Theme Issue Article

Activated partial thromboplastin time monitoring in patients receiving unfractionated heparin for venous thromboembolism in relation to clinical outcomes

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Summary

Venous thromboembolism (VTE) is a prevalent and serious condition, which requires anticoagulation treatment for prolonged time duration. The use of unfractionated heparin administered intravenously or subcutaneously for acute management of VTE has been studied with favourable clinical results. Most physicians use activated partial thromboplastin time to monitor the treatment effect, in an effort to obtain better efficacy with less bleeding complications. Recent data however does not support this practice. We set to explore the medical literature for the correlation between the level of anticoagulation and the clinical outcomes. Randomised controlled trials comparing subcutaneous unfractionated heparin to any other treatment modality in patients with venous thromboembolism were obtained and a meta-analysis was performed. Seventeen reports from 15 randomised controlled trials were included. Of these, eleven included anticoagulation measurements. Seven and six trials were included in our analysis for subcutaneous and intravenous modes of administration, respectively. No correlation between the anticoagulation level and the major clinical outcomes were found, except for the initial anticoagulation measurement and the total mortality at three months, but not to death related to treatment or disease progression. In conclusion, weight-adjusted subcutaneous unfractionated heparin without anticoagulation monitoring may be feasible for patients with acute venous thromboembolism. No differences exist between intravenous and subcutaneous modes of administration with regards to the correlation between anticoagulant measures and the clinical outcomes. More research is needed to substantiate this observation.

Keywords

Venous thromoembolism, unfractionated heparin, subcutaneous, activated partial thromboplastin time

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Introduction

Venous thromboembolism is a prevalent condition. Deep-vein thrombosis (DVT) and pulmonary embolism (PE) are usually treated with a minimum of five days of heparin, either unfractionated (UFH) of low-molecular weight (LMWH), concurrently with a vitamin K antagonist dose titration. Although LMWH has largely replaced UFH in the setting of acute venous thromboembolism treatment, many patients do not benefit from its use due to increased risk for low-molecular weight heparin induced complications, the most important of which is increased risk of bleeding in the elderly population and in patients with renal failure.

UFH has two preferred modes of administration – a continuous intravenous (IV) and an intermittent subcutaneous (SC) mode. Pharmacokinetic analyses demonstrate difficulties in attaining early laboratory anticoagulation goals with SC UFH administration (1). Nevertheless, it has been evaluated in the setting of VTE due to the ease of its application, early mobilisation and discharge, and presumably less line related complications. UFH administration requires monitoring of the activated partial thromboplastin time (aPTT). Its use in the setting of the initial treatment for VTE may be complicated by bleeding or recurrent PE. Assuring the level of anticoagulation is presumed to reduce the risks of these complications. Specifically, in certain clinical situations in which a tendency towards any of these complication exists (e.g. old age, female sex, pregnancy or coexisting diseases) (2, 3), monitoring may be perceived as crucial. The purpose of the current analysis was to assess the need for aPTT monitoring in patients treated with SC UFH for VTE by system-

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atically reviewing the medical literature and evaluating the association between aPTT levels and the clinical outcomes. This correlation was compared to the correlation gained in patients receiving IV UFH.

Materials and methods

The full description of the methodology of this study is described elsewhere (4). In short, we searched MEDLINE, The Cochrane Peripheral Vascular Diseases Group Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (until April 2009), to identify trials comparing SC UFH to other treatment modalities for the treatment of VTE. We also searched databases for ongoing trials: Current Controlled Trials, UK National Research Register, Center Watch Clinical Trials Listing Service and National Institute of Health. We tried to identify additional studies by searching the reference lists of relevant trials and reviews identified. The authors of published trials and experts in the field were contacted for further leads and clarifications. Search for identification of studies was not restricted by language or duration of follow-up. Two reviewers independently scanned the titles, abstract sections and keywords of every record retrieved. Full articles were retrieved for further assessment if the information given suggested that the study fulfilled the inclusion criteria and did not meet the exclusion criteria. Differences in opinion were resolved through open discussion.

The quality of randomised clinical trials (RCTs) was assessed with quality criteria specified by Schulz and by Jadad (5, 6): minimisation of selection bias, performance bias, attrition bias and detection bias. Based on these criteria, RCTs were broadly subdivided into the following three categories: (A) all quality criteria met: low risk of bias; (B) one or more of the quality criteria only partly met: moderate risk of bias; and (C) one or more criteria not met: high risk of bias.

In the analysis reported here, we extracted the „initial" (within 48 hours of treatment) and the „maintenance" (last measure taken, at least over 48 hours from treatment initiation, or the mean of measures, when available) values of anti-coagulation tests from the trials identified. We assessed the correlation between these parameters and the clinical outcomes for patients receiving SC UFH (DVT resolution at the end of heparin treatment, recurrent DVT at three months, new PE during heparin treatment and at three month, new PE at routine lung scan at the end of heparin treatment, major or minor bleeding during heparin treatment and at three months, as well as total death and VTE related death during heparin treatment and at three months). We also looked at these correlations for patients receiving IV UFH. The results were analysed with the *surveylogistic* procedure. This procedure fits linear logistic regression models for discrete response survey data by the method of maximum likelihood. The maximum likelihood estimation was carried out with the Fisher-scoring (7). The statistical analyses were performed on SAS system version 9.2 (SAS, Cary, NC, USA). We also looked into the impact of therapeutic versus non-therapeutic aPTT values and the clinical outcomes, applying the Inverse Variance method in order to calculate the Odds Ratio between the two groups. We performed these analyses using Review Manager (RevMan) Version 5.0 (Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration, 2008).

Results

Trials identified

The initial search identified 578 (MEDLINE) and 285 (Cochrane Peripheral Vascular Disease Group Specialised Register and CENTRAL) records. From these, 24 full papers were identified for further examination. Search through reference lists of these studies and reviews yielded 11 additional papers for full text evaluation. A search through ongoing trials databases and contact-authors queries revealed no other eligible trials. The Kappa statistic for the inter-rater agreement for study selection, that is qualifying a study as 'included' or 'potentially' relevant, was 0.639. After screening the full text of the selected papers, 17 publications from 15 RCTs finally met the inclusion criteria.

Eleven studies reported anti-coagulation measures. In eight of the included studies, the anticoagulant effect of SC UFH treatment during the initial 48 hours of treatment was reported (8–15). The anticoagulant effect after stabilisation of treatment („maintenance") was measured in nine trials (8, 10–12, 14–18). Of these, one measured anti-Xa activity (11), and one reported the aPTT ratio (14). Two additional studies reported their findings in a manner that did not allow their integration into the meta-regression model (9, 18). These four trials were thus disqualified. SC UFH was compared to IV UFH in six of the trials included in the analysis, and to LMWH in one (12). The latter was therefore omitted from the analysis of IV UFH treatment monitoring (Characteristics of included studies are given in Table 1 and Table 2).

All trials included patients with deep venous thrombosis. Three trials allowed for patients with PE in their inclusion criteria (8, 9, 18). Three trials excluded patients with PE (10–12), and one trial excluded patients with massive PE (8). In the remaining trials, PE inclusion was not clearly described. Intervention groups within studies did not differ significantly.

Only two trials utilised a double-blind design (11, 13). Intention to treat was reported by one author (9). Blinding of outcome assessors was adequately described in four studies (8, 9, 14, 18), and only partly described in three (10, 11, 17).

Outcomes

A total of 444 and 408 patients receiving SC and IV UFH, respectively, were included in the meta-regression analysis.

For patients receiving SC or IV UFH no correlation was found between aPTT and the rates of recurrent DVT at three months, or the rates of new clinical PE during heparin treatment and three months follow-up. The correlation was also non-significant for major bleeding and deaths related to treatment or VTE during heparin treatment. However, a significant correlation between the maintenance aPTT value and the resolution of thrombus per imaging at the end of heparin treatment was found for SC and for IV UFH treatments (Chi^2=14.61, *p<0.0001, and* Chi^2=4.90, *p=0.0268, respectively*). We also found significant correlation between the initial aPTT and the rate of minor bleeding during SC or IV heparin treatment (Chi^2=15.42, *p<0.001 and* Chi^2=9.31, *p=0.0023, respectively)*.

Table 1: Study characteristics.

Study	Control	Number of participants		Duration of intervention	SC UFH regimen	Duration of follow-up	Language of publication	Quality
		SC UFH	Control					
Anderson 1982	IV UFH	72	69	5 days to INR target	IV UFH bolus followed by SC UFH BID, aPTT adjusted	Acute phase	English	C
Bentley 1980	IV UFH	50	50	7 days to INR target	SC UFH 40,000IU/day followed by BID aPTT adjusted dose	Acute phase	English	C
Doyle 1987	IV UFH	51	52	10 days	SC UFH 15,000IU followed by BID aPTT adjusted dose	12 months	English	C
Holm 1986	SC LMWH	27	29	7 days	IV UFH continuous for 24 hours followed by SC UFH 10,000–15,000IU BID, aPTT adjusted	7 days	English	C
Hull 1986	IV UFH	57	58	10 days	IV UFH 5,000IU followed by SC UFH 15,000 BID, aPTT adjusted	3 months	English	B
Kearon 2006	SC LMWH	355	353	5 days to INR target	SC UFH 333IU/kg followed by 250IU/kg BID	3 months	English	C
Lopaciuk 1990	IV UFH	48	46	7 days	IV UFH 5,000IU, followed by SC UFH 500IU/kg/day BID, aPTT adjusted	3 months	Polish	C
Lopaciuk 1992	SC LMWH	72	74	10 days	IV UFH 5,000IU, followed by SC UFH 250IU/kg BID, aPTT adjusted	3 months	English	C
Peternel 2002	SC LMWH	28	31	To INR tagert	IV UFH bolus, followed by SC UFH BID/TID, aPTT adjusted	3 months	English	C
Pini 1990	IV UFH	138	133	7 days	SC UFH 250IU/kg BID	7 days	English	C
Prandoni 2004	SC LMWH	360	360	5 days to INR target	IV UFH 4,000–5,000IU followed by SC UFH BID, aPTT adjusted	3 months	English	C

UFH, unfractionated heparin; SC, subcutaneous; IV, intravenous; BID,twice daily; TID, thrice daily; IU,international units.

Table 2: Anticoagulation measures within 48 hours of heparin initiation, and after stabilisation of anticoagulant measures.

Study	Subcutaneuos unfractionated heparin		Intravenuos unfractionated heparin	
	Initial anticoagulation (Mean, SD)	Maintenance anticoagulation (Mean, SD)	Initial anticoagulation (Mean, SD)	Maintenance anticoagulation (Mean, SD)
Anderson 1982^		79 (38)		71 (30)
Bentley 1980^		94 (40)		112 (58)
Doyle 1987^	53 (10.7)	63 (14.2)	46 (17.8)	57 (21.4)
Holm 1986*	0.58 (0.07)	0.52 (0.18)		
Hull 1986^	54.8 (36.4)		71 (36.4)	
Kearon 2006^	Mean and standard deviation not reported			
Lopaciuk 1990^	65 (38)	64 (28)	78 (32)	82 (36)
Lopaciuk 1992+	1.9 (0.8)	2.3 (0.8)		
Peternel 2002^	94.1 (51.1)	105.1 (55.6)		
Pini 1990^	37 (11.7)	47 (58.7)	42 (34.5)	50 (46)
Prandoni 2004^	Mean and standard deviation not reported			

^= aPTT(seconds); *= anti Xa activity.+= aPTT ratio. SD, standard deviation.

Outcome	SC UFH		IV UFH	
	Correlation to initial aPTT	Correlation to maintenance aPTT	Correlation to initial aPTT	Correlation to maintenance aPTT
Recurrent DVT at 3 months	NS	NA	NS	NA
New clinical PE during heparin treatment	NS	NS	NS	NS
New clinical PE at 3 months	NS	NS	NS	NA
DVT resolution (partial or full) at the end of heparin treatment	NS	*p<0.0001*	NS	*p=0.0268*
Major bleeding during heparin treatment	NS	NS	NS	NS
Major bleeding during 3 months	NA	NA	NA	NA
Minor bleeding during heparin treatment	*p<0.001*	*p=0.0132*	*p=0.0023*	NS
Minor bleeding during 3 months	NA	NA	NA	NA
Total death during heparin treatment	NS	NS	NS	NS
Total death during 3 months	*p=0.002*	NA	*p=0.0035*	*p=0.0002*
VTE/bleeding related death during heparin treatment	NS	NS	NS	NS
VTE/bleeding related death during 3 months	NS	NA	NS	NS

NS, non-significant; NA, not applicable to statistical consideration.

Table 3: Correlation between aPTT and clinical outcomes.

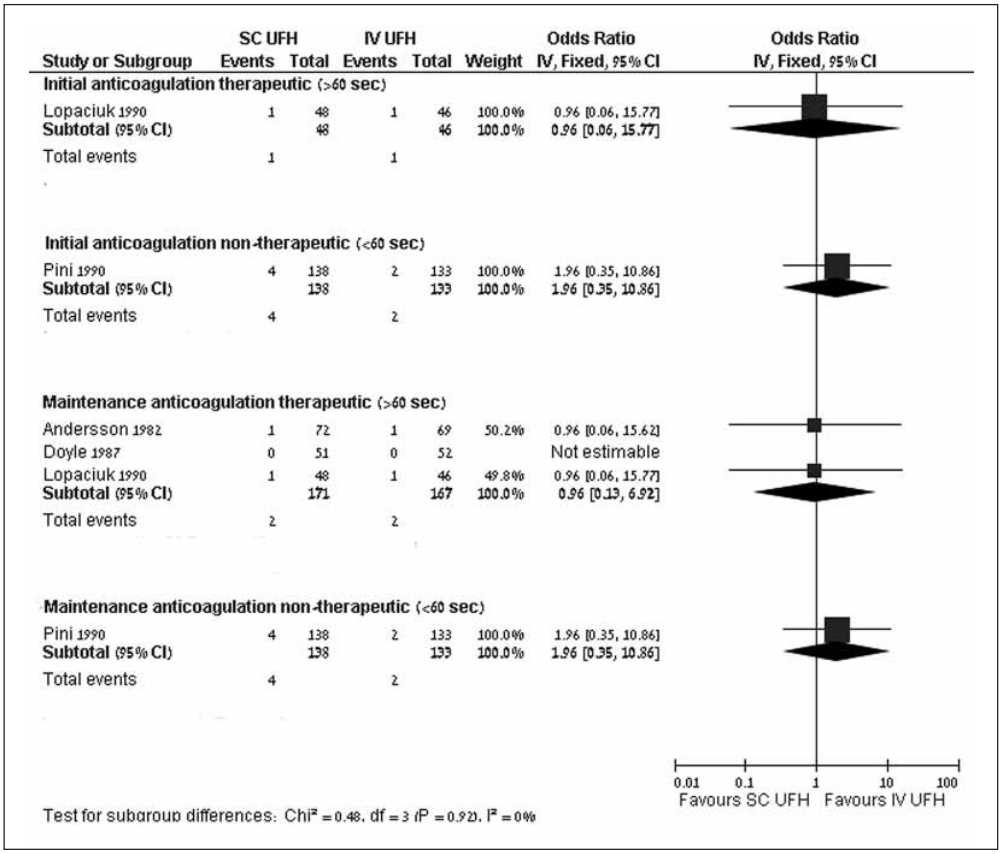

Figure 1: New clinical pulmonary embolism during subcutaneous unfractionated heparin treatment, subgrouped according to aPTT levels.

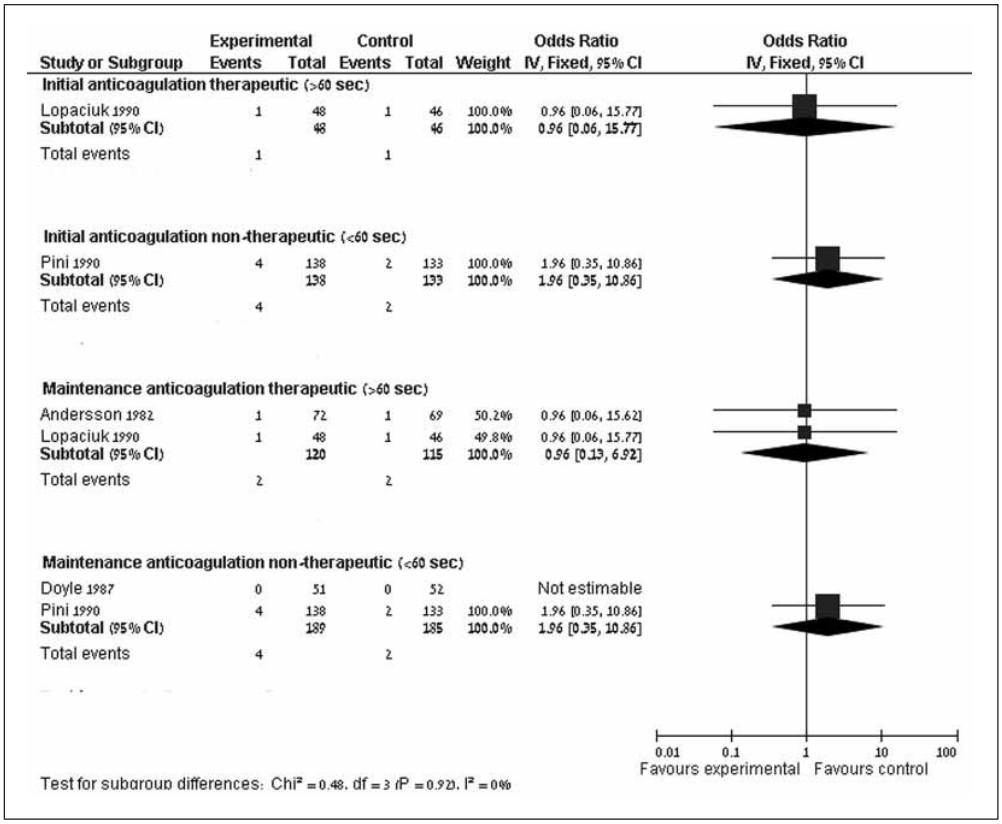

Figure 2: New clinical pulmonary embolism during intravenous unfractionated heparin, subgrouped according to aPTT levels.

The correlation between the maintenance aPTT and the rate of minor bleeding was only significant in patients receiving SC UFH *(*Chi^2=6.14, *p=0.0132)*. Correlations between the rate of total deaths (not confined to VTE or treatment) at three months follow-up and aPTT measures were significant for both treatments.

The trials that were not included in the analysis showed conflicting results. Kearon et al. (18) reported 39 patients with subtherapeutic aPTT levels and 121 patients with aPTT levels above the desired range, out of a cohort of 345 patients in the SC UFH group. The measures were taken at a mean of 2.8 days after treatment initiation, and had no influence on the rates of recurrent VTE at three months or major bleeding at 10 days. On the other hand, Prandoni et al. (9) reported that among patients allocated to the SC UFH group, recurrent VTE occurred in 2.7% of the patients reaching aPTT threshold >50 seconds within 24 hours, compared to 8.2% in patients who did not reach the desired anticoagulation threshold (p=0.02). In the remaining two trials (11, 14) the direct influence of the level of anticoagulation on the clinical outcomes was not reported.

The correlations between the initial aPTT or the maintenance aPTT with the clinical outcomes, are given in Table 3.

A subgroup analysis of the major outcomes according to whether or not the initial and the maintenance aPTT were within the desired limits or not, showed no substantial effect of this parameter on the outcomes. Figures 1–4 illustrate the rate of new clinical pulmonary embolism during subcutaneous (Fig. 1) and intravenous (Fig. 2) unfractionated heparin treatment, and the rate of major bleeding during subcutaneous (Fig. 3) and intravenous (Fig. 4) unfractionated heparin treatment, subgrouped according to initial and maintenance aPTT levels. Interaction tests between these subgroups for these clinical outcomes, as well as for all other major clinical outcomes, were non-significant.

Discussion

Venous thromboembolism is a serious clinical syndrome with potentially dire consequences. Its treatment with unfractionated heparin has been hindered by the relative complexity of continuous IV treatment and the necessity to monitor the anticoagulant effect. Nevertheless some patients mandate unfractionated heparin treatment due to relative contraindications to alternative treatment protocols.

In our present analysis, aPTT determined during the initial phase of heparin treatment, which reflects the pace by which anticoagulation is achieved, had no significant impact on most of the clinically important parameters. The correlation between this measure and the rate of minor bleeding during heparin treatment is of borderline significance after correcting for the multiple comparisons executed in this study, and its clinical importance is doubtful. The correlation between initial aPTT and total mortality at three months was also statistically significant, but the lack of correlation between the aPTT values at the beginning of heparin treatment and death related to treatment or disease propagation makes this observation clinically questionable. We also

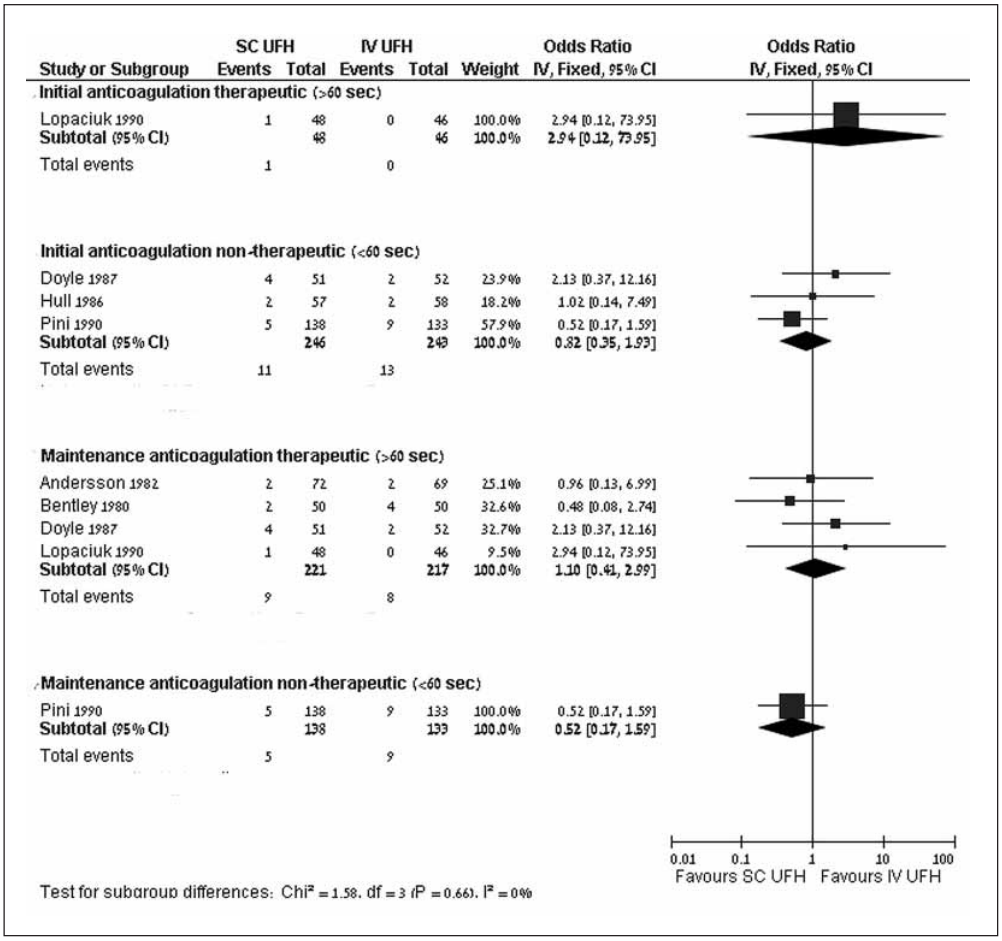

Figure 3: Major bleeding during subcutaneous unfractionated heparin treatment, subgrouped according to aPTT levels.

found the maintenance aPTT to have an impact on the rate of thrombus resolution according to imaging modalities. While this may be true, the impact of thrombus resolution at 10 days has not proved to play a role in the clinical outcome of patients (recurrent DVT or PE during and after heparin treatment).

Interestingly, no clinically significant differences in outcomes were noted, regardless of the route of UFH administration. This finding may imply SC UFH to be as efficacious as UFH. This may also imply that aPTT targeted therapy in both SC or IV administrations may not be the only determinants for successful outcomes.

A meta-analysis of randomised controlled trials comparing SC UFH to other treatment modalities in the setting of VTE, has found no significant differences in clinical outcomes (4). In 15 randomised controlled trials with a total of 1475 patients in the intervention group and 1579 patients in the control group, the results for all the major outcomes were statistically non-significant. The odds ratio (OR) for recurrent deep vein thrombosis (DVT) or pulmonary embolism (PE) during three months follow-up was 1.68 (95% confidence interval (CI) 0.92 to 3.04) and 1.18 (95% CI 0.54–2.56) in favor of the control arm. The odds ratio for developing PE during heparin treatment was not significant (OR 1.10, 95% CI 0.46–2.62), as were the ORs for major bleeding during heparin treatment and during three months follow-up (0.96, 95% CI 0.56 to 1.64, and 0.66, 95% CI 0.33 to 1.32, respectively). The risk difference for disease or treatment related deaths during heparin treatment and at three months follow-up were 0.0 (95% CI of –0.01 to 0.01). Total deaths did not differ between study groups. These non-significant differences were maintained when comparing the SC route to either SC LMWH or IV UFH separately.

The optimal dosing for SC administration of UFH was tested in several clinical trials. Kearon et al. (1) showed that weight adjusted regimen are appropriate, that heavier patients with increased heparin doses were likely to achieve aPTT levels within the desired range as were lighter patients, and that clinical outcomes were the same despite difficulties in maintaining aPTT levels within range. They advise a loading dose of 333U/kg followed by 250U/kg twice daily. Further dose adjustments were advised according to a monogram contemplated upon their data. Kearon et al. also postulated that warfarin may have had a significant effect on the aPTT results, and that a fixed dose SC UFH regimen may also be appropriate. A multicentre randomised controlled trial evaluating this assumption and regimen in a non-inferiority trial against SC LMWH, randomised 709 patients with acute VTE (18). No differences in the clinical outcomes between

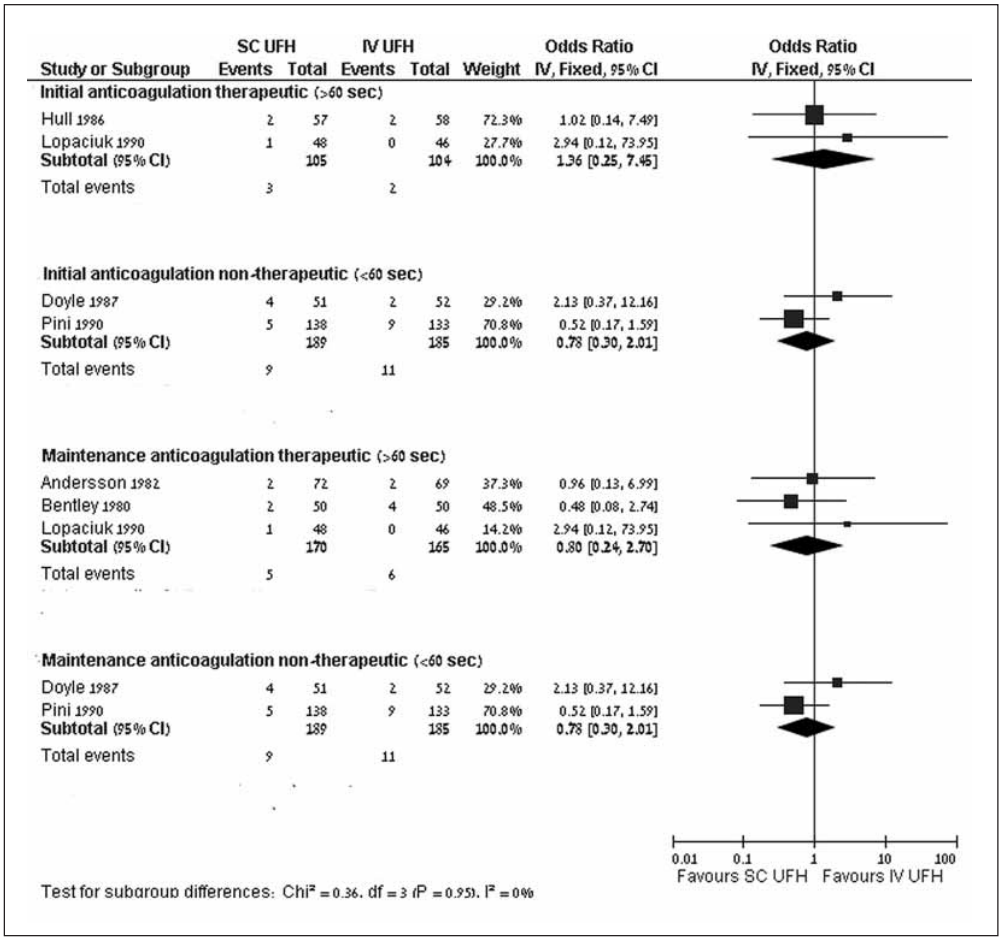

Figure 4: Major bleeding during intravenous unfractionated heparin treatment, subgrouped according to aPTT levels.

the two groups were found (recurrent VTE, bleeding and death). The lack of association between the aPTT measures and the clinical outcomes was considered by the authors to show the lack of necessity of this measure. The authors also showed their regimen to be safe and effective in an outpatient setting.

A few limitations of our analysis are worth mentioning. As mentioned above, we have performed multiple analyses in this study. Testing for multiple comparisons results in considerably more stringent threshold P-value for statistical significance (19). This may hinder the significance of the results obtained in the present analysis. It is also important to note that only seven of the 15 relevant trials were actually included in our analysis. Some of the trials included were published three decades ago, and sufficient information regarding anti-coagulation measures and some of the clinical outcomes was lacking, thus some of the planned analyses were not performed (Table 3). We also acknowledge the fact that other relevant information may be attained from non-RCTs, but these were excluded from our meta-analysis.

A recent review on the necessity for aPTT monitoring in patients receiving unfractionated heparin reassessed the data underlying this widely accepted practice. They conclude the clinical evidence to be weak and its clinical validity to be questionable. The aPTT test itself is also not well standardised, affected by many pre-analytic variables (e.g. sample collection and processing), analytic variables (e.g. reagent type), and biological variables (e.g. coagulation factors and variables affecting heparin pharmacokinetics) (20). Other laboratory assays such as the level of unfractionated heparin by either protamine titration or anti-Xa assays may be more precise, but are not widely used. Studies assessing the correlation between these assays and the clinical outcomes at the end of heparin treatment, at 30 days and at longer time duration are scarce.

The analysis presented here supports the hypothesis that subcutaneous unfractionated heparin can be administered without laboratory monitoring of its anti-coagulant effect. A formal RCT challenging this hypothesis has already been performed (18), and although the trial did not recruit enough patients to reach the desired power, its results are also supportive of this paradigm. A randomised clinical trial is needed to confirm our findings. If indeed the results of our analysis will be supported by further clinical data, a safe and efficacious option to treat VTE patients with relative contra-indications to LMWH in an out-patient setting will become available.

References

1. Kearon C, Harrison L, Crowther M, et al. Optimal dosing of subcutaneous unfractionated heparin for the treatment of deep vein thrombosis. Thromb Res 2000; 97: 395–403.

2. Clark NP. Low-molecular-weight heparin use in the obese, elderly, and in renal insufficiency. Thromb Res 2008; 123 (Suppl 1): S58–61.

3. Bates SM, Greer IA, Pabinger I, et al. ACoC. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133 (6 Suppl): 844S-886S.

4. Vardi M, Zittan E, Bitterman H. Subcutaneous unfractionated heparin for the treatment of venous thromboembolism. Cochrane Library 2009; In press.

5. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Contr Clin Trials 1996; 17: 1–12.

6. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. J Am Med Assoc 1995; 237: 408–412.

7. An AB. Performing logistic regression on survey data with the new SURVEYLOGISTIC procedure. SUGI 27; 2002; Orlando, Florida; 2002. p. 258.

8. Lopaciuk S, Misiak A, Wisawski S, et al. Subcutaneous injections and intravenous infusion of sodium salt of heparin in the treatment of thrombosis of deep veins of the lower extremities. Polski tygodnik lekarski 1990; 45: 949–952.

9. Prandoni P, Carnovali M, Marchiori A, et al. Subcutaneous adjusted-dose unfractionated heparin vs fixed-dose low-molecular-weight heparin in the initial treatment of venous thromboembolism. Arch Intern Med 2004; 164: 1077–1083.

10. Doyle DJ, Turpie AG, Hirsh J, et al. Adjusted subcutaneous heparin or continuous intravenous heparin in patients with acute deep vein thrombosis. A randomized trial. Ann Intern Med 1987; 107: 441–445.

11. Holm HA, Ly B, Handeland GF, et al. Subcutaneous heparin treatment of deep venous thrombosis: a comparison ofunfractionated and low molecular weight heparin. Haemostasis 1986; 16 (Suppl 2) : 30–37.

12. Peternel P, Terbizan M, Tratar G, et al. Markers of hemostatic system activation during treatment of deep vein thrombosis with subcutaneous unfractionated or low-molecular weight heparin. Thromb Res 2002; 105: 241–246.

13. Hull RD, Raskob GE, Hirsh J, et al. Continuous intravenous heparin compared with intermittent subcutaneous heparin in the initial treatment of proximal-vein thrombosis. New Engl J Med 1986; 315: 1109–1114.

14. Lopaciuk S, Meissner AJ, Filipeckil S, et al. Subcutaneous low molecular weight heparin versus subcutaneous unfractionated heparin in the treatment of deep vein thrombosis: A Polish multicenter trial. Thromb Haemost 1992; 68: 14–18.

15. Pini M, Pattachini C, Quintavalla R, Poli T, et al. Subcutaneous vs intravenous heparin in the treatment of deep venous thrombosis? a randomised clinical trial. Thromb Haemost 1990; 64: 222–226.

16. Andersson G, Fagrell B, Holmgren K, et al. Subcutaneous administration of heparin. A randomised comparison with intravenous administration of heparin to patients with deep-vein thrombosis. Thromb Res 1982; 27: 631–639.

17. Bentley PG, Kakkar VV, Scully MF, et al. An objective study of alternative methods of heparin administration. Thromb Res 1980; 18: 177–187.

18. Kearon C, Ginsberg JS, Julian JA, et al. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. J Am Med Assoc 2006; 296: 935–942.

19. Lagakos SW. The Challenge of Subgroup Analyses — Reporting without Distorting. New Engl J Med 2006; 354: 1667.

20. Eikelboom W, Hirsh J. Monitoring unfractionated heparin with the aPTT: Time for a fresh look. Thromb Haemost 2006; 96: 547–552.