The impact of adopting low molecular weight heparin in place of aspirin as routine thromboprophylaxis for patients with hip fracture

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Abstract

Purpose of the Study

In 2010, the National Institute of Health and Care Excellence (NICE) recommended the use of anticoagulants rather than aspirin as pharmacological thromboprophylaxis after hip fracture. We examine the impact of implementing this change in guidance on the clinical incidence of deep vein thrombosis (DVT).

Study design

Demographic, radiographic, and clinical data was retrospectively collected for 5,039 patients admitted to a single tertiary centre in the United Kingdom for hip fracture between 2007-2017. We calculated rates of lower-limb DVT and examined the impact of the June 2010 change of departmental policy, from use of aspirin to use of LMWH in hip fracture patients.

Results

Doppler scans were performed in 400 patients in the 180 days after a hip fracture, and identified 40 ipsilateral and 14 contralateral DVTs ($p<0.001$). The rate of DVT reduced significantly following the 2010 change in departmental policy from aspirin to LMWH in these patients (1.62% vs 0.83%, $p<0.05$).

Conclusions

The rate of clinical DVT halved following the change from aspirin to LMWH for pharmacological thromboprophylaxis, but the number needed to treat was 127. A figure of <1% for the incidence of clinical DVT in a unit that routinely uses LMWH monotherapy following hip fracture provides a context for discussions of alternative strategies, and for power calculations for future research. These figures are important to policy makers and to researchers as they will inform the design of the comparative studies on thromboprophylaxis agents for which NICE has called.

Introduction

Each year, there are around 80,000 hip fractures in the UK, with an annual cost to health and social services in excess of £1 billion [1]. Only a minority of patients completely regain their previous abilities, and increased dependency and difficulty walking mean that a quarter will need long-term care. Patients with hip fracture are at an increased risk of deep vein thrombosis (DVT) due to older age, co-morbidity, immobility, lower-limb fracture, and surgery [2]. This condition carries a risk of serious consequences such as post-phlebitic syndrome and chronic leg ulceration in addition to leading to pulmonary embolism and death [3, 4]. It has been suggested that DVT affects up to 60% of hip fracture patients without post-operative anticoagulation [5-8].

There remains much debate over the choice of pharmacological thromboprophylaxis for patients with hip fracture. There is a trend in the literature suggesting that low molecular weight heparins (LMWH) are superior to aspirin in preventing DVT following fragility hip fractures, but that remains inconclusive [9-13]. Two large scale meta-analysis of trials evaluating DVT thromboprophylaxis following orthopaedic surgery suggested aspirin and LWWH have similar efficacy in elective orthopaedic surgery, with less bleeding associated with aspirin [14, 15]. Looking at the hip fracture subgroup in both meta-analyses, they described inconsistent evidence and a non-significant trend favouring LMWH over aspirin [14, 15]. The National Institute of Health and Care Excellence (NICE) has issued and updated guidance on thromboprophylaxis for people with hip fracture [16, 17]; both guidelines requiring that patients are considered for treatment with low molecular weight heparin

(LMWH) or fondaparinux rather than the low dose aspirin that was commonly offered in previous years [18]. The 2010 guidance recommended that patients should also receive mechanical thromboprophylaxis such as compression stockings, but in its 2018 guideline NICE moved to only recommend this approach as an alternative, for patients who are not suitable for pharmacological thromboprophylaxis.

The topic of aspirin vs LMWH for thromboprophylaxis remains controversial and current NICE guidance identifies this as a key priority for research, asking: "What is the clinical and cost effectiveness of aspirin alone versus other pharmacological and/or mechanical prophylaxis strategies (alone or in combination) for people with fragility fractures of the pelvis, hip or proximal femur?" [17].

Another pressing issue is accurately estimating the rate of clinical DVTs in hip fracture patients with little contemporary evidence characterising the true rates of DVT in these patients and incidence estimates ranging from 1-30% for symptomatic DVT. Most of these trials are based on screening practices that are inconsistent with current clinical approaches or included populations that do not represent UK population demographics [19-24]. Older studies will fail to capture the success of trends towards prompt surgical management with surgery now being performed in 98% of cases, in most cases within 36 hours of presentation [25]. Prompt surgical intervention facilitates early mobilisation, and reduces the risk of complications such as pneumonia, pressure sores and DVT [26].

In this study we therefore set out to examine the rates of clinical DVT in a contemporary setting, to provide a better understanding of this key area of surgical controversy. We compare rates of clinical DVT before and after the publication and implementation of the 2010 NICE guidance, so that use of aspirin as pharmacological thromboprophylaxis can be set against the current recommendation of LMWH.

Methods

This study aimed to define the risk of clinical DVT among all over 60-year-olds with hip fracture presenting to a teaching hospital which serves a population of 445,000 with an age, sex, socioeconomic and ethnic composition comparable to that of the UK as a whole. National clinical audit data from our submissions to the National Hip Fracture Database (NHFD) were used to identify all over 60-year-old patients presenting with hip fracture between 1st March 2007 and the 31st of July 2017, and to define their case-mix, care, and outcome.

In June 2010, in response to new NICE guidance [16] our hospital's thromboprophylaxis policy changed from one which ensured that all patients with hip fracture received aspirin as the first line

form of pharmacological thromboprophylaxis, to one which required, audited, and ensured that all were offered LMWH.

The policy required all patients to be offered a dose of enoxaparin appropriate to their weight and renal function for a month after presentation with a hip fracture. Specific exclusions applied in a limited number of situations: risk of CNS bleed (e.g., unstable spinal injury, new-onset stroke, head injury or subarachnoid haemorrhage); severe liver disease; known bleeding disorder; heparin induced thrombocytopenia; heparin allergy. In other situations, the start of enoxaparin would be delayed and reviewed daily: active bleeding (e.g., GI bleed, 'open book' pelvic fracture); platelet count <70; patients receiving therapeutic anticoagulation; acute kidney injury; uncontrolled systolic hypertension >180mmHg.

Our policy in respect to mechanical thromboprophylaxis also followed the 2010 guidance in that it recommended the use of compression stockings. However, in practice these were very rarely used as clinical staff and patients found the stockings too painful to apply after a hip fracture, and analysis of DVT rates in our department questioned their safety [27]. Thus, our practice across the whole study period anticipated current NICE guideline which in 2018 recommended that mechanical prophylaxis is only appropriate when pharmacological measures are contraindicated [17].

As part of local clinical governance work, our Department of Medical Physics identified all lower limb Doppler ultrasound scans that been performed for any of these patients at any time in this study period. Throughout the study period health board guidance defining the criteria of clinical indications to scan patients remained consistent. We then cross-referenced the dates and results of the Doppler scans to determine rates of DVT in our population and to compare the rates before and after the change from aspirin to LMWH. We collected and analysed data from 6 months before the injury to establish baseline DVT rates within our population demographic and 6 months following the injury to assess for the effect of hip fracture and chemical thromboprophylaxis on rate of DVT. Scans that were performed within 6 months following fracture were considered clinically relevant to the hip fracture and were included in the final analysis.

Statistical analysis to determine significance in results between groups was done using Chi-Squared test with Yates correlation, statistical significance was defined as p value<0.05.

Results

Our local NHFD database identified a total of 5,583 over 60-year-old patients presenting during the 1st March 2007 to 31st of July 2017 study period (figure 1). A total of 544 of these were excluded from further analysis as they were normally resident outside the catchment and follow-up area of our

hospital. The remaining 5,039 patients had a mean age of 82.8 years (standard deviation 11.1) and included 2,754 women (54.7%), with no statistically significant differences in demographic characteristics between the groups who received aspirin and those who received LMWH as their thromboprophylaxis.

Cross-referencing these patients' medical records with the results of all Doppler ultrasounds performed by our department of Medical Physics identified a total of 913 patients (18.1%) who had required a Doppler ultrasound scan at some point during the 10-year study period (Figure 1). Many of these ultrasound scans were not related to the hip fracture; 307 which had been performed prior to their index presentation with hip fracture were used to provide baseline DVT rates in our population and 206 performed more than 6 months after the hip fracture event were excluded as not clinically related to the fracture. This left a total of 400 Doppler scans (43.8%) performed within the 'relevant' 6-month period following a hip fracture.

In total 1,542 patients presented before, and 3,497 following, the 2010 change in policy from aspirin to LMWH for thromboprophylaxis (Table 2). There was no statistically significant difference in patient demographics for those who sustained hip fracture before or after 2010. The rate of 'relevant' clinical DVTs reduced significantly following the change in thromboprophylaxis policy; from 1.62% (aspirin) to 0.83% (LMWH) of all patients with hip fracture ($p=0.012$, Figure 2).

The standardised rate of DVT in the 6 months after a hip fracture was 1.35% compared to a baseline rate of 0.98% in the 6 months prior to a hip fracture (used as a comparator time period). This implies an increase of 37.8% in the risk of DVT as a consequence of a hip fracture. Additionally, we observed a significant tendency for DVT to occur on the ipsilateral side (10/1000) compared to the contralateral side (3.5/1000) to the injury ($p<0.001$).

Discussion

Attitudes to thromboprophylaxis after hip fracture have been influenced by historical studies which screened for asymptomatic DVT. For instance, the studies described as of 'poor quality' in the Cochrane analysis reported DVT rates of 42% for controls and 26% with LMWH [28]. The initial reluctance of trauma surgeons to accept pharmacological approaches to thromboprophylaxis reflected the fact that such figures were inconsistent with their clinical experience and failed to address the surgeons' concern around overall mortality, and the risk of side-effects such as bleeding, wound healing and infection.

Despite this controversy, practice in the UK is now largely consistent with the NICE guideline. However, NICE itself recognises that the most appropriate approach to pharmacological

thromboprophylaxis is a key priority for research, asking: "What is the clinical and cost effectiveness of aspirin alone versus other pharmacological and/or mechanical prophylaxis strategies (alone or in combination) for people with fragility fractures of the pelvis, hip or proximal femur?" [17]. Our study attempts to address an often overlooked aspect of this research priority, by describing the impact of practice on clinically significant peripheral venous thrombosis. The results of this study can therefore be considered in the wider context of wound complications and more life-threatening thromboembolic complications described elsewhere.

In this study, we describe 'real world' rates of clinical DVT in patients with hip fractures, demonstrating a halving of rates of DVT in patients receiving LMWH thromboprophylaxis (0.8%) compared with those who received aspirin (1.6%). Policy makers need to be aware that these figures are much lower than those which the older literature might lead them to expect [28]. The figures are also important to researchers as they will inform the design and power calculations for the comparative studies of thromboprophylaxis agents for which NICE has called. Based on these figures, a randomised controlled trial of aspirin *vs*. LMWH for thromboprophylaxis would need to include 3,040 patients in each arm if it were to achieve a confidence interval of 95% (5% alpha) and 80% power to detect a difference in clinical DVT between them.

Such a trial might be difficult to justify explain to patients and their families given widespread public perceptions of the 'high risk' of VTE in this setting, and the fact that clinical teams have already adopted the 2010 NICE guidance. A quarter of patients presenting with hip fracture are cognitively impaired and the poorer outcome seen in such patients means that they would need to be included in any trial if it is to provide meaningful data for this patient population. Therefore, the best data we have with which to evaluate the effectiveness of these therapies in a frail trauma population remains observational in nature, including those presented in this manuscript and others [27].

Departmental policies on mechanical thromboprophylaxis, prompt surgery and prompt post-operative mobilisation were stable for the whole study period so the key change in this period was in chemical thromboprophylaxis. However, there are a number of weaknesses in this retrospective study. We did not set out to define rates of pulmonary embolism, recognising that fatal events might never be proven, and sub-clinical events might have been missed. Similarly, we did not attempt to examine rates of complications such as blood loss or wound healing or to define overall mortality. However, given the significant impact of DVT treatment on the post operative patient in addition to the common and severe implications of clinical DVTs, it is important to understand the prevalence of DVT within a frail lower limb trauma population and the effect of the current change in guidance, and

we believe that our work provides a useful 'real world' context within which to reconsider the literature and national guidance on this important clinical topic.

Conclusion

We have demonstrated that LMHW has a significant effect on reducing the rates of DVT in a typical UK hip fracture population compared with aspirin. The rates of DVT we report in this population are much lower than many would expect and mean that the number needed to treat (NNT) in adoption of a policy of using LMWH in place of aspirin would be 127.

The cost and potential for complications associated with LMWH may make it appropriate to perform further very large prospective studies to demonstrate that the current NICE guidance is clinically and cost-effective. The figures we report in this study will be useful to those considering the design of such trials.

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Tables and Figures DVT Paper

Table 1: A table summarising the number of doppler scans performed and their outcomes over the study period. Abbreviations: DVT, deep vein thrombosis

Table 1: Doppler scans and DVT	
Doppler scans (<180 days post hip fracture)	400/913 (43.8%)
No DVT identified	346/400 (86.5%)
DVT identified	54/400 (13.5%)

Table 2: The effect of change of prescribing practice (NICE 89, June 2010) on DVT rate. *indicated P-value considered significant, p=0.012. Abbreviations: DVT, deep vein thrombosis

Table 2: The effect on DVT rate of switching policy from aspirin to LMWH for thromboprophylaxis		
	Pre-June 2010 Following aspirin policy	**Post-June 2010** Following LMWH policy
Doppler scans (<180 days post hip fracture)	150/400 (37.5%)	250/400 (62.5%)
DVTs identified	25/150 (16.7%)	29/250 (11.6%)
DVTs per hip fracture admission	25/1542 (1.62%)	29/3497 (0.83%)
Difference between pre-June 2010 and post-June 2010 (p<0.05*)		

Figure 1: A flow chart demonstrating the inclusion/exclusion criteria and relevant cohort and investigation totals in our study.

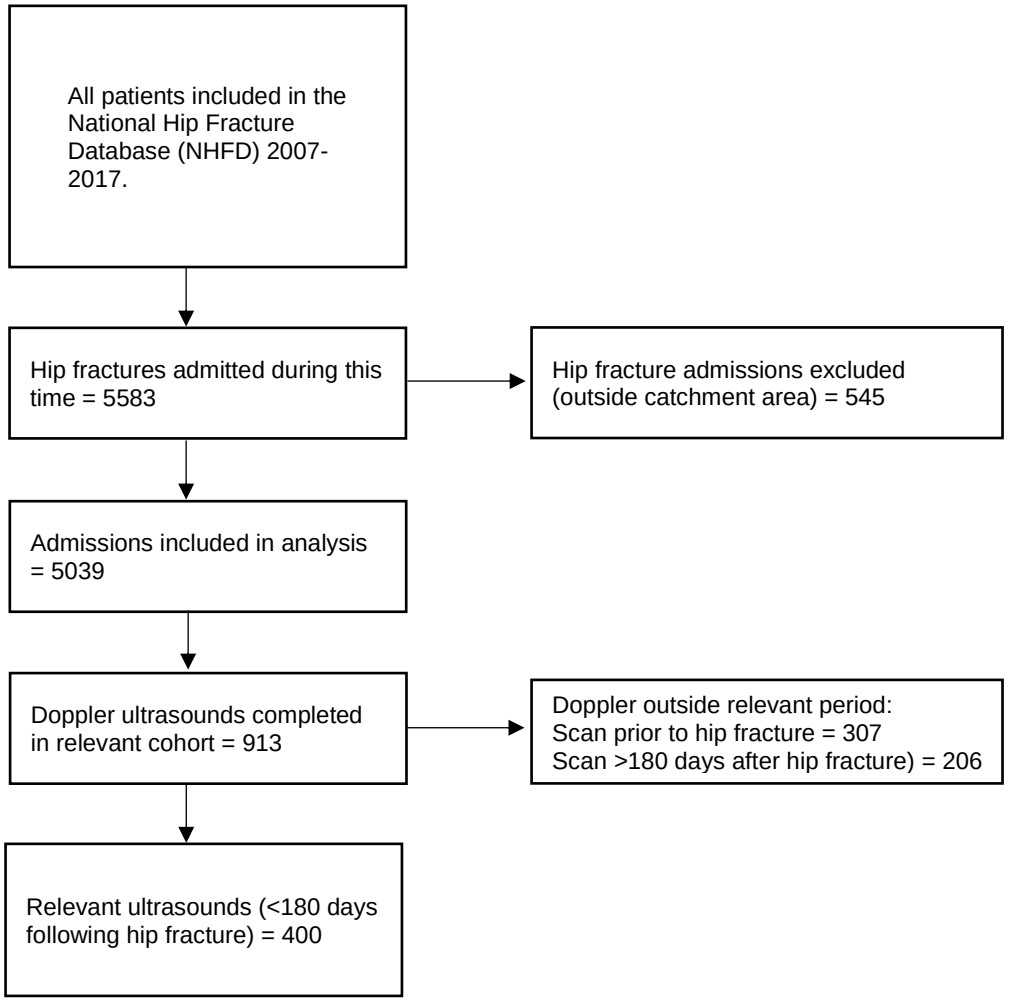
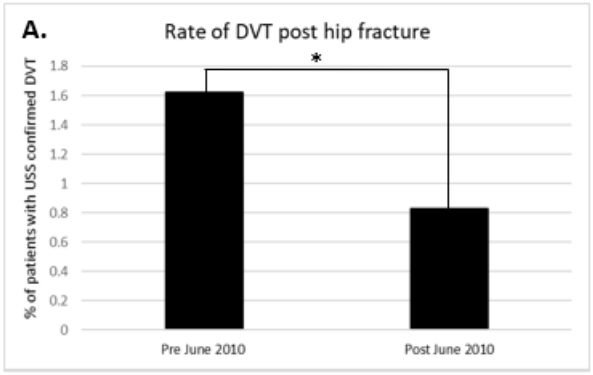
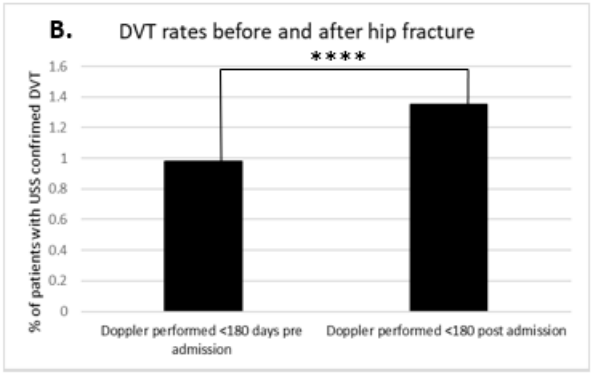
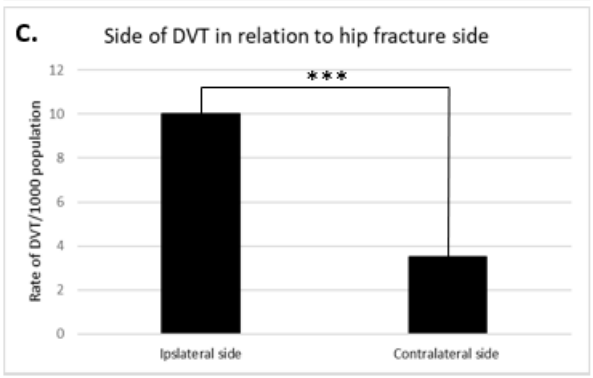


Figure 2: The effect of switching from aspirin to LMWH for thromboprophylaxis of patients with hip fractures. (A) A bar graph demonstrating the significance reduction in rates of relevant DVT before and after the change in NICE guidance of the anticoagulation preference from aspirin to LMWH (NICE 2010). (B) A bar graph demonstrating the pre-trauma baseline rate of DVT in a hip fracture population compared to post trauma. (C) A bar graph demonstrating the significant localisation of DVT when compared to site of fracture. Abbreviations *p<0.05, ***p<0.001. ****<0.0001. DVT (deep vein thrombosis), 'Relevant DVT' defined as USS confirmed DVT <180 days post admission.







Summary of figure legends

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