Hip fracture: A study of the factors influencing thromboembolic complications and mortality

Douglas Graham Mackenzie

Doctor of Medicine
University of Edinburgh
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Abbreviations

Abbreviation	Term	Notes
♀	Female	
♂	Male	
ASA grade	American Society of Anesthesiologists grade	Provides a measure of systemic disease prior to fracture (page 33)
CHD	Coronary heart disease	In the SMR analysis (chapters 3 and 5) this term represents myocardial infarction and angina
CI	Confidence interval	
CT scan	Computerised tomography scan	
CVD	Cardiovascular disease	In the SMR analysis (chapters 3 and 5) this is used as a collective term to include coronary heart disease, peripheral vascular disease and cerebrovascular disease
DVT	Deep vein thrombosis	
GEC stockings	Graduated elasticated compression stocking	
GROS	General Register Office Scotland	
HR	Hazard ratio	Output of Cox proportional hazards regression analysis (page 66)
ICD	International Classification of Diseases	
IHD	Ischaemic heart disease	In the SMR analysis (chapter 3 and 5) this is used for coronary heart disease excluding myocardial infarction
ISD	Information Services Division	A division of NHS National Services Scotland

Abbreviation	Term	Notes
LMWH	Low molecular weight heparin	
MI	Myocardial infarction	
NHS	National Health Service	
PE	Pulmonary embolism	
PEP trial	Pulmonary Embolism Prevention trial	See reference 20
RCT	Randomised controlled trial	
sd	Standard deviation	
SHFA	Scottish Hip Fracture Audit	See chapter 4
SIGN	Scottish Intercollegiate Guidelines Network	Part of NHS Quality Improvement Scotland that issues national guidelines on clinical topics
SIMD	Scottish Index of Multiple Deprivation	See page 65
SMR	Scottish Morbidity Records	See chapter 3
TED	Thromboembolic disease	
THRIFT	Thromboembolic Risk Factors	The name of a consensus group that published early guidance on TED in hip fracture patients – see page 15 and reference 24
TP	Thromboprophylaxis	
χ^2	Chi squared test	

Abstract

Background: Hip fracture in the elderly has high morbidity and mortality. Thromboembolic disease (TED) is one potential explanation for increased morbidity and mortality in hip fracture patients. National guidelines have recommended low molecular weight heparin or aspirin for thromboprophylaxis (TP) following hip fracture. While these treatments reduce clinical and radiological incidence/prevalence of TED, the Cochrane review of TP in hip fracture patients (2002), was unable to demonstrate a survival benefit with different types of TP.

Aim: To explore the effect of different types of TP in hip fracture patients after adjusting for cofactors and comorbidities.

Data sources: Prospectively collected Scottish Hip Fracture Audit (SHFA) data, linked to routinely collected Scottish Morbidity Records (SMR) providing information about hospital discharges, mortality records and cancer registry data.

Participants: 8470 patients aged 60 years and over admitted to NHS hospitals in Scotland with hip fracture (1998 to 2003).

Methods: Multivariate analysis (Cox proportional hazards regression analysis), adjusting for SHFA variables (including age, sex, residence pre-fracture, American Society of Anesthesiologists grade, delay to surgery for medical reasons, hospital, and type of TP received), and SMR variables (including the Scottish Index of Multiple Deprivation, number of hospital inpatient episodes in the five years prior to hip fracture, previous diagnoses with cardiovascular disease or respiratory disease, or cancer registration).

Main results: The mortality rate in the year following hip fracture was 30% (95% CI 29 to 31%). Clinically identified TED was uncommon in the year following hip fracture with 1.4% (95% CI 1.2 to 1.7%) patients recorded as having an inpatient episode with a primary diagnosis of TED and 0.3% (95% 0.2 to 0.4%) patients recorded with TED as the primary cause of death. There was evidence of reduced mortality in patients documented as receiving aspirin (hazard ratio 0.86; 95% CI 0.78 to 0.95) or graduated elasticated compression (GEC) stockings (HR 0.88; 95% CI 0.80 to 0.97), but there was no statistically significant effect on combined admissions/ deaths from TED or coronary artery disease with aspirin (HR 1.07; 95% CI 0.83 to 1.38) or GEC stockings (HR 1.11; 95% CI 0.90 to 1.37). Heparin did not have a statistically significant influence on outcomes.

Main conclusions: The findings of this study suggest that aspirin and GEC stockings may be beneficial following hip fracture, but the findings may be explained by residual confounding, and a randomised controlled trial of GEC stockings and/ or aspirin in elderly hip fracture patients is warranted.

Key words: Thromboembolic disease, thromboprophylaxis, hip fracture, comorbidities.

I declare that this thesis and the supporting original research is all my own work.

Signed:

Douglas Graham Mackenzie 6 September 2006

1 Introduction

1.1 Hip fracture

Hip fracture is an orthopaedic emergency. Figure 1.1 shows the site of different types of hip fracture. Compared with an age and sex matched population, the excess mortality for hip fracture patients has been estimated at 10% to 20% in the first year following the fracture, with most of the excess mortality occurring in the first 6 months after the fracture[1].

Hip fracture is common. The cumulative lifetime risk of hip fracture in economically advanced countries is estimated at 15% among women and 5% among men[2]. The majority of fractures occur as a result of falls in frail, elderly patients with osteoporosis. Hip fracture often leads to a decline in functional status, deterioration in mobility and greater dependence on carers. Hospital admissions for hip fracture can be prolonged and care involves the input of up to 50 health professionals[3].

Hip fracture is therefore expensive and care is complex. For these reasons hip fracture has been chosen as a "tracer condition" by NHS Quality Improvement Scotland, by which to examine patient journeys in older people in more detail[4]. The Scottish Hip Fracture Audit (SHFA) has collected data about quality of care for up to half of all hip fracture patients in Scotland since 1992 and this allows the detailed study of outcomes of care of hip fracture patients in Scotland.

1.2 Epidemiology of hip fracture in Scotland

The epidemiology of hip fracture in Scotland up to 1998 is summarised in the 2002 Scottish Intercollegiate Guidelines Network (SIGN) guideline for hip fracture[3]. Between 1982 and 1998 the number of hip fractures per year in Scotland in people aged 55 years and over rose from 4,000 to 5,700. This increase was not wholly attributable to the increasing age of the Scottish population as the age-standardised risk rose during the same period from 165 to 205 per 100,000 men and 500 to 593 per 100,000 women aged 55 years and over[3].

1.3 Thromboembolic disease (TED) in hip fracture patients

Thromboembolic disease (TED) is a potentially important cause of morbidity and mortality following hip fracture and includes deep vein thrombosis (DVT) and pulmonary embolism (PE). In studies of hip fracture patients who did not receive thromboprophylaxis but underwent radiological testing, DVT was identified in 40 to 60% of patients and PE in 3 to 28% of patients[5].

Over 150 years ago Virchow described a triad of factors that contribute to the pathogenesis of TED - vascular endothelial damage, stasis of blood flow, and hypercoagulability of blood[6;7]. Each of these factors is likely to have a role in the pathogenesis of TED in hip fracture patients. Hip fracture patients are often socially isolated (elderly, living alone) and may live in damp and poorly heated houses. Many hip fractures occur in the home. Following hip fracture, patients can lie for hours or days before being taken to hospital, and they can be dehydrated and hypothermic, contributing to venous stasis and abnormal clotting[8]. The trauma of the fracture and the

body's response to this trauma leads to endothelial damage and changes in clotting, and these are exacerbated by surgery and immobility during the recovery period which further contribute to venous stasis and abnormal clotting[9]. Although the precise pathophysiological mechanism through which thrombus formation occurs is not yet fully understood, it is likely to involve platelets, clotting factors, and cellular interactions with the endothelium and once the thrombus has developed there is a continual process of organisation of thrombus, with embolism occurring in some patients[10]. Thrombus formation appears to be related to both the site of the fracture and the timing of surgery as around 75% of DVT occur in the operated leg, and the peak incidence of TED occurs during the first hours and days following surgery[11]. Around one third of patients with DVT are thought to develop chronic problems (post-thrombotic syndrome) with pain, pruritis and oedema of the affected site[12]. Various aspects of hip fracture management may reduce the burden of TED following hip fracture, including thromboprophylaxis (section 1.4), reducing the delay to surgery, early mobilisation and spinal anaesthesia[3].

The clinical relevance of DVT following hip fracture depends on the method of diagnosis and the site of the clot. Studies based on radiological tests typically identify a higher rate of TED than studies based on clinical findings, but radiologically identified DVT may not be clinically important. In one review, 46% of hip fracture patients had radiological evidence of DVT, 19% had radiological evidence of proximal DVT (which is more likely to lead to PE), and 7% had clinical DVT[13]. PE may also go undetected and deaths may be attributed to other causes, so clinical studies may underestimate the true incidence of TED following hip fracture. However it is not ethical to subject

patients routinely to the invasive radiological tests required for diagnosis of PE. Historically, using data from autopsy based studies, PE appears to have been under-reported following hip fracture[14;15], and more recent autopsy studies have also shown a high prevalence of PE following hip fracture although these findings may at least partly be explained by selection of patients for autopsy who are more likely to have died from a PE due to sudden death or death soon after a surgical procedure[16].

1.4 Thromboprophylaxis in hip fracture patients

Thromboprophylaxis is a term used for a group of mechanical and pharmacological treatments that can reduce TED. Examples of mechanical thromboprophylaxis include graduated elasticated compression (GEC) stockings and foot pumps. Examples of chemical thromboprophylaxis include heparin, aspirin and warfarin. Successive SIGN guidelines for hip fracture have recommended the use of low molecular weight heparin (LMWH)[17] or aspirin[3]. GEC stockings increase mean blood velocity in leg veins and reduce venous stasis[18] and have been shown to be effective in preventing TED after major surgery[13], but their role after hip fracture has not been widely studied.

Trial evidence supporting the use of thromboprophylaxis following hip fracture is limited. The most recent Cochrane review published on thromboprophylaxis in hip fracture patients noted that, although there is evidence for reduction in TED following hip fracture with heparin, there is little evidence for a reduction in mortality[19]. The results of the Pulmonary Embolism Prevention (PEP) trial suggest that aspirin may also provide protection against fatal pulmonary embolism following hip fracture, but a similar effect on other vascular deaths or all-cause mortality was not demonstrated[20].

Nonetheless, aspirin has an established role in the primary and secondary prevention of cardiovascular disease (CVD)[21] and may also protect against breast[22] and colorectal cancer[23], all of which are common causes of morbidity and mortality in elderly patients at risk of hip fracture.

Thromboprophylaxis may also have harmful effects. For example, chemical thromboprophylaxis may increase the risk of haemorrhage or peptic ulcer disease. Understanding the balance between reducing TED and increasing haemorrhagic events is important in understanding the influence of thromboprophylaxis on morbidity and mortality following hip fracture. As noted by the THRIFT consensus group, if "the risk of adverse effects from bleeding has been underestimated, as many surgeons suspect, or if the risk of thromboembolic events were shown to be lower than the lower confidence intervals from recent data, the balance of risk and benefits would move against anticoagulation"[24].

1.5 Rationale for this study

The previous sections have highlighted some of the questions surrounding hip fracture, TED and thromboprophylaxis. The first stage of this study is therefore to perform a literature review, to explore the available data on these issues systematically. In light of the challenges in diagnosing TED, the literature review identifies descriptive studies to explore the epidemiology of clinically relevant TED following hip fracture. In order to understand the factors that may influence mortality following hip fracture, the literature review then identifies descriptive studies that explore the influence of patient factors, medical comorbidities and social influences in hip fracture patients. Finally, the literature about thromboprophylaxis in hip fracture is reviewed to provide an update to evidence from the most recent Cochrane review on this topic[19]. The findings of the literature review are used to inform the design of the rest of the study.

Evidence about the potential impact of medical, surgical and anaesthetic advances in the management of hip fracture is explored using Scottish Morbidity Records (SMR) data available for the period 1986 to 2003. SMR data are collected routinely following hospital discharge and have been linked previously to other hospital discharge data, death records, cancer registry data and the Scottish Index of Multiple Deprivation (SIMD). The modern era of hip fracture treatment, marked by the publication of the first SIGN guideline in 1997, might be expected to have led to improvements in hip fracture outcome. The age and comorbidities of patients at the time of hip fracture have, however, increased over time[25], and these influences need to be considered in the analysis. SMR data are therefore used to adjust outcomes for age, gender, number and

type of inpatient episodes during the 5 years prior to hip fracture (as a proxy for comorbidity), and deprivation category. These variables provide information about the potential impact of evidence-based treatment, including thromboprophylaxis, on hip fracture outcomes.

This study then focuses on the influence of thromboprophylaxis on all-cause mortality and other events following hip fracture. The study uses data collected between 1998 and 2003 from two Scottish databases, providing information about previous medical history, thromboprophylaxis during the hip fracture admission and outcomes following hip fracture. The two databases that have been linked to produce this database are the SHFA database, which provides information about thromboprophylaxis and other measures of quality of care, and the SMR database (see above).

In contrast to many other published research studies on this topic, this study uses data from a large number of patients, and has not excluded patients who are very ill or very old, so the findings would be expected to be more relevant to the general hip fracture population than some other epidemiological studies of selected patient groups and the selected groups of patients normally enrolled in clinical trials. As there is detailed information about patients before, during and after hip fracture it is possible to adjust for differences in age, gender and comorbidities that may influence the findings.

1.6 Aims and objectives

This work examines the influence of thromboprophylaxis on death and TED or CVD following hip fracture after adjusting for potential confounding factors. The objectives are listed in the section explaining the rationale in each of the next four chapters.

1.7 Research questions

The following research questions form the basis of this study.

1) What is the likely burden of TED following hip fracture?
2) Did outcomes in hip fracture patients alter following the launch of the first national evidence-based guidelines in 1997?
3) Is there evidence of improved survival in hip fracture patients who have received different types of thromboprophylaxis, and does this relationship persist after adjusting for cofactors?
4) If a particular type of thromboprophylaxis has an influence on survival, then is this relationship explained by changes in the incidence of secondary outcomes following hip fracture (TED, CVD and haemorrhage)?
5) How representative of elderly hip fracture patients in Scotland as a whole are the sub-set of patients included in this analysis?

1.8 Comparison with earlier work in Scotland

I have previously looked at hip fracture and TED in Scotland for a thesis submitted for the degree of Masters of Public Health (University of Glasgow, 2002)[25]. Results included descriptions of the epidemiology of hip fracture and TED following hip fracture between 1982 and 1998 using SMR data, and a description of thromboprophylaxis usage in 2788 patients participating in SHFA in 1998. It was not possible at that time to link the SMR and SHFA databases together, so only limited conclusions were possible in that thesis. Additionally, as the national guidelines on hip fracture were published in 1997[17] and updated in 2002[3], these findings may not be relevant to current practice.

The current study has been made possible by recent improvements in the Scottish data on hip fracture. SHFA records have now been linked to SMR records providing longitudinal data for over 18,000 SHFA participants admitted between 1998 and 2003. Linkage to SMR records has been performed for the 5 years prior to hip fracture and the year following hip fracture, providing information about previous inpatient episodes, socio-economic status and subsequent outcomes. The conclusions available from this new analysis are therefore based on a more detailed analysis of a larger number of patients and are based entirely on the period following publication of the first SIGN guideline in 1997[17].

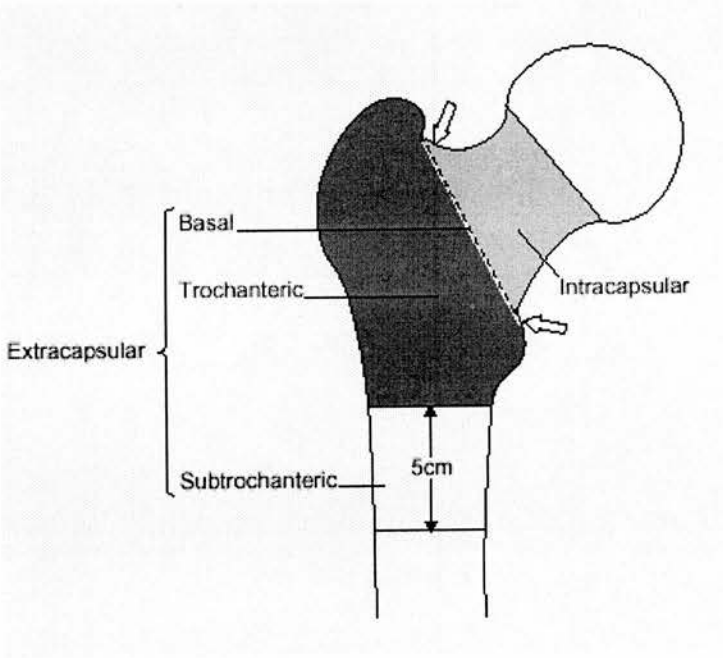
1.9 Statistical power

The primary outcome of interest for this study is all-cause mortality in the year following hip fracture admission. Estimating the sample size required to identify a statistically significant reduction in mortality with thromboprophylaxis is not straightforward, because a substantial proportion of patients receive more than one type of thromboprophylaxis, the proportion of patients receiving thromboprophylaxis varies by type of treatment, and there are inadequate data from previously published studies to estimate the likely reduction in mortality with thromboprophylaxis. The estimation of sample size is therefore based on a series of assumptions.

The findings of previously published studies suggest that heparin has the largest treatment effect of conventional types of thromboprophylaxis, with a 40% reduction in radiologically identified TED[19] and use of heparin is documented in approximately 50% of SHFA participants[25]. With an expected mortality rate of 30% during the year following hip fracture, and assuming a 10% reduction in mortality with heparin compared to patients receiving other thromboprophylaxis regimes, the sample size required to detect a reduction in mortality with heparin is estimated at 3570 patients per study limb (5% significance level, 80% power)[26]. There are data available for 18,000 patients in this analysis. Therefore this study is likely to be adequately powered for heparin. However, the sample size for other types of thromboprophylaxis will vary by the size of the treatment effect (which cannot be quantified using existing evidence) and the proportion of patients receiving that type of thromboprophylaxis.

1.10 Figures

Figure 1.1
Different types of hip fracture[3]



2 Literature review

2.1 Introduction

The aim of this thesis is to examine the influence of thromboprophylaxis on death and other outcomes following hip fracture, adjusting for confounding factors. This chapter reviews the published literature relating to this topic.

2.2 Background

The previous chapter has highlighted the potential importance of TED following hip fracture. There is considerable uncertainty, however, about the incidence of clinically apparent TED following hip fracture.

A Cochrane review published in 2002 studied the influence of heparin and mechanical thromboprophylaxis on outcomes following hip fracture and identified a number of gaps in the literature. There were few studies identified that looked at the influence of thromboprophylaxis on mortality following hip fracture, and there were few studies of the influence of GEC stockings[19]. This is despite evidence from studies of other types of major surgery that GEC stockings may reduce TED[13]. Aspirin, which is the preferred type of thromboprophylaxis in the most recent SIGN guideline on hip fracture[3], may also reduce TED but has not been demonstrated to reduce mortality in hip fracture patients[20].

There therefore remain a number of unanswered questions, particularly relating to the influence of different types of thromboprophylaxis on mortality following hip fracture.

The findings of the literature review described here inform the design of the study described in subsequent chapters in order to fill gaps in the existing literature.

2.3 Rationale

2.3.1 Objective 1a. To review the published literature to identify the incidence of thromboembolic disease (TED) following hip fracture

Understanding the epidemiology of clinically apparent, radiologically confirmed TED following hip fracture is of major importance in this study. The findings will be used to assess the accuracy of hospital discharge data (chapter 3), and will be used to estimate the sample size required in the study of the influence of thromboprophylaxis on secondary outcomes (chapter 5).

2.3.2 Objective 1b. To review the published literature to identify demographic, medical and social factors that influence mortality following hip fracture

Chapters 4 and 5 study the influence of different types of thromboprophylaxis on outcomes following hip fracture. There may, however, be important variation in the characteristics of patients receiving different types of thromboprophylaxis that could also influence outcome. The factors that have been shown to be most important in predicting outcome following hip fracture will be identified from the published literature. This information will be used to identify relevant variables from routinely collected hospital discharge data (chapter 3) and SHFA data (chapter 4).

2.3.3 Objective 1c. To update the findings of previous reviews of thromboprophylaxis in hip fracture

Papers published since the time of the most recent Cochrane review of thromboprophylaxis in hip fracture and the SIGN guideline on hip fracture will be reviewed to examine whether any subsequent trials have demonstrated the superiority of different types of thromboprophylaxis over placebo on long-term survival following hip fracture.

2.4 Methods

The literature review was performed in December 2004 and involved the steps shown in figure 2.1, adapting search strategies from the Cochrane review for thromboprophylaxis in hip fracture[19] using MEDLINE and EMBASE databases (appendix). Additional references were identified from the bibliographies of key references identified in the search. Objectives 1a and 1b were explored by reviewing descriptive studies and objective 1c was explored by reviewing randomised controlled trials, using inclusion and exclusion criteria listed in table 2.1. Figure 2.1 shows the number of studies that were excluded at each stage to give the final number of papers selected for further study (n=35). Authors of potentially useful studies of lower limb surgery were contacted with requests for further information for hip fracture alone. Of the authors contacted, Barrett[27] responded with additional data, and Ollendorf[28] replied but was unable to provide additional data.

Of the 35 selected papers, 23 provided data relevant to objective 1a (of which 2 provided additional data for objective 1b and 1 provided data for objective 1c). These

studies were divided into clinical studies (n=19) and autopsy studies (n=4). An additional 12 papers provided information about comorbidities (objective 1b).

2.5 Results

2.5.1 Objective 1a: To identify the incidence of clinical DVT and PE following hip fracture

In total 19 papers that provided information about the incidence of TED following hip fracture were identified. These included 11 studies where the main aim of the study was to identify the incidence of TED or other medical complications following hip fracture, of which 5 studies recruited patients prospectively (table 2.2) and 6 studies collected data retrospectively (table 2.3). The remaining 8 studies were conducted for other purposes, but included information about the incidence of TED following hip fracture (table 2.4). The key studies are described and appraised below.

2.5.1.1 Studies estimating the incidence of TED in the year following hip fracture

Two papers described TED and other complications in the year following hip fracture (the follow-up period studied in subsequent chapters).

Gerber *et al* studied TED in the year following hip fracture, identifying clinical PE in 3.3% (95% confidence intervals (CI) 1.5 to 5.0%) of patients. These data were collected at patient review four months and one year after hip fracture. This study had a number of limitations. The study was conducted between 1972 and 1988 and may not therefore be relevant to current practice. A lower proportion of patients received thromboprophylaxis than in many other studies (45%). There was no information about whether radiological tests were performed to confirm diagnosis in patients with suspected PE[29].

Vajanto *et al* studied outcomes at around one year of follow up, with 2.1% (95% CI 0.6 to 3.7%) of patients identified with PE and 1.5% (95% CI 0.2 to 2.8%) with DVT during an average follow-up period of 58 weeks. There was no indication of how many patients developed both DVT and PE so the overall burden of TED in this study can not be estimated. Data were collected retrospectively from patient records of patients admitted with hip fracture between 1990 and 1993. All patients were given LMWH before and after surgery. There was no information about the radiological techniques used to investigate patients with suspected TED. Information was available about other complications one year after hip fracture, but not mortality[30].

2.5.1.2 Large studies of the incidence of TED following hip fracture, using administrative data

The most precise estimates of the incidence of TED following hip fracture came from two very large retrospective studies conducted in the United States using administrative data.

Ollendorf *et al* used hospital discharge records collected from 220 hospitals between 1998 and 1999, identifying DVT in 0.82% (95% CI 0.7 to 0.9%) of patients and PE in 0.5% (95% CI 0.5 to 0.6%) during the hip fracture admission; overall 1.4% (95% CI 1.2 to 1.5%) of patients developed TED during the hospital admission[28].

Barrett *et al* used Medicare billing information to follow up hip fracture patients identified in the 5% United States standard sample of the Medicare population between 1986 and 1990, with PE identified in 1.6% (95% CI 1.5 to 1.7%) of patients within 90 days of hip fracture[27].

While both these studies specifically examined the epidemiology of TED in fracture patients, both relied on administrative data and there were no data about thromboprophylaxis usage or methods of radiological confirmation.

2.5.1.3 Studies estimating the overall burden of DVT and PE following hip fracture

In most papers there was insufficient detail to estimate the overall proportion of patients with TED. The following studies did however provide some information about the overall incidence of TED following hip fracture.

Todd *et al* used prospectively collected East Anglian Audit data to study outcomes following hip fracture. In common with the findings presented in chapter 4, this study used the results of a prospective audit based on the Standardised Audit of Hip Fractures in Europe. Use of chemical thromboprophylaxis was reported in 45% of patients, but use of mechanical thromboprophylaxis was not described. Data collected from hospital records showed that 5.3% (95% CI 3.5 to 7.2%) of patients were diagnosed with "postoperative thrombosis", but there were no details about radiological testing or the

anatomical distribution of thrombus*. 2.2% (95% CI 1.0 to 3.5%) of patients developed fatal PE during the 90 days following hip fracture but it is not clear whether these patients underwent autopsy‡[31]. Uncertainties about definitions and methodology in this study make it difficult to compare the findings with other studies.

Lawrence *et al* retrospectively identified TED in 1.0% (95% CI 0.8 to 1.2%) of patients during hospital admission, with full details about radiological testing. This estimate was based on data collected between 1982 and 1993, and information about thromboprophylaxis was not available[32].

Ollendorf *et al* also provided information about the overall burden of TED (see section 2.5.1.2 above), as did the two studies described in section 2.5.1.4 below.

2.5.1.4 Recent studies focusing on TED and haemorrhagic complications

Few published studies provide detailed information about complications of hip fracture (and its management) in the modern era of hip fracture treatment. Two studies provided

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* There were no details about the proportion of these patients who experienced proximal DVT and/ or PE. It is possible therefore that this estimate included superficial thrombus and distal DVT which are of less clinical importance.

‡ The paper states: "Although few patients were identified at postmortem examination as having had a fatal pulmonary embolism, whether the patient had received prophylactic treatment was highly significant".

recent and detailed information about TED, haemorrhagic complications and use of thromboprophylaxis following hip fracture.

Thaler *et al* prospectively studied hip fracture patients admitted between 1997 and 1999, identifying radiologically confirmed TED in 0.8% (95% CI 0.2 to 1.4%) of patients during the hospital admission, with no TED deaths recorded. Major haemorrhagic events[#] were recorded in 4.7% (95% CI 3.3 to 6.1%) of patients, and one death (0.1%, 95% CI 0 to 0.3%) was recorded as being due to intracerebral haemorrhage. The study also provided information about the accuracy of clinical diagnosis in detection of TED. Only 14% of suspected DVT and 50% of suspected PE were confirmed when patients underwent radiological testing. Younger patients were included in this study which may have resulted in an underestimate of postoperative complications. However, the majority of patients were elderly, and a high level of previous medical illness was documented in the study participants. Consequently, these findings are probably reasonably representative of the elderly hip fracture population[33].

[#] Major haemorrhagic events were defined as clinically overt intracranial or retroperitoneal bleeding unrelated to trauma that led to transfusion of 4 or more units of packed red blood cells within the first 24 hours of operation, or bleeding at the operative site leading to re-operation for bleeding and transfusion of 2 or more units.

Ennis *et al* looked retrospectively for TED and haemorrhagic complications during the three months following hip fracture in a group of patients admitted to hospital between 1995 and 1999. Patients received a variety of types of mechanical and chemical thromboprophylaxis, and 0.6% (95% CI 0.1 to 1.2%) of patients developed TED, including one fatal PE. In total 0.8% (95% CI 0.2 to 1.3%) of patients had a major bleeding episode[‡], including one death (0.1%, 95% CI 0 to 0.3%) from gastrointestinal bleeding. This study also included some younger patients, but the majority of patients were elderly and the average age was similar to that expected in a population of elderly hip fracture patients[34].

2.5.1.5 Autopsy studies

Some additional information about the burden of TED is provided in studies reporting autopsy findings. Table 2.5 summarises the results from the four autopsy studies identified in the literature search. The majority of data in these studies were collected more than ten years ago, and some were collected more than 50 years ago, so the relevance to current practice is not clear. There was considerable heterogeneity between

‡ Major bleeding episode defined as one that causes death, intra-organ bleeding, or bleeding that necessitated re-operation.

studies. Depending on the study, between 11.1 and 19.0% of autopsies identified PE as causing or contributing to death at a maximum of 3 months follow up.

Table 2.6 shows the combined findings of three of the autopsy studies that provided data about all causes of mortality. PE was the most common thrombotic cause of death and third most common cause of death overall (only pneumonia and congestive cardiac failure were more common). Overall 25.7% deaths were attributed to thrombotic events and 2.8% deaths to haemorrhagic events.

2.5.1.6 Other studies

The remaining studies summarised in tables 2.2 to 2.4 were, typically, smaller studies of the period of the hip fracture admission. The studies listed in table 2.4 had diverse aims and methodologies. Many studies had limitations for this particular objective including incomplete documentation[35;36] and a high proportion of drop-outs[37]. In some studies there was over representation of particular groups including men[37;38], and more physically able patients[39]. In one study there was under-representation of patients with a previous history of TED or haemorrhage[37].

2.5.2 Objective 1b: to identify medical and social factors that influence mortality following hip fracture

Some studies explored the impact of comorbidities on mortality following hip fracture. The most important findings are summarised below.

2.5.2.1 Demographics

Age was an important predictor of mortality[31;35;40]. Patients aged 85 years and over had a higher mortality at one year than patients aged under 85 years (hazard ratio 2.7; 95% CI 1.7-4.4)[41]. Sex was also an important predictor of mortality with men more likely to die than women within the first 90 days following hip fracture (odds ratio 2.9; 95% CI 1.5 to 5.4)[31].

2.5.2.2 Social circumstances and functional characteristics

Patients who required assistance for basic activities of daily living had a higher mortality than those who did not require such assistance. In one study, mortality at 90 days was higher for patients with poorer function (odds ratio 1.07 per unit increase in activities of daily living scale†; 95% CI 1.04 to 1.10)[31]. In another study, mortality at one year was higher in patients who required assistance with activities of daily living than among those who did not require assistance (hazard ratio 2.4; 95% CI 1.5-3.9)[41]. Patients in residential care had higher mortality than other patients at 24 months for patients aged 50 to 79 years (odds ratio 1.7; 95% CI 1.4 to 2.1), and for patients aged 80 and over (odds ratio 2.7; 95% CI 1.8-4.0)[42].

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† Activities of daily living scale ranged from 0-38, with higher scores representing poorer function.

2.5.2.3 Medical conditions

Patients with severe systemic illness prior to fracture (American Society of Anesthesiologists (ASA) grades 3 or 4[‡]) had higher mortality at one year (hazard ratio 3.9; 95% CI 2.3-6.7)[41] a finding that was consistent with other studies[43]. Cancer (excluding skin cancer) was an important predictor of mortality at one year (hazard ratio 3.1; 95% CI 1.8-5.4)[41] while a prior history of the following conditions increased adverse outcomes at 30 days following hip fracture: congestive cardiac disease (odds ratio 32.3; 95% CI 5.4-192.0), angina (odds ratio 25.7; 95% CI 3.6 to 184.0) and chronic obstructive pulmonary disease (odds ratio 11.1; 95% CI 2.0 to 62.0)[44]. Prior CVD was associated with increased mortality at 90 days compared to those with no history of CVD (odds ratio 2.13; 95% CI 1.25 to 3.64)[31]. Patients with diabetes had a higher mortality during the hospital admission than those without diabetes (odds ratio 3.0; 95% CI 1.1 to 8.0) but no difference in mortality was found after one year of follow up[45].

[‡] ASA grade documents the level of systemic disease prior to hip fracture: grade 1 = a healthy patient; grade 2 = a patient with mild systemic illness; grade 3 = a patient with severe systemic disease that is not incapacitating; grade 4 = a patient with incapacitating systemic disease that is a constant threat to life; grade 5 = a moribund patient not expected to survive for 24 hours[43].

The medical conditions listed above that had an important influence on mortality appear to have been relatively common in hip fracture patients. A summary of the prevalence of these conditions, as derived from the reviewed studies, is shown in table 2.7. Different studies used different diagnostic groupings, and there is likely to have been some overlap between some conditions, for example between CVD, CHD and stroke.

2.5.2.4 Quality of care

Other aspects of hip fracture management may also have also influenced outcome. Operative delay to hip fracture surgery of more than 48 hours had an adverse effect on outcome (hazard ratio 1.63; 95% CI 1.11 to 2.40) in one study, but surgical delay may be due either to the patient's condition or hospital factors relating to quality of care and findings in other studies are contradictory[43]. Speed of mobilisation following surgery was identified as an important influence on mortality 90 days post-operatively in a re-audit of hip fracture care in the East Anglian Audit[#].

[#] Freeman C, Todd C, Camilleri-Ferrante C, et al. Quality improvement for patients with hip fracture: experience from a multi-site audit. *Qual Saf Health Care* 2002;11:239-245.

2.5.3 Objective 1c: to update the findings of previous reviews of thromboprophylaxis in hip fracture

Chapter 1 provided a summary of existing evidence about thromboprophylaxis in hip fracture patients, including the findings of the most recent Cochrane review on this topic[19] (section 1.4). In the literature search, one randomised controlled trial comparing thromboprophylaxis with placebo was identified which was published after the most recent update of the Cochrane review. Eriksson *et al* showed an apparent protective effect with fondaparinux (a novel pentasaccharide/ heparinoid) with a 95.9% (87.2 to 99.7%) relative risk reduction in combined clinical and radiological TED during the first 32 days following hip fracture admission and an 88.8% (95% CI 67.7 to 100%) relative risk reduction in symptomatic TED[37]. There were a number of limitations to this study. The study did not have a true placebo limb, as all patients received open label LMWH for 6 to 8 days prior to randomisation to fondaparinux or placebo. Overall 42% of those initially recruited were excluded or dropped out of the study. Most importantly, the primary endpoint included the results of mandatory bilateral venography in all patients, so the clinical relevance is unclear. In the control limb of the study, for example, 35% of patients had radiological evidence of DVT, but only 1.8% had clinical evidence of DVT and 0.9% had clinical evidence of PE. The influence of fondaparinux on all-cause mortality was not assessed in this study[37].

Eriksson *et al*'s study does not therefore alter the conclusions of the Cochrane review of thromboprophylaxis in hip fracture, which showed no statistically significant influence of different types of thromboprophylaxis on mortality[19]. Indeed the funnel plot of the studies included in the Cochrane review (figure 2.2) shows evidence of publication bias

favouring studies that suggested a beneficial effect of heparin, with lower precision estimates to the left of the pooled estimate, and more precise estimates to the right.

2.6 Discussion

2.6.1 Objective 1a. To identify the incidence of DVT and PE following hip fracture

There were limited data describing the long-term burden of TED following hip fracture. The considerable variation in estimates of incidence of TED in different studies reflected differences in casemix and methodology. Few studies collected data prospectively and many were studies of the general complications of hip fracture, providing limited detail about TED, including thromboprophylaxis regimes and/or radiological tests. The majority of studies used data collected more than ten years ago and no study of outcomes for the full year after hip fracture included more recently collected data, so the findings may not reflect current practice, particularly with the increase in the use of chemical thromboprophylaxis more recently. Acknowledging these limitations, the incidence of clinically apparent TED in the year following hip fracture is estimated to be around 3%[29;30] (section 2.5.1.1).

TED was relatively common at autopsy. The studies listed in table 2.5 can be divided into two groups: studies in Scandinavian countries where autopsy was performed in the majority of patients (over 60%), and studies in English speaking countries where autopsy is performed infrequently (under 30%, where stated). Scandinavian studies would be expected therefore to have been more representative of all hip fracture patients who died following hip fracture, while the studies from English speaking countries may

be expected to have included more sudden and unexplained deaths, thereby overestimating the burden of fatal PE (see section 1.3). It is therefore interesting to note that the proportion of autopsies identifying PE as the cause of death or contributing factor was high, at between 10-20%, regardless of the autopsy rate. PE therefore appears to have been a common cause of death in the postoperative period, although it should be noted that the findings of these studies may not be relevant to current practice as the data were predominantly collected more than ten years ago, and often many decades ago, before the widespread use of thromboprophylaxis.

The more recent studies identified for the literature review reveal that there remains a discrepancy between radiologically diagnosed TED and clinical events. Eriksson *et al* identified radiological TED in 35% of patients but clinically apparent TED in less than 3%[37]. Thaler *et al* showed that the majority of patients with clinically suspected TED tested negative on venography and/or spiral CT scan[33]. This finding may be explained by the fact that elderly hip fracture patients commonly have a number of other medical conditions leading to leg swelling and/or chest pain and breathlessness that can be mistaken for TED. Such misclassification bias is a problem common to all studies of TED following hip fracture. There is also the possibility that TED may occur silently. If this is the case then TED may be an important but unsuspected cause of morbidity and mortality, and thromboprophylaxis would be expected to have an influence on morbidity and mortality beyond that expected from the observed incidence of TED.

2.6.2 Objective 1b. To identify medical and social factors that have the greatest influence on mortality following hip fracture

The findings of the studies exploring the impact of comorbidities and cofactors on outcomes following hip fracture were plausible, showing higher mortality in older patients, dependent patients and patients with medical comorbidities. There was unfortunately no information about smoking status in these studies. There was considerable heterogeneity in the odds ratios for some medical conditions. Nettleman *et al* identified very high odds ratios for a number of medical comorbidities, including an odds ratio of 32 for patients with congestive cardiac failure[44]. These findings may be explained by the fact that the medical comorbidities were identified using records relating to the hip fracture admission. Events identified during the admission may have progressed to contribute to the patient's death within that same admission, so these findings could be biased.

There was also considerable heterogeneity in the prevalence of some medical conditions in the different studies listed in table 2.7, with an almost ten-fold difference in the reported prevalence of diabetes and dementia across studies. The wide range of estimates reflects differences in the design and recruitment to studies, and the age of the population.

2.6.3 Objective 1c. To update the findings of previous reviews of thromboprophylaxis in hip fracture

As identified in the most recent Cochrane review of hip fracture and thromboprophylaxis[19] there remains a shortage of adequately powered studies exploring the effect of thromboprophylaxis on mortality. Results from the one randomised

controlled trial identified in this literature review suggested a large reduction in TED with fondaparinux[37] but there is to date no evidence of a survival benefit with this treatment[5].

The possibility of publication bias in the papers published on the effect of heparin on mortality following hip fracture may be of importance when comparing the findings of the analysis presented in chapter 5 with the published literature. However it should be noted that funnel plots such as the one shown in fig 2.2 are a relatively crude approach in the detection of publication bias[46].

2.7 Studies published after completing the literature review

One prospective cohort study published after completing the literature review provides additional relevant information. Roche *et al* followed up hip fracture patients admitted between 1999 and 2003 (n=2448, mean age 82) for a year in order to study the influence of a number of cofactors and comorbidities on mortality. Previously diagnosed CVD was not found to have a statistically significant effect on mortality in multivariate analysis, but this finding was perhaps explained by the strong effect of cardiac failure postoperatively (HR 5.0; 95% CI 3.9 to 6.5), an observation that has parallels with the discussion around Nettleman *et al*'s study in section 2.6.2. A minority of patients (10%) were recorded as being current smokers, but smoking status did not appear to influence mortality in either univariate or multivariate analysis. This provides information that was missing in the papers identified for the literature review. All patients received LMWH as thromboprophylaxis. Clinically apparent TED was

identified during the inpatient stay in 1.7% (95% CI 1.2 to 2.2) of patients, each of whom underwent radiological testing to confirm the clinical diagnosis[47].

2.8 Grey literature published after completing the literature review

The House of Commons Health Committee produced a report in 2005 about thromboprophylaxis in hospitalised patients[48]. The report provides expert opinion about use of thromboprophylaxis in different contexts.

Mr David Warwick summarised the evidence for and against different types of thromboprophylaxis in orthopaedic surgery for the Health Committee, on behalf of the Royal College of Surgeons. His advice contrasts with that of the most recent SIGN guidelines on hip fracture[3] but concurs with the most recent American College of Chest Physicians guidelines[5] by recommending against use of aspirin and advising use of LMWH as thromboprophylaxis. SIGN has specifically addressed the difference between the advice in its own guidelines and that of the American guidelines in the most recent SIGN guideline on thromboprophylaxis[18]. However, as identified earlier, there are insufficient data in existing trials to prove or disprove a survival benefit with aspirin, heparin or different types of mechanical thromboprophylaxis following hip fracture[19;20]. Warwick also stated that, in the case of fondaparinux, "risk reductions presented for DVT are enticing"[48]. However, as identified in section 2.5.3, existing trials with fondaparinux are based on clinical and radiological evidence of TED rather than survival.

A manufacturer of graduated elasticated compression stockings and other mechanical devices also provided evidence to the Health Committee. They presented an argument

for the use of mechanical thromboprophylaxis based on the theoretical influence on the pathogenesis of TED using Virchow's triad, and trial evidence-based on clinical endpoints rather than survival.

In summary, while the House of Commons Health Committee report does not add to the evidence base for thromboprophylaxis following hip fracture, it reinforces that thromboprophylaxis is, as stated at the beginning of Warwick's evidence, "a controversial and changing topic"[48].

2.9 Implications of the findings of the literature review for the design of the study described in subsequent chapters

Estimates of the incidence of TED from the literature review can be used to estimate the sample size required to detect a treatment effect of thromboprophylaxis on secondary outcomes for use in chapter 5 (see section 1.9 for the equivalent calculation for all cause mortality). The Cochrane review of thromboprophylaxis in hip fracture patients identified a 40% relative risk reduction in DVT with heparin, but there were insufficient data to provide the equivalent estimate for PE[19]. With an estimated incidence of TED of 3% during the year following hip fracture[29;30], the estimated sample size to detect a 40% reduction in TED with heparin is 2500 per study limb (alpha = 5%, power = 80%)[26]. However, based on earlier work, the incidence of TED following hip fracture identified using SMR data is between 1 and 2%[25], so the required sample size may be substantially higher. The sample size for different types of thromboprophylaxis including aspirin and GEC stockings is also likely to be higher as fewer patients are documented as receiving these types of thromboprophylaxis than heparin in the SHFA database[25].

Chemical thromboprophylaxis, including heparin and aspirin, may also influence cardiovascular outcomes following hip fracture. Including these outcomes in the secondary endpoint would increase the statistical power of the study. In the studies identified in the literature review, Gerber *et al* identified cardiovascular events in 8% of patients in the year following hip fracture[29], Vajanto identified myocardial infarction (MI) in 1.5% and cerebral infarct in 1.2% of patients respectively[30], while the results of autopsy studies suggest that about one quarter of hip fracture deaths are attributable to TED or MI in the first three months following hip fracture (table 2.6).

Ideally, all cardiovascular events would be included in the analysis described in subsequent chapters. However, the consequences of using chemical thromboprophylaxis on the two most common types of stroke (thrombotic and haemorrhagic) are very different, and details about the type of stroke are often incomplete in the SMR database[25]. As a result the only type of CVD included in the secondary endpoint is coronary heart disease (CHD) – combined deaths and inpatient episodes due to MI or angina.

Fatal haemorrhage was rare both in clinical studies (0.1% at up to 3 months follow up[33;34]) and autopsy studies (2.8% autopsies – table 2.6), regardless of whether the studies were conducted prior to the widespread use of thromboprophylaxis or in later studies where thromboprophylaxis was used in the majority of patients. Major haemorrhage and use of transfusion were also recorded infrequently. These results are consistent with the findings of the Cochrane review of thromboprophylaxis in hip fracture, which observed no evidence of significant or clinically important excess blood

loss or haemorrhagic events with heparin[19]. A preliminary investigation of Scottish Morbidity Records data also identified that haemorrhagic events were rare in the hip fracture patients studied in subsequent chapters*. Haemorrhagic events will not therefore be included as a secondary outcome in the analysis presented in subsequent chapters.

2.10 Conclusions

There is a lack of recent data about the long-term incidence of TED following hip fracture in the modern era of hip fracture treatment, which will be studied further using SMR data (chapter 3).

The literature review has identified a number of cofactors and comorbidities that have an important influence on morbidity and mortality following hip fracture. The majority of these factors are included in SMR (chapter 3) and/or SHFA data (chapter 4).

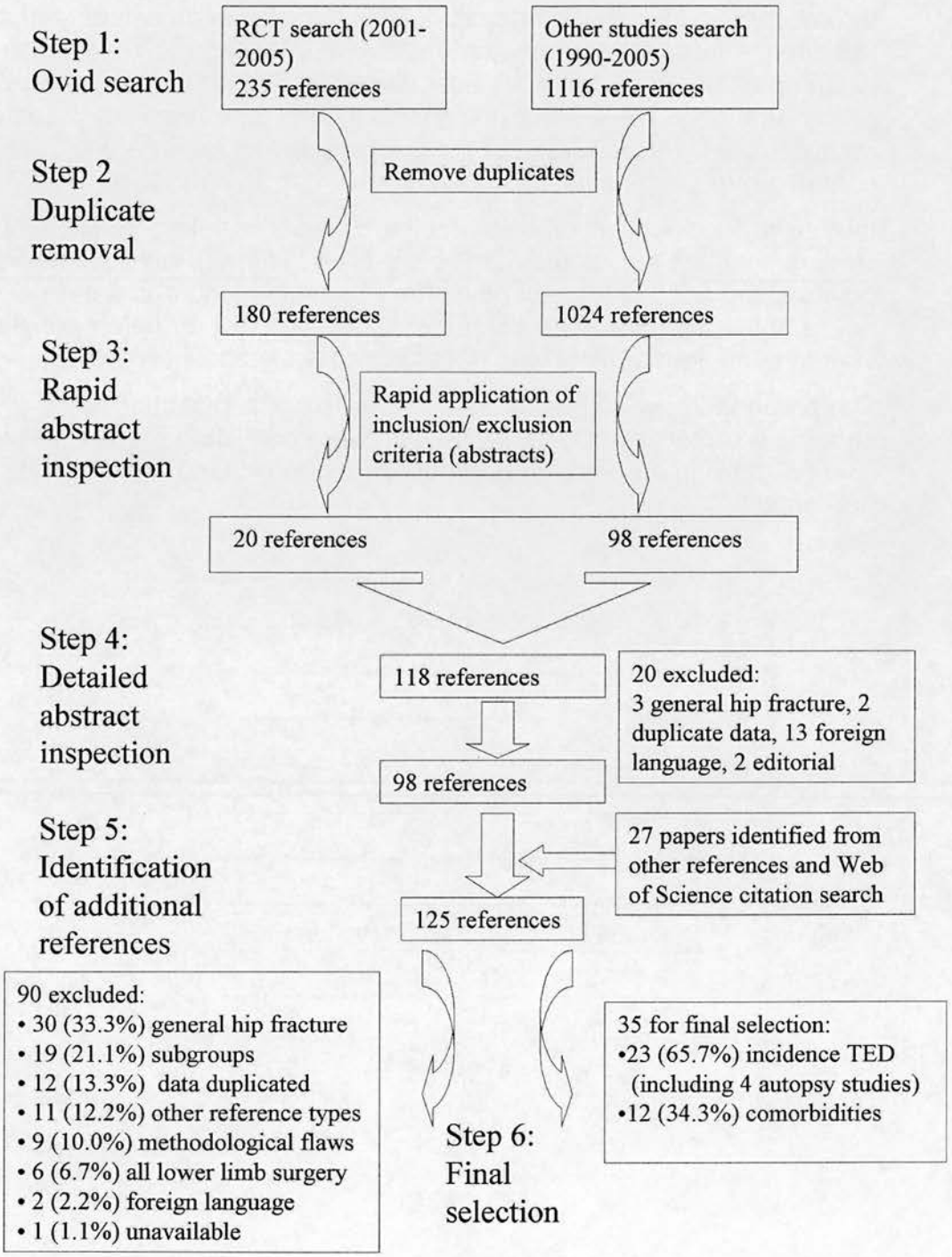
There remains limited information about the effectiveness of different types of thromboprophylaxis over placebo in reducing mortality following hip fracture. The

* Haemorrhage (gastrointestinal, intracerebral or general haemorrhage) was identified during the index admission with hip fracture or in death records during the year following hip fracture admission in 86/8470 patients (1.02%; 95% CI 0.80 to 1.23%).

findings of the analysis presented using SHFA data (chapter 4) and linked SHFA-SMR data (chapter 5) may therefore provide evidence that is not available from the existing published literature.

2.11 Figures and tables

Figure 2.1 Selection of studies in the literature review



At stage 6, "other reference types" include letters, reviews and comment.

Figure 2.2 Funnel plot of studies of the influence of heparin on mortality in hip fracture patients identified in the Cochrane review of thromboprophylaxis in hip fracture

The funnel plot shown uses data from the Cochrane review of thromboprophylaxis in hip fracture[19]. The plot shows an estimate of the treatment effect with heparin (log (relative risk)) along the x-axis against an estimate of the precision of the estimate (standard error of log (relative risk)) along the y-axis. The vertical line shows the log of the pooled estimate of relative risk. Overall, 42/356 of the group receiving heparin and 38/374 of the control group died – equivalent to a relative risk of 1.16 (95% CI 0.77 to 1.74).

If there was no publication bias and there was little heterogeneity between studies, then the plot would resemble a filled in funnel, with a wide spread of points at the base of the plot (low precision estimates), and a narrow spread of points at the top (high precision estimates). The test for heterogeneity using a standard chi-squared test was not statistically significant (χ^2 =0.16, p=0.69).

The preponderance of points on the left side of the plot suggests that studies showing a protective effect with heparin were published preferentially, and that studies showing a neutral or harmful effect with heparin were less likely to be published.

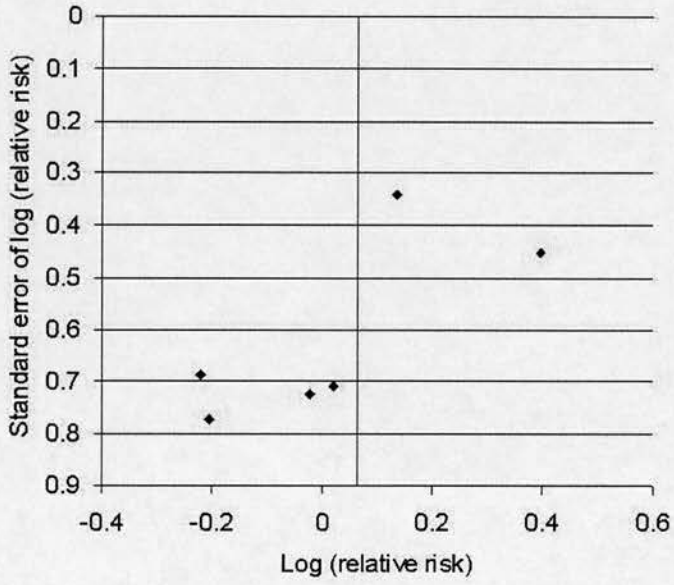


Table 2.1 Inclusion and exclusion criteria used at stage 4 (rapid assessment) and stage 6 (detailed assessment) of literature review (see also figure 2.1)

Objectives 1a (incidence of TED) and 1b (identification of demographic, medical and social factors that may influence outcome following hip fracture)		
Inclusion criteria	**Exclusion criteria**	**For more detailed inspection (stages 4 & 6)**
• Well-designed studies of general hip fracture population (randomised controlled trials, cohort studies, cross sectional studies).	• Studies with high probability of confounding or bias. • Reviews. • Arthroplasty and other types of elective orthopaedic surgery. • In vitro studies.	• Include only studies with clear documentation about the population being studied (including age and gender) and the way that TED was identified (clinical, laboratory or radiological). • Give preference to studies that clearly document whether patients received thromboprophylaxis or not.
Objective 1c. Interventions aimed at reducing the burden of TED following hip fracture		
Inclusion criteria	**Exclusion criteria**	**For more detailed inspection (stages 4 & 6)**
• Well-designed randomised controlled trials in hip fracture patients, comparing patients receiving chemical or mechanical thromboprophylaxis with control group.	• Studies with high probability of confounding or bias. • Reviews. • Arthroplasty and other types of elective orthopaedic surgery. • In vitro studies. • Studies comparing one method of chemical thromboprophylaxis with another.	• Include only those studies with clear documentation about that population being studied (including age and gender) and the way that TED was identified (clinical, laboratory or radiological).

Table 2.2 Studies where patients were recruited prospectively and the aim was to study TED or medical complications following hip fracture

CT = Computerised tomography scan, ♀ = female, ♂ = male, # = fracture, sd = standard deviation.

Authors, country and year of publication of study	N patients	DVT N (%)	PE N (%)	TED N (%)	Thrombo-prophylaxis	Study design	Radiology	Duration of follow-up	Mean age in years (range)	Notes – including potential sources of bias
Dahl et al[49] Norway 2003	1907		28 (1.5)		All patients received LMWH on admission	Prospective study using data from patients admitted to a single hospital between 1989 and 1998, to identify the incidence of PE following major orthopaedic surgery	Ventilation perfusion scan +/- spiral CT	6 mnths	81 (29-90)	Numbers stated here are for hip fracture only. Included some young patients. 14 (50%) PE developed following discharge. Assumed that patients would be re-admitted to the same hospital with PE.
Gerber et al[29] Switzerland 1993	397		13 (3.3)		45% of patients received un-fractionated heparin until mobilised	Prospective register collected between 1972 and 1988, used to compare outcomes between age groups.	Not stated	1 year	79 (60 and over)	Examination at 1 year. Cardiovascular outcomes recorded in 32 patients (8.1%)

Authors, country and year of publication of study	N patients	DVT N (%)	PE N (%)	TED N (%)	Thrombo-prophylaxis	Study design	Radiology	Duration of follow-up	Mean age in years (range)	Notes – including potential sources of bias
Thaler et al[33] Austria 2001	897	5 (0.6)	2 (0.2)		All patients received LMWH from admission	Prospective study of consecutive patients admitted between 1997 and 1999 looking at TED and haemorrhagic outcomes.	Veno-graphy or CT scan	Hip # adm-ission	Mean 82 ♀, 71 ♂. Range 19-101	Some young patients. High proportion of CHD (50%), diabetes (44%), malignancy (10%), dementia (7%). Numbers stated here exclude the patients who did not receive LMWH.
Tjeenk et al[50] Netherlands 2001	268	2 (0.7)			Not stated	Prospective study conducted between 1996 and 1998 looking at complications following hip fracture.	Not stated	Hip # adm-ission	81 (range 24-97)	Some young patients.
Todd et al[31] UK 1995	580		13 fatal PEs (2.2)	31 (5.3)	46% of patients received chemical thrombo-prophylaxis	Prospective audit of mortality following hip fracture conducted between 1996 and 1997.	Not stated	90 days	80.3 (sd 10.4)	8 patients lost to follow up.

Table 2.3 Retrospective studies (using medical records unless otherwise stated) where aim was to study TED or medical complications following hip fracture. See table 2.2 for abbreviations

Authors, country and year of study	N patients	DVT N (%)	PE N (%)	TED N (%)	Thrombo-prophylaxis	Study design	Radiology	Duration of follow-up	Mean age in years	Notes – including potential sources of bias
Barrett et al[27] USA 2003	32286		511 (1.6)		Not stated	Retrospective study using data collected between 1986 and 1990 to identify incidence of PE following hip fracture	Not stated	90 days	82 (sd 7.6)	Medicare bill based analysis. Contacted authors for additional information. Old data
Ennis[34] USA 2003	939	5 (0.5)	1 (0.1)		94% of patients received TP (mechanical or chemical)	Retrospective study using data collected between 1995 and 1999 to identify the incidence of TED following hip fracture	Ultrasound or ventilation perfusion scan	3 mnths	83 ♀ (range 50-104), 78 ♂ (range 16-98)	Includes some younger patients. 61 patients excluded due to missing information.
Larsson et al[51] Sweden 1990	563	10 (1.6)	11 (1.8)		47% of patients received dextran	Retrospective study using data collected between 1976 and 1985 to identify complications following hip fracture	Veno-graphy or ventilation-perfusion scan	Hip # adm-ission	76 (range 22-92)	607 fractures. Includes some younger patients and about 1/3 were men.

Authors, country and year of study	N patients	DVT N (%)	PE N (%)	TED N (%)	Thrombo-prophylaxis	Study design	Radiology	Duration of follow-up	Mean age in years	Notes – including potential sources of bias
Lawrence et al[32] USA 2003	8930			89 (1.0)	Not stated	Retrospective study using data collected between 1982 and 1993 to identify medical complications following hip fracture	Ultra-sound, venogram, ventilation-perfusion scan or pulmonary angiogram	Hip # admission	80.2	Provides detailed information (including diagnostic information) about medical problems identified during the hip fracture admission.
Ollendorf et al[28] USA 2002	38269	314 (0.8)	205 (0.5)		Not stated	Retrospective study using data collected between 1998 and 1999 looking at TED following orthopaedic surgery.	Not stated	Hip # admission	N/A	Used information recorded in discharge summary. Age and gender not provided for hip fracture patients on their own.
Vajanto et al[30] Finland 1998	329	5 (1.5)	7 (2.1)		All patients given LMWH pre- and post-op	Retrospective study using data collected between 1990 and 1993 to study complications following hip fracture	Not stated	Average 58 weeks	77.8 (range 29-94)	334 fractures. Includes some younger patients.

Table 2.4 Other studies that provided data about TED following hip fracture

See table 2.2 for abbreviations

Authors, country and year of study	N patients	DVT N (%)	PE N (%)	Thrombo-prophylaxis	Study design	Radiology	Duration of follow up	Mean age (years)	Notes – including potential sources of bias
Bettelli et al[35] Italy 2004	493	5 (1.0)		Heparin on admission	Prospective study of risk factors associated with mortality (1990 to 1999)	Ultrasound	Not clearly stated	81-82 (range 65-96)	Data for DVT likely to be for the hospital admission but this is not clearly stated.
Eriksson et al[37] Denmark 2003	656	7 (1.1)	2 (0.3) 1 fatal (0.2)	Open label LMWH prior to randomisation	Double blind RCT (LMWH versus placebo) conducted between 2001 and 2002	Extensive radiological investigation as part of RCT	32 days	79 (range 23-96)	Number of exclusions and drop-outs including previous TED. Included younger patients and more men than expected (28%).
Gregory et al[52] UK 1992	46	1 (2.2)	1 (2.2)	Not stated	Prospective study of functional status conducted between 1986 and 1997	Venography or ventilation-perfusion scan	Hip # admission	Range 65-79	Only 10% male, exclusions included dementia and poor mobility.

Authors, country and year of study	N patients	DVT N (%)	PE N (%)	Thrombo-prophylaxis	Study design	Radiology	Duration of follow up	Mean age (years)	Notes – including potential sources of bias
Lykke et al[53] Norway 2002	278	2 (0.7)		LMWH on admission	Randomised trial of orthopaedic tech-nique (1997 to 1998)		Hip # adm-ission	81 (range 56-96)	9 patients declined to participate.
Parker et al[36] UK 2002	455	6 (1.3)	4 (0.9)	Not stated	Randomised trial of orthopaedic technique conducted (1991 to 2001)	Not stated	Hip # adm-ission	82.3 (range 71-103)	Excluded patients younger than 71.
Roberts et al[54] UK 2004	730	16 (2.2)	9 (1.2)	Not stated	Prospective audit of care pathway conducted between 1998 and 2001	Not stated	Hip # adm-ission	83 (sd 7)	More men than exp-ected (23.4%). Teaching hospital. Excluded patients with previous/ multiple fractures.
Shabat et al[38] Israel 2003	191	1 (0.5)		Not stated	Retrospective study of the consequences of operative delay	Not stated	Hip # adm-ission	81 (men), 77 (women)	Almost 30% men - who were older than the women.
Zuckerman et al[39] USA 1992	491		7 (1.4)	All patients received dextran or aspirin	Prospective study of interdisciplinary hospital care programme conducted in 2000	Not stated	Hip # adm-ission	80.3	Excluded patients unable to participate in the programme.

Table 2.5 Autopsy studies providing data about the proportion of deaths attributable to PE following hip fracture

Study	Description	Period of follow up	Autopsy rate n/N (%)	Fatal/ major PE at autopsy n/N (%)
Bergqvist et al Sweden 1991[55]	Prospective study of 806 hip fracture patients admitted to hospital between 1986 and 1988	Up to 3 months	42/66 (63.6)	8/42* (19.0)
Parvizi et al USA 2004[56]	Retrospective study of 7774 hip fracture patients admitted to hospital between 1969 and 1997	30 days	54/186 (29.0)	6/54 (11.1)
Perez et al UK 1995[57]	Retrospective review of autopsy reports of 581 hip fracture patients who died between 1953 and 1992	N/A	N/A	80/581 (13.8)
Schroder et al Denmark 1993[58]	Prospective study of 1812 hip fracture patients admitted to hospital between 1969 and 1983	90 days	180/273 (65.9)	27/180# (15.0)

* 3 fatal PE, 5 contributed to death. Median time to death 31 days.

The majority of fatal PE occurred in the first 30 days.

Table 2.6 All causes of death identified at autopsy in patients with recent hip fracture[55-57]

Diagnostic category	Diagnosis	Number of cases	% (95% CI)
Non haemorrhagic/ thrombotic complications	**Bronchopneumonia**	290	42.8 (39.1 to 46.6)
	Congestive cardiac failure	97	14.3 (11.7 to 17.0)
	Not known/ other	40	5.9 (4.1 to 7.7)
	Sepsis	27	4.0 (2.5 to 5.5)
	Stroke (other)*	3	0.4 (0 to 0.9)
	Multiple	15	2.2 (1.1 to 3.3)
	Renal failure	9	1.3 (0.5 to 2.2)
	Cancer	2	0.3 (0 to 0.7)
	Fat embolism	1	0.1 (0 to 0.4)
TED/ other thrombotic complications	**Pulmonary embolism**	89	13.1 (10.6 to 15.7)
	Myocardial infarction	71	10.5 (8.2 to 12.8)
	Stroke (thrombotic)	11	1.6 (0.7 to 2.6)
	Other arterial thrombosis	3	0.4 (0 to 0.9)
	Total thrombosis	174	25.7 (22.4 to 29.0)
Haemorrhagic complications	**Erosive gastritis/ gastrointestinal bleed**	13	1.9 (0.9 to 3.0)
	Aneurysm	4	0.6 (0 to 1.2)
	Stroke (haemorrhagic)	2	0.3 (0 to 0.7)
	Total haemorrhage	19	2.8 (0 to 4.1)
Total		**677**	**100.0%**

* This category was used when it was not clearly stated whether the stroke was haemorrhagic or thrombotic.

Table 2.7 Common medical problems documented prior to hip fracture admission

There was considerable heterogeneity between papers so the figures shown are the median proportion of the different papers and the range.

Group	Condition	Median (%)	Range (%)	References
Diseases of the heart and circulation	**Ischaemic heart disease**	36.4	17.7 to 50.3	32;33;39;59
	Congestive cardiac failure	11.7	7.6 to 15.8	32;59;63;64
	Stroke	9.7	8.1 to 19.2	32;59
	Myocardial infarction in the 6 months prior to hip fracture	4.1		51
Other conditions	**Diabetes**	10.4	5.9 to 43.9	33;39;51;59;61; 63;64
	Dementia	10.0	4.5 to 39.6	30;32;33;51;64
	Respiratory disease	10.0	4.3 to 14.9	32;39;51;59-64
	Cancer	8.5	1.2 to 12.0	30;33;51;59; 60;63;64

3 Scottish Morbidity Records (SMR)

3.1 Introduction

The literature review (chapter 2) has demonstrated the association between various patient factors, social factors and medical comorbidities on outcome following hip fracture. Routinely collected hospital discharge records provide one potential method of identifying medical comorbidities in hip fracture patients. Changes in the quality of these data over time are explored. The identification of variables that have been collected consistently over time provides the opportunity to test whether hip fracture outcomes have changed with the introduction of modern treatment. Subsequent chapters focus on the analysis of a subgroup of SHFA participants with complete SHFA and SMR data admitted with hip fracture between 1998 and 2003 (see section 4.4.1). Data from the complete SMR extract collected during the same period is used to compare the characteristics of this subgroup of SHFA participants, to assess the representativeness of these patients.

3.2 Background

SMR records are routinely completed for each inpatient episode under the care of a consultant in NHS hospitals in Scotland. SMR records can be linked together for individual patients, allowing the study of continuous inpatient stays under the care of successive hospital consultants. Additionally, SMR data are now linked to the cancer register and mortality records. Using the postcode of the patient, it is also possible to link to area-based measures of socio-economic status.

SMR data are collected for administrative purposes. In the 1990s there was an increase in the accuracy of the data collected. Reasons for this increase in accuracy included the

introduction of a Data Quality Assurance team at the Information Services Division (ISD) of National Services Scotland in 1990[65], and the introduction of the Internal Market in 1991. The Internal Market depended on high quality information to allow the calculation of costs for reimbursement and commissioning purposes. The Internal Market was, however, short lived, ending with legislation passed in 1998[66]. While earlier work has shown the increased detail available from SMR records for hip fracture patients during the period of the Internal Market[25], it is not clear whether this trend has reversed since the dissolution of the Internal Market. SMR data also provide data about outcome, by linking to subsequent inpatient episodes and death records. Using SMR data, therefore, it is possible to study the influence of comorbidities on long-term outcomes. Combining these findings with those presented for SHFA participants in chapter 4 allows comprehensive adjustment for multiple cofactors and comorbidities, as detailed in chapter 5.

The first national evidence-based hip fracture guideline in Scotland was published by SIGN in 1997[17]. The publication of this guideline in July 1997 and its dissemination at a national hip fracture conference in August 1997 pinpoints the time at which thromboprophylaxis and other aspects of modern hip fracture care were first documented on a national basis in Scotland. The recommendations of these new guidelines were audited using a new expanded SHFA form from the start of 1998. Nonetheless, SHFA reports published since 1998 have shown variable uptake of the advice given in successive hip fracture guidelines in hospitals across Scotland[67]. The impact of this move to an audited evidence-based approach for hip fracture care on outcomes for patients has not been studied previously.

3.3 Rationale

3.3.1 Objective 2a. To assess the quality and reliability of SMR data collected for hip fracture patients between 1986 and 2003

The quality and reliability of SMR data collected for patients admitted with hip fracture between 1986 and 2003, is explored in order to identify the variables most suitable for inclusion in the analysis of the linked SHFA–SMR database in chapter 5.

3.3.2 Objective 2b. To assess how survival following hip fracture has changed since the publication of the first hip fracture guideline, using SMR data collected between 1986 and 2003

The evidence-based approach to hip fracture care documented in hip fracture guidelines[17;18] should have resulted in an improvement in outcomes. However, over the past twenty years, the age and comorbidities of patients at the time of hip fracture have increased. Using the results presented for objective 2a, survival following hip fracture is modelled, adjusting for age, sex and other comorbidities and cofactors.

3.3.3 Objective 2c. To assess the representativeness of a subgroup of SHFA participants using SMR data collected between 1998 and 2003

In this chapter, SMR data for all hip fracture patients admitted between 1998 and 2003 (n=34012) are used to assess the representativeness of a subgroup of SHFA participants (n=8470), comparing demographics, comorbidities and outcomes. Since this subgroup of patients is studied in further detail in subsequent chapters, this analysis tests how well the findings of subsequent chapters can be generalised to the elderly hip fracture population in Scotland.

3.4 Methods

3.4.1 Participants

Figure 3.1 shows the number of patients included in the various analyses presented in this thesis. Cases were identified as "the first discharge for a patient aged 60 years and over with a principal diagnosis of Fractured Neck of Femur for 1986-2003 in a non-obstetric, non-psychiatric Scottish Hospital", using the following codes for hip fracture (International Classification of Diseases (ICD)-9 code 820 or ICD-10 code S72.0-S72.2). Private hospitals do not return SMR records and patients treated for hip fracture in these institutions are therefore not included in this analysis. Data were available for 93520 patients aged 60 years and over admitted with a primary diagnosis of hip fracture between 1986 and 2003 inclusive.

There were 34012 patients aged 60 and over recorded with hip fracture in the SMR database between 1998 and 2003 inclusive. More detailed analysis of SMR data was performed for a subgroup of SHFA participants (n=8470) admitted between 1998 and 2003 (section 4.4.1), representing 25% of hip fracture patients admitted between 1998 and 2003.

3.4.2 Ethical and privacy considerations

Analysis was performed according to current ethical and legal guidelines. SMR data were anonymised following record linkage and prior to analysis. The study protocol was discussed with the Caldicott Guardian of National Services Scotland. The record linkage between SMR and SHFA databases was approved by the Privacy Advisory Committee of National Services Scotland.

3.4.3 Data collection

SMR data are collected routinely at the time of hospital discharge. Coding staff based in hospitals use medical notes and consultant discharge letters to identify up to six diagnostic codes per hospital discharge. Each consultant episode results in an SMR discharge record. For example, a patient admitted to a general medical ward, transferred to orthopaedics and discharged via a rehabilitation ward will have three separate discharge records completed for that particular continuous inpatient stay. The data recorded in the SMR database include the name, address, age and sex of the patient, dates of admission and discharge, hospital, ward and speciality, a primary diagnosis and up to five secondary diagnoses, and postcode. Data are then collected centrally and quality assurance checks are carried out by the Data Quality Assurance team at ISD which checks 1% of SMR returns. Most recently the accuracy rate for the main diagnosis was 88%, but this has varied during the period 1990 to 2003[65].

3.4.4 Record linkage

Analysts at ISD have developed considerable experience in linking SMR records, as has been described elsewhere[68]. The process of record linkage aims to bring together all records for the same person, using probability matching to correct for factors that may hinder the process including name changes, moving house and human error in entering patient details. Automated algorithms have been developed that first produce a code (New York State Intelligence Information System) and then compress the name (Soundex) to circumvent problems with spelling. Records with similar blocks of information such as Soundex code, postcode and age are brought together and then matched in pairs within these blocks using probability matching. Thus, to continue the example from section 3.4.3, the three separate records would, following record linkage,

be considered together as a continuous inpatient stay. The record linkage for this study used the approach laid out in figure 3.2.

The SMR records for each hip fracture patient were linked to SMR records for the five years prior to the hip fracture admission and one year subsequent to the hip fracture admission. Up until 1981, SMR used ICD-8, which does not map adequately to subsequent coding systems (ICD-9 and ICD-10). As a result, the earliest date of study was chosen as the start of 1986, allowing the study of previous inpatient episodes for five years using ICD-9. The latest date of study (end of 2003) was chosen because the end of 2004 was the last date for which complete SMR data were available from all NHS Trusts in Scotland, providing outcomes up to one year following the date of the hip fracture admission for each patient.

3.4.5 Data coding and extraction

Extraction and coding was performed following record linkage during July and August 2005. SMR records linked to the hip fracture admission were searched using a computer programme written by analysts at ISD. Primary and secondary diagnostic positions were searched using ICD codes listed in table 3.1*. Cancer register data were

* ICD-9 codes were used between 1982 and end of March 1996 in SMR and between 1982 and end of December 1999 in GRO death records. Thereafer ICD-10 codes were used.

also searched for common types of cancer (excluding skin cancers other than melanoma) and cancers that are known to metastasise to the bone (table 3.2).

Diagnoses recorded during inpatient episodes in the five years prior to hip fracture were searched to identify factors that may influence outcome following hip fracture, as identified for the literature review (objective 1b). Examples of conditions that have previously been shown to be associated with an adverse outcome include a prior diagnosis of heart disease, respiratory disease, cancer and dementia. Secondary diagnoses recorded during the index admission with hip fracture were also searched to document pre-existing or concurrent medical conditions.

The SMR database also provides some information about social factors, in the form of the Scottish Index of Multiple Deprivation (SIMD) which is assigned to individuals based on their postcode[69]. This provides information on area-based measures of deprivation using 31 indicators from six domains: current income, employment, housing, health, education, skills and training and geographic access to services and telecommunications. The information is based on data from a range of administrative data collected by a number of central government departments, local government and agencies including ISD. Data are available for 6505 "data zones" ranked in order of deprivation, and are expressed in deciles of SIMD score in the SMR database.

Outcomes in the year following hip fracture admission were identified in two ways. All-cause mortality (the primary endpoint) was identified from General Register Office Scotland (GROS) records that are routinely linked to SMR. The secondary endpoint was identified by searching GROS and SMR records for deaths and/or inpatient episodes with CHD or TED.

3.4.6 Statistical analysis

Statistical analysis was performed in Statistical Package for the Social Sciences (SPSS version 11.5). Continuous variables were grouped as follows: for age, patients aged 60 to 69 years, 5-year groupings for patients aged 70 to 89 years, and 90 years and over; for number of inpatient episodes in the five years prior to hip fracture, in groupings of 0 episodes, 1 episode, 2-3 episodes, 4-7 episodes and 8+ episodes.

The independent samples T test was used to compare means for continuous variables in two groups. Analysis of variance was used to compare means for continuous variables in more than two groups. The chi squared (χ^2) test was used to compare proportions between two or more groups, testing for trend where appropriate. Where distributions were highly skewed (for example the number of inpatient episodes and bed days spent in hospital over the five years prior to hip fracture admission), further statistical analysis was not attempted. Comparisons of patients included in SHFA and SMR data between 1998 and 2003 did not include testing for statistical significance because the majority of patients recorded in SHFA were also recorded in SMR, so these were not independent samples.

Cox proportional hazards regression analysis was performed using the forward conditional method, checking for the assumption of proportional hazards using the log minus log plot, and testing for interaction between age category, sex, and number/ type of prior inpatient episodes for medical reasons. The outcome used in the Cox proportion hazards regression analysis described in this chapter was all-cause mortality at up to 365 days following the date of hip fracture admission identified from General Register Office Scotland (GROS) records linked to SMR.

3.5 Results

3.5.1 Objective 2a. To assess the quality of SMR data collected for hip fracture patients between 1986 and 2003 (n=93520)

3.5.1.1 Characteristics of hip fracture patients admitted between 1986 and 2003

Between 1986 and 1998 the number of hip fractures increased from 4380 to 5644 hip fractures per annum, a 29% increase. Since 1999, however, the number of hip fractures in Scotland per year has not increased, with a mean of 5674 fractures (range 5562 to 5816) per annum between 1999 and 2003.

The mean age of patients at hip fracture increased slightly from a mean of 79.9 years (95% confidence interval (CI) 79.8 to 80.0) between 1986 and 1991, 80.5 years (95% CI 80.4 to 80.6) between 1992 and 1997, and 80.9 years (95% CI 80.4 to 80.5) between 1998 to 2003 ($p<0.001$). Men were on average 3.3 years (95% CI 3.2 to 3.4 years) younger than women at the time of hip fracture ($p<0.001$). The proportion of males increased slightly from 18.6% between 1986 and 1991, to 20.2% between 1992 and 1997 and 21.8% between 1998 and 2003 ($p<0.001$).

3.5.1.2 Outcomes following hip fracture

Between 1986 and 2003 there were 28112 deaths (representing 30% of all hip fracture patients) recorded in the year following hip fracture admission. The crude mortality rate at a year following hip fracture increased slightly over time, from 29.6% (95% CI 29.1 to 30.1%) between 1986 and 1991, 29.8% (95% CI 29.3 to 30.3%) between 1992 and 1997, and 30.7% (95% CI 30.2 to 31.1%) between 1998 and 2003 ($p=0.003$). Mortality one year after hip fracture admission was higher in men than women at 39.2% (95% CI

38.5 to 39.9%) and 27.7% (95% CI 27.4 to 28.1%) respectively (p<0.001). Mortality did not change significantly over time for men, but increased for women from 27.3% (95% CI 26.8 to 27.9%) between 1986 and 1991, to 27.5% (95% CI 26.9 to 28.0%) between 1992 and 1997, and 28.3% (95% CI 27.8 to 28.9%) between 1998 and 2003 (p=0.01).

3.5.1.3 Inpatient episodes in the five years prior to hip fracture

The median number of inpatient episodes in the five years prior to hip fracture increased between 1986 and 2003 from 1 to 2 episodes. The median number of days spent in hospital over the five years prior to hip fracture also increased, from 6 days for patients admitted with hip fracture between 1986 and 1991 to 8 days for patients admitted with hip fracture between 1998 and 2003.

3.5.1.4 Types of previous and current medical problems recorded for hip fracture patients.

Tables 3.3a and 3.3b show the proportion of hip fracture patients with a primary or secondary diagnosis of different groupings of medical diagnoses during the five years prior to hip fracture. Figure 3.3 shows the proportion of patients with a primary or secondary diagnosis of these medical conditions in the five years prior to hip fracture - the proportion of patients with these conditions increased by 91% from 34.9 to 66.7% (p<0.001).

Cancer data presented in tables 3.3a and 3.3b show that there was a 221% increase in coding for prior inpatient episodes where cancer was documented using SMR data between 1986 and 2003. However, using cancer registration data included in the SMR

database, the proportion of patients with previous episodes with any of the cancer types listed in table 3.2 increased by only 14% from 4.1% for the period 1986 to 1991 to 4.7% for the period 1998 to 2003 (χ^2 for linear trend = 10.5, p<0.001).

3.5.2 Objective 2b. To assess how survival following hip fracture has changed since the publication of the first hip fracture guideline, using SMR data collected between 1986 and 2003 (n=93520)

As described above, the crude mortality rate up to a year following hip fracture increased slightly between 1986 and 2003. However, other characteristics of hip fracture patients changed over the same period, including distribution of age, sex and the number of co-existing medical conditions. Cox proportional hazards regression was used to adjust for age, sex and previous inpatient episodes. Results of univariate and multivariate analysis are shown in tables 3.4 and 3.5 and figure 3.4.

Compared to hip fracture patients admitted between 1986 and 1991, unadjusted mortality at a year following hip fracture did not change for hip fracture patients admitted between 1992 and 1998, but increased for hip fracture patients admitted between 1998 and 2003 (hazard ratio 1.04; 95% CI 1.01 to 1.07; p=0.01). However after adjusting for age, sex, number of previous inpatient episodes, inpatient episodes with CVD or respiratory disease, or prior registration with cancer, mortality appeared to reduce over time, with a hazard ratio 0.91 (95% CI 0.89-0.94; p<0.001) for hip fracture patients admitted between 1992 and 1997 and a hazard ratio of 0.87 (95% CI 0.85 to 0.90; p<0.001) for hip fracture patients admitted between 1998 and 2003. The log minus log curves ran closely parallel to each other suggesting that the assumption of proportional hazards with this model was valid. The model showed that age, male sex, and previous cancer registration were the strongest predictors of mortality. There were

significant interactions between age and sex, number of previous inpatient episodes and previous diagnoses, but these did not influence the hazard ratios presented above. The analysis was repeated, replacing previous inpatient episodes with CVD with inpatient episodes with a primary diagnosis of acute MI but this did not influence the hazard ratios presented above. Similarly, including previous inpatient episodes with dementia and/ or diabetes as an additional covariate did not influence the findings.

3.5.3 Objective 2c. To assess the representativeness of a subgroup of SHFA participants using SMR data collected between 1998 and 2003 (n=8470)

A subgroup of SHFA participants admitted between 1998 and 2003 (n=8470) had complete SMR and SHFA data and are compared here with the hip patients identified from the complete SMR extract during the same period.

The subgroup of SHFA participants were older (81.6 years; 95% CI 81.4 to 81.8 years) than hip fracture patients in the complete SMR extract (80.9 years; 95% CI 80.8 to 81.0 years). A higher proportion of the subgroup of SHFA participants were women (80.7%; 95% CI 79.8 to 81.6%) compared with the complete SMR extract (78.2%; 95% CI 77.7 to 78.6%). The geographic distribution of cases was different between the groups with under-representation from more deprived areas such as Greater Glasgow for the subgroup of SHFA participants (figure 3.5). SIMD data recorded in SMR provide further evidence that patients from more deprived areas were under-represented in the subgroup of SHFA participants. For the complete SMR extract, 33533 (98.6%) hip fracture patients had SIMD data available and of these patients 15636 (46.6%) were from SIMD deciles 1-5 (more affluent). All the subgroup of SHFA participants had SIMD data and 4525 (53.4%) were from SIMD deciles 1-5.

Table 3.6 shows a comparison of the number of inpatient episodes with medical conditions in the five years prior to hip fracture for hip fracture patients from the complete SMR extract and the subgroup of SHFA participants. A higher proportion of the SHFA participants had previous inpatient episodes documented than hip fracture patients from the complete SMR extract. Table 3.7 shows that previous inpatient episodes with cardiovascular disease were more common in the subgroup of SHFA participants, but that they were slightly less likely to have had previous inpatient episodes with respiratory disease or cancer registration.

The mortality rate at a year was lower for the subgroup of SHFA participants (29.9%; 95% CI 28.9 to 30.9%) than for hip fracture patients from the complete SMR extract (30.7%; 95% CI 30.2 to 31.1%). The primary causes of death for the 2531 SHFA participants who died in the year following hip fracture admission are listed in table 3.8. The most commonly recorded causes of death following hip fracture were diseases of the heart and circulation (37%) and trauma (18%). Inpatient episodes and deaths recorded for the secondary endpoint are summarised in table 3.9 (3.9a shows hospital inpatient episodes and 3.9b shows deaths). Overall, 7.4% (95% CI 6.9 to 7.8%) of hip fracture patients from the subgroup of SHFA participants had the secondary endpoint recorded during the year following hip fracture, compared to 7.5% (95% CI 7.2 to 7.8%) of hip fracture patients from the complete SMR extract.

3.6 Discussion

3.6.1 Quality of data

Understanding the potential influences on quality of SMR data is central to the analysis presented in subsequent sections and chapters. Consistent with earlier work[25], the proportion of patients with medical comorbidities recorded during inpatient episodes in the five years prior to hip fracture increased during the 1990s (figure 3.3). There were large increases in the documentation of a number of medical conditions including dementia and diabetes, particularly in the secondary diagnostic positions (table 3.3b). While there would have been expected to be some increase in the proportion of patients with these conditions over time as the age of patients at the time of hip fracture increased, a substantial part of the increase is likely to be explained by the changes in recording of routinely collected hospital discharge data. Possible reasons include the introduction of the Internal Market, increased use of computer technology in hospital record management, and changes in medical management. These questions about the quality of data for some medical conditions may explain why inclusion of diabetes mellitus and dementia did not influence the multivariate analysis of trends in hip fracture survival (section 3.5.2).

There were more modest increases in other conditions including inpatient episodes with CVD* or a primary diagnosis of respiratory disease. Cardiovascular conditions such as acute MI, unstable angina or stroke, and respiratory conditions such as pneumonia and acute exacerbation of chronic obstructive pulmonary disease frequently lead to hospitalisation and may therefore have been more accurately recorded than other conditions principally managed in primary care. However, it is difficult to assess the accuracy of these data. Secular trends in CVD suggest that while mortality due to CVD decreased rapidly in men and fell slightly in women during the last two decades[70], the consequences of ischaemic heart disease, including heart failure, are increasing[71]. However, data describing trends in morbidity and inpatient episodes related to CHD in many parts of the UK are limited, particularly for the elderly and for women[72], the groups at highest risk of hip fracture. The relatively large increase in respiratory disease may reflect high smoking rates in Scottish women in the latter half of the twentieth century[73]. Cancer registry data collected during the period of this study has been collected using an extended and quality assured data collection system, based on

* Based on the findings of tables 3.3a and 3.3b this was defined as primary or secondary diagnosis of acute MI or stroke or primary diagnosis of IHD, other heart disease or peripheral vascular disease. There was a 32% increase in the proportion of patients with previous admissions with documentation of CVD, from 17.2% between 1986 and 1991 to 22.7% between 1998 and 2003). This definition did not include surgical codes for coronary artery bypass grafting, and did not include patients admitted as day cases for coronary angioplasty.

notifications from multiple sources, so the accuracy of cancer diagnoses is likely to have been high[74].

The primary endpoint, all-cause mortality, is likely to have been recorded accurately, as death certification is required by law. The secondary endpoint was studied in order to explore the influence of thromboprophylaxis on CHD and TED. However these outcomes are likely to have been less accurately identified or recorded than all-cause mortality. The quality of recording for primary and secondary endpoints is considered further in chapter 5.

3.6.2 Trends in mortality following hip fracture

The data presented in tables 3.4 and 3.5 illustrate the importance of adjusting for cofactors and comorbidities. In univariate analysis, mortality following hip fracture appeared to increase over time. However, after adjusting for age, sex and comorbidities in multivariate analysis, mortality following hip fracture appeared to fall over time. While the cofactors and comorbidities included in the analysis have been shown in the literature review to be important in predicting hip fracture outcomes, there remains the possibility of residual confounding.

The apparent fall in adjusted mortality over time may be explained by evidence-based changes to medical, anaesthetic and/ or surgical management. However mortality following hip fracture remains high and the challenge now is to maximise the use of interventions that have the greatest impact on mortality. Unfortunately many randomised controlled trials study surrogate endpoints and are underpowered to detect an influence on mortality. In the case of TED following hip fracture, for example, firm recommendations cannot be made about thromboprophylaxis regimes based on existing

evidence as discussed in the literature review. Therefore, despite publication of national hip fracture guidelines and evidence of a reduction in mortality in this study, further adequately powered studies of survival following hip fracture survival are required.

Cox proportional hazards regression analysis, used in the study of trends in mortality in this chapter, also forms the basis of statistical analysis in subsequent chapters. Cox proportional hazards regression analysis uses the time from hip fracture admission to death, providing an instantaneous estimate of the hazard ratio at all time points. The technique depends on the assumption that the reduction in hazard is the same at all time points, whether during the period immediately following surgery when mortality rates were likely to have been high, or during the period of recuperation when mortality rates were likely to have started to decrease. This assumption was tested by examining the log minus log plot, which, in this analysis, showed that the assumption of proportional hazards was valid. A number of models were fitted to the data, testing for interactions between variables. There were therefore a number of benefits to using Cox proportional hazards regression analysis: it used all the available information including time to outcome, allowed sophisticated adjustment for a number of cofactors and comorbidities, and was quick to perform in SPSS. Alternative approaches such as logistic regression would not have used some of the information available (time to event), while the

analysis required to perform a cohort study would be time consuming and would have had less statistical power as patients would need to be matched for other comorbidities and cofactors*.

3.6.3 Representativeness of patients included in the analysis

The SMR data described above do not include information about patients who were treated conservatively at home or community hospitals, patients who died before admission to a hospital ward (including patients who died in Accident and Emergency), or patients admitted to private hospitals. However there are likely to have been very small numbers in each of these categories so the findings are likely to be applicable to the majority of elderly hip fracture patients. Patients under 60 years old were excluded from analysis because the reasons for fracture and the subsequent outcomes in younger patients differ substantially from elderly patients with hip fracture.

There were some differences between the total population of hip fracture patients described using SMR data and the subgroup of SHFA participants studied in subsequent

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* A cohort study *was* conducted, matching patients for age category, sex, previous admissions with cardiovascular disease or respiratory disease, cancer registration, and number of hospital admissions in the previous five years. The comparison was for patients admitted between 1986 and 1997 and patients admitted between 1998 and 2003. Matching was achieved for 64408 (66.7%) of the 93520 patients aged 60 years and over. The relative risk comparing mortality between 1998 and 2003 with mortality between 1986 and 1997 was estimated at 0.93 (95% CI 0.91 to 0.95), and is therefore consistent with the findings of multivariate analysis (table 3.5).

chapters. Compared to all hip fracture patients recorded in SMR and admitted between 1998 and 2003, the subgroup of SHFA participants were older, were more likely to be women, had a lower mortality rate at a year and were less likely to have lived in deprived areas. The difference in mortality rates may reflect differences in the proportions of men between the groups, as men were much more likely to die than women in the year following hip fracture. The subgroup of SHFA participants were also more likely to have been admitted to hospital in the past and this may reflect age and sex differences between the two groups, but it is also possible that these differences are explained by the inverse care law, where patients from deprived areas are less able to access medical services[75]. Overall, however, the differences between the subgroup of SHFA participants and other hip fracture patients were relatively small and the subgroup of SHFA participants is likely to have been reasonably representative of the general population of elderly hip fracture patients.

3.7 Conclusions

The analysis presented in this chapter was performed primarily to assess the completeness and accuracy of SMR data for use in subsequent chapters. There are a number of limitations to using hospital discharge data, relating to accuracy, changes in quality over time, and completeness. Nonetheless, these data provide potentially useful information about comorbidities and outcomes in hip fracture patients that will be explored in subsequent chapters. The findings of this chapter suggest that results for the subgroup of SHFA participants can be generalised to the general elderly hip fracture population. The analysis presented in this chapter has also provided data on trends in mortality, adjusted for cofactors and comorbidities.

3.8 *Figures and tables*

Figure 3.1 Summary of participants included in the various analyses presented in this thesis

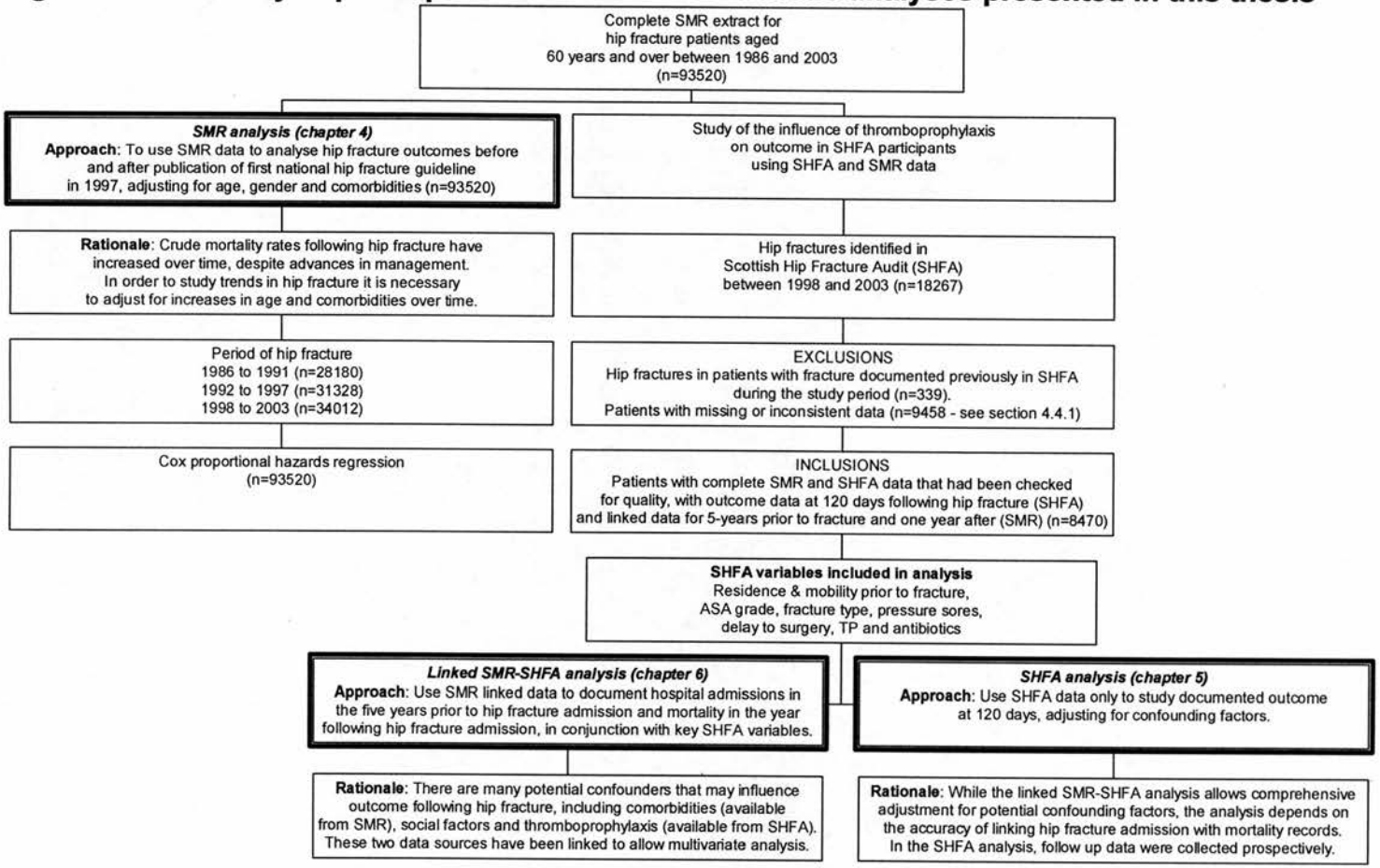


Figure 3.2 Approach used for record linkage

After identifying the index admission with hip fracture, inpatient episodes in the five years prior to hip fracture, and inpatient episodes and deaths in the year following hip fracture were identified.

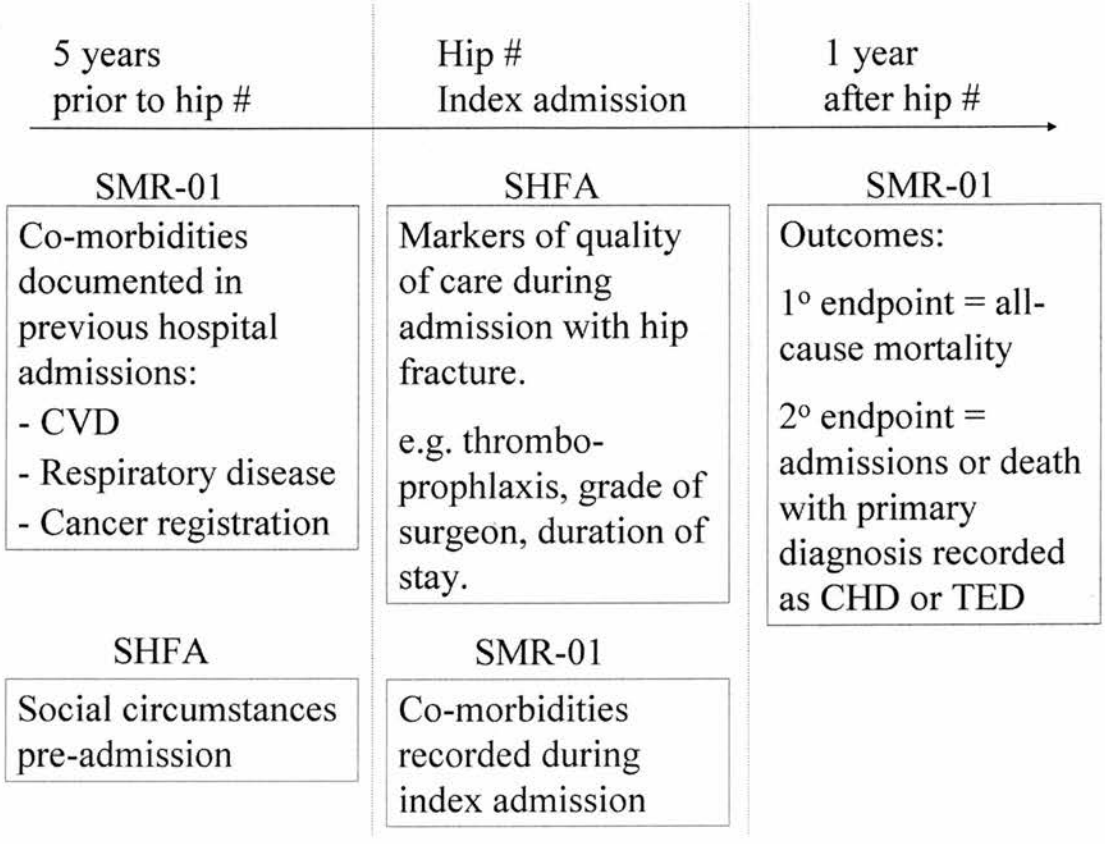


Figure 3.3 Proportion of hip fracture patients aged 60 and over with inpatient episodes documented for medical reasons in the five years prior to hip fracture

n=93520

Source: Scottish Morbidity Records (1986 to 2003)

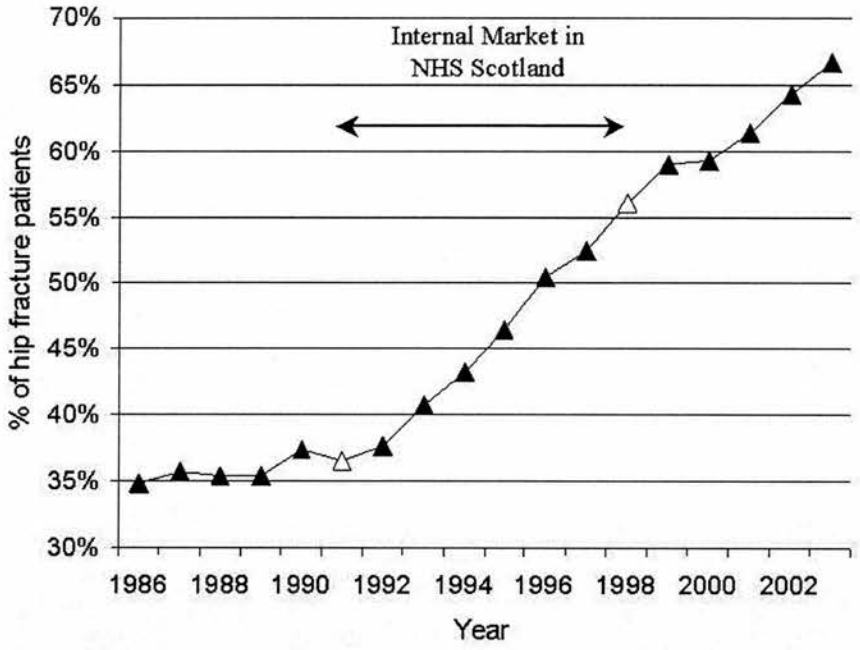


Figure 3.4 Cox proportion hazards survival functions (plotted at mean of covariates) for patients admitted with hip fracture during three different time periods, adjusted for cofactors shown in table 3.5

n=93520

Source: Scottish Morbidity Records (1986 to 2003)

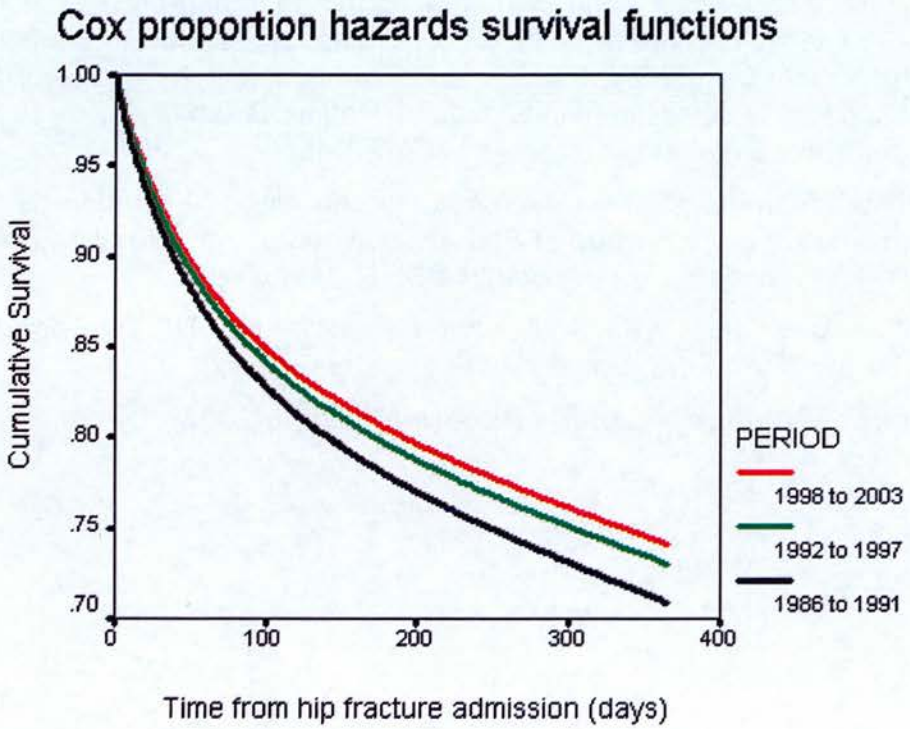


Figure 3.5 Geographical distribution of patients aged 60 years and over admitted to NHS hospitals in Scotland with hip fracture between 1998 and 2003, by health board of residence, in SMR and SHFA databases

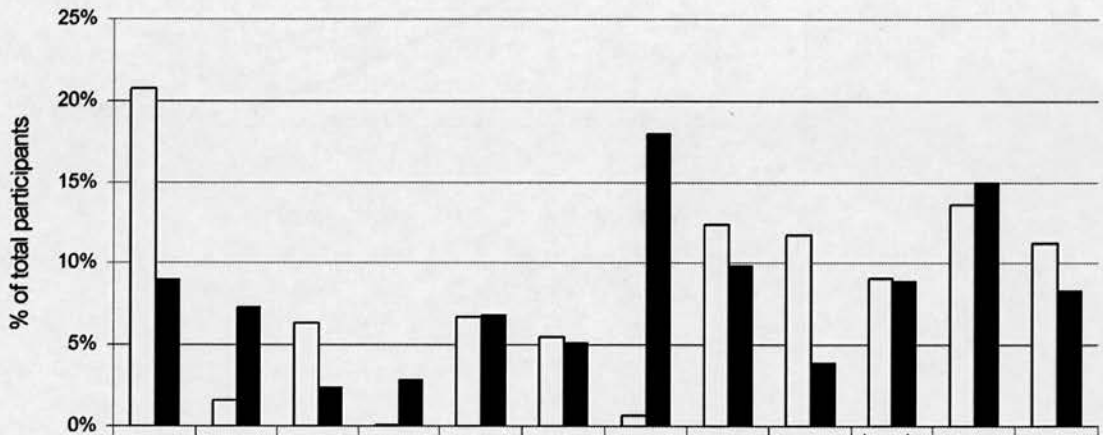
Results are shown for all patients admitted with hip fracture (labelled "SMR", n=34012) and a subgroup of patients with complete SMR and SHFA data (labelled "SHFA", n=8470).

The graph shows the proportion of the total number of patients in each group who were resident in each of the mainland health boards. For example, while 18% of all hip fracture patients were resident in Glasgow in the complete SMR extract, only 1% of hip fractures patients included in the subgroup of SHFA participants were resident in Glasgow. Patients from Glasgow were therefore underrepresented in the analysis of SHFA data.

This graph does not show the results for the island health boards. Data were complete for the subgroup of SHFA participants, but data were not available for 479 (1.4%) patients in the complete SMR database.

A&C = Argyll and Clyde, A&A = Ayrshire and Arran, D&G = Dumfries and Galloway, FV = Forth Valley, GG = Greater Glasgow.

Source: Scottish Morbidity Records (1998 to 2003)



	A&C	A&A	Borders	D&G	Fife	FV	Glasgow	Grampian	Highland	Lanark-shire	Lothian	Tayside
□ SHFA	21%	2%	6%	0%	7%	5%	1%	12%	12%	9%	14%	11%
■ SMR	9%	7%	2%	3%	7%	5%	18%	10%	4%	9%	15%	8%

Table 3.1 List of diagnoses identified in SMR analysis

Diagnosis	ICD-9 codes	ICD-10 codes
Acute myocardial infarction (MI)	410	I21-I22
Ischaemic heart disease (IHD) other than MI	411-414	I20, I23-I25
Pulmonary embolism	415	I26
Heart disease (other than IHD or PE)	393-398, 416-429	I05-I09, I27-I52
Hypertension	401-405	I10-I15
Deep vein thrombosis	451.0-451.2	I80.0-I80.3
Diseases of the circulatory system (other than heart disease, hypertension or DVT)	390-392, 438-450, 430-437, 451.3-459.9	G45, I00-I02, I60-I67, I68-I79, I80.4-I99.9
Diseases of the respiratory system including pneumonia and chronic obstructive pulmonary disease	460-519	J00-J99
Cancer (excluding non melanoma skin cancer)	140-172, 174-208	C00-C43, C45-C97
Diseases of the musculo-skeletal system	710-730, 731.1-739.9	M00-M87, M89-M99
Dementia	290	F00-F03
Diabetes	250	E10-E14

Table 3.2 List of cancer diagnoses used for cancer registration search

Cancer type	ICD-10 code
Bone	C40-C41
Breast	C50
Pancreas	C25
Lung	C35
Colorectal	C18-C20
Stomach	C16
Bladder	C67
Uterus	C53-C55
Thyroid	C73
Kidney	C64-C65
Melanoma	C43

Table 3.3 Medical diagnoses recorded on hospital discharge records in the five years prior to hip fracture admission

Primary (table 3.3a) and secondary (table 3.3b) diagnoses on discharge records in the five years prior to hip fracture admission for patients aged 60 years and over admitted to NHS hospitals in Scotland with hip fracture (n=93520). Primary and secondary diagnoses are mutually exclusive, so, for example, a patient with a primary diagnosis of respiratory disease was not counted again if they also had coding for an admission with a secondary diagnosis of respiratory disease.

n=93520

Source: Scottish Morbidity Records (1986 to 2003)

Table 3.3a

Primary diagnoses in the five years prior to hip fracture

Diagnoses	Number (%)			% Increase
	1986 to 1991 (n=28180)	1992 to 1997 (n=31328)	1998 to 2003 (n=34012)	
Respiratory disease	1939 (6.9)	2658 (8.5)	3510 (10.3)	50
Stroke	1917 (6.8)	2295 (7.3)	2551 (7.5)	10
Other heart disease	1122 (4.0)	1793 (5.7)	2349 (6.9)	74
Cancer	475 (1.7)	696 (2.2)	1769 (5.2)	209
PVD	892 (3.2)	1181 (3.8)	1354 (4.0)	26
IHD (other than MI)	507 (1.8)	882 (2.8)	1292 (3.8)	111
MI	621 (2.2)	779 (2.5)	845 (2.5)	13
Dementia	586 (2.1)	793 (2.5)	811 (2.4)	15
Diabetes mellitus	356 (1.3)	303 (1.0)	346 (1.0)	-20
DVT	78 (0.3)	178 (0.6)	299 (0.9)	218
Hypertension	128 (0.5)	142 (0.5)	173 (0.5)	12
PE	43 (0.2)	81 (0.3)	127 (0.4)	145

Table 3.3b

Secondary diagnoses in the five years prior to hip fracture admission or during the index admission for hip fracture.

n=93520

Diagnosis	Number (%)			% increase
	1986 to 1991 (n=28180)	1992 to 1997 (n=31328)	1998 to 2003 (n=34012)	
Respiratory disease	1494 (5.3)	2357 (7.5)	4275 (12.6)	137
Other heart disease	1367 (4.9)	2258 (7.2)	4146 (12.2)	151
Dementia	1051 (3.7)	2334 (7.5)	4119 (12.1)	225
IHD (other than MI)	748 (2.7)	1756 (5.6)	3667 (10.8)	306
Hypertension	369 (1.3)	1000 (3.2)	3047 (9.0)	584
PVD	560 (2.0)	1167 (3.7)	2456 (7.2)	263
Diabetes mellitus	570 (2.0)	957 (3.1)	1814 (5.3)	164
Stroke	323 (1.1)	405 (1.3)	591 (1.7)	52
Cancer	108 (0.4)	212 (0.7)	490 (1.4)	276
MI	359 (1.3)	343 (1.1)	475 (1.4)	10
DVT	79 (0.3)	186 (0.6)	242 (0.7)	154
PE	159 (0.6)	177 (0.6)	203 (0.6)	6

Table 3.4 Results of Cox proportion hazards regression analysis for patients admitted with hip fracture during three different time periods between 1986 and 2003 (univariate analysis).

n=93520

Source: Scottish Morbidity Records (1986 to 2003)

Variable	Category	Frequency (% of total)	Hazard ratio (95% CI)	p value
Age (years)*	60-64	4141 (4)	1.0	
	65-69	6735 (7)	1.3 (1.2 to 1.4)	<0.001
	70-74	10989 (12)	1.7 (1.6 to 1.9)	<0.001
	75-79	17332 (19)	2.2 (2 to 2.4)	<0.001
	80-84	21953 (23)	2.7 (2.5 to 3)	<0.001
	85-89	19826 (21)	3.4 (3.1 to 3.7)	<0.001
	90+	12544 (13)	4.6 (4.2 to 5.1)	<0.001
Sex	Men	18982 (20)	1.0	
	Women	74538 (80)	0.7 (0.6 to 0.7)	<0.001
Inpatient episodes in previous five years	0 episodes	31678 (34)	1.0	
	1 episodes	17563 (19)	1.4 (1.3 to 1.4)	<0.001
	2-3 episodes	22064 (24)	1.6 (1.6 to 1.7)	<0.001
	4-7 episodes	15905 (17)	2 (1.9 to 2)	<0.001
	8+ episodes	6310 (7)	2.4 (2.3 to 2.5)	<0.001
Admission with respiratory condition	No	85413 (91)	1.0	
	Yes	8107 (9)	1.9 (1.8 to 1.9)	<0.001
Admission with CVD	No	74652 (80)	1.0	
	Yes	18868 (20)	1.7 (1.7 to 1.8)	<0.001
Cancer registration	No	89352 (96)	1.0	
	Yes	4168 (4)	2.2 (2.1 to 2.2)	<0.001
Period of hip fracture	1986 to 1991	28180 (30)	1.0	
	1992 to 1997	31328 (33)	1 (0.98 to 1.03)	0.8
	1998 to 2003	34012 (36)	1.04 (1.01 to 1.07)	0.01

* Due to the large size of the dataset available for the analysis presented in tables 3.4 and 3.5 it was possible to divide 60 to 69 year olds into two groups. Elsewhere in this thesis patients aged 60 to 69 years old have been analysed as a single group (see section 3.4.6).

Table 3.5 Results of Cox proportion hazards regression analysis for patients admitted with hip fracture during three different time periods between 1986 and 2003 (multivariate analysis).

n=93520

Source: Scottish Morbidity Records (1986 to 2003)

Variable	Category	Hazard ratio (95% CI)	p value
Age (years)	60-64	1.0	
	65-69	1.3 (1.2 to 1.4)	<0.001
	70-74	1.8 (1.6 to 2.0)	<0.001
	75-79	2.3 (2.1 to 2.5)	<0.001
	80-84	3 (2.7 to 3.3)	<0.001
	85-89	3.8 (3.5 to 4.2)	<0.001
	90+	5.4 (4.9 to 5.9)	<0.001
Sex	Male	1.0	
	Female	0.6 (0.6 to 0.6)	<0.001
Inpatient episodes in previous five years	0 episodes	1.0	
	1 episode	1.2 (1.1 to 1.2)	<0.001
	2-3 episodes	1.3 (1.3 to 1.3)	<0.001
	4-7 episodes	1.4 (1.4 to 1.5)	<0.001
	8+ episodes	1.6 (1.5 to 1.7)	<0.001
Previous admissions with respiratory disease	No	1.0	
	Yes	1.4 (1.4 to 1.5)	<0.001
Previous admissions with CVD	No	1.0	
	Yes	1.4 (1.4 to 1.5)	<0.001
Cancer registration	No	1.0	
	Yes	1.9 (1.9 to 2.0)	<0.001
Period of hip fracture	1986 to 1991	1.0	
	1992 to 1997	0.91 (0.89 to 0.94)	<0.001
	1998 to 2003	0.87 (0.85 to 0.9)	<0.001

Table 3.6 Number of inpatient episodes in the 5-years prior to hip fracture admission comparing all SMR patients admitted with hip fracture between 1998 and 2003 with a subgroup of SHFA participants

Comparison of the number of inpatient episodes in the five years prior to hip fracture admission, for all patients aged 60 years and over admitted with hip fracture to NHS hospitals in Scotland (SMR) between 1998 and 2003 (n=34012) and a subgroup of patients participating in the Scottish Hip Fracture Audit (SHFA) between 1998 and 2003 (n=8470)

Source: Scottish Morbidity Records (1998 to 2003)

	All hip fracture patients in SMR database (n=34012)		**Patients with complete SMR and SHFA data (n=8470)**	
Inpatient episodes in the five years prior to hip fracture	**Number**	**% (95% CI)**	**Number**	**% (95% CI)**
0 episodes	9538	28.0 (27.6 to 28.5)	2170	23.7 (22.8 to 24.5)
1 episode	5680	16.7 (16.3 to 17.1)	1549	16.9 (16.1 to 17.7)
2-3 episodes	8280	24.3 (23.9 to 24.8)	2391	26.1 (25.2 to 27.0)
4-7 episodes	7021	20.6 (20.2 to 21.1)	2058	22.4 (21.6 to 23.3)
8+ episodes	3493	10.3 (9.9 to 10.6)	994	10.8 (10.2 to 11.5)
Total	34012	100	8470	100

Table 3.7 Admissions with selected medical diagnoses in the 5-years prior to the hip fracture admission comparing all SMR patients admitted with hip fracture between 1998 and 2003 with a subgroup of SHFA participants

Comparison of the proportion of patients admitted with common medical diagnoses in the five years prior to hip fracture, for all patients aged 60 years and over admitted with hip fracture to NHS hospitals in Scotland (SMR) between 1998 and 2003 (n=34012) and a subgroup of patients participating in the Scottish Hip Fracture Audit (SHFA) between 1998 and 2003 (n=8470).

Source: Scottish Morbidity Records

	All hip fracture patients in SMR database (n=34012)		**Patients with complete SMR and SHFA data (n=8470)**	
Diagnosis	**Number**	**% (95% CI)**	**Number**	**% (95% CI)**
Cardiovascular	7735	22.7 (22.3 to 23.2)	2098	24.8 (23.9 to 25.7)
Respiratory	3510	10.3 (10.0 to 10.6)	844	10.0 (9.3 to 10.6)
Cancer registration	1592	4.7 (4.5 to 4.9)	361	4.3 (3.8 to 4.7)

Table 3.8 Primary cause of death in the year following hip fracture for SHFA participants

Primary cause of death (using groupings based on ICD-10 chapters) for a subgroup of SHFA participants between 1998 and 2003 (n=2531 deaths/ 8470 participants)

Source: Scottish Morbidity Records (1998 to 2003)

Cause of death	Number (%)
Diseases of the heart / circulation*	929 (36.7)
Trauma‡	456 (18.0)
Respiratory	412 (16.3)
Neoplasm	233 (9.2)
Neurological/ Neuropsychiatric	217 (8.6)
Gastrointestinal	87 (3.4)
Renal/ genitourinary	61 (2.4)
Endocrine/metabolic/haematological	52 (2.1)
Orthopaedic	31 (1.2)
Infection	25 (1.0)
Other (including iatrogenic)	20 (0.8)
Skin	8 (0.3)

* Includes coronary heart disease, stroke, other cardiovascular disease, valvular heart disease and cardiomyopathy.

‡ The majority of deaths attributed to trauma are likely to be related to the episode causing the hip fracture, though a small proportion of patients may have suffered a subsequent trauma resulting in death.

Table 3.9 CHD and TED outcomes following hip fracture

Patients with inpatient episodes where the primary diagnosis was recorded as the conditions listed, in the year following hip fracture admission.

Source: Scottish Morbidity Records

Table 3.9a

Inpatient episodes in the year following hip fracture admission.

	SMR extract 1998 to 2003 (n=34012)		Patients with complete SMR and SHFA data (n=8470)	
Inpatient episodes	**Number**	**% (95% CI)**	**Number**	**% (95% CI)**
Inpatient episodes with MI	409	1.2 (1.1 to 1.3)	95	1.1 (0.9 to 1.4)
Inpatient episodes with any CHD (including MI)	671	2.0 (1.8 to 2.1)	157	1.9 (1.6 to 2.1)
Inpatient episodes with PE	174	0.51 (0.44 to 0.59)	53	0.63 (0.46 to 0.79)
Inpatient episodes with any TED (including PE)	417	1.2 (1.1 to 1.3)	121	1.4 (1.2 to 1.7)
Inpatient episodes with CHD or TED	1078	3.2 (3.0 to 3.4)	275	3.3 (2.8 to 3.6)

Table 3.9b

Deaths in the year following hip fracture admission.

	SMR extract 1998 to 2003 (n=34012)		Patients with complete SMR and SHFA data (n=8470)	
Deaths	**Number**	**% (95% CI)**	**Number**	**% (95% CI)**
Deaths due to MI	921	2.7 (2.5 to 2.9)	201	2.4 (2.0 to 2.7)
Deaths due to any CHD (including MI)	1682	4.9 (4.7 to 5.2)	399	4.7 (4.3 to 5.2)
Deaths due to PE	92	0.27 (0.22 to 0.33)	18	0.21 (0.11 to 0.31)
Deaths due to any TED (including PE)	94	0.28 (0.22 to 0.33)	23	0.27 (0.16 to 0.38)
Deaths due to CHD or TED	1776	5.2 (5.0 to 5.5)	422	5.0 (4.5 to 5.4)

4 Scottish Hip Fracture Audit 1998-2003

4.1 Introduction

The analysis of routinely collected hospital discharge data (chapter 3) has provided information about previous inpatient episodes with medical diagnoses, and socio-economic status. SHFA data are described in this chapter, providing prospectively collected information unavailable from the SMR database.

4.2 Background

The SHFA started in two pilot hospitals in Scotland in 1992. Based on the Standardised Audit of Hip Fractures in Europe, the audit collects data about patient circumstances and quality of care. Typically around half the elderly hip fracture patients admitted with hip fracture in Scotland are included in the audit, though, as shown in chapter 3 there is under-representation of patients from more deprived areas.

The main focus of this work is to understand how different types of thrombo-prophylaxis have influenced outcomes following hip fracture. The SHFA database includes information about thromboprophylaxis as well as other factors identified in the literature review that influence outcome (chapter 2). These include residence and walking ability prior to hip fracture, and the American Society of Anesthesiologists (ASA) grade, a measure of physical health prior to fracture (1 = fit, 5 = moribund – see section 2.5.2.3 for more information). Each of these factors has been shown previously to be a strong predictor of outcome following hip fracture as described in chapter 2.

4.3 Rationale

4.3.1 Objective 3a. To use SHFA variables to describe characteristics of SHFA participants receiving different types of thromboprophylaxis

Many of the potential confounding factors identified in the literature review (chapter 2) are described in the SHFA database. These potential confounding factors are described here, dividing the results by the types of thromboprophylaxis administered. These findings will be used in the final analysis presented in chapter 5.

4.3.2 Objective 3b. To study the association between different types of thromboprophylaxis and mortality before and after adjusting for comorbidities and cofactors using SHFA data

SHFA data include outcomes at 120 days. These data are collected by local audit co-ordinators, during telephone or face-to-face interviews with the patient or carer. These outcome data may be more accurate than the linked outcomes used in the analysis presented in chapter 5. A separate analysis using just SHFA data is therefore presented in this chapter.

4.4 Methods

4.4.1 Participants

SHFA data were available for 18267 hip fractures in 17928 patients aged 60 years and over (339 patients were included twice in SHFA, and the second hip fracture was excluded for this analysis). For these 17928 patients, a number of exclusions were necessary: 7640 (42.6%) because there were data missing for one or more SHFA variable, 525 (2.9%) because they had no information about whether operation was performed, and 135 (0.7%) because they were recorded as having pathological fracture. Patients with pathological fracture were excluded because the most likely cause was cancer that had metastasised to the bone. Hip fracture patients with metastatic cancer are likely to have a higher mortality rate, a higher incidence of TED, and may be given different thromboprophylaxis regimes when compared with hip fracture patients in general.

In order to simplify the presentation of results in this and subsequent chapters, other patients were excluded following a comparison of SHFA data with SMR data. The process of linking SHFA and SMR records is described in section 5.4. After comparing the two databases, 63 (0.3%) patients were excluded because there was a discrepancy

between SMR and SHFA*, 789 (4.4%) because of uncertainties about the accuracy of record linkage to an SMR record, and 306 (1.7%) because they did not have a health board of residence recorded in SMR and did not therefore appear to be resident in Scotland.

In total, 8470 (47.2%) SHFA participants aged 60 years and over, with hip fracture admission between 1998 and 2003, were included in the final analysis. SHFA data were collected separately from SMR data, so it would have been possible to perform the SHFA analysis without excluding patients identified above for whom there were uncertainties within the SMR database about record linkage (n=789)‡ or health board of residence (n=306)†. However, even using SHFA outcome data exclusively, mortality at 120 days was significantly different for these excluded patients when compared with the rest of the SHFA patients included in the analysis. Patients without record linkage data had a death rate at 120 days of 35.0% (95% CI 31.6 to 38.5%), compared to 9.2% (95% CI 5.7 to 12.7%) for patients without heath board of residence recorded, and 18.9%

* Discrepancy of more than one year in age, more than one month for date of hip fracture admission or date of death, or difference in recorded sex.

‡ For these patients, the SHFA record had had been linked to a patient record set in SMR01, but it was not possible to link to a matching admission within that record set.

† These patients had a lower mortality and a lower rate of hospital episodes both before and after the index admission with hip fracture. One possible explanation is that while the patient was admitted to a hospital in Scotland, he or she was not normally resident in Scotland. This would explain the lack of information about health board of residence, and the lower than expected hospitalization and mortality rates.

(95% CI 18.0 to 19.7%) for the patients included in the final analysis ($\chi^2 = 132$, $p<0.001$). It was not possible to corroborate findings between SHFA and SMR databases or to identify duplicate information for these patients. For these reasons, both groups have been excluded from further analysis.

Fourteen hospitals participated in the audit during the period of study. The number of patients contributed by different hospitals varied considerably, reflecting differences in size and type of hospital. The hospital contributing the smallest number of cases (n=51) was a district general hospital. Three hospitals contributed over 40% of cases including in the analysis – a district general hospital in the West of Scotland (n=1298), a large teaching hospital in the South East of Scotland (n=1138), and a district general hospital in the North of Scotland (n=1034).

4.4.2 Ethical and privacy considerations

Participants in the SHFA gave consent to having their data used for audit purposes and were given the opportunity to opt out from having their data used for research purposes. The study protocol was agreed by the Privacy Advisory Committee of National Services Scotland. Records were anonymised following record linkage and prior to analysis (chapter 5).

4.4.3 Data collection

SHFA data were collected at the time of acute hip fracture admission by local audit co-ordinators, using forms based on the Standardised Audit of Hip Fractures in Europe[76]. SHFA data provided pre-fracture status (residence and mobility) and aspects of medical, surgical and anaesthetic care during the hip fracture admission. Between 1998 and 2003 SHFA forms included detailed information about thromboprophylaxis during the

hospital admission including up to three types of thromboprophylaxis, the timing of the first thromboprophylaxis treatment in relation to surgery and the combined duration of all thromboprophylaxis.

The audit forms were collected centrally at ISD, and inconsistencies in the information explored further with hospital audit staff before entering data in mutually exclusive categories into a database.

4.4.4 Data coding

Variables of potential interest that were identified from the literature review were explored and, for categories with small numbers or redundant information, regrouped into the categories shown in tables 4.1 and 4.2. Data for age and sex were complete, but other variables had missing values and there were some ambiguities for some variables. For example, heparin could be coded as LMWH, heparin – type unspecified, or conventional heparin. For the latter two categories the type of heparin and route of administration was not clear. As a result information about heparin was grouped into a single category. The multivariate analysis described in this chapter and the subsequent chapter was repeated for LWMH and other types of heparin separately, but this did not change the findings (results not shown).

Information about timing and duration of thromboprophylaxis was only available for the period of the index admission, and not for subsequent episodes within the same continuous inpatient stay. The inability to match information about type, timing and duration of thromboprophylaxis for patients receiving more than one type of thromboprophylaxis limits the usefulness of these findings and would have reduced the

statistical power, so neither variable has been explored further, beyond a basic description.

4.4.5 Statistical analysis

Statistical analysis was carried out with SPSS (version 11.5) using a number of different techniques described in chapter 3 (section 3.4.6). Cox proportional hazards regression analysis was performed using outcome at up to 120 days following hip fracture admission. Hospital was included as a variable in multivariate analysis, but to simplify the presentation of results the hazard ratios for individual hospitals are not shown in this chapter or chapter 5.

Some patients may have died before thromboprophylaxis was administered or had the chance to take effect, potentially resulting in an under-estimate of the effectiveness of thromboprophylaxis. To explore this further, patients who died within 5 days of admission (n=96) were excluded and multivariate analysis repeated.

4.5 Results

4.5.1 Objective 3a. To describe characteristics of SHFA participants receiving different types of thromboprophylaxis (n=8470)

The mean age of patients admitted with hip fracture was 81.6 years (95% CI 81.4 to 81.8 years). This analysis has been restricted to the three most commonly used types of thromboprophylaxis – heparin, GEC stockings and aspirin. For these types of thromboprophylaxis, 4584 (54.1%) received one type of thromboprophylaxis, 2668 (31.5%) received two types of thromboprophylaxis and 220 (2.6%) received three types of thromboprophylaxis. The analysis also included 954 (11.3%) patients who were documented as having received no thromboprophylaxis and 44 (0.5%) patients who were documented as receiving exclusively warfarin or foot pumps for thromboprophylaxis*.

Data about the timing of thromboprophylaxis in relation to surgery were available for 7107 (84%) patients. Of these patients, 2678 (38%) received thromboprophylaxis prior to surgery. The median duration of thromboprophylaxis was 9 days (interquartile range 5-14 days, n=7136). The proportion of patients recorded as receiving different types of thromboprophylaxis varied between hospitals with ranges of 13 to 96% for heparin, 0 to

* In total, 191 (2.3%) patients were documented as having received warfarin and 69 (0.8%) patients were documented as having received foot pumps.

84% for GEC stockings, 0.3 to 82% for aspirin, and 0 to 68% received no thromboprophylaxis.

The characteristics of patients who received either heparin, GEC stockings, and/or aspirin are shown in tables 4.1 and 4.2. Patients documented as receiving GEC stockings may have been fitter prior to hip fracture than other patients – they tended to be younger and were more likely to have lived in their own home pre-fracture. Patients documented as receiving heparin were also more likely to have lived in their own home pre-fracture. Patients documented as having received aspirin may have been less fit, as fewer walked without aids pre-fracture, fewer had favourable ASA grades, and a slightly higher proportion of men were documented as receiving aspirin than expected overall. Patients who were documented as having received GEC stockings were more likely to have also received aspirin, and vice versa. However, patients who received heparin were less likely to have received either aspirin or stockings.

4.5.2 Objective 3b. To study the association between different types of thromboprophylaxis and mortality before and after adjusting for comorbidities and cofactors using SHFA data.

There were 1597 deaths (18.9%, 95% CI 18.0 to 19.7) in the 120 days following hip fracture admission. The recorded death rate for individual hospitals varied from 13.6% to 24.2%. Cox proportional hazards regression analysis was used to estimate the risk of death at 120 days, adjusting for sex, age, residence pre-fracture, walking ability pre-fracture, ASA grade, fracture type, delay to surgery and prophylaxis (antibiotic or thromboprophylaxis). Table 4.3 and 4.4 show the results for univariate and multivariate analysis respectively.

The results of univariate analysis showed that there were strong relationships between mortality and the following variables: sex, age, ASA grade, residence and mobility prior to surgery, delay to surgery for medical reasons, use of antibiotics and thromboprophylaxis. The Cox model identified in multivariate analysis included each of these variables apart from mobility prior to surgery and antibiotics.

Aspirin and GEC stockings were associated with a lower mortality in univariate analysis with hazard ratios of 0.82 (95% CI 0.73 to 0.91) and 0.74 (95% CI 0.66 to 0.82) respectively. Patients receiving heparin or no thromboprophylaxis had a higher mortality with hazard ratios of 1.15 (95% CI 1.04 to 1.27) and 1.32 (95% CI 1.15 to 1.52) respectively. However, only aspirin remained in the model in multivariate analysis with a hazard ratio of 0.81 (95% CI 0.71 to 0.93). The survival function is plotted in figure 4.1. Excluding patients who died within five days of hospital admission did not influence the findings (results not shown). However aspirin was no longer included in the model once interaction terms were included (results not shown).

4.6 Discussion

There are a number of strengths to this analysis of SHFA data. SHFA data, including outcomes at 120 days, were collected prospectively by trained audit co-ordinators, using an internationally recognised audit form designed specifically for the purpose of documenting information related to the function status, health and management of hip fracture patients. As a result, the variables available for the analysis were relevant to hip fracture outcomes, as identified in the literature review (chapter 2). The use of prospective data collection by trained personnel is likely to have minimised the potential for bias though there remains the possibility that recording practices varied between hospitals.

Adjusting for cofactors and comorbidities was important in understanding the potential influence of thromboprophylaxis on mortality. Some SHFA variables had more of an influence on the multivariate analysis than others. Mobility prior to fracture and antibiotic prophylaxis did not influence multivariate analysis and have not therefore been included in further analysis. For delay to surgery, only delay for medical reasons had a significant influence on the multivariate model, perhaps explaining the contradictory findings for studies based on duration of delay rather than cause of delay[43]. For fracture type only intertrochanteric fracture had a statistically significant and detrimental influence, a finding that is consistent with other studies and may be explained by the increased blood loss observed with extracapsular fractures[56] and the more complex surgical procedures required, including internal fixation.

There are, however, a number of limitations to using SHFA data. A number of variables, including ASA grade and thromboprophylaxis were incompletely recorded in

some hospitals, leading to a large number of exclusions as documented in section 4.4.1. Patients recorded as receiving different types of thromboprophylaxis may not have received these treatments reliably or consistently. Thus, a patient prescribed aspirin may not have been well enough to swallow the medication, and a patient prescribed GEC stockings may not have worn the GEC stockings for the majority of the hospital admission, whether due to problems fitting the GEC stockings or patient preference*. Furthermore, the wide range in thromboprophylaxis use between hospitals (section 4.5.1) may reflect differences in recording rather than differences in management between hospitals. However, where data about thromboprophylaxis were unavailable, patients were excluded from the analysis. There were no data in SHFA about speed of mobilisation following hip fracture surgery (see section 2.5.2.4).

There are also potential inconsistencies in the documentation of physical status in SHFA. ASA grade is the only measure of physical status recorded in SHFA and is meant to document the presence of serious medical conditions prior to hip fracture. However, there is evidence from the published literature that some centres use ASA

* There is some anecdotal evidence for this. Presentation of some early findings from this work at a national hip fracture conference in 2004 led some nursing staff on orthopaedic wards to observe that they would not put GEC stockings on a patient, even if recommended by a consultant, if the patient had poor skin condition or circulation. Others noted that stockings are sometimes poorly fitted, limiting their usefulness.

grade as a measure of physical condition during the hospital admission[77]. If ASA was used in this way in some centres, then this would lead to an overestimation of ASA grade, and would result in a biased estimate of the influence of ASA grade on outcome. However, there is no evidence of overestimation of ASA grade in this current study, as only 14% of patients were recorded as ASA grades 4 or 5. Additionally, there was an increase in hazard ratio with increasing ASA grade (tables 4.3 and 4.4).

The results of multivariate analysis presented in table 4.4 show that use of aspirin was associated with a lower mortality rate following hip fracture. These findings are consistent with existing guidelines[3], which used the findings of the PEP study to recommend aspirin, though this was based on clinical evidence of TED rather than all-cause mortality[20]. Aspirin also has a potentially beneficial influence on cardiovascular outcomes, breast cancer and colorectal cancer, which are commonly recorded in elderly hip fracture patients (see section 1.4).

The findings for aspirin may, however, be explained by residual confounding, either due to factors that were not recorded in SHFA or by factors that were incompletely or inaccurately recorded in SHFA. The difference in outcome and aspirin usage in different hospitals provides one potential source of confounding. However, hospital was included as a variable in the multivariate analysis which should have minimised this influence. The lack of high quality and unambiguous information about physical health provides another potential source of confounding and there therefore remains the possibility that frailer and/or sicker patients were underrepresented in the group documented as receiving aspirin.

Heparin did not appear to have a statistically significant influence on mortality, in apparent contradiction to advice in the guidlines[5;17;48]. A potential explanation for this finding is that heparin might increase serious haemorrhage following surgery, but the Cochrane review of thromboprophylaxis suggests that this is not the case[19].

Finally, there remains the possibility that a substantial proportion of patients died before thromboprophylaxis had a chance to take effect. If this was the case, then there would be a strong case for excluding these patients from the analysis. Indeed, when the analysis was repeated after excluding patients who had died within 5 days of hospital admission, the apparently protective influence of aspirin on survival persisted.

4.7 Conclusions

There is evidence, using SHFA data, of a protective influence of aspirin on all-cause mortality in the first 120 days following hip fracture admission. This analysis has shown some of the strengths and limitations of using SHFA data. Some variables were missing or the information recorded was potentially ambiguous, while others did not appear to influence the findings of the analysis. These findings have been used in the design of the study described in the next chapter. The findings may be explained by residual confounding, particularly relating to the physical status of hip fracture patients, a possibility that is explored using more detailed information about physical health in the following chapter.

4.8 Figures and tables

Figure 4.1 Cox proportional hazards survival functions for aspirin / no aspirin using SHFA data

Figure 4.1a shows the Cox proportion hazards survival functions (plotted at mean of covariates) for aspirin, based on the Cox proportional hazards regression model shown in table 4.4. Figure 4.1b shows the log minus log curves used to test the assumption of proportional hazards.

n=8470

Source: SHFA (1998 to 2003)

Figure 4.1a

Cox proportional hazards survival functions, plotted at the mean of covariates, for patients documented as receiving aspirin compared to patients not documented as receiving aspirin.

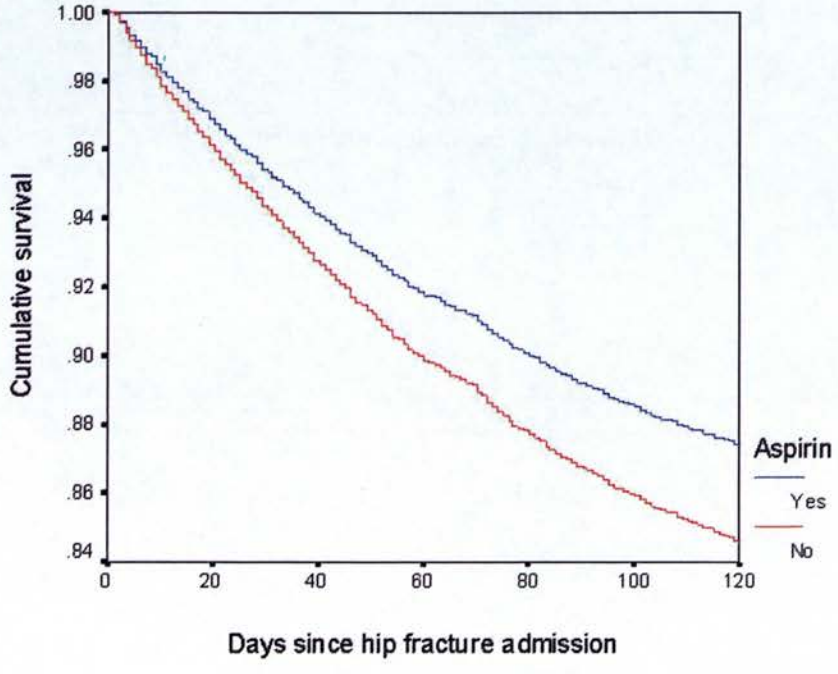


Figure 4.1b

Log minus log curves, testing for the assumption of proportional hazards. The curves run closely parallel, suggesting that this assumption is justified.

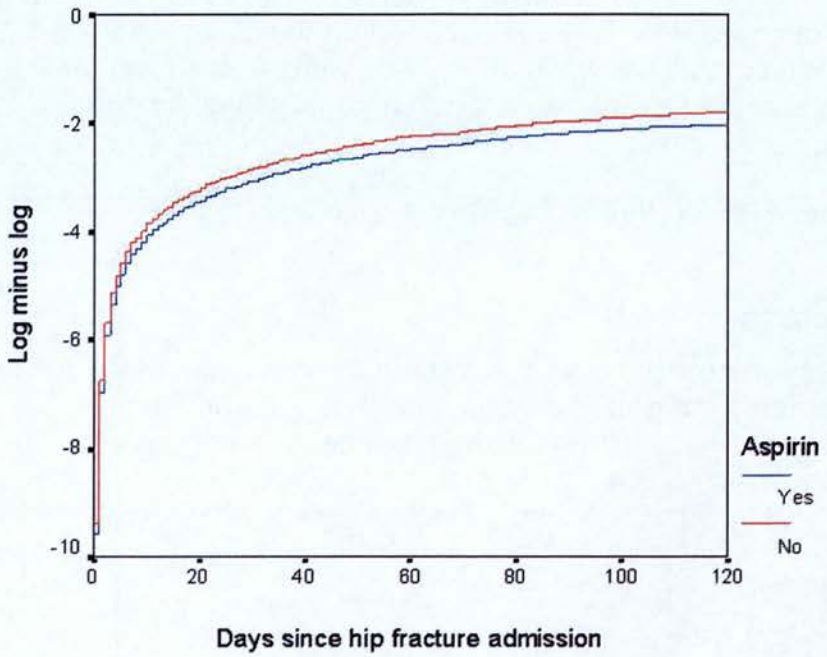


Table 4.1 Patient details and pre-fracture functional status using SHFA data

Number and % of patients receiving different types of thromboprophylaxis for each variable included in the Cox proportional hazards regression analysis. Where there are significant differences in the findings for a particular variable and type of thromboprophylaxis using the Chi squared test this is indicated as follows: * = p<0.05, ** = p<0.001.

n=8470

Source: SHFA (1998 to 2003)

Variable	Category	N (% of total)	Thromboprophylaxis (some patients received more than one type) N (%) of patients receiving thromboprophylaxis for each category			
			Aspirin	Heparin	Stocking	None
Sex	Female	6837 (81)	2171 (31.8) *	3677 (53.8) **	2696 (39.4)	756 (11.1)
	Male	1633 (19)	564 (34.5) *	850 (52.1) **	622 (38.1)	198 (12.1)
Age (years)	60 to 69 years	752 (9)	227 (30.2)	418 (55.6) **	326 (43.4) *	76 (10.1)
	70 to 74 years	922 (11)	303 (32.9)	479 (52) *	393 (42.6) *	95 (10.3)
	75 to 79 years	1504 (18)	470 (31.3)	824 (54.8) **	594 (39.5)	160 (10.6)
	80 to 84 years	1884 (22)	611 (32.4)	997 (52.9) **	724 (38.4)	212 (11.3)
	85 to 89 years	1963 (23)	638 (32.5)	1059 (53.9) **	745 (38)	233 (11.9)
	90+ years	1445 (17)	486 (33.6)	750 (51.9) *	536 (37.1)	178 (12.3)
Residence prior to fracture	Own home or sheltered housing	5522 (65)	1782 (32.3)	2998 (54.3) **	2269 (41.1) **	568 (10.3) **
	Residential care/ hospital	2948 (35)	953 (32.3)	1529 (51.9) **	1049 (35.6) **	386 (13.1) **
Walking ability prior to fracture	Walked without aids	3754 (44)	1165 (31.0) *	2027 (54.0) **	1512 (40.3)	421 (11.2)
	Walked with aids	4522 (53)	1508 (33.3) *	2400 (53.1) **	1740 (38.5)	509 (11.3)
	Chair/ bed bound	194 (2)	62 (32.0)	100 (51.5)	66 (34)	24 (12.4)
Total		8470 (100)	2735 (32.3)	4527 (53.4)	3318 (39.2)	954 (11.3)

Table 4.2 Details of surgical admission using SHFA data

Number and % of patients receiving different types of thromboprophylaxis for each variable included in the Cox proportional hazards regression analysis. Where there are significant differences in the findings for a particular variable and type of thromboprophylaxis using the Chi squared test this is indicated as follows: * = p<0.05, ** = p<0.001.
Source: SHFA (1998 to 2003)

Variable	Category	N and % of total	Thromboprophylaxis (some patients received more than one type) N and % of patients receiving thromboprophylaxis by category			
			Aspirin	Heparin	Stocking	None
ASA grade	Grades 1 to 2	2811 (33)	778 (27.7) **	1598 (56.8) **	1102 (39.2)	317 (11.3)
	Grade 3	4510 (53)	1569 (34.8) **	2341 (51.9) **	1782 (39.5)	509 (11.3)
	Grades 4 to 5	1149 (14)	388 (33.8)	588 (51.2) *	434 (37.8)	128 (11.1)
Fracture type	Undisplaced intracapsular	838 (10)	284 (33.9)	392 (46.8)	358 (42.7) *	94 (11.2)
	Displaced intracapsular	3648 (43)	1168 (32)	1968 (53.9) **	1447 (39.7)	405 (11.1)
	Basocervical	395 (5)	133 (33.7)	193 (48.9)	135 (34.2) *	49 (12.4)
	Intertrochanteric (2 fragments)	2192 (26)	694 (31.7)	1195 (54.5) **	877 (40)	253 (11.5)
	Intertrochanteric (multifragment)	1151 (14)	374 (32.5)	645 (56) **	414 (36) *	124 (10.8)
	Subtrochanteric	246 (3)	82 (33.3)	134 (54.5) *	87 (35.4)	29 (11.8)
Pressure sores pre surgery	No	6682 (79)	1813 (27.1) **	3836 (57.4) **	2476 (37.1) **	838 (12.5) **
	Yes	1788 (21)	922 (51.6) **	691 (38.6) **	842 (47.1) **	116 (6.5) **
Delay to surgery	No delay	5106 (60)	1695 (33.2) *	2641 (51.7) **	2014 (39.4)	567 (11.1)
	Administrative	1432 (17)	380 (26.5) **	916 (64.0) **	564 (39.4)	135 (9.4) *
	Medically unfit	1315 (16)	446 (33.9)	704 (53.5) **	516 (39.2)	149 (11.3)
	Other	617 (7)	214 (34.7)	266 (43.1) *	224 (36.3)	103 (16.7) **
Prophylaxis	Antibiotics	7623 (90)	2588 (33.9) **	4088 (53.6) **	3101 (40.7) **	706 (9.3) **
	Aspirin	2735 (32)		526 (19.2) **	1289 (47.1) **	
	Heparin	4088 (48)	526 (12.9) **		1513 (37) **	
	Stockings	3318 (39)	1289 (38.8) **	1513 (45.6) **		
Total		8470 (100)	2735 (32.3)	4527 (53.4)	3318 (39.2)	954 (11.3)

Table 4.3 Results of univariate Cox proportional hazards regression analysis describing the association between key SHFA variables and mortality in the 120 days following hip fracture admission

n=8470

Source: SHFA (1998 to 2003)

Variable	Category	Hazard ratio (95% CI)	p value
Sex	**Male**	1.00	
	Female	0.56 (0.51 to 0.63)	<0.001
Age (years)	**60-69**	1.00	
	70-74	1.93 (1.37 to 2.72)	0.001
	75-79	2.19 (1.60 to 3.02)	<0.001
	80-84	3.22 (2.37 to 4.37)	<0.001
	85-89	4.24 (3.14 to 5.72)	<0.001
	90+	5.41 (4.00 to 7.31)	<0.001
Residence pre fracture	**Own home or sheltered housing**	1.00	
	Residential care or other hospital	2.74 (2.48 to 3.02)	<0.001
Walking ability pre fracture	**Walked unaided**	1.00	
	Walked with aids	1.59 (1.43 to 1.76)	<0.001
	Bed/ chair bound	2.42 (1.86 to 3.16)	<0.001
ASA grade	**ASA grades 1-2**	1.00	
	ASA grade 3	2.57 (2.23 to 2.96)	<0.001
	ASA grades 4-5	5.42 (4.63 to 6.35)	<0.001
Fracture type	**Displaced capsular**	1.00	
	Undisplaced intracapsular	0.78 (0.64 to 0.94)	0.01
	Basocervical	1.27 (1.01 to 1.59)	0.04
	Intertrochanteric (2 fragments)	1.16 (1.03 to 1.31)	0.02
	Intertrochanteric (>2 frags)	1.36 (1.18 to 1.57)	<0.001
	Subtrochanteric	1.21 (0.91 to 1.61)	0.2
Pressure sores	**Present pre fracture**	1.52 (1.36 to 1.69)	<0.001
Delay to surgery	**No delay**	1.00	
	Administrative delay	0.96 (0.83 to 1.11)	0.6
	Patient medically unfit	1.85 (1.64 to 2.09)	<0.001
	Other reason for delay	1.29 (1.07 to 1.55)	0.008
Prophylaxis	**Antibiotics**	1.19 (1.02 to 1.39)	0.02
	Aspirin	0.82 (0.73 to 0.91	<0.001
	Heparin	1.15 (1.04 to 1.27)	0.005
	GEC stockings	0.74 (0.66 to 0.82)	<0.001
	No thromboprophylaxis	1.32 (1.15 to 1.52)	<0.001

Table 4.4 Results of multivariate Cox proportional hazards regression analysis describing the association between key SHFA variables and mortality in the 120 days following hip fracture admission

n=8470

Hospital was also included in the analysis but the results are not shown.

Source: SHFA (1998 to 2003)

Variable	Category	HR (95% CI)	p value
Sex	**Female**	0.50 (0.45 to 0.56)	<0.001
Age	**70-74**	1.78 (1.26 to 2.51)	0.001
	75-79	2.01 (1.46 to 2.77)	<0.001
	80-84	2.87 (2.11 to 3.90)	<0.001
	85-89	3.56 (2.63 to 4.83)	<0.001
	90+	4.21 (3.10 to 5.72)	<0.001
Residence	**Residential care or other hospital setting**	1.90 (1.71 to 2.11)	<0.001
ASA grade	**ASA grade 3**	2.00 (1.73 to 2.31)	<0.001
	ASA grades 4-5	3.63 (3.06 to 4.31)	<0.001
Fracture type	**Displaced capsular**		
	Undisplaced intracapsular	0.88 (0.72 to 1.07)	0.2
	Basocervical	1.12 (0.90 to 1.41)	0.3
	Intertrochanteric (2 fragments)	1.06 (0.94 to 1.20)	0.3
	Intertrochanteric (multifragment)	1.33 (1.15 to 1.54)	<0.001
	Subtrochanteric	1.16 (0.87 to 1.55)	0.3
Pressure sores	**Present prior to surgery**	1.32 (1.17 to 1.50)	<0.001
Delay to surgery	**Administrative delay**	0.90 (0.77 to 1.05)	0.2
	Medically unfit	1.35 (1.18 to 1.53)	<0.001
	Other	1.09 (0.90 to 1.32)	0.4
Thrombo-prophylaxis	**Aspirin**	0.81 (0.71 to 0.92)	0.002

5 SHFA-SMR linked database 1998-2003

5.1 Introduction

Using SHFA data, the results set out in the previous chapter suggested that use of aspirin as thromboprophylaxis may reduce mortality in the first four months following admission with hip fracture. Additional information is available from the SMR database as described in chapter 3, and SHFA and SMR records have been linked to provide a more detailed analysis.

5.2 Background

Previous chapters have set the context and described the methodology used in this chapter. The importance of adjusting for various cofactors and comorbidities was highlighted in the literature review (chapter 2). The options for studying these cofactors and comorbidities have been discussed in chapters describing SMR (chapter 3) and SHFA (chapter 4). The principals behind record linkage are described in chapter 3.

5.3 Rationale

5.3.1 Objective 4a. To describe relevant SMR variables for SHFA participants receiving different types of thromboprophylaxis

The characteristics of patients receiving different types of thromboprophylaxis have been described for SHFA variables (chapter 4). Linked SHFA-SMR data offer the opportunity to combine the detailed information relevant to hip fracture and short term (120 day) follow-up data from SHFA with comorbidity, socio-economic status and long-term follow-up data available through SMR.

5.3.2 Objective 4b. To study the association between different types of thromboprophylaxis and mortality before and after adjusting for comorbidities and cofactors

The literature review has identified a need for more evidence relating to the influence of different types of thromboprophylaxis on long-term survival following hip fracture. The influence of thromboprophylaxis on mortality during the year following hip fracture is assessed using the linked SHFA–SMR database.

5.3.3 Objective 4c. To study the association between different types of thromboprophylaxis and secondary endpoint before and after adjusting for comorbidities and cofactors

There is evidence using SHFA data of a survival benefit over 120 day follow-up with aspirin (chapter 4). The proposed mechanism is through a reduction in TED and CHD. The influence of thromboprophylaxis on combined inpatient episodes or deaths from TED or CHD over a one year period is studied, adjusting for the cofactors and comorbidities identified in preceding chapters.

5.4 Methods

Analysis was performed using the approaches already described in chapters 3 and 4. The categories selected for the analysis (listed in tables 5.1 and 5.2) were based on the findings of the two previous chapters. The index admission was identified from SHFA, and the SHFA record linked to SMR records using probability matching, as described in section 3.4.4. The SMR record identified by record linkage had to be related to hip fracture (ICD-10 codes S70-79) and had to occur within one month of the SHFA record. Complete data were identified for 8470 SHFA participants (section 4.4.1).

Cox proportional hazards regression analysis was performed using the forward conditional method, as described in chapter 3, but using all-cause mortality (primary endpoint) and deaths or inpatient episodes with TED or CHD (secondary endpoint) during the year following hip fracture admission. Tests for interactions between variables included in the Cox analysis were undertaken. The analysis was repeated after excluding patients who died within 5 days of hip fracture admission to explore the possibility that patients may have died before thromboprophylaxis was administered or had a chance to take effect (see section 4.4.5).

5.5 Results

5.5.1 Objective 4a. To describe relevant SMR variables for SHFA participants receiving different types of thromboprophylaxis (n=8470)

Overall 6495 (76.7%) patients had been admitted to hospital at least once in the five years prior to the hip fracture admission. Details of these inpatient episodes are shown in table 5.1, dividing results for patients documented as having received aspirin, heparin, GEC stockings or no thromboprophylaxis. Patients with previous inpatient episodes with CVD were more likely to be documented as having received aspirin during the hip fracture admission, while the reverse was true for patients with previous inpatient episodes with respiratory disease. Patients with previous inpatient episodes with respiratory disease were more likely to receive heparin during the hospital admission. Patients with no previous hospital inpatient episodes in the previous five years were less likely to be documented as having received aspirin during the hip fracture admission but were more likely to be documented as having received heparin. The median length of the hip fracture admission recorded in the SHFA-SMR database was 23 days (interquartile range 11 to 49 days).

5.5.2 Objective 4b. To study the association between different types of thromboprophylaxis and mortality before and after adjusting for comorbidities and cofactors (n=8470)

There were 2531 deaths in the year following hip fracture admission (29.9%; 95% CI 28.9 to 30.9%). Results of univariate analysis for the association of SHFA variables with all-cause mortality are shown in table 5.2. Mortality at one year was associated strongly with age, residence, ASA grade, intertrochanteric fracture, pressure sores, and

delay for medical reasons. For SMR variables (table 5.3), mortality at one year was associated strongly with the number of previous inpatient episodes, previous inpatient episodes with CVD or respiratory disease and documentation of cancer registration. There was no apparent association however between mortality and the Scottish Index of Multiple Deprivation.

Both aspirin and GEC stockings were associated with lower mortality in univariate analysis and multivariate analysis. Compared to the results of univariate analysis, however, adjusting for cofactors in multivariate analysis attenuated the apparent protective effect of GEC stockings (HR increased from 0.80 to 0.88) and amplified the apparent protective effect of aspirin (HR decreased from 0.92 to 0.86). The findings persisted after interaction terms* were included in the model. After repeating the analysis to exclude patients who died in the first 5 days following hip fracture, however, neither the association between aspirin nor GEC stockings and mortality remained statistically significant.

* There were statistically significant interactions between age category and each of the following: ASA grade, no thromboprophylaxis and cancer registration. There were also statistically significant interactions between number of inpatient episodes in the 5-years prior to hip fracture admission and documentation of previous inpatients episodes with CVD or cancer registration.

5.5.3 Objective 4c. To study the association between different types of thromboprophylaxis and the secondary endpoint before and after adjusting for comorbidities and cofactors (n=8470)

As described in section 3.5.3, 275 (3.3%; 95% CI 2.8 to 3.6%) patients had at least one inpatient episode attributed to CHD/ TED and 422 (5.0%; 95% CI 4.5 to 5.4%) patients had the primary cause of death recorded as CHD and/ or TED in the year following hip fracture. In total 628 (7.4%; 95% CI 6.9 to 7.8%) patients had the secondary endpoint recorded in SMR in the year following hip fracture admission. Figure 5.1 shows Kaplan Meier curves for inpatient episodes and deaths in the year following hip fracture recorded as being due to TED or CHD, while figure 5.2 shows the Kaplan Meier curve for all-cause mortality. The highest event rate (deaths or inpatient episodes) was in the period immediately after hip fracture admission. The rate of inpatient episodes due to CHD or TED fell following discharge from hospital as indicated by the sharp fall in the gradient of the curve for inpatient episodes with CHD or TED in figure 5.1. No equivalent fall in gradient was observed for deaths from CHD or TED or all-cause mortality (figure 5.2).

Using Cox proportional hazards regression analysis there was no statistically significant influence of either aspirin, heparin, GEC stockings or receiving no thromboprophylaxis on the secondary endpoint within one year of hip fracture admission, using either univariate or multivariate analysis (results not shown).

5.6 Discussion

The analysis presented in this chapter has a number of factors in common with the analysis presented in chapter 4. Both analyses used Cox proportional hazards regression analysis and both used the same number of SHFA participants. There were, however some important differences between the analyses. The linked SHFA-SMR database provided information about previous inpatient episodes and cancer registrations, and provided information about both primary and secondary endpoints for a whole year following the hip fracture admission. However the outcomes in the SHFA-SMR analysis were based on retrospective identification using record linkage whereas the SHFA data were collected prospectively and may therefore have been more accurate.

The number of previous inpatient episodes, previous inpatient episodes with CVD or respiratory disease and cancer registration had an important influence on univariate analysis (table 5.3) and multivariate analysis (table 5.4). However, in multivariate analysis the hazard ratio for previous inpatient episodes with CVD was only modestly increased at 1.14 (95% CI 1.04 to 1.25) and was lower than previous inpatient episodes with respiratory disease (HR 1.28; 95% CI 1.14 to 1.44) and registration with cancer (HR 1.74; 95% CI 1.49 to 2.04). The lower than expected association between CVD and mortality is consistent with the findings of the recent study by Roche *et al* discussed in section 2.7[47].

Socio-economic status, measured by SIMD, did not have an independent effect on mortality in multivariate analyses. The absence of an influence with SIMD may be explained in two ways. First, the estimate of SIMD for an area may not have accurately

reflected the socio-economic status of hip fracture patients living in that area as hip fracture patients are typically elderly, retired, may be socially isolated and commonly have high levels of dependency and medical illness. Secondly, socio-economic status may have influenced the Cox regression models through other variables including the number of previous inpatient episodes and the type of medical conditions, hence masking the influence of SIMD on mortality. The former explanation appears to be the most likely, as death rates following hip fracture in more deprived areas were not significantly higher than more affluent areas in univariate analysis.

This analysis, using SHFA-SMR linked data, suggests that aspirin and GEC stockings are associated with lower mortality following hip fracture. This finding is independent of potential confounding factors recorded in the SMR and SHFA databases. Heparin did not have a statistically significant influence on mortality. The findings for aspirin and heparin are consistent with those presented in chapter 4. The finding that GEC stockings had a statistically significant protective effect was not observed in the analysis of SHFA data alone, but may be explained by the higher event rate during the longer period of follow up using linked SHFA-SMR data, resulting in greater statistical power. The apparent protective effect observed with GEC stockings demonstrated in the linked SHFA-SMR data provides evidence for an intervention that has been little studied to date (as noted in systematic reviews and guidelines[19]), but would be consistent with the findings of a meta-analysis of studies of general surgery, though these studies used TED as the endpoint rather than all-cause mortality[13].

There may be other explanations for the apparent protective effect of aspirin and/or GEC stockings. In common with the analysis presented in chapter 4, the findings may be explained by residual confounding. Patients who received GEC stockings were younger and had better functioning prior to hip fracture (table 4.1), explaining why the apparent protective effect of GEC stockings was attenuated in multivariate analysis. However, patients documented as receiving GEC stockings may have been fitter in other ways that were not measured in the SHFA or SMR databases – for example, patients may not have received GEC stockings if they had leg swelling or poor skin condition, factors that may be associated with unfavourable states including heart failure, prolonged immobility, peripheral vascular disease or systemic steroid treatment. However, in one recent study of the elderly hip fracture population in the UK only 2% of patients received steroids[47].

Patients documented as receiving aspirin may have been at higher risk than other patients, with a higher proportion of patients documented with previous inpatient episodes due to CVD, but as discussed on page 107 the opposite may also be true. Indeed, patients documented as taking aspirin were less likely to have documentation of respiratory disease or cancer (table 5.1).

The reliance on SMR data to identify patients with pre-existing CVD is a potential source of bias. It is possible, for example, that patients with severe pre-existing CVD would have been less likely to have been admitted to hospital with CVD if they were elderly or had inoperable disease, and as a result these patients could be underrepresented in SMR data. Younger and fitter patients and those with first onset of symptoms of CVD may have been more likely to have been admitted to hospital for

investigation and treatment (including revascularisation) and this group may have had a better prognosis following hip fracture surgery.

Despite the apparent reduction in mortality with GEC stockings and aspirin there was no evidence of a reduction in the secondary endpoint of combined deaths or inpatient episodes from TED or CHD with use of thromboprophylaxis. This is in contrast to other studies, which have typically identified an influence of thromboprophylaxis on TED but not all-cause mortality (chapter 2). If the apparent protective influence of aspirin and/or GEC stockings on all-cause mortality was spurious, then no influence on the secondary endpoint would be expected. However, there remains the possibility that different diagnoses recorded for the secondary endpoint were inaccurately or incompletely recorded, so the potential impact of thromboprophylaxis was underestimated. Figure 5.1 provides some evidence for this: while the incidence and detection of CHD and TED is likely to have been highest during the period immediately following hip fracture, there was a noticeable reduction in inpatient episodes due to TED or CHD following discharge from hospital. This suggests either that there was a lower detection rate of these complications in the community, or that patients were being managed in primary care without being admitted to hospital. Deaths recorded in SMR as being caused by TED or CHD may also have had inaccuracies. Myocardial infarction is a common cause of death in Scotland, and it may have been documented as the cause of death where no further exploration of cause was undertaken (the autopsy rate during the period of study was around 6% of deaths). These points provide further evidence of the challenges in dealing with routinely collected data.

5.7 Conclusions

This analysis of the linked SHFA-SMR database provides further evidence that aspirin may protect against all-cause mortality and also provides evidence of a survival benefit with GEC stockings. There were, however, some potential sources of bias and confounding. A randomised controlled trial would be necessary to explore the apparent protective influence of aspirin and GEC stockings further.

5.8 Figures and tables

Figure 5.1 Kaplan Meier curves for inpatient episodes and deaths with CHD/TED in the year following hip fracture

The dotted line shows the median length of hospital stay (23 days)

n=8470 with 275 inpatient episodes and 422 deaths attributed to CHD or TED

Source: SHFA-SMR linked database (1998 to 2003)

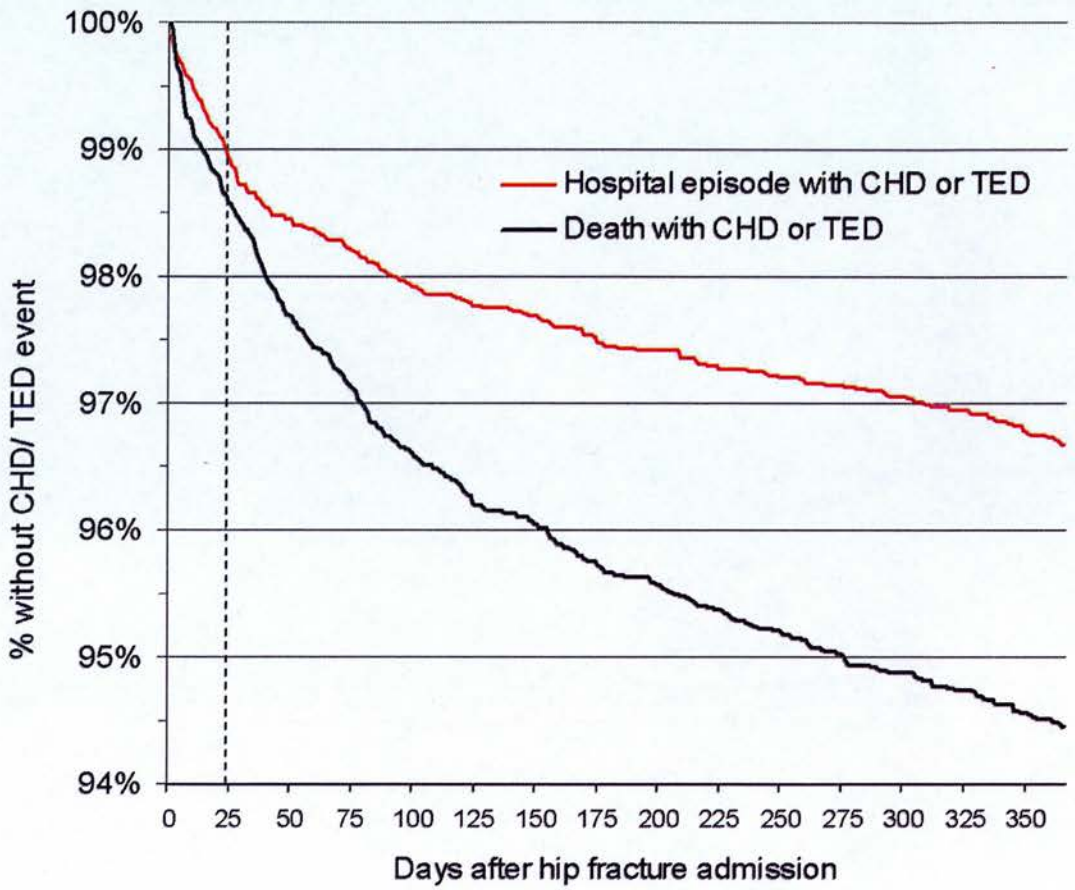


Figure 5.2 Kaplan Meier curves for all cause mortality in the year following hip fracture

The dotted line shows the median length of hospital stay (23 days)

n=8470, with 2531 deaths from all causes

Source: SHFA-SMR linked database (1998 to 2003)

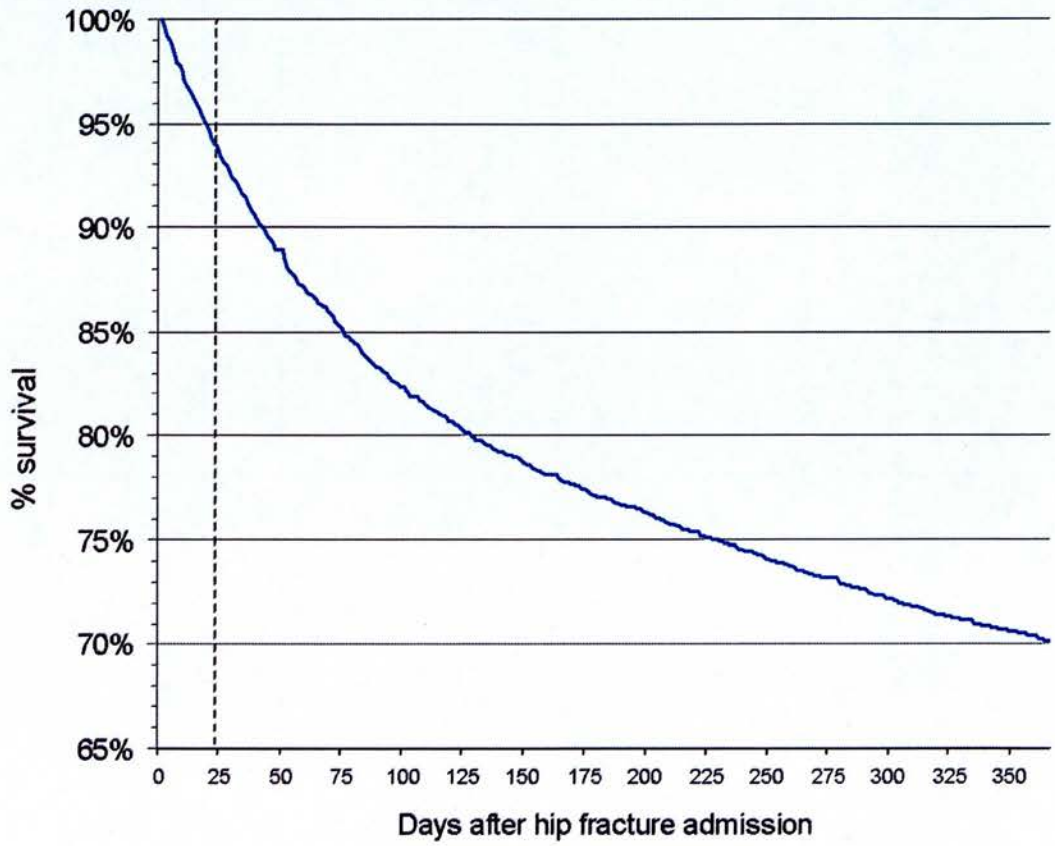


Table 5.1 Number and proportion (%) of patients receiving different types of thromboprophylaxis for each variable included in the Cox proportional hazards regression analysis described in tables 5.2 to 5.4

Where there were significant differences in the findings for a particular variable and type of thromboprophylaxis using the Chi squared test this is indicated as follows: * = p<0.05,** = p<0.001. See tables 4.1 and 4.2 for equivalent data for SHFA variables.

Source: SHFA-SMR linked database (1998 to 2003)

Variable	Category	N and % of total	Thromboprophylaxis (some patients received more than one type) N (%) of patients receiving thromboprophylaxis by category			
			Aspirin	Heparin	GEC stockings	None
Documented medical conditions in the 5-years prior to hip fracture admission	Admission with CVD	2098 (25)	810 (38.6) **	1091 (52.0) **	780 (37.2)	232 (11.1%)
	Admission with respiratory disease	844 (10)	246 (29.1) *	473 (56.0) **	298 (35.3)	108 (12.8%)
	Cancer registration	361 (4)	101 (28.0)	198 (54.8) *	152 (42.1)	38 (10.5%)
Inpatient episodes in the 5-years prior to hip fracture admission	None	1975 (23)	596 (30.2) *	1101 (55.7) **	810 (41.0)	201 (10.2%)
	One	1475 (17)	492 (33.4)	769 (52.1) *	583 (39.5)	169 (11.5%)
	Two to three	2242 (26)	769 (34.3) *	1158 (51.7) **	899 (40.1)	235 (10.5%)
	Four to seven	1875 (22)	605 (32.3)	999 (53.3) **	721 (38.5)	228 (12.2%)
	Eight or more	903 (11)	273 (30.2)	500 (55.4) **	305 (33.8)	121 (13.4%)
Scottish Index of Multiple Deprivation	1-5 (less deprived)	4525 (53)	1450 (32)	2366 (52.3) **	1772 (39.2)	583 (12.9%)
	6-10 (more deprived)	3945 (47)	1285 (32.6)	2161 (54.8) **	1546 (39.2)	371 (9.4%)
Total		8470 (100)	2735 (32.3)	4527 (53.4)	3318 (39.2)	954 (11.3%)

Table 5.2 Univariate analyses describing the association between key SHFA variables and mortality in the year following hip fracture

Source: SHFA-SMR linked database (1998 to 2003)

Variable	Category	Hazard ratio (95% CI)	p value
Sex	**Male**	1.00	
	Female	0.59 (0.54 to 0.65)	<0.001
Age (years)	**60-69**	1.00	
	70-74	1.45 (1.14 to 1.85)	0.003
	75-79	1.68 (1.35 to 2.09)	<0.001
	80-84	2.41 (1.95 to 2.97)	<0.001
	85-89	3.13 (2.55 to 3.85)	<0.001
	90+	4.00 (3.26 to 4.93)	<0.001
Residence prior to hip fracture	**Own home or sheltered housing**	1.00	
	Residential care or other hospital	2.54 (2.35 to 2.75)	<0.001
ASA grade	**ASA grades 1-2**	1.00	
	ASA grade 3	2.31 (2.08 to 2.57)	<0.001
	ASA grades 4-5	4.70 (4.16 to 5.32)	<0.001
Intertrochanteric fracture	**No**	1.00	
	Yes	1.20 (1.11 to 1.30)	<0.001
Delay to surgery	**No**	1.00	
	Yes	1.70 (1.55 to 1.87)	<0.001
Pressure sore pre surgery	**No**	1.00	
	Yes	1.51 (1.39 to 1.65)	<0.001
Prophylaxis	**Heparin**	1.05 (0.97 to 1.13)	0.3
	GEC stockings	0.80 (0.74 to 0.87)	<0.001
	Aspirin	0.92 (0.84 to 1.00	0.04
	No thromboprophylaxis	1.24 (1.10 to 1.39	<0.001

Table 5.3 Univariate analysis describing the association between key SMR variables and mortality in the year following hip fracture

Source: SHFA-SMR linked database (1998 to 2003)

Variable	Category	Hazard ratio (95% CI)	p value
Inpatient episodes in the 5 years prior to hip fracture admission	**None**	1.00	
	1 episode	1.40 (1.22 to 1.62)	<0.001
	2-3 episodes	1.79 (1.57 to 2.02)	<0.001
	4-7 episodes	2.16 (1.90 to 2.45)	<0.001
	8+	2.83 (2.46 to 3.25)	<0.001
Prior hospital episodes with CVD	**No**	1.00	
	Yes	1.60 (1.47 to 1.74)	<0.001
Prior hospital episodes with respiratory disease	**No**	1.00	
	Yes	1.84 (1.65 to 2.05)	<0.001
Cancer registration	**No**	1.00	
	Yes	1.82 (1.56 to 2.12)	<0.001
Scottish Index of Multiple Deprivation	**Deciles 1-5**	1.00	
	Deciles 6-10	0.95 (0.88 to 1.03)	0.2

Table 5.4 Multivariate analysis looking at the association between key SHFA and SMR variables and mortality in the year following hip fracture

The analysis included each of the variables listed in tables 5.2 and 5.3, but the model included only those identified as being statistically significant using the forward conditional method. Hospital was also included (data are not shown).

Source: SHFA-SMR linked database (1998 to 2003)

Variable	Category	HR (95% CI)	p value
Sex	**Male**	1.00	
	Female	0.55 (0.50 to 0.60)	<0.001
Age	**60 to 69 years**	1.00	
	70 to 74 years	1.37 (1.07 to 1.75)	0.01
	75 to 79 years	1.54 (1.24 to 1.93)	<0.001
	80 to 84 years	2.22 (1.79 to 2.74)	<0.001
	85 to 89 years	2.76 (2.24 to 3.40)	<0.001
	90+ years	3.30 (2.66 to 4.08)	<0.001
Pre-fracture residence	**Own home or sheltered housing**	1.00	
	Nursing home or other hospital	1.77 (1.63 to 1.93)	<0.001
ASA grade	**ASA grade 1-2**	1.00	
	ASA grade 3	1.72 (1.54 to 1.92)	<0.001
	ASA grade 4-5	2.83 (2.47 to 3.24)	<0.001
Pressure sores prior to surgery	**No**	1.00	
	Yes	1.25 (1.13 to 1.38)	<0.001
Delayed to surgery because medically unfit	**No**	1.00	
	Yes	1.27 (1.15 to 1.41)	<0.001
Number of inpatient episodes prior to hip fracture	**None**	1.00	
	1 episode	1.16 (1.00 to 1.34)	0.05
	2-3 episodes	1.19 (1.04 to 1.35)	0.01
	4-7 episodes	1.26 (1.10 to 1.45)	0.001
	8+ episodes	1.41 (1.20 to 1.66)	<0.001
Prior hospital episodes with CVD	**No**	1.00	
	Yes	1.14 (1.04 to 1.25)	0.007
Prior hospital episodes with respiratory disease	**No**	1.00	
	Yes	1.28 (1.14 to 1.44)	<0.001
Cancer registration	**No**	1.00	
	Yes	1.74 (1.49 to 2.04)	<0.001
Thromboprophylaxis	**GEC stockings**	0.88 (0.80 to 0.97)	0.01
	Aspirin	0.86 (0.78 to 0.95)	0.004

6 Interpretation

6.1 Introduction

This chapter brings together the findings of the literature review (chapter 2) and the results of SHFA and SMR databases (chapters 3 to 5) to answer the research questions identified in chapter 1. The plausibility of the findings is explored by considering the pathogenesis of TED and the wider effects of different types of thromboprophylaxis. Finally, recommendations for further research are made based on the findings of this work.

6.2 Background

Studies based on radiological and/or autopsy findings suggest that TED is common following hip fracture, as highlighted in guidelines internationally[3;5]. Unfortunately, however, there have been no large long-term follow up studies of hip fracture patients that adequately document TED in the modern era of hip fracture treatment (see objective 1a, chapter 2). Additionally, there remains uncertainty about the influence of thromboprophylaxis on all-cause mortality following hip fracture (see objective 1c, chapter 2). Scottish data (chapters 3 to 5) may provide information about the epidemiology of TED and effectiveness of thromboprophylaxis that is not available from the published literature.

6.3 Research questions

6.3.1 Question 1. What is the likely burden of TED following hip fracture?

Two studies identified in the literature review provided information about the long-term incidence of TED following hip fracture. Between 2 and 3% of hip fracture patients developed clinical PE in the year following hip fracture, but the overall burden of TED was not documented (section 2.5.1.1). Chapter 3 provides data about the proportion of patients developing TED following hip fracture in Scotland using SMR data (table 3.9), and figure 5.1 shows the timing of these events in relation to the date of the hip fracture admission. Almost 90% of patients included in the analysis presented in chapters 4 and 5 were documented as having received thromboprophylaxis but information about radiological testing was not available.

The incidence of pulmonary embolism following hip fracture identified using SMR data was lower than previous studies. The difference, however, is as likely to be explained by the reliance on routinely collected hospital discharge data as by differences in the incidence of TED (see section 5.6). Overall, findings from the published literature (chapter 2) and SMR data (chapter 3) suggest that clinically identified TED is uncommon in the year following hip fracture. However, the estimated incidence of clinical TED identified in the literature review and from SMR data do not necessarily accurately estimate the overall burden of TED and it remains possible that there is a high incidence of undetected TED contributing to morbidity and mortality following hip fracture, which would be consistent with the findings of studies based on radiological or autopsy findings (section 2.5.1.5).

There is therefore an unresolved paradox in the study of TED following hip fracture. Studies based on clinical findings are likely to underestimate the burden of clinically relevant TED, regardless of the use of radiological investigation to confirm the diagnosis. In contrast, studies based purely on radiological findings or autopsy examination are likely to overestimate the burden of clinically relevant TED as autopsies are likely to be performed on an unrepresentative sub-group of the population. The burden of TED following hip fracture is therefore unclear, particularly in the era of widespread thromboprophylaxis, and this research question is unlikely to be answered satisfactorily using existing methods of investigation.

6.3.2 Question 2. Did outcomes in hip fracture patients alter following the launch of the first national evidence-based guidelines in 1997?

Trends in hip fracture mortality between 1986 and 2003 provide some information with which to answer this research question (objective 2b). Compared to patients admitted with hip fracture between 1986 and 1991, patients admitted between 1998 and 2003 had a lower mortality at one year (hazard ratio 0.87; 95% CI 0.85 to 0.90, $p<0.001$). It is not possible, however, to prove that the guidelines, and specifically the advice about thromboprophylaxis, have led to the apparent reduction in mortality. There remains the possibility that the findings may be explained by residual confounding, a potential drawback of all epidemiological research and one that limits any further interpretation of these data. More sophisticated approaches are therefore required to study the effect of thromboprophylaxis on mortality, as described below.

6.3.3 Question 3. Is there evidence of improved survival in hip fracture patients who have received different types of thromboprophylaxis, and does this relationship persist after adjusting for cofactors?

This study provides evidence for a protective effect of aspirin (chapters 4 and 5) and GEC stockings (chapter 5), before and after adjusting for cofactors. There was no evidence of a protective effect of heparin (chapters 4 and 5) and this remained the case when the analysis was repeated for LMWH (results not shown). Each of these findings may however be explained by residual confounding. The plausibility of these findings is explored in section 6.4.

The apparent protective effect of aspirin and GEC stockings following hip fracture is a potentially important finding. Each year in Scotland there are around 5,700 hip fractures in patients aged 60 years and over (section 1.2). Approximately 1710 (30%) of these patients would be expected to die in the first year following hip fracture admission (section 5.5.2). The findings of this study suggest that use of GEC stockings or aspirin could reduce mortality by 12% and 14% respectively (table 5.4). If the estimated 44% of hip fracture patients* who do not currently receive GEC stockings or

* See table 4.2. Of the 8470 SHFA participants included in the analysis 2029 (24%) were documented as receiving GEC stockings, 1446 (17%) were documented as receiving aspirin and 1289 (15%) were documented as receiving both GEC stockings and aspirin. Overall 4764 (56%) SHFA participants included in this analysis were documented as receiving GEC stockings and/ or aspirin.

aspirin were to be treated with these types of thromboprophylaxis, then the additional number of deaths prevented in the year following hip fracture in Scotland is estimated at 90 (for GEC stockings) and 105 (for aspirin).

6.3.4 Question 4. If a particular type of thromboprophylaxis has an influence on survival, then is this relationship explained by changes in the incidence of secondary outcomes following hip fracture (thromboembolic disease, CVD and haemorrhage)?

As explained in section 2.9, the analysis of secondary outcomes focused on CHD rather than CVD and did not include haemorrhagic events. Despite an apparent reduction in mortality with GEC stockings and/or aspirin following hip fracture there was no detectable influence of GEC stockings and/or aspirin on combined TED and CHD following hip fracture. There are a number of possible explanations for the lack of an apparent reduction in the secondary endpoint with different types of thromboprophylaxis, particularly relating to the reliance on hospital discharge data (section 5.6).

6.3.5 Question 5. How representative of elderly hip fracture patients were the patients included in this analysis?

The results presented in section 3.5.3 suggest that the group of SHFA participants included in this study were very similar to the general population of hip fracture patients aged 60 years and over in Scotland. Although there were differences between the groups, these were minor and the groups were similar in terms of age, sex, prevalence of comorbidities and mortality. More important differences were identified for socio-economic class, with an under-representation of patients from more deprived areas. This may not be a major limitation given the observed lack of association between

deprivation and mortality following fracture. Overall however, with certain caveats, the findings of this study can be generalised to the general population of hip fracture patients in Scotland aged 60 years and over.

The findings of this study are likely to be more representative of the general elderly hip fracture patients than many other studies. In the literature review (chapter 2) for example, patients with severe systemic illness were excluded from some studies, and some studies excluded patients with prior TED or very elderly patients. The mortality rate in some studies was much lower than expected, and the median mortality at a year in the studies identified at stage 6 of the literature review (figure 2.1) was 20%, much lower than that expected from Scottish data (30%)[3]. The paper by Roche *et al* was one recent exception, recording a mortality rate of 33% at one year[47].

6.4 Plausibility of the findings

There are insufficient data from randomised controlled trials to assess the plausibility of the findings of this study. The Cochrane review of thromboprophylaxis in hip fracture patients identified no adequately powered studies of mechanical methods of thromboprophylaxis including stockings[19], and the most recent SIGN guideline on hip fracture states that there is "no evidence for [the use of graduated elasticated support stockings] in hip fracture patients"[3] despite evidence suggesting a reduction in TED associated with their use in patients undergoing general surgery[13]. While low dose aspirin is recommended in the SIGN guideline for hip fracture[3], this guidance was based on the PEP trial which identified a reduction in clinical TED rather than all-cause mortality[20]. Much of the existing trial evidence for thromboprophylaxis in hip fracture relates to the use of different types of heparin, studying clinical and radiological TED rather than mortality. There is evidence of publication bias in the limited number of studies that have studied the influence of heparin on mortality following hip fracture (section 2.5.3).

The plausibility of the findings of this study can, however, be explored further by considering the pathogenesis of TED. Virchow proposed that TED was the result of a triad of factors: vascular endothelial damage, stasis of blood flow, and hypercoagulability of blood[6], each of which occur in the natural history of hip fracture, whether during the initial trauma surgical repair, or recuperation period (section 1.3).

In theory, different types of thromboprophylaxis could have an influence on Virchow's triad and therefore potentially reduce the burden of fatal and non-fatal TED and CHD. Aspirin and heparin may influence endothelial function and the hypercoagulability of

blood, thereby increasing vascular flow in veins and arteries. The same is true of more modern treatments including the novel pentasaccharide/ heparinoid fondaparinux[78]. GEC stockings and other mechanical forms of thromboprophylaxis increase venous flow and this might have an indirect influence on clotting factors and vascular distension, and may reduce endothelial dysfunction as a result[48]. However, each of these interventions act on thrombus formation and development, but do not actively break down clot that has already formed (thrombolysis)[79], so some TED would be expected even in patients receiving these treatments.

It is possible, therefore, that GEC stockings and aspirin *could* reduce TED, but whether they could plausibly cause a reduction in mortality of the magnitude observed in this study is less clear. Aspirin has the advantage that it may be taken long-term, potentially reducing TED and CHD in the elderly population at greatest risk of hip fracture. GEC stockings have the advantage that they do not increase the risk of haemorrhage and may therefore be applied more readily prior to surgery with a resultant reduction in mortality peri-operatively and immediately post-operatively, the period during which most pulmonary emboli occur. However there is no guarantee that stockings are worn properly for the intended period, and there is some anecdotal evidence that they can be poorly fitted and poorly tolerated, reducing compliance and the effectiveness of treatment[3]. A recent qualitative study showed that in palliative care, patients prefer LMWH to GEC stockings[80]. There are also potential explanations for the apparent lack of a treatment effect with heparin. Heparin may not be administered pre-operatively because of concerns about haemorrhage and it is not routinely administered long-term as it is a parenteral treatment.

6.5 *Implications for future research*

This study has illustrated how little is known about interventions that may reduce mortality following hip fracture. Despite many hundreds of randomised controlled trials, dozens of systematic reviews, meta-analyses, and evidence-based guidelines, there remain many inconsistencies in the evidence and gaps in our knowledge of this topic. Indeed many studies included in evidence-based guidelines are now largely of historical interest only as they were conducted in the period before techniques available in modern hip fracture management were commonly available. Hip fracture remains a common condition with a poor prognosis (excess mortality 10 to 20% in the first year following hip fracture compared to an age and sex matched population[1]) so it remains important that these unanswered questions are considered further. Deaths attributed to diseases of the heart or circulation were twice as common in the year following hip fracture admission as deaths attributed to trauma (table 3.8) highlighting the potential importance of medical treatment in hip fracture patients.

This study demonstrates that epidemiological research has an important place in generating and testing hypotheses. However, there is limited potential for further record linkage to study thromboprophylaxis in hip fracture patients in more detail using epidemiological methods. Thromboprophylaxis is no longer adequately documented in the SHFA (since 2004). While there are moves to link SMR records to prescribing data this would only provide limited additional information for hip fracture as the data relate only to primary care and would not include information about GEC stockings (which are dispensed under local arrangements without prescription) or aspirin purchased over the counter.

This work has illustrated the importance of studying mortality rather than surrogate endpoints, reinforcing points made in the Cochrane review of thromboprophylaxis following hip fracture[19]. A reduction in surrogate endpoints such as radiological findings does not necessarily translate to an improvement in survival. This is particularly relevant to hip fracture because of the challenges in the identification of TED. This study suggests that the use of aspirin and GEC stockings after hip fracture should be studied further. Additionally, neither this study nor the Cochrane review of thromboprophylaxis in hip fracture[19] have been able to identify a survival benefit with different types of heparin. This is of importance because heparin is commonly used as thromboprophylaxis (48% of patients in this study). If heparin was proved to be ineffective in reducing mortality and clinical events following hip fracture, this could have important implications for health services and for patients. The use of heparin involves considerable expense to health services, both in prescribing costs (for LMWH) and in the monitoring required to ensure therapeutic levels (for unfractionated heparin). Heparin treatment can also be a source of pain for the patient, requiring repeated injections or intravenous access.

There is therefore an urgent need for an adequately powered randomised control trial (RCT) looking at the impact of each of these different types of thromboprophylaxis on mortality following hip fracture. This study is unlikely to be funded by a pharmaceutical company, so it would depend on support from the Chief Scientist Office or other public sector funding. Such a study would be a major undertaking. In order to detect a reduction in mortality of 10% with aspirin or GEC stockings compared to heparin in the year following hip fracture admission, the minimum estimated sample

size would be 3,500 participants in each treatment limb (patients would receive aspirin, GEC stockings or heparin). In order to recruit all these participants (minimum number=10,500) in Scotland it would be necessary to involve all 15 hospitals participating in SHFA over a period of three years, but this assumes that all patients would agree to participate in the study, which is unrealistic. Given these long timescales and caveats a multicentre international RCT may be more appropriate.

6.6 Proposed research papers resulting from this work

The five research questions addressed above form the focus of a number of research papers that are being prepared for publication in peer-reviewed medical journals. Table 6.1 summarises the papers in preparation at the time of writing (March 2006).

6.7 Conclusions

This study has shown that routinely collected data linked to other relevant data sources can be invaluable, not only in generating hypotheses, but also in estimating the size of treatment effects for therapies and interventions that have, to date, been incompletely investigated using randomised controlled trials. The findings of this study suggest that GEC stockings and/or aspirin (but not heparin) may reduce mortality in the year following hip fracture in patients aged 60 years and over: GEC stockings are estimated to reduce mortality by 12%, while aspirin is estimated to reduce mortality by 14%. These findings are in apparent contradiction to international guidelines and the House of Commons Health Committee report on thromboprophylaxis[5;17;48]. The findings may, however, be explained by residual confounding, and adequately powered multi-centre randomised controlled trials of different types of thromboprophylaxis are necessary to test this. In the interim, hip fracture patients should continue to receive aspirin as

thromboprophylaxis, as recommended in the most recent SIGN guideline for hip fracture[3]. The findings of this study suggest that these patients should also receive GEC stockings, a recommendation that is consistent with advice for other types of major surgery[13].

Mortality following hip fracture remains high in the modern era of hip fracture treatment, and the burden of TED following hip fracture remains uncertain. In the future, studies should concentrate on all-cause mortality rather than surrogate endpoints including clinical and radiological evidence of TED. It will not be possible to improve the survival of hip fracture patients in the future without understanding which treatments and interventions are most effective at reducing mortality. This applies as much to existing treatments including heparin, aspirin and GEC stockings as to novel and expensive treatments including fondaparinux.

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Table 6.1 Proposed research papers resulting from this work

Working title	Summary	Journal for initial submission
The influence of thromboprophylaxis on mortality following hip fracture: results from a prospective cohort study	Uses only prospectively collected data from SHFA (1998 to 2003) studying mortality 120 days after hip fracture admission (see objective 3b). This paper will have more participants than included in this thesis, as fewer exclusions will be necessary: the analysis will include fewer variables and it will not be necessary to exclude all patients with missing SMR data.	Lancet
Hip fracture between 1986 and 2003 in Scotland: Has mortality fallen over time?	Short paper (600 words). Uses SMR data collected between 1986 and 2003 to describe trend data adjusting for age, sex and comorbidities (see objective 2d).	British Medical Journal
The influence of thromboprophylaxis on survival at one year following hip fracture: results from a unique Scottish database	Uses linked SMR and SHFA (1998 to 2003) data to study 1° and 2° outcomes in the year following hip fracture admission (see objectives 4b and 4c).	British Medical Journal or Journal of Bone & Joint Surgery
The epidemiology of TED following hip fracture: literature review and update using hospital discharge data	Systematic literature review identifying existing gaps in the literature, followed by exploration of the role of routinely collected data in addressing these gaps (see objectives 1a and 2c).	Epidemiology

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8 Appendix

8.1 Search strategy (see section 2.4)

8.1.1 MEDLINE

The following search identified descriptive studies for objectives 1a and 1b. The search for randomised controlled trials used the results of step 51 of the search and limited the results to the period between 2001 and 2005 (n=86).

Database: Ovid MEDLINE(R) <1966 to November Week 3 2004>

Search Strategy:

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1 Pulmonary Embolism/ (20839)
2 Thromboembolism/ (13720)
3 Thrombosis/ (36320)
4 Thrombophlebitis/ (18196)
5 Venous Thrombosis/ (6707)
6 Thrombolytic Therapy/ (11393)
7 exp Heparin/ (40952)
8 ((venous or vein$1 or pulmonary) adj25 (thrombo$ or embol$)).tw. (51311)
9 or/1-8 (142297)
10 exp Hip Fractures/ (10147)
11 ((hip$ or femur$ or femoral$ or trochant$ or pertrochant$ or intertrochant$ or subtrochant$ or intracapsular$ or extracapsular$) adj5 fracture$).tw. (15538)
12 or/10-11 (18052)
13 and/9,12 (705)
14 randomized controlled trial.pt. (198393)
15 controlled clinical trial.pt. (68298)
16 randomized controlled trials/ (35630)
17 random allocation/ (52749)
18 double-blind method/ (81218)
19 single-blind method/ (8672)
20 14 or 15 or 16 or 17 or 18 or 19 (336624)
21 limit 20 to animal (25726)
22 limit 20 to human (316495)
23 21 and 22 (7668)
24 21 not 23 (18058)
25 20 not 24 (318566)
26 clinical trial.pt. (399808)
27 exp clinical trials/ (162674)
28 clin$ with trial$.tw. (83384)
29 placebos/ (23656)
30 placebo$.tw. (87925)
31 random$.tw. (301887)
32 exp research design/ (188452)

33 26 or 27 or 28 or 29 or 30 or 31 or 32 (737686)
34 limit 33 to animal (93078)
35 limit 33 to human (653829)
36 34 and 35 (34437)
37 34 not 36 (58641)
38 33 not 37 (679045)
39 comparative study/ (1178202)
40 exp evaluation studies/ (510452)
41 follow-up studies/ (293938)
42 prospective studies/ (182927)
43 (control$ or prospectiv$ or volunteer$).tw. (1515193)
44 39 or 40 or 41 or 42 or 43 (3021424)
45 limit 44 to animal (906149)
46 limit 44 to human (2088953)
47 45 and 46 (201490)
48 45 not 47 (704659)
49 44 not 48 (2316765)
50 25 or 38 or 49 (2535115)
51 13 and 50 (366)
52 graduated elasticated support stockings.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (0)
53 stockings.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (838)
54 stockings.mp. (838)
55 compres$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (52211)
56 stock$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (16450)
57 ted.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (239)
58 aspirin.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (33842)
59 exp ASPIRIN/ (26196)
60 thromboproph$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading] (764)
61 warfarin.mp. or WARFARIN/ (10660)
62 heparin.mp. (58231)
63 Dextrans/ or low molecular heparin.mp. (15700)
64 mobili$.mp. (88626)
65 or/52-64 (264660)
66 65 and 12 (1672)
67 9 and 12 (705)
68 66 or 67 (2097)
69 68 not 51 (1731)
70 from 69 keep 1-274 (274)
71 limit 70 to yr=1990 - 2005 (269)
72 from 71 keep 1-269 (269)

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8.1.2 EMBASE

The following search identified descriptive studies for objectives 1a and 1b. The search for randomised controlled trials used the results of step 32 of the search and limited the results to the period between 2001 and 2005 (n=149).

Database: EMBASE <1988 to 2004 Week 47>

Search Strategy:

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1 Lung Embolism/ (13173)
2 Thromboembolism/ (14638)
3 thrombosis/ or deep vein thrombosis/ or leg thrombosis/ or postoperative thrombosis/ (34396)
4 anticoagulant therapy/ or fibrinolytic therapy/ (13814)
5 exp Anticoagulant Agent/ (149160)
6 Heparin/ (40514)
7 ((venous or vein$1 or pulmonary) adj25 (thrombo$ or embol$)).tw. (33919)
8 or/1-7 (195176)
9 exp Hip Fracture/ (7087)
10 ((hip$ or ((femur$ or femoral$) adj3 (neck or proximal))) adj4 fracture$).tw. (6367)
11 or/9-10 (8949)
12 and/8,11 (655)
13 controlled-study.sh. (1820979)
14 crossover-procedure.sh. (15520)
15 double-blind-procedure.sh. (49197)
16 phase-3-clinical-trial.sh. (6077)
17 placebo$.tw. (68324)
18 randomized-controlled-trial.sh. (89760)
19 single-blind-procedure.sh. (4986)
20 blind$.tw. (83889)
21 comparative study.tw. (17061)
22 (control$ adj1 trial$).tw. (29994)
23 cross?over$.tw. (17205)
24 factorial$.tw. (4645)
25 random$.tw. (231910)
26 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 (1973007)
27 human.sh. (3975960)
28 nonhuman.sh. (2008321)
29 27 and 28 (310044)
30 28 not 29 (1698277)
31 26 not 30 (1185495)
32 12 and 31 (247)
33 stockings.mp. or Compression Therapy/ or elastic stockings/ or Leg Compression/ (3131)
34 ted.mp. (243)
35 aspirin.mp. or Acetylsalicylic Acid/ (50317)
36 thromboprophylaxis.mp. or Thrombosis Prevention/ (2118)

37 thromboproph$.mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (730)
38 warfarin.mp. or WARFARIN/ (18991)
39 low molecular heparin.mp. or Low Molecular Weight Heparin/ (8776)
40 heparin.mp. (51273)
41 DEXTRAN SULFATE/ or DEXTRAN 70/ or DEXTRAN/ or DEXTRAN 60/ or dextran.mp. or DEXTRAN 40/ or DEXTRAN DERIVATIVE/ (13360)
42 mobili$.mp. (63349)
43 or/33-42 (179265)
44 43 or 8 (276460)
45 44 and 11 (1125)
46 45 not 32 (878)
47 limit 46 to yr=1990 - 2005 (847)
48 Breast Cancer/ or Hormone Substitution/ or Estrogen/ or Sex Hormone/ or hrt.mp. or Estradiol/ (125617)
49 47 not 48 (741)
50 from 47 keep 1-10 (10)
51 from 47 keep 1-847 (847)

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