur Respir J.* 2009;33(1):85-91.

54. Velthuis S, Buscarini E, Mager JJ, et al. Predicting the size of pulmonary arteriovenous malformations on chest computed tomography: a role for transthoracic contrast echocardiography. *Eur Respir J.* 2014;44(1):150-159.

55. Hanneman K, Faughnan ME, Prabhudesai V. Cumulative radiation dose in patients with hereditary hemorrhagic telangiectasia and pulmonary arteriovenous malformations. *Can Assoc Radiol J.* 2014;65(2):135-140.

56. Shovlin CL. Pulmonary Arteriovenous Malformations. *Am J Respir Crit Care Med.* 2014;190(11):1217-1228.

57. Caselitz M, Bahr MJ, Bleck JS, et al. Sonographic criteria for the diagnosis of hepatic involvement in hereditary hemorrhagic telangiectasia (HHT). *Hepatology.* 2003;37(5):1139-1146.

58. Buonamico P, Suppressa P, Lenato GM, et al. Liver involvement in a large cohort of patients with hereditary hemorrhagic telangiectasia: echo-color-Doppler vs multislice computed tomography study. *J Hepatol.* 2008;48(5):811-820.

59. Vase P. Estrogen treatment of hereditary hemorrhagic telangiectasia. A double-blind controlled clinical trial. *Acta Med Scand.* 1981;209(5):393-396.

60. Van Cutsem E, Rutgeerts P, Geboes K, et al. Estrogen-progesterone treatment of Osler-Weber-Rendu disease. *J Clin Gastroenterol.* 1988;10(6):676-679.

61. Albinana V, Bernabeu-Herrero ME, Zarrabeitia R, et al. Estrogen therapy for hereditary haemorrhagic telangiectasia (HHT): Effects of raloxifene, on Endoglin and ALK1 expression in endothelial cells. *Thromb Haemost.* 2010;103(3):525-534.

62. Jameson JJ, Cave DR. Hormonal and Antihormonal Therapy for Epistaxis in Hereditary Hemorrhagic Telangiectasia. *The Laryngoscope.* 2004;114(4):705-709.

63. Yaniv E, Preis M, Hadar T, et al. Antiestrogen therapy for hereditary hemorrhagic telangiectasia: a double-blind placebo-controlled clinical trial. *The Laryngoscope.* 2009;119(2):284-288.

64. Klepfish A, Berrebi A, Schattner A. Intranasal tranexamic acid treatment for severe epistaxis in hereditary hemorrhagic telangiectasia. *Arch Int Med.* 2001;161(5):767.

65. Sabba C, Gallitelli M, Palasciano G. Efficacy of unusually high doses of tranexamic acid for the treatment of epistaxis in hereditary hemorrhagic telangiectasia. *N Engl J Med.* 2001;345(12):926.

66. Boyer H, Fernandes P, Duran O, et al. Office-based sclerotherapy for recurrent epistaxis due to hereditary hemorrhagic telangiectasia: a pilot study. *Int Forum Allergy Rhinol.* 2011;1(4):319-323.

67. Chen St, Karnezis T, Davidson TM. Safety of intranasal Bevacizumab (Avastin) treatment in patients with hereditary hemorrhagic telangiectasia-associated epistaxis. *The Laryngoscope.* 2011;121(3):644-646.

68. Lebrin F, Srun S, Raymond K, et al. Thalidomide stimulates vessel maturation and reduces epistaxis in individuals with hereditary hemorrhagic telangiectasia. *Nat Med.* 2010;16(4):420-428.

69. Ghaheri BA, Fong KJ, Hwang PH. The utility of bipolar electrocautery in hereditary hemorrhagic telangiectasia. *Otolaryngol Head Neck Surg.* 2006;134(6):1006-1009.

70. Harvey RJ, Kanagalingam J, Lund VJ. The impact of septodermoplasty and potassium-titanyl-phosphate (KTP) laser therapy in the treatment of hereditary hemorrhagic telangiectasia-related epistaxis. *Am J Rhinol.* 2008;22(2):182-187.

71. Shah RK, Dhingra JK, Shapshay SM. Hereditary hemorrhagic telangiectasia: a review of 76 cases. *Laryngoscope.* 2002;112(5):767-773.

72. Layton KF, Kallmes DF, Gray LA, et al. Endovascular treatment of epistaxis in patients with hereditary hemorrhagic telangiectasia. *Am J Neuroradiol.* 2007;28(5):885-888.

73. Lund VJ, Howard DJ. Closure of the nasal cavities in the treatment of refractory hereditary haemorrhagic telangiectasia. *J Laryngol Otol.* 1997;111(1):30-33.

74. Bown SG, Swain CP, Storey DW, et al. Endoscopic laser treatment of vascular anomalies of the upper gastrointestinal tract. *Gut.* 1985;26(12):1338-1348.

75. Sargeant IR, Loizou LA, Rampton D, et al. Laser ablation of upper gastrointestinal vascular ectasias: long term results. *Gut.* 1993;34(4):470-475.

76. Román G, Fisher M, Perl DP, et al. Neurological manifestations of hereditary hemorrhagic telangiectasia (rendu-osler-weber disease): Report of 2 cases and review of the literature. *Ann Neurol.* 1978;4(2):130-144.

77. Hodgson CH, Kaye RL. Pulmonary arteriovenous fistula and hereditary hemorrhagic telangiectasia: a review and report of 35 cases of fistula. *Dis Chest.* 1963;43:449-455.

78. Press OW, Ramsey PG. Central nervous system infections associated with hereditary hemorrhagic telangiectasia. *Am J Med.* 1984;77(1):86-92.

79. Angle JF, Siddiqi NH, Wallace MJ, et al. Quality improvement guidelines for percutaneous transcatheter embolization: Society of Interventional Radiology Standards of Practice Committee. *J Vasc Interv Radiol.* 2010;21(10):1479-1486.

80. Shovlin CL, Jackson JE, Bamford KB, et al. Primary determinants of ischaemic stroke/brain abscess risks are independent of severity of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia. *Thorax.* 2008;63(3):259-266.

81. van Beijnum J, van der Worp HB, Buis DR, et al. Treatment of brain arteriovenous malformations: a systematic review and meta-analysis. *JAMA.* 2011;306(18):2011-2019.

82. Mohr JP, Parides MK, Stapf C, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. *The Lancet.* 2014;383(9917):614-621.

83. Buscarini E, Plauchu H, Garcia Tsao G, et al. Liver involvement in hereditary hemorrhagic telangiectasia: consensus recommendations. *Liver Int.* 2006;26(9):1040-1046.

84. Lis Y, Mann RD. The VAMP Research multi-purpose database in the U.K. *J Clin Epidemiol.* 1995;48(3):431-443.

85. British Medical Association. Framework Guidance for GMS Contract. 2013. http://bma.org.uk/practical-support-at-work/contracts/gp-contracts-and-funding/independent-contractors/qof-guidance. Accessed 01-06-2015.
86. Chisholm J. The Read clinical classification. *BMJ.* 1990;300(6732):1092.
87. Townsend P. Deprivation. *Journal of Social Policy.* 1987;16(02):125-146.
88. EPIC. THIN Data Guide for Researchers. 2011.
89. Bourke A, Dattani H, Robinson M. Feasibility study and methodology to create a quality-evaluated database of primary care data. *Informatics in Primary Care.* 2004;12(3):171-177.
90. Blak BT, Thompson M, Dattani H, et al. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Informatics in Primary Care.* 2011;19(4):251-255.
91. Lo Re V, Haynes K, Forde KA, et al. Validity of The Health Improvement Network (THIN) for epidemiologic studies of hepatitis C virus infection. *Pharmacoepidemiol Drug Saf.*18(9):807-814.
92. Denburg MR, Haynes K, Shults J, et al. Validation of The Health Improvement Network (THIN) database for epidemiologic studies of chronic kidney disease. *Pharmacoepidemiol Drug Saf.* 20(11):1138-1149.
93. Ruigomez A, Martin-Merino E, Rodriguez LAG. Validation of ischemic cerebrovascular diagnoses in the health improvement network (THIN). *Pharmacoepidemiol Drug Saf.*19(6):579-585.
94. Lewis JD, Schinnar R, Bilker WB, et al. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf.* 2007;16(4):393-401.
95. Langley TE, Szatkowski L, Gibson J, et al. Validation of The Health Improvement Network (THIN) primary care database for monitoring prescriptions for smoking cessation medications. *Pharmacoepidemiol Drug Saf.*19(6):586-590.

96. Szatkowski L, Lewis S, McNeill A, et al. Can data from primary care medical records be used to monitor national smoking prevalence? *J Epidemiol Community Health.* 2012;66(9):791-795.

97. Khadjesari Z, Marston L, Petersen I, et al. Alcohol consumption screening of newly-registered patients in primary care: a cross-sectional analysis. *Br J Gen Pract.* 2013;63(615):e706-712.

98. Love TJ, Zhu Y, Zhang Y, et al. Obesity and the risk of psoriatic arthritis: a population-based study. *Ann Rheum Dis.* 2012;71(8):1273-1277.

99. Taggar JS, Coleman T, Lewis S, Szatkowski L. The impact of the Quality and Outcomes Framework (QOF) on the recording of smoking targets in primary care medical records: cross-sectional analyses from The Health Improvement Network (THIN) database. *BMC Public Health.* 2012;12:329.

100. The Information Centre for Health and Social Care. Hospital Episodes Statistics (HES): Improving the quality and value of hospital data. 2011. http://www.hscic.gov.uk/media/1593/Hospital-Episode-Statistics-Improving-the-quality-and-value-of-hospital-data/pdf/HES_-_Improving_the_quality_and_value_of_hospital_data.pdf. Accesssed 01-06-2015.

101. Audit Commission. Improving data quality in the NHS annual report on the PbR assurance programme. 2010. http://archive.audit-comission.gov.uk/auditcommission/sitecollectiondocuments/Downloads/26082010pbrnhsdataqualityreport.pdf. Accesssed 01-06-2015.

102. Wright F, Green J, Canoy D, et al. Vascular disease in women: comparison of diagnoses in hospital episode statistics and general practice records in England. *BMC Med Res Methodol.* 2012;12(1):161.

103. Britton A, Milne B, Butler T, et al. Validating self-reported strokes in a longitudinal UK cohort study (Whitehall II): Extracting information from

hospital medical records versus the Hospital Episode Statistics database. *BMC Med Res Methodol.* 2012;12(1):83.

104. Health and Social Care Information Centre. 2010. HES-ONS linked mortality data guide. 2010. http://www.hscic.gov.uk/article/2677/Linked-HES-ONS-mortality-data. Accesssed 01-06-2015.

105. Pounder D, Jones M, Peschel H. How can we reduce the number of coroner autopsies? Lessons from Scotland and the Dundee initiative. *J R Soc Med.* 2011;104(1):19-24.

106. Sington JD, Cottrell BJ. Analysis of the sensitivity of death certificates in 440 hospital deaths: a comparison with necropsy findings. *J Clin Pathol.* 2002;55(7):499-502.

107. Porteous ME, Burn J, Proctor SJ. Hereditary haemorrhagic telangiectasia: a clinical analysis. *J Med Genet.* 1992;29(8):527-530.

108. Donaldson JW, McKeever TM, Hall IP, et al. The UK prevalence of hereditary haemorrhagic telangiectasia and associations with sex, region of residence and socioeconomic status: A population-based study. *Thorax.* 2014(69):161-167.

109. Grosse SD, Boulet SL, Grant AM, et al. The use of US health insurance data for surveillance of rare disorders: hereditary hemorrhagic telangiectasia. *Genet Med.* 2014;16(33-39).

110. Westermann CJJ, Rosina AF, De Vries V, et al. The prevalence and manifestations of hereditary hemorrhagic telangiectasia in the Afro-Caribbean population of the Netherlands Antilles: a family screening. *Am J Med Genet Part A.* 2003; 116A(4):324-328.

111. Dakeishi M, Shioya T, Wada Y, et al. Genetic epidemiology of hereditary hemorrhagic telangiectasia in a local community in the northern part of Japan. *Hum Mutat.* 2002;19(2):140-148.

112. Kjeldsen AD, Vase P, Green A. Hereditary haemorrhagic telangiectasia: a population-based study of prevalence and mortality in Danish patients. *J Intern Med.* 1999;245(1):31-39.

113. Guttmacher AE, McKinnon WC, Upton MD. Hereditary hemorrhagic telangiectasia: a disorder in search of the genetics community. *Am J Med Genet.* 1995;52(2):252-253.

114. Jessurun GA, Nossent JC. [Cerebrovascular accidents at a young age in Rendu-Osler-Weber disease; a survey in the Netherlands Antilles]. *Ned Tijdschr Geneeskd.* 1992;136(9):428-431.

115. Bideau A, Plauchu H, Brunet G, Robert J. Epidemiological investigation of Rendu-Osler disease in France: its geographical distribution and prevalence. *Popul.* 1989;44(1):3-22.

116. Plauchu H, Bideau, A. Epidemiologie et constitution d'un registre de population a propros d'une concentration geographique d'une maladie hereditaire rare. *Popul.* 1984;4-5:765-786.

117. Gossage JR, Kanj G. Pulmonary arteriovenous malformations. A state of the art review. *Am J Respir Crit Care Med.* 1998;158(2):643-661.

118. Plauchu H, de Chadarevian JP, Bideau A, et al. Age-related clinical profile of hereditary hemorrhagic telangiectasia in an epidemiologically recruited population. *Am J Med Genet.* 1989;32(3):291-297.

119. Adams J, Ryan V, White M. How accurate are Townsend Deprivation Scores as predictors of self-reported health? A comparison with individual level data. *Journal of Public Health.* 2005;27(1):101-106.

120. Kapur N, Hunt I, Lunt M, etal. Primary care consultation predictors in men and women: a cohort study. *Br J Gen Pract.* 2005;55(511):108-113.

121. Hippisley-Cox J, Vinogradova Y. Trends in Consultation rates in General Practice 1995/1996 to 2008/2009: Analysis of the Q Research database. Report to The Health and Social Care Information Centre. 1999.

http://www.hscic.gov.uk/catalogue/PUB01077/tren-cons-rate-gene-prac-95-09-95-09-rep.pdf. Accesssed 01-06-2015.

122. Shovlin CL, Winstock AR, Peters AM, et al. Medical complications of pregnancy in hereditary haemorrhagic telangiectasia. *QJM.* 1995;88(12):879-887.

123. Shovlin CL, Sodhi V, McCarthy A, et al. Estimates of maternal risks of pregnancy for women with hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu syndrome): suggested approach for obstetric services. *BJOG.* 2008;115(9):1108-1115.

124. Rich S, Dantzker DR, Ayres SM et al. Primary Pulmonary Hypertension: A National Prospective Study. *Ann Int Med.* 1987;107:216-223.

125. Abenhaim L, Moride Y, Brenot F, et al. Appetite-Suppressant Drugs and the Risk of Primary Pulmonary Hypertension. *N Engl J Med.* 1996;335:609-616.

126. Peacock AJ, Murphy NF, McMurray JJV, et al. An epidemiological study of pulmonary arterial hypertension. *Eur Respir J.* 2007;30(1):104-109.

127. Humbert M SO, Chaouat A et al. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med.* 2006;173(9):1023-1030.

128. Austin ED, Lahm T, West J, et al. Gender, sex hormones and pulmonary hypertension. *Pulm Circ.* 2013;3(2):294-314.

129. Dempsie Y, MacLean MR. The influence of gender on the development of pulmonary arterial hypertension. *Exp Physiol.* 2013;98(8):1257-1261.

130. Ventetuolo CE, Ouyang P, Bluemke DA, et al. Sex hormones are associated with right ventricular structure and function: The MESA-right ventricle study. *Am J Respir Crit Care Med.* 2011;183(5):659-667.

131. Butler DC, Petterson S, Phillips RL, et al. Measures of Social Deprivation That Predict Health Care Access and Need within a Rational Area of Primary Care Service Delivery. *Health Serv Res.* 2012:1-21.

132. Trinder PM, Croft PR, Jones M, et al. Social deprivation and patterns of consultation for respiratory symptoms: a population-based cohort study. *J Epidemiol Community Health.* 1999;53(4):251-252.

133. Hart JT. The inverse care law. *Lancet.* 1971;1(7696):405-412.

134. Brunet G, Lesca G, Genin E, et al. Thirty Years of Research into Rendu-Osler-Weber Disease in France: Historical Demography, Population Genetics and Molecular Biology. *Popul.* 2009;64(2):273-292.

135. Bideau A, Brunet G, Heyer E, et al. An abnormal concentration of cases of Rendu-Osler disease in the Valserine valley of the French Jura: a genealogical and demographic study. *Ann Hum Biol.* 1992;19(3):233-247.

136. Office for National Statistics. Annual mid-year population estimates. 2010. http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/mid-2010-population-estimates/index.html. Accesssed 01-06-2015.

137. Woodall MN, McGettigan M, Figueroa R, et al. Cerebral vascular malformations in hereditary hemorrhagic telangiectasia. *J Neurosurg.* 2014;120(1):87-92.

138. Cottin V, Plauchu H, Bayle J-Y, Barthelet M, Revel D, Cordier J-F. Pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. *Am J Respir Crit Care Med.* 2004;169(9):994-1000.

139. Dupuis-Girod S, Giraud S, Decullier E, et al. Hemorrhagic hereditary telangiectasia (Rendu-Osler disease) and infectious diseases: an underestimated association. *Clin Infect Dis.* 2007;44(6):841-845.

140. Kjeldsen AD, Oxhoj H, Andersen PE, et al. Prevalence of pulmonary arteriovenous malformations (PAVMs) and occurrence of neurological

symptoms in patients with hereditary haemorrhagic telangiectasia (HHT). *J Intern Med.* 2000;248(3):255-262.

141. Haitjema T, Balder W, Disch FJ, et al. Epistaxis in hereditary haemorrhagic telangiectasia. *Rhinology.* 1996;34(3):176-178.

142. Hoag JB, Terry P, Mitchell S, et al. An epistaxis severity score for hereditary hemorrhagic telangiectasia. *The Laryngoscope.* 2010;120(4):838-843.

143. Hosman A, Devlin H, Silva B, et al. Specific cancer rates may differ in patients with hereditary haemorrhagic telangiectasia compared to controls. *Orphanet J Rare Dis.* 2013;8(1):195.

144. O'Malley M, LaGuardia L, Kalady MF, et al. The prevalence of hereditary hemorrhagic telangiectasia in juvenile polyposis syndrome. *Dis Colon Rectum.* 2012;55(8):886-892.

145. Brosens LAA, van Hattem A, Hylind LM, et al. Risk of colorectal cancer in juvenile polyposis. *Gut.* 2007;56(7):965-967.

146. Cottin V, Dupuis-Girod S, Lesca G, et al. Pulmonary vascular manifestations of hereditary hemorrhagic telangiectasia (Rendu-Osler disease). *Respiration.* 2007;74(4):361-378.

147. Drouet T, Muresan IP, Maro B, et al. Neurologic phenotype assocoated with Hereditary Haemorrhagic Telangiectasia in a monocentric cohort of 154 patients. 2012. International Stroke Conference.

148. Kjeldsen AD, Torring PM, Nissen H, et al. Cerebral abscesses among Danish patients with hereditary haemorrhagic telangiectasia. *Acta Neurol Scand.* 2014;129(3):192-197.

149. Vase P, Grove O. Gastrointestinal lesions in hereditary hemorrhagic telangiectasia. *Gastroenterology.* 1986;91(5):1079-1083.

150. Marziniak M, Jung A, Guralnik V, et al. An association of migraine with hereditary haemorrhagic telangiectasia independently of pulmonary right-to-left shunts. *Cephalalgia.* 2009;29(1):76-81.

151. Thenganatt J, Schneiderman J, Hyland RH, et al. Migraines Linked to Intrapulmonary Right-to-Left Shunt. *Headache.* 2006;46:439-443.

152. Post MC, Letteboer TGW, Mager JJ, et al. A pulmonary right-to-left shunt in patients with hereditary hemorrhagic telangiectasia is associated with an increased prevalence of migraine. *Chest.* 2005;128(4):2485-2489.

153. Sabba C, Pasculli G, Suppressa P, et al. Life expectancy in patients with hereditary haemorrhagic telangiectasia. *QJM.* 2006;99(5):327-334.

154. Kjeldsen AD, Moller TR, Brusgaard K, Vase P, Andersen PE. Clinical symptoms according to genotype amongst patients with hereditary haemorrhagic telangiectasia. *J Intern Med.* 2005;258(4):349-355.

155. Edwards CP, de Gussem EM, Mager JJ, Westermann CJJ, Faughnan ME. Life expectancy of parents with hereditary hemorrhagic telangiectasia in a Canadian population. *Can Respir J.* 2010;17:49A.

156. Lantz PM, House JS, Lepkowski JM, et al. Socioeconomic factors, health behaviors, and mortality: Results from a nationally representative prospective study of us adults. *JAMA.* 1998;279(21):1703-1708.

157. Stringhini S, Sabia S, Shipley M, et al. ASsociation of socioeconomic position with health behaviors and mortality. *JAMA.* 2010;303(12):1159-1166.

158. Gupta S, Faughnan ME, Bayoumi AM. Embolization for pulmonary arteriovenous malformation in hereditary hemorrhagic telangiectasia: a decision analysis. *Chest.* 2009;136(3):849-858.

159. Hsu CC, Kwan GN, Thompson SA, Evans-Barns H, van Driel ML. Embolisation for pulmonary arteriovenous malformation. *Cochrane database of systematic reviews (Online).* 2012;8:CD008017.

160. Pollak JS, Saluja S, Thabet A, et al. Clinical and anatomic outcomes after embolotherapy of pulmonary arteriovenous malformations. *J Vasc Interv Radiol.* 2006;17(1):35-44.

161. Albrecht J, Werth VP, Bigby M. The role of case reports in evidence-based practice, with suggestions for improving their reporting. *J Am Acad Dermatol.* 2009;60(3):412-418.

162. Saluja S, Sitko I, Lee DW, et al. Embolotherapy of pulmonary arteriovenous malformations with detachable balloons: long-term durability and efficacy. *J Vasc Interv Radiol.* 1999;10(7):883-889.

163. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials.*7(3):177-188.

164. National Institure for Health Research. International prospective register of systematic reviews. 2013. http://www.crd.york.ac.uk/Prospero/. Accessed 01-06-2015.

165. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *Open Med.* 2009;3(3):e123-130.

166. Allison DJ, Jackson JE. Coil embolization of pulmonary arteriovenous malformations. *Radiology: proceedings of the 17th International Congress of Radiology.* 1990;ICS876:219-224.

167. Andersen PE, Kjeldsen AD. Clinical and radiological long-term follow-up after embolization of pulmonary arteriovenous malformations. *Cardiovasc Interven Radiol.* 2006;29(1):70-74.

168. Dutton JAE, Jackson JE, Hughes JMB, et al. Pulmonary arteriovenous malformations: Results of treatment with coil embolization in 53 patients. *Am J Roentgenol.* 1995;165(5):1119-1125.

169. Grosso M, Groppo Marchisio F, Testa F, et al. Pulmonary arteriovenous malformations: percutaneous treatment preserving parenchyma in high-flow fistulae. *Radiologia Medica.* 2008;113(3):395-413.

170. Gupta P, Mordin C, Curtis J, et al. Pulmonary arteriovenous malformations: effect of embolization on right-to-left shunt, hypoxemia,

and exercise tolerance in 66 patients. *Am J Roentgenol.* 2002;179(2):347-355.

171. Haitjema TJ, Overtoom TT, Westermann CJ, et al. Embolisation of pulmonary arteriovenous malformations: results and follow up in 32 patients. *Thorax.* 1995;50(7):719-723.

172. Hart JL, Aldin Z, Braude P, et al. Embolization of pulmonary arteriovenous malformations using the Amplatzer vascular plug: successful treatment of 69 consecutive patients. *Eur Radiol.* 2010;20(11):2663-2670.

173. Hayashi S, Baba Y, Senokuchi T, et al. Efficacy of venous sac embolization for pulmonary arteriovenous malformations: comparison with feeding artery embolization. *J Vasc Interv Radiol.* 2012;23(12):1566-1577.

174. Lacombe P, Lagrange C, Beauchet A, et al. Diffuse pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia long-term results of embolization according to the extent of lung involvement. *Chest.* 2009;135(4):1031-1037.

175. Lee DW, White Jr RI, Egglin TK, et al. Embolotherapy of large pulmonary arteriovenous malformations: Long-term results. *Ann Thorac Surg.* 1997;64 (4):930-940.

176. Letourneau-Guillon L, Faughnan ME, Soulez G, et al. Embolization of pulmonary arteriovenous malformations with amplatzer vascular plugs: safety and midterm effectiveness. *J Vasc Interv Radiol.* 2010;21(5):649-656.

177. Liu FY, Wang MQ, Fan QS, et al. Endovascular embolization of pulmonary arteriovenous malformations. *Chinese Medical Journal.* 2010;123 (1):23-28.

178. Mager JJ, Overtoom TTC, Blauw H, et al. Embolotherapy of pulmonary arteriovenous malformations: long-term results in 112 patients. *J Vasc Interv Radiol.* 2004;15(5):451-456.

179. Pierucci P, Murphy J, Henderson KJ, et al. New definition and natural history of patients with diffuse pulmonary arteriovenous malformations: Twenty-seven-year experience. *Chest.* 2008;133 (3):653-661.

180. Pollak JS, Egglin TK, Rosenblatt MM, et al. Clinical results of transvenous systemic embolotherapy with a neuroradiologic detachable balloon. *Radiology.* 1994;191 (2):477-482.

181. Prasad V, Chan RP, Faughnan ME. Embolotherapy of pulmonary arteriovenous malformations: efficacy of platinum versus stainless steel coils. *J Vasc Interv Radiol.* 2004;15(2 Pt 1):153-160.

182. Puskas JD, Allen MS, Moncure AC, et al. Pulmonary arteriovenous malformations: Therapeutic options. *Ann Thorac Surg.* 1993;56 (2):253-258.

183. Remy-Jardin M, Dumont P, Brillet PY, et al. Pulmonary arteriovenous malformations treated with embolotherapy: Helical CT evaluation of long-term effectiveness after 2-21-year follow-up. *Radiology.* 2006;239 (2):576-585.

184. Saluja S, Sitko I, Lee DW, Pollak J, White Jr RI. Embolotherapy of pulmonary arteriovenous malformations with detachable balloons: Long-term durability and efficacy. *J Vasc Interv Radiol.* 1999;10 (7):883-889.

185. Swanson KL, Prakash UB, Stanson AW. Pulmonary arteriovenous fistulas: Mayo Clinic experience, 1982-1997. *Mayo Clin Proc.* 1999;74(7):671-680.

186. Tapping CR, Ettles DF, Robinson GJ. Long-term follow-up of treatment of pulmonary arteriovenous malformations with AMPLATZER Vascular Plug and AMPLATZER Vascular Plug II devices. *J Vasc Interv Radiol.* 2011;22(12):1740-1746.

187. Trerotola SO, Pyeritz RE, Bernhardt BA. Outpatient single-session pulmonary arteriovenous malformation embolization. *J Vasc Interv Radiol.* 2009;20(10):1287-1291.

188. White Jr RI, Lynch-Nyhan A, Terry P, et al. Pulmonary arteriovenous malformations: Techniques and long-term outcome of embolotherapy. *Radiology.* 1988;169 (3):663-669.

189. Wong HH, Chan RP, Klatt R, et al. Idiopathic pulmonary arteriovenous malformations: clinical and imaging characteristics. *Eur Respir J.* 2011;38(2):368-375.

190. Woodward CS, Pyeritz RE, Chittams JL, et al. Treated pulmonary arteriovenous malformations: patterns of persistence and associated retreatment success. *Radiology.* 2013;269:919-926.

191. Lacombe P, Lagrange C, Beauchet A, et al. Diffuse pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia: long-term results of embolization according to the extent of lung involvement. *Chest.* 2009;135(4):1031-1037.

192. Pierucci P, Murphy J, Henderson KJ, et al. New definition and natural history of patients with diffuse pulmonary arteriovenous malformations: twenty-seven-year experience. *Chest.* 2008;133(3):653-661.

193. Lee DW, White RI, Jr., Egglin TK, et al. Embolotherapy of large pulmonary arteriovenous malformations: long-term results. *Ann Thorac Surg.* 1997;64(4):930-939.

194. Andersen PE, Kjeldsen AD, Oxhoj H, et al. Percutaneous transluminal treatment of pulmonary arteriovenous malformations. *J Vasc Interv Radiol.* 1999;14 (4):164-170.

195. Brillet P-Y, Dumont P, Bouaziz N, et al. Pulmonary arteriovenous malformation treated with embolotherapy: systemic collateral supply at multidetector CT angiography after 2-20-year follow-up. *Radiology.* 2007;242(1):267-276.

196. Chilvers ER, Whyte MK, Jackson JE, et al. Effect of percutaneous transcatheter embolization on pulmonary function, right-to-left shunt,

and arterial oxygenation in patients with pulmonary arteriovenous malformations. *Am Rev Respir Dis.* 1990;142(2):420-425.

197. Faughnan ME, Thabet A, Mei-Zahav M, et al. Pulmonary arteriovenous malformations in children: outcomes of transcatheter embolotherapy. *J Pediatr.* 2004;145(6):826-831.

198. Jackson JE, Whyte MK, Allison DJ, et al. Coil embolization of pulmonary arteriovenous malformations. *Cor et Vasa.* 1990;32(3):191-196.

199. White Jr RI, Mitchell SE, Barth KH. Angioarchitecture of pulmonary arteriovenous malformations: An important consideration before embolotherapy. *Am J Roentgenol.* 1983;140 (4):681-686.

200. Dutton JA, Jackson JE, Hughes JM, et al. Pulmonary arteriovenous malformations: results of treatment with coil embolization in 53 patients. *Am J Roentgenol.* 1995;165(5):1119-1125.

201. Whyte MK, Peters AM, Hughes JM, et al. Quantification of right to left shunt at rest and during exercise in patients with pulmonary arteriovenous malformations. *Thorax.* 1992;47(10):790-796.

202. Sagara K, Miyazono N, Inoue H, et al. Recanalization after coil embolotherapy of pulmonary arteriovenous malformations: study of long-term outcome and mechanism for recanalization. *Am J Roentgenol.* 1998; 170(3):727-730.

203. NHS Connecting for Health. OPCS-4 Classification. 2011. http://webarchive.nationalarchives.gov.uk/20130502102046/http://connectingforhealth.nhs.uk/systemsandservices/data/clinicalcoding/codingstandards/opcs4/index_html. Accessed 01-06-2015.

204. World Health Organisation. International Classification of Diseases Tenth Revision. 2000. http://apps.who.int/classifications/icd10/browse/2010/en. Accessed 01-06-2015.

205. Health and Social Care Information Centre. Methodology for creation of the HES Patient ID (HESID). 2014. http://www.hscic.gov.uk/media/1370/HES-Hospital-Episode-Statistics-Replacement-of-the-HES-patient-ID/pdf/HESID_Replacement_Nov09.pdf. Accessed 01-06-2015.

206. Cottin V, Chinet T, Lavole A, et al. Pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia: a series of 126 patients. *Medicine.* 2007;86(1):1-17.

207. Avendano M, Kunst AE, Huisman M, et al. Socioeconomic status and ischaemic heart disease mortality in 10 western European populations during the 1990s. *Heart.* 2006;92(4):461-467.

208. Woods LM, Rachet B, Coleman MP. Origins of socio-economic inequalities in cancer survival: a review. *Annals of Oncology.* 2006;17(1):5-19.

209. Prescott E, Godtfredsen N, Vestbo J, Osler M. Social position and mortality from respiratory diseases in males and females. *Eur Respir J.* 2003;21(5):821-826.

210. HHT Mutation Database. University of Utah. 2013. http://www.arup.utah.edu/database/hht/index.php. Accessed 01-06-2015.

211. 1000 Genomes Project. 2015. http://www.1000.genomes.org. Accessed 01-06-2015.

212. Majewski J, Schwartzentruber J, Lalonde E, et al. What can exome sequencing do for you? *J Med Genet.* 2011;48:580-589.

213. Hanneman K, Faughnan ME, Prabhudesai V. Cumulative Radiation Dose in Patients With Hereditary Hemorrhagic Telangiectasia and Pulmonary Arteriovenous Malformations. *Can Assoc Radiol J.* 65(2):135-140.

214. Lee WL, Graham AF, Pugash RA, et al. Contrast echocardiography remains positive after treatment of pulmonary arteriovenous malformations. *Chest.* 2003;123(2):351-358.

215. UK Department of Health. The UK Strategy for Rare Diseases. 2013. http://www.gov.uk/government/uploads/system/uploads/attachment_data/file/260562/Uk_Strategy_for_Rare_Diseases.pdf. Accessed 01-06-2015.

216. University of Aix-Marseille. 2015. http://rd-connect.eu/. Accessed 01-06-2015.

217. UK Biobank. 2015. http://www.ukbiobank.ac.uk/. Accessed 01-06-2015.

APPENDICES

10.1 APPENDIX 1 - OPCS-4 codes for interventional procedures that may have been undertaken as treatment of pulmonary arteriovenous malformations.

Procedure	OPCS-4 code
Percutaneous transluminal embolisation of pulmonary artery	L13.2
Percutaneous transluminal embolisation of major systemic to pulmonary collateral artery	L69.3
Percutaneous transluminal embolisation of artery	L71.3
Embolisation of arteriovenous abnormality NEC	L75.3
Percutaneous transluminal embolisation of arteriovenous malformation NEC	L75.4
Percutaneous transluminal venous embolisation of arteriovenous malformation	L75.5
Percutaneous transluminal arterial and venous embolisation of arteriovenous malformation	L75.6
Percutaneous transluminal coil embolisation of small aneurysm of artery	O01.1
Percutaneous transluminal coil embolisation of medium aneurysm of artery	O01.2
Percutaneous transluminal coil embolisation of large aneurysm of artery	O01.3
Percutaneous transluminal coil embolisation of giant aneurysm of artery	O01.4
Other specified transluminal coil embolisation of aneurysm of artery	O01.8
Unspecified transluminal coil embolisation of aneurysm of artery	O01.9
Percutaneous transluminal balloon assisted coil embolisation of three or more aneurysms of artery	O02.1
Percutaneous transluminal balloon assisted coil embolisation of two aneurysms of artery	O02.2
Percutaneous transluminal balloon assisted coil embolisation of single aneurysm of artery	O02.3

Other specified transluminal balloon assisted coil embolisation of three or more aneurysms of artery	O02.8
Unspecified transluminal balloon assisted coil embolisation of three or more aneurysms of artery	O02.9
Percutaneous transluminal stent assisted coil embolisation of three or more aneurysms of artery	O03.1
Percutaneous transluminal stent assisted coil embolisation of two aneurysms of artery	O03.2
Percutaneous transluminal stent assisted coil embolisation of single aneurysm of artery	O03.3
Other specified transluminal stent assisted coil embolisation of aneurysm of artery code	O03.8
Unspecified transluminal stent assisted coil embolisation of aneurysm of artery	O03.9
Percutaneous transluminal liquid polymer embolisation of aneurysm of artery	O04.1
Percutaneous transluminal stent assisted liquid polymer embolisation of aneurysm of artery	O04.2
Other specified other transluminal embolisation of aneurysm of artery	O04.8
Unspecified other transluminal embolisation of aneurysm of artery	O04.9

10.2 APPENDIX 2 - Read codes used to identify potential complications of HHT and associated cardiovascular comorbidities and malignancies

Anaemia

Description	Medcode
H/O: anaemia	145..11
H/O: anaemia - iron deficient	1451.00
Iron deficiency anaemias	D00..00
Hypochromic - microcytic anaemia	D00..11
Microcytic - hypochromic anaemia	D00..12
Iron deficiency anaemia due to chronic blood loss	D000.00
Normocytic anaemia due to chronic blood loss	D000.11
Iron deficiency anaemia due to blood loss	D000.12
Other specified iron deficiency anaemia	D00y.00
Microcytic hypochromic anaemia	D00y100
Other specified iron deficiency anaemia NOS	D00yz00
Unspecified iron deficiency anaemia	D00z.00
Iron deficiency anaemia NOS	D00zz00
[X]Other iron deficiency anaemias	Dyu0000
Acute posthaemorrhagic anaemia	D211.00
Normocytic anaemia following acute bleed	D211.11
Chronic anaemia	D214.00

Arteriovenous Malformations

Description	Medcode
Arteriovenous fistula of pulmonary vessels	G420.00
Arteriovenous malformation	P76D.00
Congenital cerebral arteriovenous aneurysm	P7y0100
Congenital arteriovenous fistula of brain	P7y0111
Pulmonary arterio-venous aneurysm	P736.00
Pulmonary arterio-venous fistula	P736.11
Pulmonary arterio-venous malformation	P736.12
Pulmonary artery aneurysm	P737.00
Percutaneous transluminal embolisation of arteriovenous malformation NEC	7A61500
Percutaneous transluminal venous embolisation of arteriovenous malformation	7A61600
Percutaneous transluminal arterial venous embolisation of arteriovenous malformation	7A61700

Breast Cancer

Description	Medcode
Juvenile breast carcinoma	BB94.00
Secretory breast carcinoma	BB94.11
Malignant neoplasm of female breast	B34..00
Ca female breast	B34..11
Malignant neoplasm of nipple and areola of female breast	B340.00
Malignant neoplasm of nipple of female breast	B340000
Malignant neoplasm of areola of female breast	B340100
Malignant neoplasm of nipple or areola of female breast NOS	B340z00
Malignant neoplasm of central part of female breast	B341.00
Malignant neoplasm of upper-inner quadrant of female breast	B342.00
Malignant neoplasm of lower-inner quadrant of female breast	B343.00
Malignant neoplasm of upper-outer quadrant of female breast	B344.00
Malignant neoplasm of lower-outer quadrant of female breast	B345.00

Malignant neoplasm of axillary tail of female breast	B346.00
Malignant neoplasm, overlapping lesion of breast	B347.00
Malignant neoplasm of other site of female breast	B34y.00
Malignant neoplasm of ectopic site of female breast	B34y000
Malignant neoplasm of other site of female breast NOS	B34yz00
Malignant neoplasm of female breast NOS	B34z.00
Carcinoma in situ of breast and genitourinary system	B83..00
Carcinoma in situ of breast	B830.00
Lobular carcinoma in situ of breast	B830000
Intraductal carcinoma in situ of breast	B830100
Paget's disease and infiltrating breast duct carcinoma	BB9K.00
Paget's disease and intraductal carcinoma of breast	BB9K000
Personal history of malignant neoplasm of breast	ZV10300
Lobular carcinoma in situ	BB9E.00
Intraductal carcinoma and lobular carcinoma in situ	BB9E000
Lobular carcinoma NOS	BB9F.00
Infiltrating ductular carcinoma	BB9G.00

Cardiac Failure

Description	Medcode
Heart failure	G58..00
Cardiac failure	G58..11
Congestive heart failure	G580.00
Congestive cardiac failure	G580.11
Right heart failure	G580.12
Right ventricular failure	G580.13
Biventricular failure	G580.14
Acute congestive heart failure	G580000
Chronic congestive heart failure	G580100
Decompensated cardiac failure	G580200
Compensated cardiac failure	G580300
Congestive heart failure due to valvular disease	G580400

Left ventricular failure	G581.00
Asthma - cardiac	G581.11
Pulmonary oedema - acute	G581.12
Impaired left ventricular function	G581.13
Acute left ventricular failure	G581000
Acute heart failure	G582.00
Heart failure with normal ejection fraction	G583.00
HFNEF - heart failure with normal ejection fraction	G583.11
Right ventricular failure	G584.00
Heart failure NOS	G58z.00

Cerebral Abscess

Description	Medcode
Drainage of abscess of brain tissue	7004000
Aspiration of abscess of brain tissue	7008100
Intracranial abscess	F040.00
Brain abscess	F040.11
Cerebral intracranial abscess	F040000
Cerebral abscess	F040011
Cerebellar intracranial abscess	F040100
Cerebellar abscess	F040111
Intracranial abscess NOS	F040z00

Colonic Cancer

Description	Medcode
Malignant neoplasm of colon	B13..00
Malignant neoplasm of hepatic flexure of colon	B130.00
Malignant neoplasm of transverse colon	B131.00
Malignant neoplasm of descending colon	B132.00
Malignant neoplasm of sigmoid colon	B133.00
Malignant neoplasm of caecum	B134.00

Carcinoma of caecum	B134.11
Malignant neoplasm of appendix	B135.00
Malignant neoplasm of ascending colon	B136.00
Malignant neoplasm of splenic flexure of colon	B137.00
Malignant neoplasm, overlapping lesion of colon	B138.00
Dukes stage A	4M10.00
Dukes stage B	4M11.00
Dukes stage C1	4M12.00
Dukes stage C2	4M13.00
Dukes stage D	4M14.00
Personal history of malignant neoplasm of large intestine	ZV10014
Personal history of malignant neoplasm of rectum	ZV10017

Dyspnoea

Description	Medcode
Breathlessness	173..00
Breathlessness symptom	173..11
Dyspnoea - symptom	173..12
Shortness of breath symptom	173..13
Breathless - moderate exertion	1732.00
Breathless - mild exertion	1733.00
Breathless - at rest	1734.00
Shortness of breath	1739.00
Short of breath on exertion	173C.00
Dyspnoea on exertion	173C.11
SOBOE	173C.12
Breathless - strenuous exertion	173G.00
MRC Breathlessness Scale: grade 1	173H.00
MRC Breathlessness Scale: grade 2	173I.00
MRC Breathlessness Scale: grade 3	173J.00
MRC Breathlessness Scale: grade 4	173K.00
MRC Breathlessness Scale: grade 5	173L.00

Breathlessness NOS	173Z.00
O/E - dyspnoea	2322.00
Dyspnoea	R060A00
Breathlessness	R060D00

Epistaxis

Description	Medcode
Epistaxis symptom	1C6..11
O/E - epistaxis	2D25.00
Epistaxis	R047.00
Nose bleed symptom	1C6..00
Has nose bleeds - epistaxis	1C62.00
Nose bleed symptom NOS	1C6Z.00
Nosebleed	R047.11

Epilepsy

Description	Medcode
H/O: epilepsy	1473.00
Epilepsy confirmed	1O30.00
Epilepsy monitoring	667..00
Epilepsy drug side effects	6677.00
Epilepsy treatment changed	6678.00
Epilepsy treatment started	6679.00
Epilepsy control good	667C.00
Epilepsy control poor	667D.00
Epilepsy management plan given	667M.00
Epilepsy monitoring NOS	667Z.00
Seen in epilepsy clinic	9N0r.00
Epilepsy monitoring call first letter	9Of5.00
Epilepsy monitoring call second letter	9Of6.00
Epilepsy monitoring call third letter	9Of7.00

Epilepsy	F25..00
Generalised nonconvulsive epilepsy	F250.00
Petit mal (minor) epilepsy	F250000
Epileptic absences	F250011
Epileptic seizures - atonic	F250200
Epileptic seizures - akinetic	F250300
Juvenile absence epilepsy	F250400
Other specified generalised nonconvulsive epilepsy	F250y00
Generalised nonconvulsive epilepsy NOS	F250z00
Generalised convulsive epilepsy	F251.00
Grand mal (major) epilepsy	F251000
Tonic-clonic epilepsy	F251011
Epileptic seizures - clonic	F251200
Epileptic seizures - myoclonic	F251300
Epileptic seizures - tonic	F251400
Tonic-clonic epilepsy	F251500
Other specified generalised convulsive epilepsy	F251y00

Family history of Ischaemic heart disease

Description	Medcode
No FH: Ischaemic heart disease	1226.00
No relevant family history	122..00
No relevant FH: family history	122..11
No FH: Cardiovascular disease	1224.00
FH: Cardiovascular disease	12C..00
FH: Angina	12C..14
FH: Ischaemic heart dis. <60	12C2.00
FH: Myocardial infarction < 60	12C2.11
FH: MI- Myocardial infarct <60	12C2.12
FH: Angina < 60yrs	12C2.13
FH: Ischaemic heart dis. >60	12C3.00
FH: Myocardial infarction > 60	12C3.11

FH: MI- myocardial infarct >60	12C3.12
FH: Angina > 60yrs	12C3.13
FH: Myocardial infarction	12C5.00
FH: Coronary thrombosis	12C5.11
FH: Ischaemic heart disease	12C5.12
FH: Atherosclerosis	12C6.00
FH myocardial infarction male first degree age known	12CA.00
FH myocardial infarction male first degree age unknown	12CB.00
FH myocardial infarction female first degree age known	12CC.00
FH myocardial infarction female first degree age unknown	12CD.00
FH angina male first degree age known	12CE.00
FH angina male first degree age unknown	12CF.00
FH angina female first degree age known	12CG.00
FH angina female first degree age unknown	12CH.00

Gastrointestinal bleeding

Description	Medcode
GIB - Gastrointestinal bleeding	J68z.11
Gastric haemorrhage NOS	J68z000
Intestinal haemorrhage NOS	J68z100
Gastrointestinal tract haemorrhage NOS	J68zz00

Haemoptysis

Description	Medcode
Blood in sputum - haemoptysis	172..00
Blood in sputum - symptom	172..11
Haemoptysis - symptom	172..12
Haemoptysis	R063.00
Haemoptysis NOS	R063z00

Haemothorax

Description	Medcode
Haemothorax	H51y200

Headache

Description	Medcode
Headache	1B1G.00
C/O - a headache	1B1G.11
Cephalgia	1B1G.12
Generalised headache	1BA2.00
Unilateral headache	1BA3.00
Bilateral headache	1BA4.00
Frontal headache	1BA5.00
Occipital headache	1BA6.00
Parietal headache	1BA7.00
Temporal headache	1BA8.00
Headache site NOS	1BAZ.00
Aching headache	1BB1.00
Throbbing headache	1BB2.00
Shooting headache	1BB3.00
Headache character NOS	1BBZ.00
Referral to headache special interest general practitioner	8H4c.00
Seen by general practitioner with special interest headache	9Nl7.00
Vascular headache, not elsewhere classified	F2X..00
Vascular headache, not elsewhere classified	Fyu5A00
Chronic headache disorder	Fyu5E00
Headache	R040.00

Hypertension

Description	Medcode
On treatment for hypertension	662O.00
Hypertension monitoring	662..12
Good hypertension control	6627.00
Poor hypertension control	6628.00
Hypertension:follow-up default	6629.00
Moderate hypertension control	662b.00
Hypertension six month review	662c.00
Hypertension annual review	662d.00
Hypertension treatment. started	662F.00
Hypertensive treatment changed	662G.00
Hypertension clinical management plan	8CR4.00
Referral to hypertension clinic	8HT5.00
Hypertension treatment refused	8I3N.00
Seen in hypertension clinic	9N03.00
Hypertension monitored	9OIA.11
Hypertensive disease	G2...00
BP - hypertensive disease	G2...11
Essential hypertension	G20..00
High blood pressure	G20..11
Malignant essential hypertension	G200.00
Benign essential hypertension	G201.00
Systolic hypertension	G202.00
Diastolic hypertension	G203.00
Essential hypertension NOS	G20z.00
Hypertension NOS	G20z.11

Hypoxaemia

Description	Medcode
Hypoxaemia	R2y0100

Intracerebral bleed

Description	Medcode
Haemorrhagic stroke monitoring	662o.00
Stroke due to intracerebral haemorrhage	G61..12
Intracerebral haemorrhage	G61..00
CVA - cerebrovascular accid due to intracerebral haemorrhage	G61..11
Cortical haemorrhage	G610.00
Internal capsule haemorrhage	G611.00
Basal nucleus haemorrhage	G612.00
Cerebellar haemorrhage	G613.00
Pontine haemorrhage	G614.00
Bulbar haemorrhage	G615.00
External capsule haemorrhage	G616.00
Intracerebral haemorrhage, intraventricular	G617.00
Intracerebral haemorrhage, multiple localized	G618.00
Intracerebral haemorrhage in hemisphere, unspecified	G61X.00
Left sided intracerebral haemorrhage, unspecified	G61X000
Right sided intracerebral haemorrhage, unspecified	G61X100
Intracerebral haemorrhage NOS	G61z.00
Other and unspecified intracranial haemorrhage	G62..00
Intracranial haemorrhage NOS	G62z.00
Subarachnoid haemorrhage	G60..00
Subarachnoid haemorrhage NOS	G60z.00
Sequelae of subarachnoid haemorrhage	G680.00
Sequelae of intracerebral haemorrhage	G681.00
Sequelae of other nontraumatic intracranial haemorrhage	G682.00

Ischaemic Heart Disease

Description	Medcode
Ischaemic heart disease	G3...00
Arteriosclerotic heart disease	G3...11
Atherosclerotic heart disease	G3...12
IHD - Ischaemic heart disease	G3...13
Acute myocardial infarction	G30..00
Attack - heart	G30..11
Coronary thrombosis	G30..12
Cardiac rupture following myocardial infarction (MI)	G30..13
Heart attack	G30..14
MI - acute myocardial infarction	G30..15
Thrombosis - coronary	G30..16
Silent myocardial infarction	G30..17
Acute anterolateral infarction	G300.00
Other specified anterior myocardial infarction	G301.00
Acute anteroapical infarction	G301000
Acute anteroseptal infarction	G301100
Anterior myocardial infarction NOS	G301z00
Acute inferolateral infarction	G302.00
Acute inferoposterior infarction	G303.00
Posterior myocardial infarction NOS	G304.00
Lateral myocardial infarction NOS	G305.00
True posterior myocardial infarction	G306.00
Acute subendocardial infarction	G307.00
Acute non-Q wave infarction	G307000
Acute non-ST segment elevation myocardial infarction	G307100
Inferior myocardial infarction NOS	G308.00
Acute Q-wave infarct	G309.00
Mural thrombosis	G30A.00
Acute posterolateral myocardial infarction	G30B.00
Acute transmural myocardial infarction of unspecified site	G30X.00
Acute ST segment elevation myocardial infarction	G30X000

Other acute myocardial infarction	G30y.00
Acute atrial infarction	G30y000
Acute papillary muscle infarction	G30y100
Acute septal infarction	G30y200
Other acute myocardial infarction NOS	G30yz00
Acute myocardial infarction NOS	G30z.00
Other acute and subacute ischaemic heart disease	G31..00
Postmyocardial infarction syndrome	G310.00
Dressler's syndrome	G310.11
Preinfarction syndrome	G311.00
Crescendo angina	G311.11
Impending infarction	G311.12
Unstable angina	G311.13
Angina at rest	G311.14
Myocardial infarction aborted	G311000
MI - myocardial infarction aborted	G311011
Unstable angina	G311100
Angina at rest	G311200
Refractory angina	G311300
Worsening angina	G311400
Acute coronary syndrome	G311500
Preinfarction syndrome NOS	G311z00
Coronary thrombosis not resulting in myocardial infarction	G312.00
Other acute and subacute ischaemic heart disease	G31y.00
Acute coronary insufficiency	G31y000
Microinfarction of heart	G31y100
Subendocardial ischaemia	G31y200
Transient myocardial ischaemia	G31y300
Other acute and subacute ischaemic heart disease NOS	G31yz00
Angina pectoris	G33..00
Angina decubitus	G330.00
Nocturnal angina	G330000
Angina decubitus NOS	G330z00
Prinzmetal's angina	G331.00

Variant angina pectoris	G331.11
Coronary artery spasm	G332.00
Angina pectoris NOS	G33z.00
Status anginosus	G33z000
Stenocardia	G33z100
Syncope anginosa	G33z200
Angina on effort	G33z300
New onset angina	G33z600
Stable angina	G33z700
Angina pectoris NOS	G33zz00
Other chronic ischaemic heart disease	G34..00
Coronary atherosclerosis	G340.00
Triple vessel disease of the heart	G340.11
Coronary artery disease	G340.12
Single coronary vessel disease	G340000
Double coronary vessel disease	G340100
Atherosclerotic cardiovascular disease	G342.00
Ischaemic cardiomyopathy	G343.00
Silent myocardial ischaemia	G344.00
Other specified chronic ischaemic heart disease	G34y.00
Chronic myocardial ischaemia	G34y100
Other specified chronic ischaemic heart disease NOS	G34yz00
Other chronic ischaemic heart disease NOS	G34z.00
Asymptomatic coronary heart disease	G34z000
Subsequent myocardial infarction	G35..00
Subsequent myocardial infarction of anterior wall	G350.00
Subsequent myocardial infarction of inferior wall	G351.00
Subsequent myocardial infarction of other sites	G353.00
Subsequent myocardial infarction of unspecified site	G35X.00
Certain current complications following acute myocardial infarction	G36..00
Haemopericardium as current complication following acute myocardial infarction	G360.00
Atrial septal defect as current complication following acute	G361.00

myocardial infarction	
Ventricular septal defect as current complication following acute myocardial infarction	G362.00
Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction	G363.00
Rupture of chordae tendinae as current complication following acute myocardial infarction	G364.00
Rupture of papillary muscle as current complication following acute myocardial infarction	G365.00
Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction	G366.00
Cardiac syndrome X	G37..00
Coronary microvascular disease	G39..00
Other specified ischaemic heart disease	G3y..00
Ischaemic heart disease NOS	G3z..00

Lung Cancer

Description	Medcode
Malignant neoplasm of trachea, bronchus and lung	B22..00
Malignant neoplasm of trachea	B220.00
Malignant neoplasm of cartilage of trachea	B220000
Malignant neoplasm of mucosa of trachea	B220100
Malignant neoplasm of trachea NOS	B220z00
Malignant neoplasm of main bronchus	B221.00
Malignant neoplasm of carina of bronchus	B221000
Malignant neoplasm of hilus of lung	B221100
Malignant neoplasm of main bronchus NOS	B221z00
Malignant neoplasm of upper lobe, bronchus or lung	B222.00
Pancoast's syndrome	B222.11
Malignant neoplasm of upper lobe bronchus	B222000
Malignant neoplasm of upper lobe of lung	B222100
Malignant neoplasm of upper lobe, bronchus or lung NOS	B222z00

Malignant neoplasm of middle lobe, bronchus or lung	B223.00
Malignant neoplasm of middle lobe bronchus	B223000
Malignant neoplasm of middle lobe of lung	B223100
Malignant neoplasm of middle lobe, bronchus or lung NOS	B223z00
Malignant neoplasm of lower lobe, bronchus or lung	B224.00
Malignant neoplasm of lower lobe bronchus	B224000
Malignant neoplasm of lower lobe of lung	B224100
Malignant neoplasm of lower lobe, bronchus or lung NOS	B224z00
Malignant neoplasm of overlapping lesion of bronchus & lung	B225.00
Malignant neoplasm of other sites of bronchus or lung	B22y.00
Malignant neoplasm of bronchus or lung NOS	B22z.00
Lung cancer	B22z.11
Carcinoma in situ of trachea	B811.00
Carcinoma in situ of bronchus and lung	B812.00
Carcinoma in situ of carina of bronchus	B812000
Carcinoma in situ of main bronchus	B812100
Carcinoma in situ of upper lobe bronchus and lung	B812200
Carcinoma in situ of middle lobe bronchus and lung	B812300
Carcinoma in situ of lower lobe bronchus and lung	B812400
Carcinoma in situ of bronchus or lung NOS	B812z00
Bronchiolo-alveolar adenocarcinoma	BB5S200
Alveolar cell carcinoma	BB5S211
Personal history of malig neop of trachea/bronchus/lung	ZV10100
Personal history of malignant neoplasm of bronchus	ZV10111
Personal history of malignant neoplasm of lung	ZV10112
Personal history of malignant neoplasm of trachea	ZV10113

Migraine

Description	Medcode
Migraine	F26..00
Classical migraine	F260.00

Common migraine	F261.00
Atypical migraine	F261000
Common migraine NOS	F261z00
Migraine variants	F262.00
Basilar migraine	F262300
Ophthalmic migraine	F262400
Migraine variant NOS	F262z00
Other forms of migraine	F26y.00
Hemiplegic migraine	F26y000
Ophthalmoplegic migraine	F26y100
Other forms of migraine NOS	F26yz00
Migraine NOS	F26z.00
Other migraine	Fyu5300

Myocardial Infarction

Description	Medcode
Acute myocardial infarction	G30..00
Attack - heart	G30..11
Coronary thrombosis	G30..12
Cardiac rupture following myocardial infarction (MI)	G30..13
Heart attack	G30..14
MI - acute myocardial infarction	G30..15
Thrombosis - coronary	G30..16
Silent myocardial infarction	G30..17
Acute anterolateral infarction	G300.00
Other specified anterior myocardial infarction	G301.00
Acute anteroapical infarction	G301000
Acute anteroseptal infarction	G301100
Anterior myocardial infarction NOS	G301z00
Acute inferolateral infarction	G302.00
Acute inferoposterior infarction	G303.00
Posterior myocardial infarction NOS	G304.00

Lateral myocardial infarction NOS	G305.00
True posterior myocardial infarction	G306.00
Acute subendocardial infarction	G307.00
Acute non-Q wave infarction	G307000
Acute non-ST segment elevation myocardial infarction	G307100
Inferior myocardial infarction NOS	G308.00
Acute Q-wave infarct	G309.00
Mural thrombosis	G30A.00
Acute posterolateral myocardial infarction	G30B.00
Acute transmural myocardial infarction of unspecified site	G30X.00
Acute ST segment elevation myocardial infarction	G30X000
Other acute myocardial infarction	G30y.00
Acute atrial infarction	G30y000
Acute papillary muscle infarction	G30y100
Acute septal infarction	G30y200
Other acute myocardial infarction NOS	G30yz00
Acute myocardial infarction NOS	G30z.00
Other acute and subacute ischaemic heart disease	G31..00
Postmyocardial infarction syndrome	G310.00
Dressler's syndrome	G310.11
Myocardial infarction aborted	G311000
MI - myocardial infarction aborted	G311011
Acute coronary syndrome	G311500
Preinfarction syndrome NOS	G311z00
Coronary thrombosis not resulting in myocardial infarction	G312.00
Other acute and subacute ischaemic heart disease	G31y.00
Acute coronary insufficiency	G31y000
Microinfarction of heart	G31y100
Subendocardial ischaemia	G31y200
Transient myocardial ischaemia	G31y300
Subsequent myocardial infarction	G35..00
Subsequent myocardial infarction of anterior wall	G350.00
Subsequent myocardial infarction of inferior wall	G351.00
Subsequent myocardial infarction of other sites	G353.00

Subsequent myocardial infarction of unspecified site	G35X.00
Certain current complications following acute myocardial infarction	G36..00
Haemopericardium as current complication following acute myocardial infarction	G360.00
Atrial septal defect as current complication following acute myocardial infarction	G361.00
Ventricular septal defect as current complication following acute myocardial infarction	G362.00
Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction	G363.00
Rupture of chordae tendinae as current complication following acute myocardial infarction	G364.00
Rupture of papillary muscle as current complication following acute myocardial infarction	G365.00
Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction	G366.00

Portal hypertension

Description	Medcode
Portal hypertension	J623.00

Prostate Cancer

Description	Medcode
Gleason grading of prostate cancer	4M0..00
Gleason prostate grade 2-4 (low)	4M00.00
Gleason prostate grade 5-7 (medium)	4M01.00
Gleason prostate grade 8-10 (high)	4M02.00
Radioactive seed implantation into prostate	7B3CB00
Seed implantation into prostate	7B3C900

Malignant neoplasm of prostate	B46..00
Carcinoma in situ of prostate	B834.00
High grade prostatic intraepithelial neoplasia	B834000
Neoplasm of uncertain behaviour of prostate	B915.00
Personal history of malignant neoplasm of prostate	ZV10415

Pulmonary hypertension

Description	Medcode
Secondary pulmonary hypertension	G41y000

Seizure

Description	Medcode
O/E - fit/convulsion	282..00
O/E - a convulsion	282..11
O/E - a fit	282..12
O/E - a seizure	282..13
O/E - grand mal fit	2822.00
O/E - petit mal fit	2823.00
O/E - focal (Jacksonian) fit	2824.00
O/E - Jacksonian fit	2824.11
O/E - focal fit	2824.12
O/E - psychomotor fit	2825.00
O/E - fit/convulsion NOS	282Z.00
Seizure free >12 months	667F.00
Myoclonic seizure	F132z12
Grand mal seizure	F251600
Nocturnal seizure	R003400
Seizure NOS	R003z11
Fit frequency	6675.00
Last fit	6676.00
Fit	R003200

Fit (in non-epileptic) NOS	R003211

Smoking

Description	Medcode	Smoking habit
Tobacco consumption	137..00	Unknown
Smoker - amount smoked	137..11	Current
Never smoked tobacco	1371.00	Never
Non-smoker	1371.11	Unknown
Trivial smoker - < 1 cig/day	1372.00	Current
Occasional smoker	1372.11	Current
Light smoker - 1-9 cigs/day	1373.00	Current
Moderate smoker - 10-19 cigs/d	1374.00	Current
Heavy smoker - 20-39 cigs/day	1375.00	Current
Very heavy smoker - 40+cigs/d	1376.00	Current
Ex-trivial smoker (<1/day)	1377.00	Ex
Ex-light smoker (1-9/day)	1378.00	Ex
Ex-moderate smoker (10-19/day)	1379.00	Ex
Ex-heavy smoker (20-39/day)	137A.00	Ex
Ex-very heavy smoker (40+/day)	137B.00	Ex
Keeps trying to stop smoking	137C.00	Current
Admitted tobacco cons untrue ?	137D.00	Unknown
Tobacco consumption unknown	137E.00	Unknown
Ex-smoker - amount unknown	137F.00	Ex
Trying to give up smoking	137G.00	Current
Pipe smoker	137H.00	Current
Cigar smoker	137J.00	Current
Stopped smoking	137K.00	Ex
Current non-smoker	137L.00	Unknown
Rolls own cigarettes	137M.00	Current
Ex pipe smoker	137N.00	Ex
Ex cigar smoker	137O.00	Ex
Cigarette smoker	137P.00	Current

Smoker	137P.11	Current
Smoking started	137Q.00	Current
Smoking restarted	137Q.11	Current
Current smoker	137R.00	Current
Ex smoker	137S.00	Ex
Date ceased smoking	137T.00	Ex
Smoking reduced	137V.00	Current
Cigarette consumption	137X.00	Unknown
Cigar consumption	137Y.00	Unknown
Tobacco consumption NOS	137Z.00	Unknown
Pipe tobacco consumption	137a.00	Unknown
Ready to stop smoking	137b.00	Current
Thinking about stopping smoking	137c.00	Current
Not interested in stopping smoking	137d.00	Current
Smoking restarted	137e.00	Current
Reason for restarting smoking	137f.00	Current
Cigarette pack-years	137g.00	Unknown
Minutes from waking to first tobacco consumption	137h.00	Current
Smoking cessation milestones	13p..00	Unknown
Negotiated date for cessation of smoking	13p0.00	Current
Smoking status at 4 weeks	13p1.00	Unknown
Smoking status between 4 and 52 weeks	13p2.00	Unknown
Smoking status at 52 weeks	13p3.00	Unknown
Smoking free weeks	13p4.00	Unknown
Smoking cessation programme start date	13p5.00	Current
Carbon monoxide reading at 4 weeks	13p6.00	Unknown
Expired carbon monoxide concentration	4I90.00	Unknown
Health ed. - smoking	6791.00	Current
Pregnancy smoking advice	67A3.00	Current
Lifestyle advice regarding smoking	67H1.00	Current
Tobacco usage screen	6893.00	Unknown
Tobacco usage screen	68T..00	Unknown
Smoking cessation therapy	745H.00	Unknown
Nicotine replacement therapy using nicotine patches	745H000	Current

Nicotine replacement therapy using nicotine gum	745H100	Current
Nicotine replacement therapy using nicotine inhalator	745H200	Current
Nicotine replacement therapy using nicotine lozenges	745H300	Current
Smoking cessation drug therapy	745H400	Current
Other specified smoking cessation therapy	745Hy00	Current
Smoking cessation therapy NOS	745Hz00	Unknown
Nicotine replacement therapy	8B2B.00	Current
Over the counter nicotine replacement therapy	8B3Y.00	Current
Nicotine replacement therapy provided free	8B3f.00	Current
Nicotine replacement therapy provided by community pharmacis	8BP3.00	Current
Smoking cessation advice	8CAL.00	Current
Smoking cessation advice provided by community pharmacist	8CAg.00	Current
Referral to smoking cessation advisor	8H7i.00	Current
Referral to stop-smoking clinic	8HTK.00	Current
Nicotine replacement therapy contraindicated	8I2I.00	Current
Nicotine replacement therapy refused	8I39.00	Current
Seen by smoking cessation advisor	9N2k.00	Unknown
DNA - Did not attend smoking cessation clinic	9N4M.00	Unknown
Anti-smoking monitoring admin.	9OO..00	Unknown
Stop smoking clinic admin.	9OO..11	Unknown
Stop smoking monitoring admin.	9OO..12	Unknown
Attends stop smoking monitor.	9OO1.00	Unknown
Refuses stop smoking monitor	9OO2.00	Unknown
Stop smoking monitor default	9OO3.00	Unknown
Stop smoking monitor 1st lettr	9OO4.00	Unknown
Stop smoking monitor 2nd lettr	9OO5.00	Unknown
Stop smoking monitor 3rd lettr	9OO6.00	Unknown
Stop smoking monitor verb.inv.	9OO7.00	Current
Stop smoking monitor phone inv	9OO8.00	Current
Stop smoking monitoring delete	9OO9.00	Unknown

Stop smoking monitor.chck done	9OOA.00	Unknown
Stop smoking monitor admin.NOS	9OOZ.00	Unknown
Exception reporting: smoking quality indicators	9hG..00	Exception
Excepted from smoking quality indicators: Patient unsuitable	9hG0.00	Exception
Excepted from smoking quality indicators: Informed dissent	9hG1.00	Exception
Nicotine withdrawal	E023.00	Unknown
Tobacco dependence	E251.00	Current
Tobacco dependence, continuous	E251100	Current
Tobacco dependence in remission	E251300	Ex
Tobacco dependence NOS	E251z00	Current
Advice on smoking	ZG23300	Current
Fagerstrom test for nicotine dependence	ZRBm200	Current
FTND - Fagerstrom test for nicotine dependence	ZRBm211	Current
Motives for smoking scale	ZRaM.00	Current
MFS - Motives for smoking scale	ZRaM.11	Current
Occasions for smoking scale	ZRao.00	Current
Reasons for smoking scale	ZRh4.00	Current
RFS - Reasons for smoking scale	ZRh4.11	Current
Personal history of tobacco abuse	ZV11600	Unknown
Tobacco use	ZV4K000	Unknown
Tobacco abuse counselling	ZV6D800	Current
Ex-cigarette smoker	137j.00	Ex

Stroke

Description	Medcode
H/O: Stroke in last year	14AK.00
Stroke monitoring	662M.00
Delivery of rehabilitation for stroke	7P24200
Ref to multidisciplinary stroke function improvement service	8HHM.00
Referral to stroke clinic	8HTQ.00

Seen in stroke clinic	9N0p.00
Stroke and cerebrovascular accident unspecified	G66..00
Cerebral arterial occlusion	G64..00
CVA - cerebral artery occlusion	G64..11
Infarction - cerebral	G64..12
Stroke due to cerebral arterial occlusion	G64..13
Cerebral thrombosis	G640.00
Cerebral infarction due to thrombosis of cerebral arteries	G640000
Cerebral embolism	G641.00
Cerebral embolus	G641.11
Cerebral infarction due to embolism of cerebral arteries	G641000
Cerebral infarction NOS	G64z.00
Brainstem infarction NOS	G64z.11
Cerebellar infarction	G64z.12
Brainstem infarction	G64z000
Left sided cerebral infarction	G64z200
Right sided cerebral infarction	G64z300
Infarction of basal ganglia	G64z400
CVA unspecified	G66..11
Stroke unspecified	G66..12
CVA - Cerebrovascular accident unspecified	G66..13
Middle cerebral artery syndrome	G660.00
Anterior cerebral artery syndrome	G661.00
Posterior cerebral artery syndrome	G662.00
Brain stem stroke syndrome	G663.00
Cerebellar stroke syndrome	G664.00
Pure motor lacunar syndrome	G665.00
Pure sensory lacunar syndrome	G666.00
Left sided CVA	G667.00
Right sided CVA	G668.00
Sequelae of cerebral infarction	G683.00
Cerebral infarct due unspecified occlusion/stenosis of precerebral arteries	G6W..00
Cerebral infarction due to unspecified occlusion/stenosis of	G6X..00

cerebral arteries

Telangiectasia

Description	Medcode
Telangiectasia	G771300

Transient Ischaemic Attack

Description	Medcode
Transient ischaemic attack clinical management plan	8CRB.00
Transient ischaemic attack	G65..12
Other transient cerebral ischaemia	G65y.00
Transient cerebral ischaemia NOS	G65z.00
Intermittent cerebral ischaemia	G65z100
Transient cerebral ischaemia NOS	G65zz00
Personal history of transient ischaemic attack	ZV12D00

Venous Thromboembolism

Description	Medcode
H/O: pulmonary embolus	14AC.00
Open embolectomy of pulmonary artery	7A09300
Trendelenburg pulmonary embolectomy	7A09311
Pulmonary embolism	G401.00
Pulmonary embolus	G401.12
Recurrent pulmonary embolism	G401100
Personal history deep vein thrombosis	ZV12800
Personal history DVT- deep vein thrombosis	ZV12811
Personal history of pulmonary embolism	ZV12900
H/O: Deep Vein Thrombosis	14A8100
Deep vein thrombosis	G801.11
Deep vein thrombosis, leg	G801.12

DVT - Deep vein thrombosis	G801.13
Deep vein thrombosis of lower limb	G801D00

10.3 APPENDIX 3 - Selected bias assessment plots (funnel plots) for assessment of publication bias in meta-analysis

Figure 1. Funnel plot to identify publication bias in studies estimating prevalence of pleuritic chest pain/pleurisy after embolisation

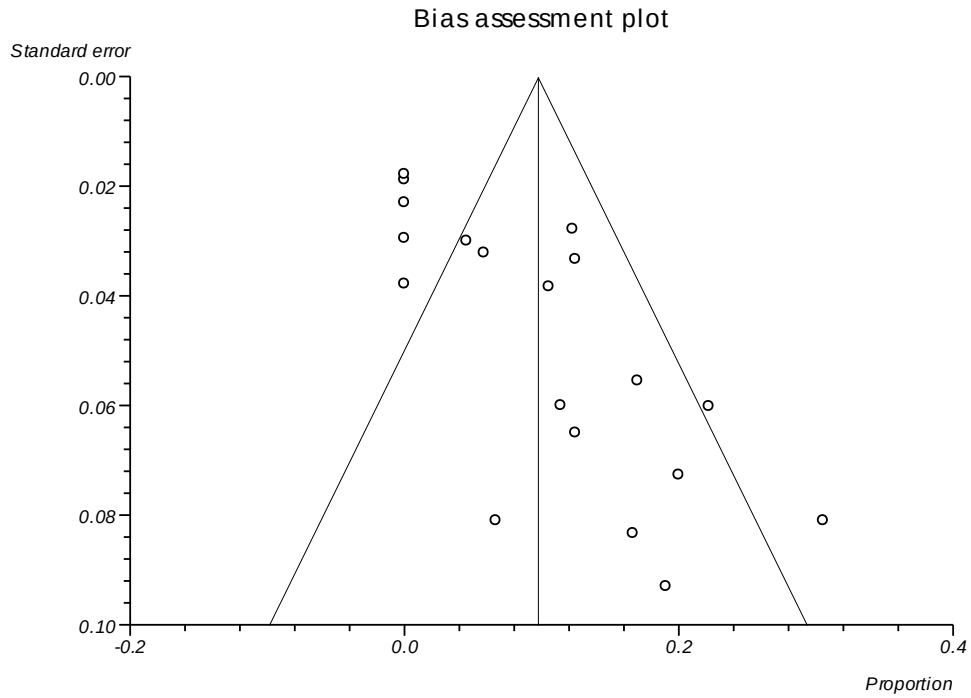


Figure 2. Funnel plot to identify publication bias in studies estimating prevalence of ischaemic chest pain after embolisation

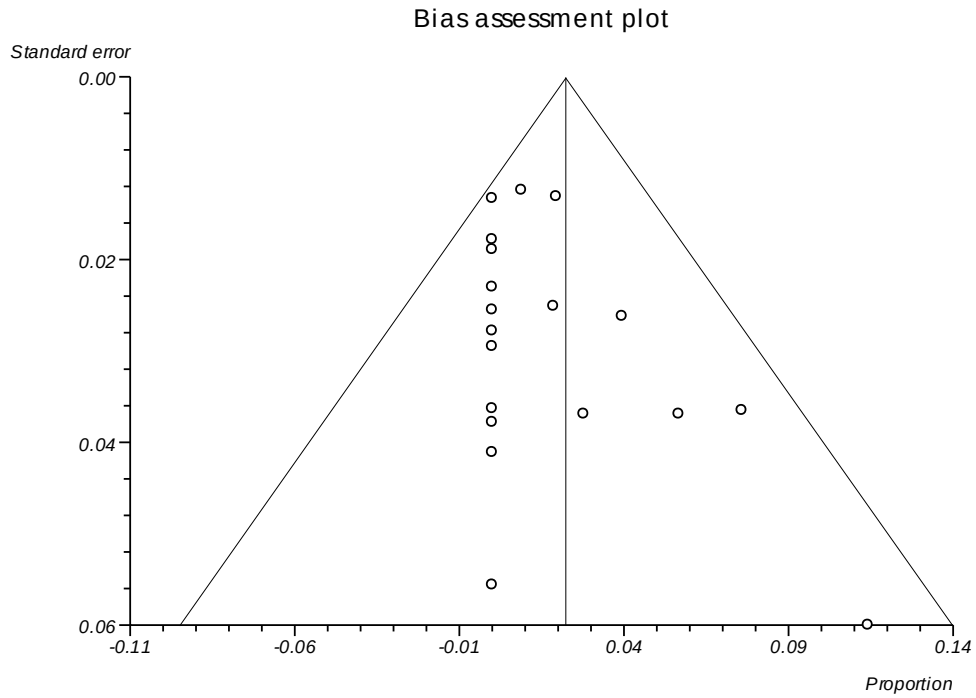


Figure 3. Funnel plot to identify publication bias in studies estimating prevalence of haemoptysis after embolisation

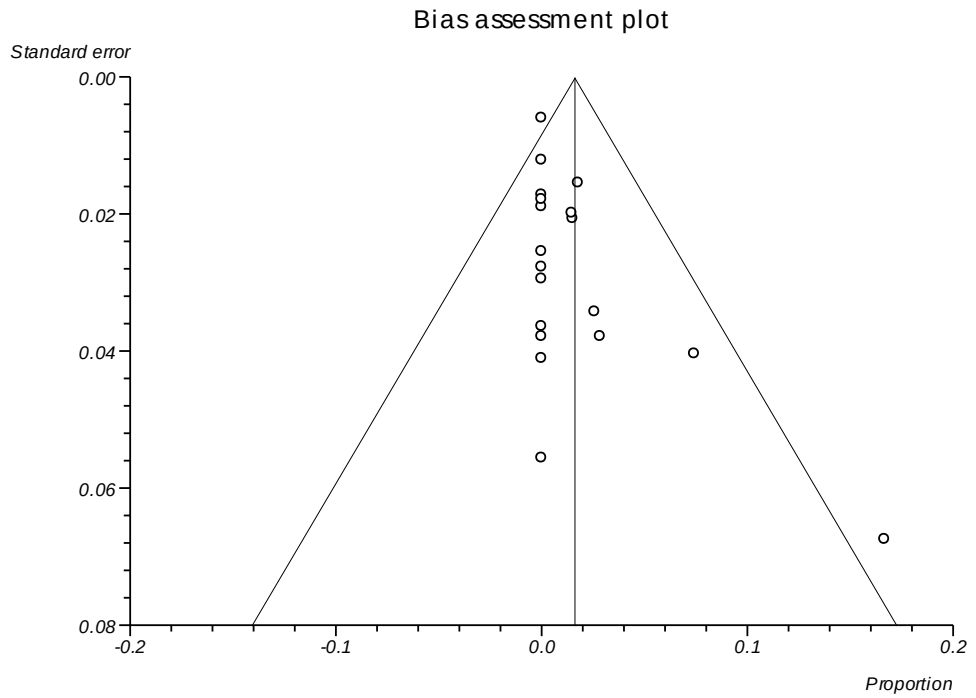


Figure 4. Funnel plot to identify publication bias in studies estimating prevalence of pulmonary infarct after embolisation

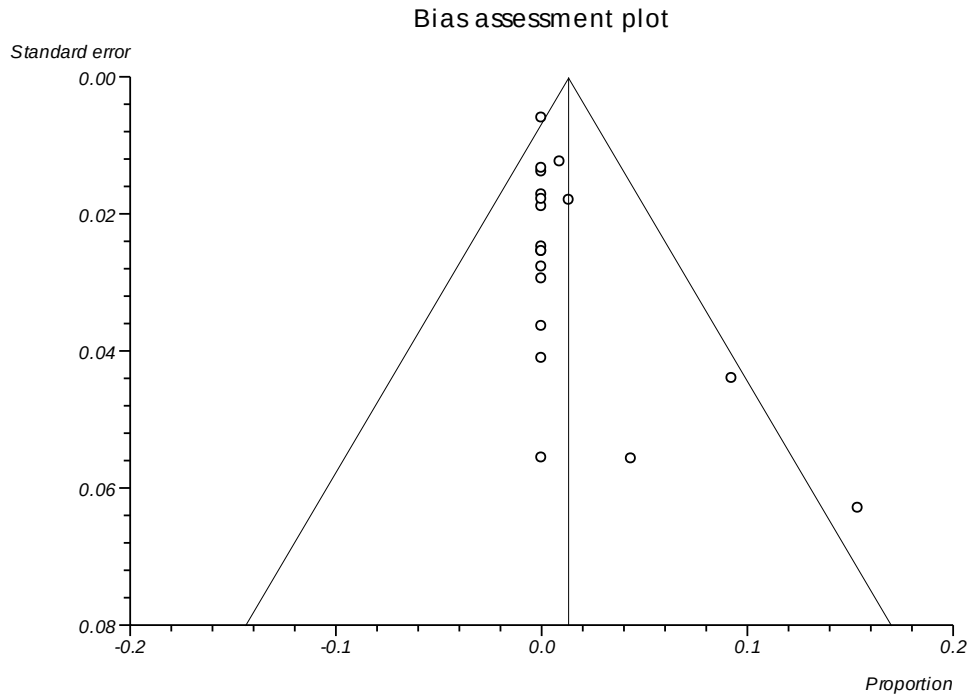


Figure 5. Funnel plot to identify publication bias in studies estimating prevalence of an uncatheterisable/unoccludable PAVM during embolisation

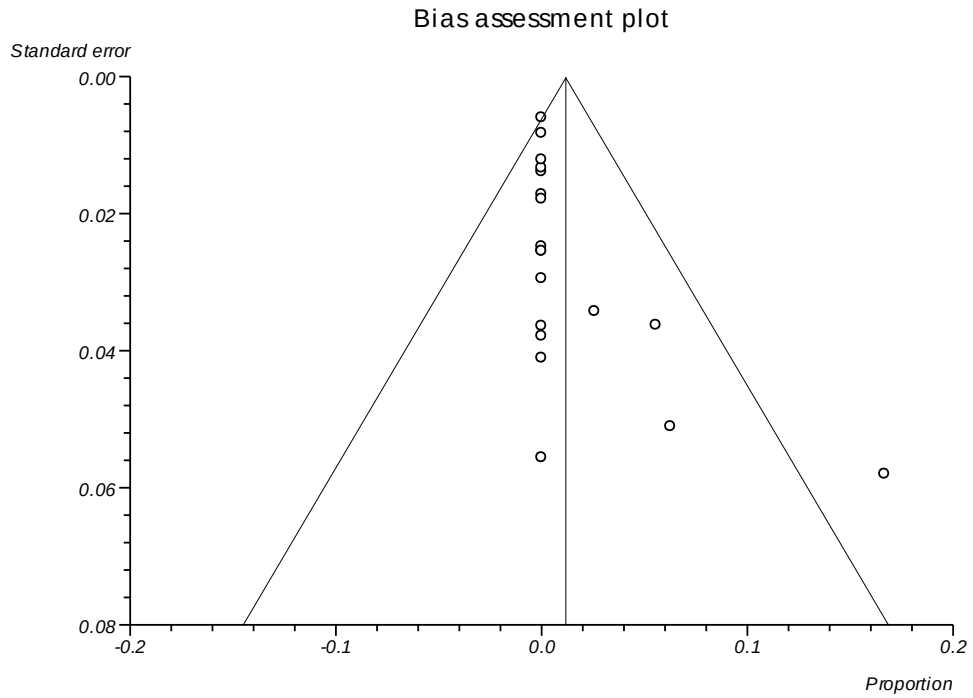


Figure 6. Funnel plot to identify publication bias in studies estimating prevalence of device embolism during embolisation procedure

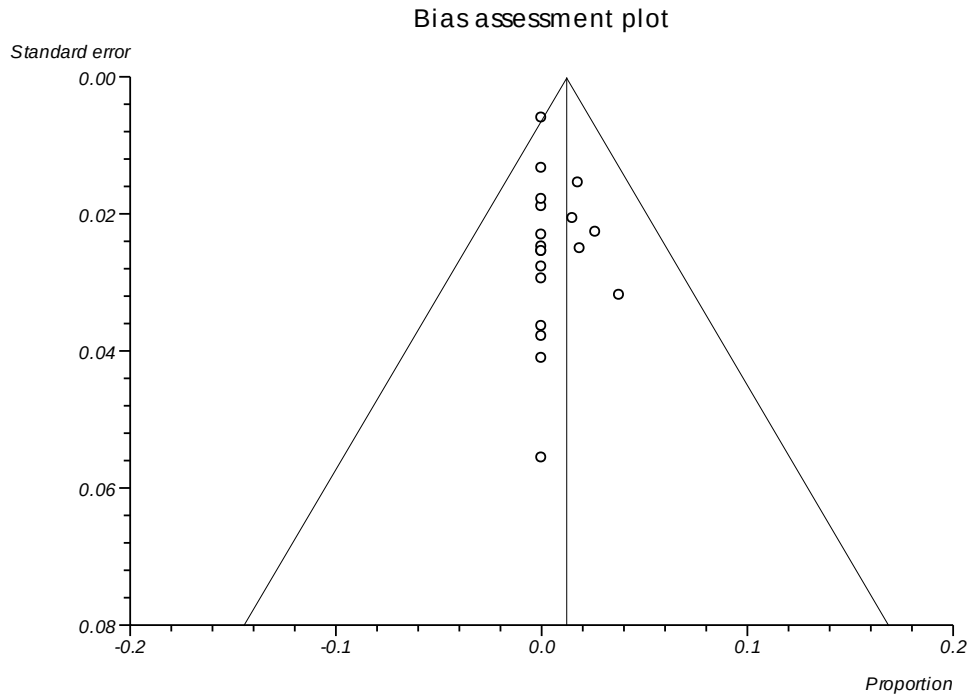


Figure 7. Funnel plot to identify publication bias in studies estimating prevalence of device migration during embolisation procedure

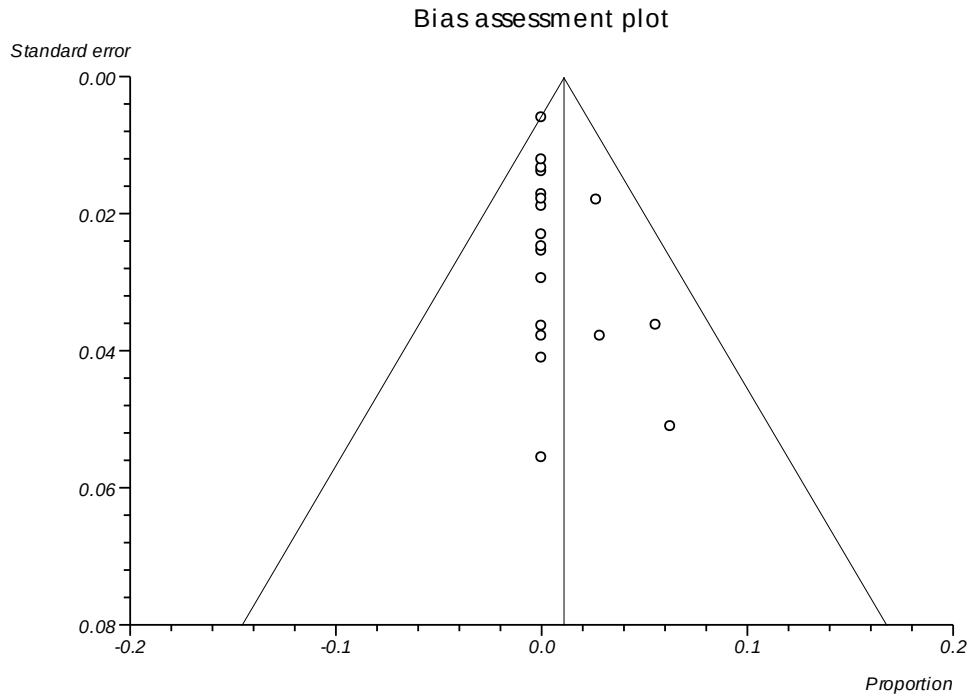


Figure 8. Funnel plot to identify publication bias in studies estimating prevalence of stroke during/after embolisation

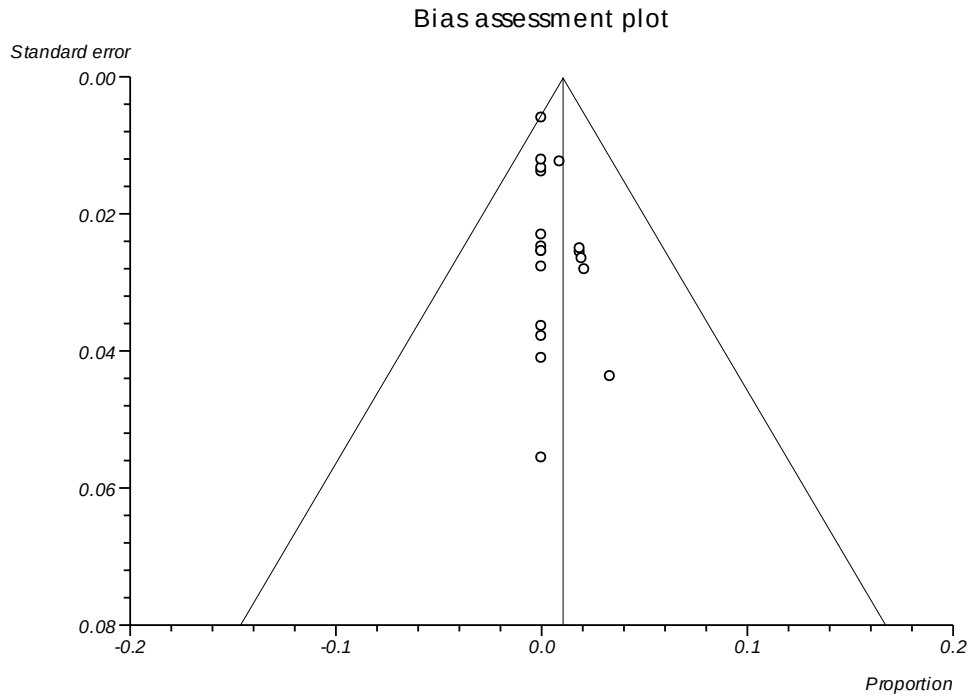


Figure 9. Funnel plot to identify publication bias in studies estimating prevalence of arrhythmia during/after embolisation

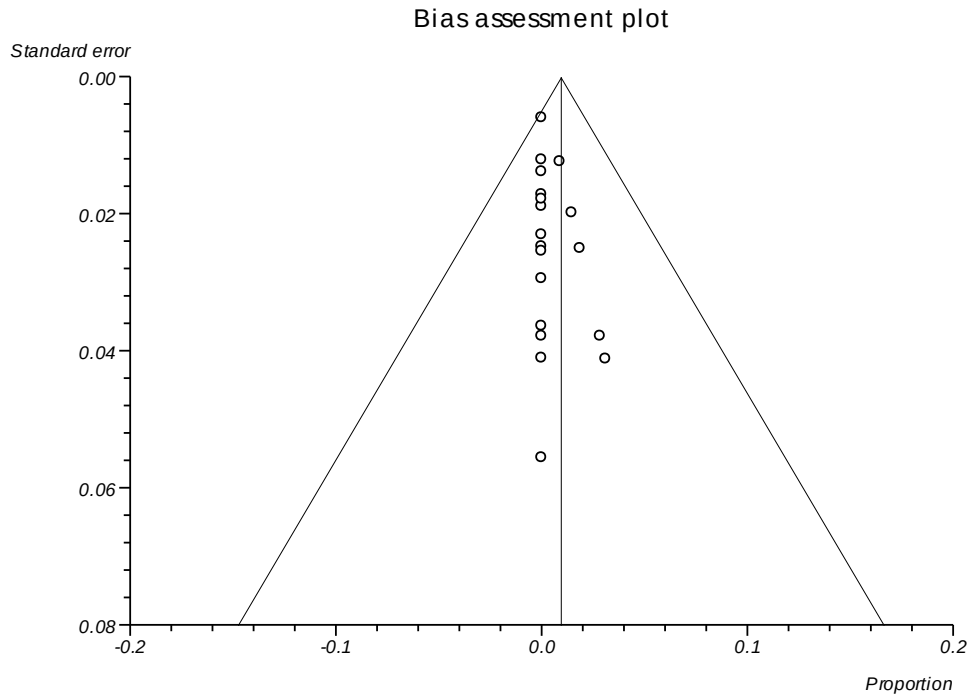


Figure 10. Funnel plot to identify publication bias in studies estimating prevalence of TIA during/after embolisation

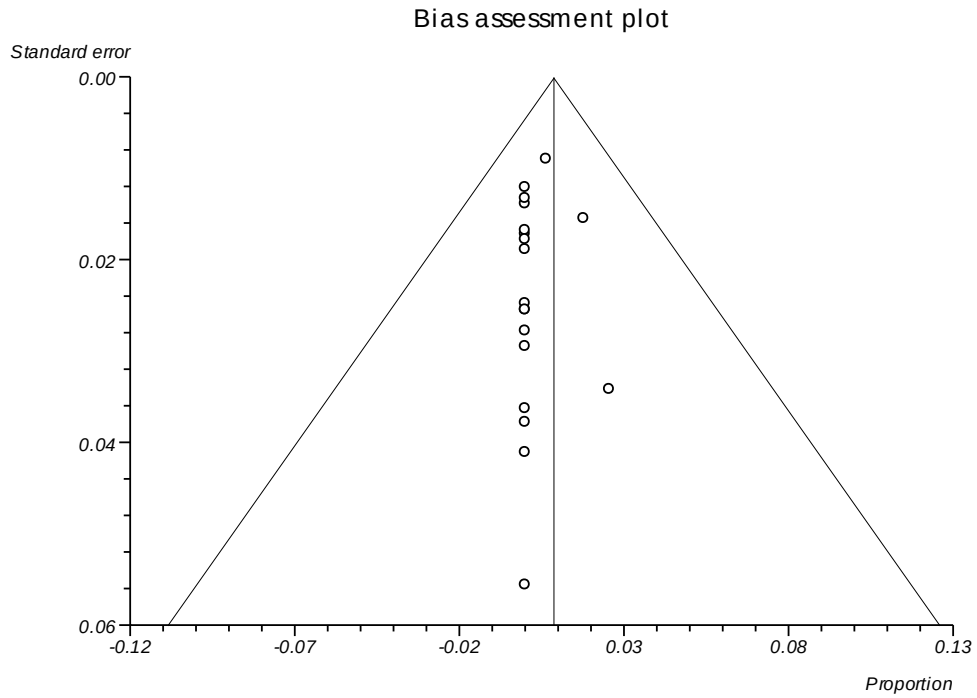


Figure 11. Funnel plot to identify publication bias in studies estimating prevalence of groin haematoma during/after embolisation

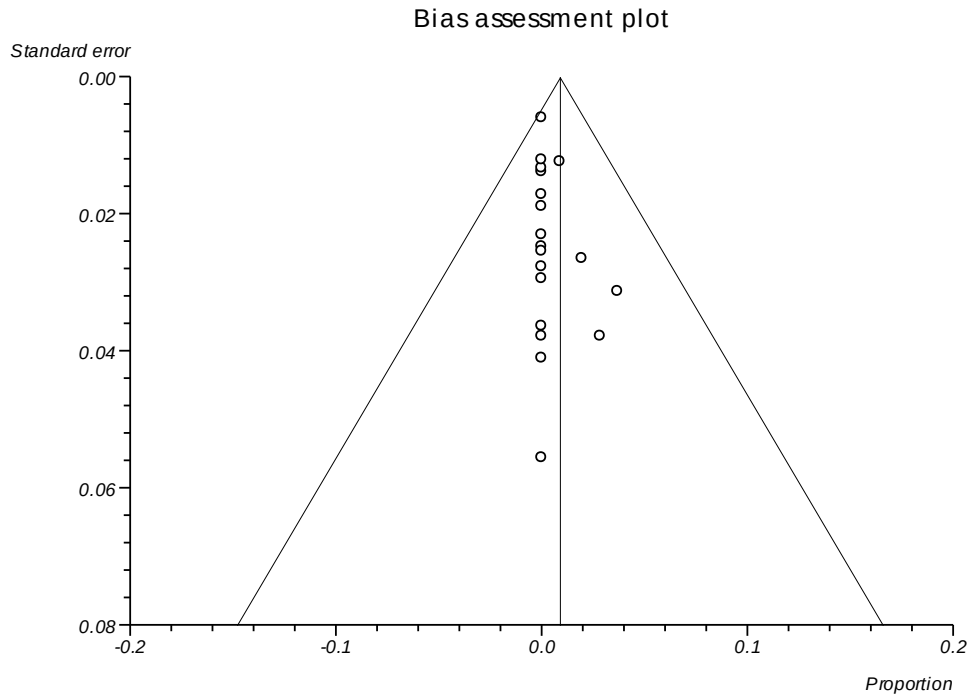


Figure 12. Funnel plot to identify publication bias in studies estimating prevalence of air embolism during embolisation

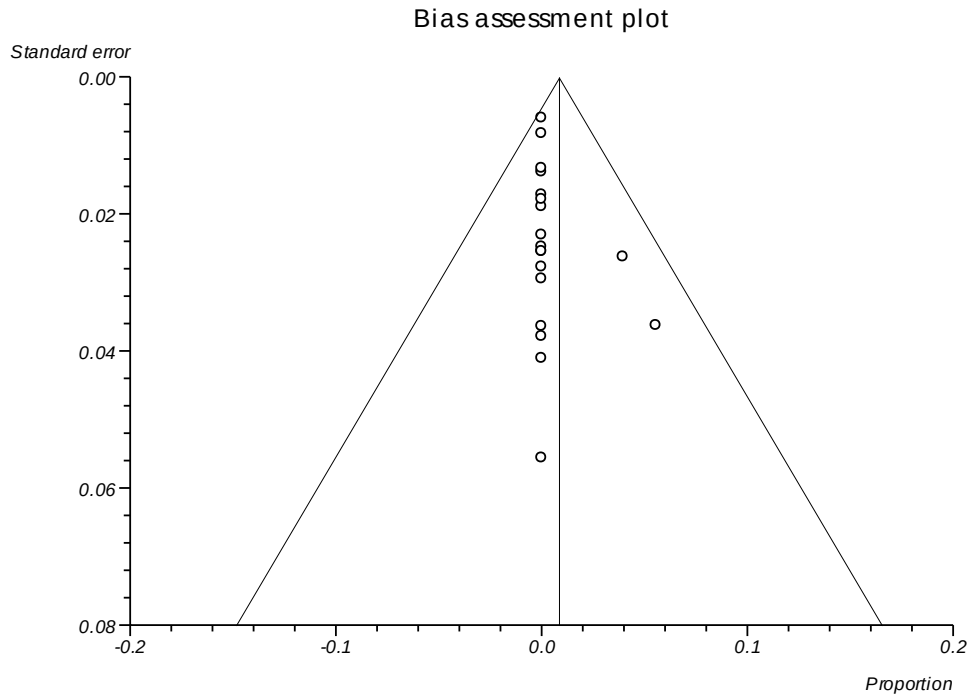


Figure 13. Funnel plot to identify publication bias in studies estimating prevalence of venous thromboembolism after embolisation

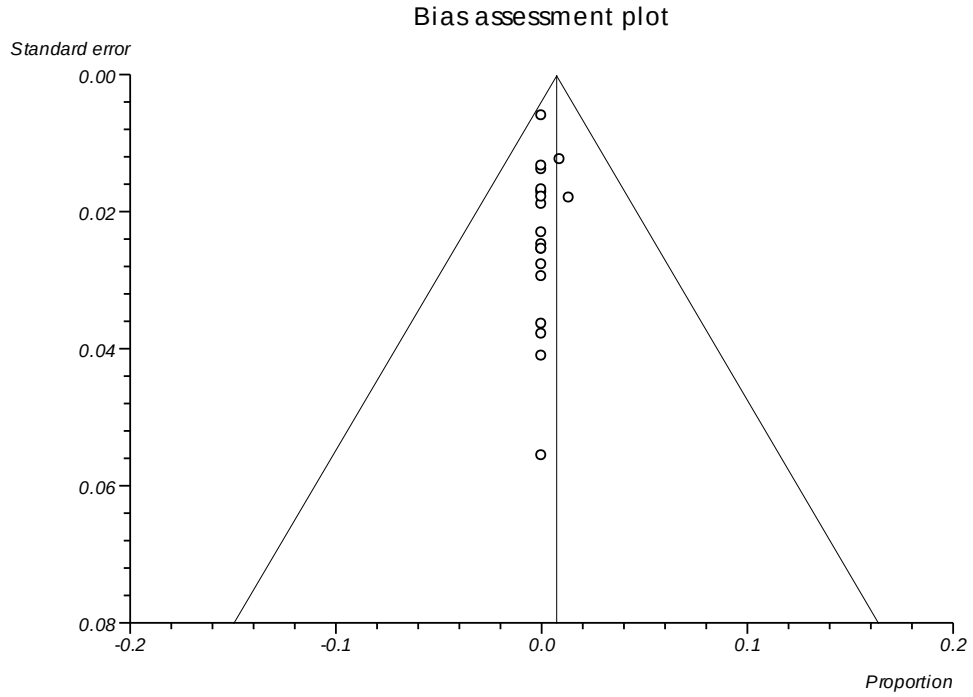


Figure 14. Funnel plot to identify publication bias in studies estimating prevalence of haemopericardium during/after embolisation

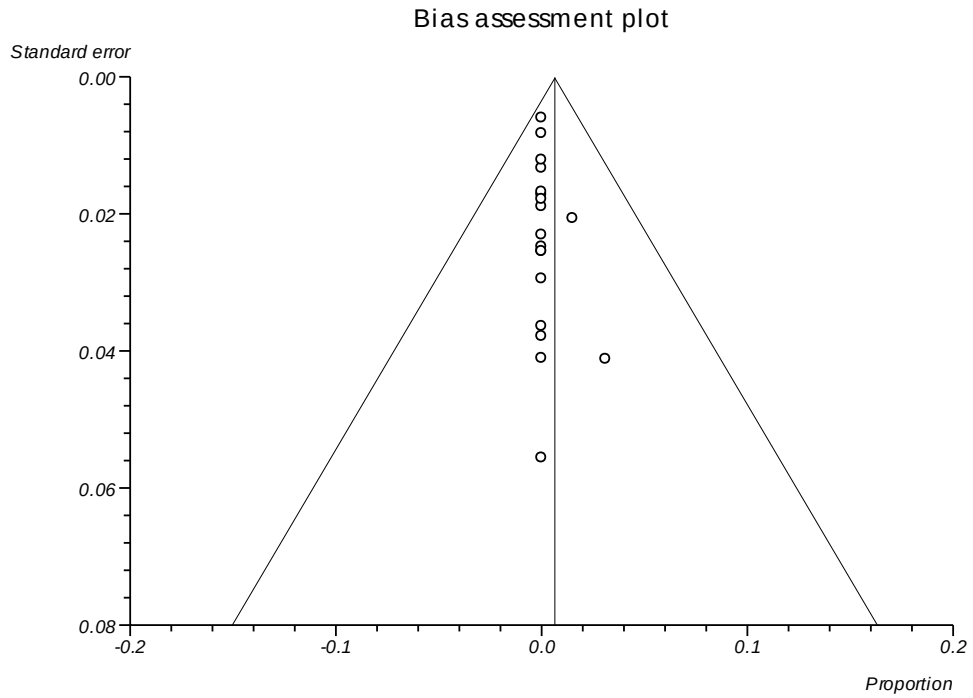


Figure 15. Funnel plot to identify publication bias in studies estimating prevalence of ectopic device deposition during embolisation

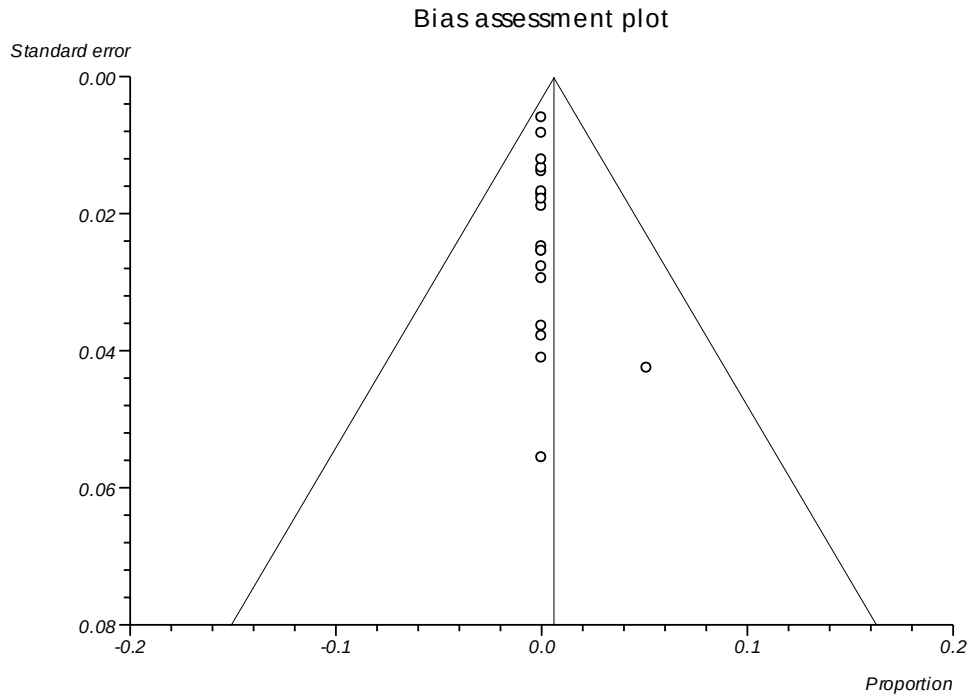


Figure 16. Funnel plot to identify publication bias in studies estimating prevalence of death during/after embolisation

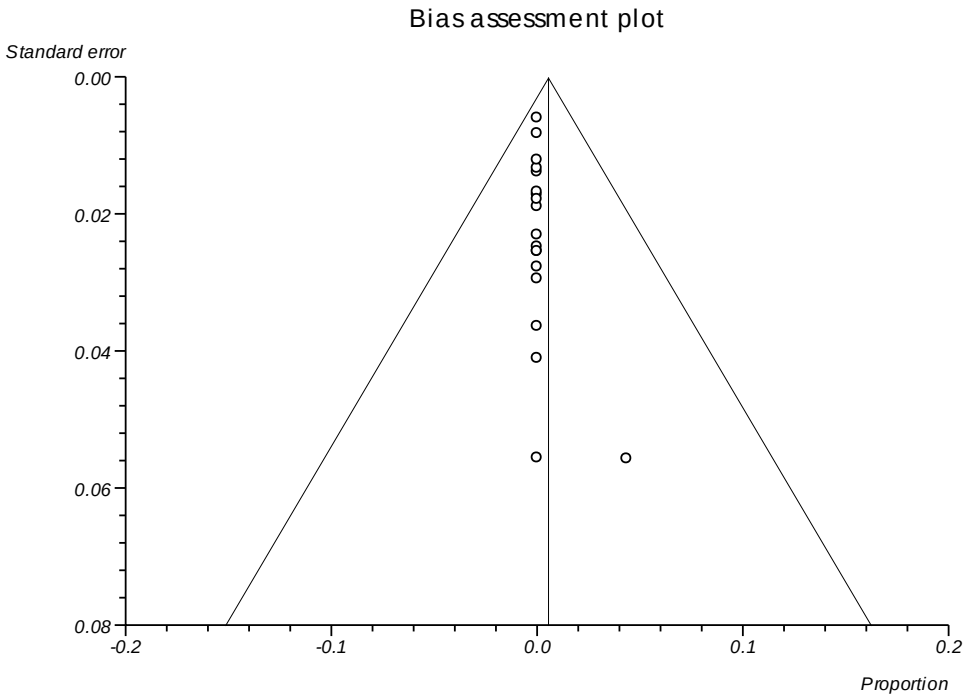


Figure 17. Funnel plot to identify publication bias in studies estimating overall embolisation success rate (by patient)

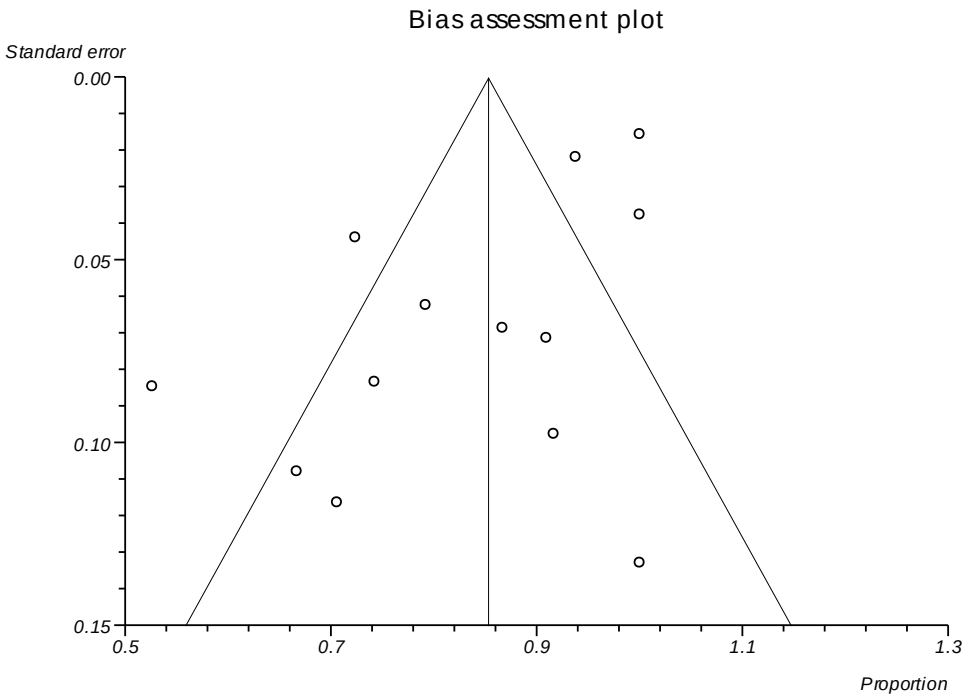


Figure 18. Funnel plot to identify publication bias in studies estimating overall embolisation success rate (by PAVM)

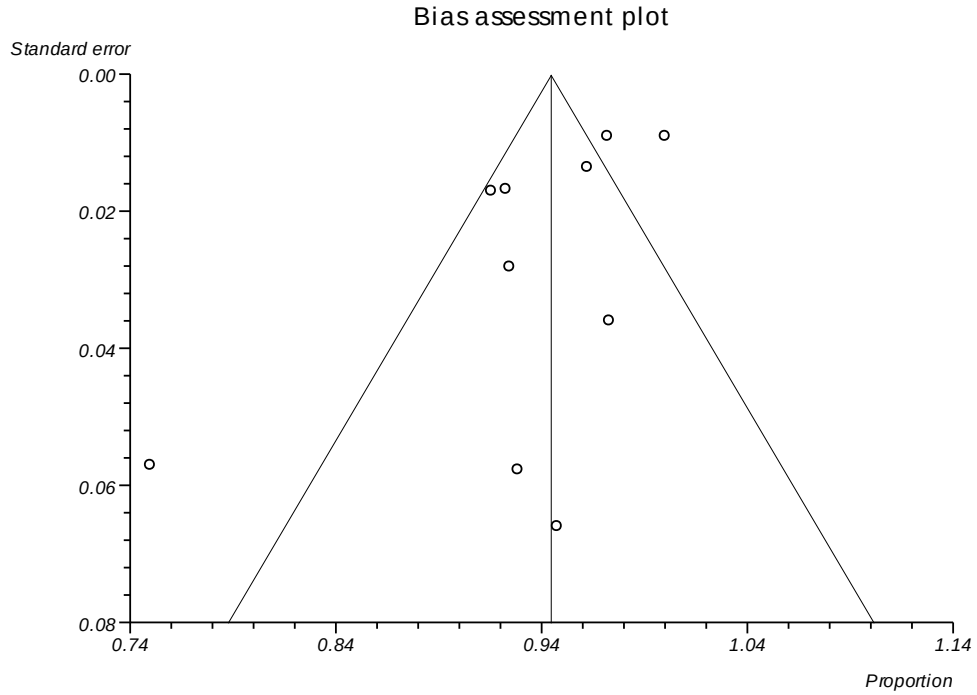


Figure 19. Funnel plot to identify publication bias in studies estimating embolisation success rate (by PAVM) when coils alone were used

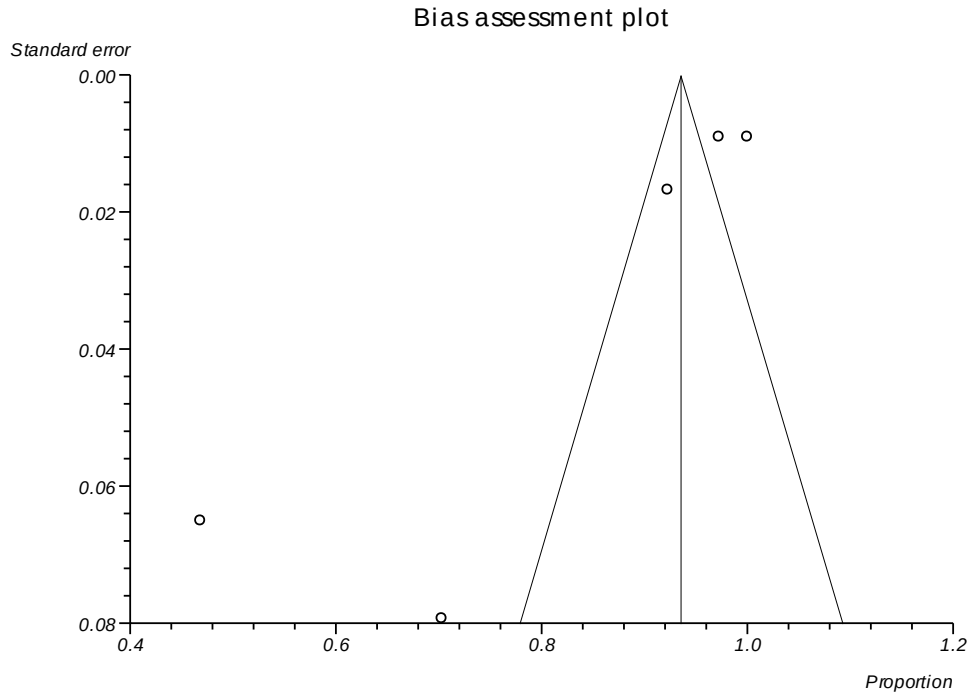


Figure 20. Funnel plot to identify publication bias in studies estimating embolisation success rate (by PAVM) when follow-up protocol included CT thorax or pulmonary angiography, follow-up exceeded 12 months, and < 20% of patients were lost to follow-up

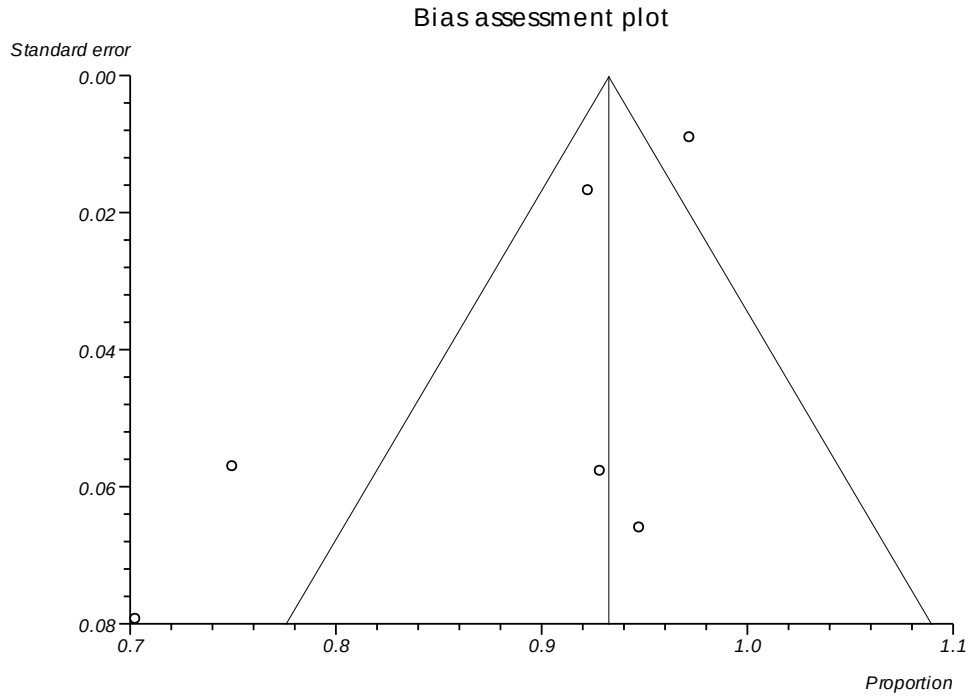
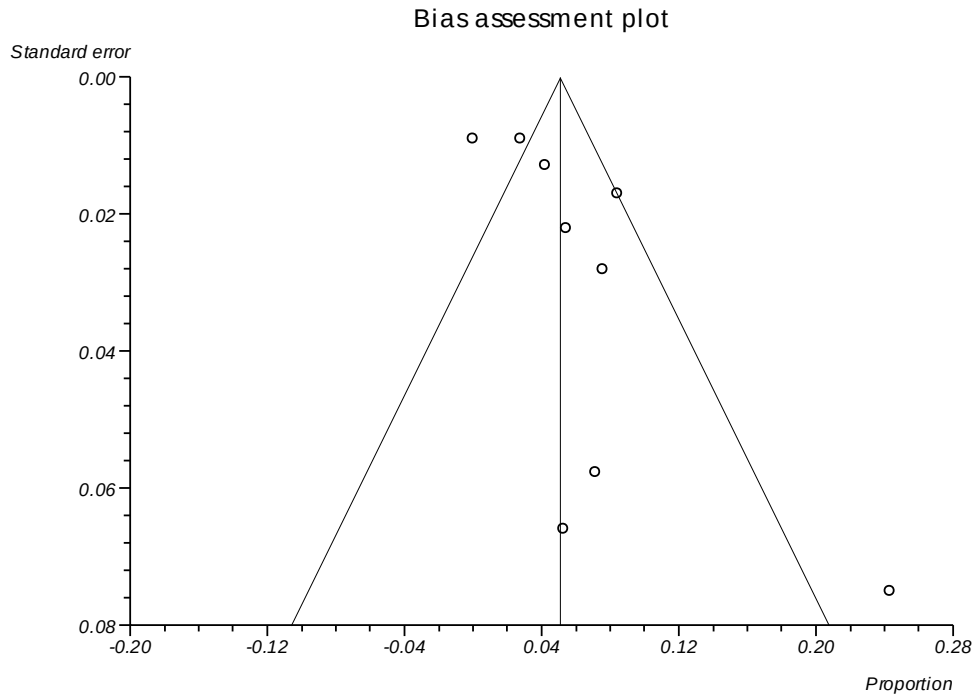


Figure 21. Funnel plot to identify publication bias in studies estimating overall recanalisation rate (by PAVM)



10.4 APPENDIX 4 - THIN Ethics approval letter

National Research Ethics Service
South East Research Ethics Committee
South East Coast Strategic Health Authority
Preston Hall
Aylesford
Kent
ME20 7NJ

Telephone: 01622 713097
Facsimile: 01622 885966

06 March 2008

Mrs Alison Bourke
Managing Director
EPIC
Regeneration House
York Way
London
N1 0UZ

Dear Mrs Bourke

Full title of study: **The Health Improvement network (Data Collection Scheme)**
REC reference number: **07/H1102/103**

Thank you for your letter of 13 February 2008, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair and named members who were present at the meeting.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

In point (a) of our letter dated 18 October 2007, we said that the Committee would draw up a set of conditions. These are as follows:

The Committee need assurance that the details will either be incorporated into, presumably, the contract they have between them, or some other acknowledgement that the researchers will comply with the requirements. If sent by letter, a signed copy of the letter would be sufficient. If sent by email, a definite reply, printed out and kept, would be needed or something like that. The same applies to researchers outside the UK (as per your point 5 bullet point 3).

Ethical review of research sites

The Committee has designated this study as exempt from site-specific assessment (SSA. There is no requirement for [other] Local Research Ethics Committees to be informed or for site-specific assessment to be carried out at each site.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application		19 September 2007
Investigator CV		
Protocol		
Advertisement	Poster content for GP surgeries	
Response to Request for Further Information		13 February 2008
Protocol review checklist	1	01 February 2008
Letter to Inps		31 January 2008
Practice visit checklist	1	01 February 2008
Suggested wording for practice patient leaflet	2	01 February 2008
Practice poster	2	01 February 2008
Research agreement for supply of THIN data subsets		
sub licence agreement		
Data audit procedures		
Scientific review of research		

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from http://www.rdforum.nhs.uk/rdform.htm.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

Here you will find links to the following

a) Providing feedback. You are invited to give your view of the service that you have received from the National Research Ethics Service on the application procedure. If you wish to make your views known please use the feedback form available on the website.

b) Progress Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
c) Safety Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
d) Amendments. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
e) End of Study/Project. Please refer to the attached Standard conditions of approval by Research Ethics Committees.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nationalres.org.uk .

07/H1102/103	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

pp **Dr L. Alan Ruben**
Chair

Email: nicki.watts@nhs.net

Enclosures: *Standard approval conditions*

Copy to:

10.5 APPENDIX 5 – Genetic study: ethical approval and sponsor letter

NHS
Health Research Authority

NRES Committee East Midlands - Nottingham 2
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Tel: 0115 883 9390

19 December 2012

Dr Andrew Fogarty
Room C113
Clinical Sciences Building
Nottingham City Hospital,
Hucknall Road,
Nottingham
NG5 1PB

Dear Dr Fogarty

Study title:	**Exploring the genetic basis of Hereditary Haemorrhagic Telangiectasia and its associated complications.**
REC reference:	**12/EM/0020**
Protocol number:	**11112**
Amendment number:	**signed by A Fogarty**
Amendment date:	**23 November 2012**
IRAS project ID:	**91384**

The above amendment was reviewed at the meeting of the Sub-Committee held on 17 December 2012.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Participant Information Sheet: Instructions for Participants	3.0	23 November 2012
Notice of Substantial Amendment (non-CTIMPs)	signed by A Fogarty	23 November 2012
Covering Letter	Email from James Donaldson	26 November 2012

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

12/EM/0020:	Please quote this number on all correspondence

Yours sincerely,

pp

Dr Martin Hewitt
Chair

E-mail: NRESCommittee.EastMidlands-Nottingham2@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Dr Maria Koufali, Nottingham University Hospitals NHS Trust*

Our reference:
RGS 11112
Your reference:
12/EM/0020

0115 9515679
angela.shone@nottingham.ac.uk

Research and Graduate Services
University of Nottingham
King's Meadow Campus
Lenton Lane Nottingham
NG7 2NR

Nottingham 2 REC
East Midlands REC centre
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Dr Andrew Fogarty, Chief Investigator
Room C113
Clinical Sciences Building
Nottingham City Hospital
NG5 1PB

14th December 2011

Dear sir or madam,

Sponsorship Statement

Re: Exploring the genetic basis of Hereditary Haemorrhagic Telangiectasia (HHT) and its associated complications

I can confirm that this research proposal has been discussed with the Chief Investigator and agreement to sponsor the research is in place.

An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.*

Any necessary indemnity or insurance arrangements will be in place before this research starts. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

The duties of sponsors set out in the NHS Research Governance Framework for Health and Social Care will be undertaken in relation to this research.**

* Not applicable to student research (except doctoral research).
** Not applicable to research outside the scope of the Research Governance Framework.

Yours faithfully

Angela Shone
Research Governance Manager
University of Nottingham

10.6 APPENDIX 6 - Genetic study: patient information leaflet, consent form and patient questionnaire

PARTICIPANT INFORMATION SHEET

Final Version 1.0, 13th December 2011

Exploring the genetic basis of Hereditary Haemorrhagic Telangiectasia and its associated complications

Name of researchers: Dr J Donaldson / Dr A Fogarty / Prof I Hall

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you.

Please read through this information sheet and if you have any questions contact us using the details given on the last page.

- **What is the purpose of the study?**

The purpose of this study is to try and give us a better understanding of how hereditary haemorrhagic telangiectasia (HHT) is passed on between families. HHT is a genetic (inherited) disease that can cause a variety of complications including severe nosebleeds and strokes. In up to 20% of people with HHT we cannot identify what type of mutation in their genes is causing the disease. This study involves looking at DNA (genetic material) from saliva (spit) samples to search for new undiscovered genes that may cause the disease. We hope the results from this study will help us to diagnose and treat HHT more effectively in the future.

- **Why have I been invited to participate?**

You have been invited to take part in this study for one of two reasons;

- Either you are known to the Nottingham Clinical Genetics Service with a possible or definite diagnosis of HHT,
- Or, you are a close relative of a person with HHT but you do not have the disease yourself.

In this study we are looking for around 60 people with HHT and 60 people without the disease to take part.

- **What will happen to me if I take part?**

This study is conducted by post and will not require you to travel to the hospital or to your GP surgery at any point.

If you are happy to take part then we would ask you to;

- **Complete (by putting your initials) and sign the consent form that will be sent to you**
- **Complete the confidential health questionnaire (should take 5 minutes)**

- **Provide a single sample of saliva (spit), approximately 10ml (or two teaspoons), in the enclosed specimen pot.**
- **Post the saliva sample, questionnaire and consent form back to us free of charge in the prepaid envelope.**

By agreeing to take part you would also be giving us permission to access your hospital medical records to find out information about your health – these records would remain confidential.

- **Do I have to take part?**

It is up to you to decide whether to join the study. This information sheet is designed to explain the study. If you agree to take part but later on change your mind you are free to withdraw at any time, without giving a reason. This would not affect the standard of any medical care you receive.

- **Will I be compensated in any way for my time?**

On receipt of your completed consent form, questionnaire and adequate saliva sample we will post to you a £15 voucher in recognition of your assistance with this study.

- **What will happen to any samples I give?**

The DNA (genetic material) in your saliva sample will be analysed to look for variations in the genes that cause HHT. With your permission, any remaining saliva will be kept and stored securely under our licence and without your details associated with it to maintain confidentiality.

In addition, if you agree, we may contact you directly in the future about further HHT related research projects although you have no obligation to take part in either this or any future study.

- **Will any genetic tests be done?**

Yes. DNA (genetic material) in your saliva will be analysed to look for variations in the genes that cause HHT. These tests will be done at the Sanger Institute in Cambridge on our behalf.

- **What are the possible advantages, disadvantages and risks of taking part?**

We cannot promise the study will help you directly and you will not receive any individual results of tests performed but we hope the information we get from this study will help improve the diagnosis and treatment of patients with HHT in the future and give us a better understanding of the cause of the disease.

There are no significant disadvantages in taking part other than the time it will take to collect and post the saliva samples to us. Any medical treatment you normally receive will be entirely unaffected by participation in this research study.

- **What will happen if I don’t want to carry on with the study?**

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw then the information collected so far cannot be erased and this information may still be used in the project analysis. Any remaining samples will be destroyed if you wish.

- **What if there is a problem?**

If you have a concern about any aspect of this study, you should ask to speak to Dr James Donaldson or another member of the research team who will do their best to answer your questions (telephone 0115 823 1379 or e-mail james.donaldson@nottingham.ac.uk).

- **Will my GP be informed about my involvement in this study?**

We will not contact your GP to inform them of your participation in this study.

- **Will my taking part in the study be kept confidential?**

All information which is collected about you during the course of the research will be kept strictly confidential.

The genetic study data will be anonymous as the DNA (genetic material) of many participants will be combined and analysed simultaneously. This means that it will not be possible to identify which genetic results are from which participant. The results of genetic testing will not be available and as such your participation in the study should not affect insurance policies.

Study data on the results of analysing the genetic material will be stored in a secure database labelled with only your initials and the participant number we will allocate to you.

We may, if you consent (optional), also use the DNA (genetic material) from your saliva samples for further genetic sequencing (analysis) with new genetic techniques as they become available, either within the University of Nottingham or with collaborators at other institutions. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

- **What will happen to the results of the research study?**

Our results will be published in scientific journals however it will not be possible to identify individuals who have taken part. The detailed nature of this research and the tests involved means that it may be a year or more before results are published.

A summary of the study results will be on our departmental website when they are available. The website address is:

http://www.nottingham.ac.uk/scs/divisions/therapeuticsmoleculermedicine/index.aspx

- **Who is organising and funding the research?**

This research is organised by clinical academic researchers at the University of Nottingham and is funded by a research grant from the National Institute of Health Research (an NHS research body).

- **Who has reviewed this study?**

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the Nottingham Research Ethics Committee East Midlands – Nottingham.

- **Contact details for any queries or further information;**

Dr James Donaldson, Division of Epidemiology and Public Health, Clinical Sciences Building, Nottingham City Hospital Campus, Hucknall Road, Nottingham, NG5 1PB.
E-mail: james.donaldson@nottingham.ac.uk, Telephone: 0115 823 1379.

The contact details of the chief investigator are: Dr A Fogarty, Division of Epidemiology and Public Health, Clinical Sciences Building, Nottingham City Hospital Campus, Hucknall Road, Nottingham, NG5 1PB.
E-mail: andrew.fogarty@nottingham.ac.uk, tel: 0115 823 1715

CONSENT FORM

Final version 2.0, 17th February 2012

Title of Study: **Exploring the genetic basis of Hereditary Haemorrhagic Telangiectasia and its associated complications**

PLEASE KEEP ONE COPY OF THIS FORM AND RETURN THE SECOND BY POST

Name of Researchers: Dr James Donaldson / Dr A Fogarty / Prof Ian Hall

Participant Name: …… **Please initial**

1. I have read and understand the information sheet for the above study (dated 17th February 2012) and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

3. I give permission for access to my medical and other health-related records, and for long term storage and use of this information for health-related research purposes, including publication. I understand that my personal details will be kept confidential. ☐

4. I understand and agree that a saliva sample will be taken for analysis of DNA (genetic material). I understand that the results will *not* be given to me as the sample will be analysed anonymously. ☐

5. I agree to my GP being informed of my participation in this study. ☐

6. I agree to take part in the above study. ☐

7. Consent for storage and use in possible future research;

I agree that the samples I have given and the information gathered about me can be stored by Dr Andrew Fogarty at the Clinical Sciences Building, Nottingham City Hospital for possible use in future studies. I understand that some of these studies may be carried out by researchers other than the current team of Dr Fogarty, who ran the first study, including researchers working for commercial companies. Any samples or data used will be anonymised, and I will not be identified in any way. ☐

I agree to be contacted directly in the future regarding other HHT related research projects.

(please tick) Yes ☐ No ☐

_____	_____	_____
Name of Participant	**Date**	**Signature**

_____	_____	_____
Name of Person taking consent	**Date**	**Signature**

2 copies: 1 for participant, 1 for the project file

PARTICIPANT QUESTIONNAIRE

Final version 2.1, 3rd April 2012

Title of Study: **Exploring the genetic basis of Hereditary Haemorrhagic Telangiectasia and its associated complications**

Please complete this short questionnaire about you and your health.

Any information you provide will be stored securely and kept confidential.

Participant Name: ……..

1. What is your date of birth? ……

2. What sex are you? (please circle) Male / Female

3. To which ethnic group do you belong? (please tick)

White British ☐

Mixed race

White and Black Caribbean / African ☐

White and Asian ☐

Any other Mixed background (please specify) ……...

Asian or Asian British ☐

Black or Black British ☐

Chinese or Chinese British ☐

Other background (please specify) ……

4. Question 4 applies **only** to females completing this form (please circle); **If you are male, please continue to question 5.**

a) Are you currently using or have you ever used a contraceptive containing oestrogen (such as the combined pill, contraceptive implant or patch)? Yes / No

b) As far as you are aware, are you currently pregnant? Yes / No

c) How many previous times have you been pregnant (whether resulting in giving birth or not)? ……

5. Have you been diagnosed with Hereditary Haemorrhagic Telangiectasia, also known as HHT? Yes / No

If you *have not* been diagnosed with HHT please continue to answer the questions below. If you have HHT please skip to question 9.

6. Have you suffered from any of the following symptoms in the last 2 years? **(please circle)**

   a) Severe nosebleeds that happen repeatedly Yes / No / Unsure

   b) Anaemia Yes / No / Unsure

   c) Bleeding from the gut Yes / No / Unsure

   d) Shortness of breath Yes / No / Unsure

   e) Migraine Yes / No / Unsure

   f) Coughing up blood Yes / No / Unsure

7. Have you ever noticed small (less than 1cm) spider-shaped lesions on your skin that are cherry red in colour, normally on the nose, lips, inside of the mouth or fingers?

   Yes / No / Unsure

8. Have you ever had a stroke or a mini stroke in the past?

   Yes / No / Unsure

If, having answered the above questions, you are at all concerned about whether

you may have symptoms of HHT, we can offer further medical support.

Please contact us via the details provided on the patient information sheet

The following questions apply only to those people who have HHT.

9. Do you currently attend a hospital outpatient clinic for any treatment or monitoring for your HHT?

   Yes / No / Unsure

10. If yes, are you seen in the respiratory / chest clinic for any lung problems related to your HHT?

    Yes / No / Unsure

11. If no, please detail which specialist clinic you attend (eg. gastroenterology, clinical genetics)

    ……

12. Have you received information about what symptoms to look out for in HHT (such as nose bleeds or shortness of breath)?

    Yes / No / Unsure

13. If you are female and of childbearing age have you ever received any advice on HHT and pregnancy?

Yes / No / Unsure

14. Have you ever had the following complications of HHT?

a) Severe nosebleeds that happen repeatedly Yes / No / Unsure

b) Coughing up blood Yes / No / Unsure

c) Bleeding from the gut Yes / No / Unsure

d) Anaemia Yes / No / Unsure

e) Malformations of blood vessels, also known as AVMs in your:

I. Lungs Yes / No / Unsure

II. Brain Yes / No / Unsure

III. Liver Yes / No / Unsure

IV. Gut Yes / No / Unsure

V. Spine Yes / No / Unsure

f) Skin lesions (known as telangiectasia) on the nose, tongue or lips? Yes / No / Unsure

g) Stroke or mini stroke Yes / No / Unsure

h) Brain abscess Yes / No / Unsure

i) Migraine headaches Yes / No / Unsure

15. Have you ever had a coil embolisation procedure to close off an abnormal blood vessel in your lungs? Yes / No / Unsure

THANKYOU FOR COMPLETING THIS QUESTIONNAIRE