Bleeding Risk during Treatment of Acute Thrombotic Events with Subcutaneous LMWH Compared to Intravenous Unfractionated Heparin; A Systematic Review

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Abstract

Background: Low Molecular Weight Heparins (LMWH) are at least as effective antithrombotic drugs as Unfractionated Heparin (UFH). However, it is still unclear whether the safety profiles of LMWH and UFH differ. We performed a systematic review to compare the bleeding risk of fixed dose subcutaneous LMWH and adjusted dose UFH for treatment of venous thromboembolism (VTE) or acute coronary syndromes (ACS). Major bleeding was the primary end point.

Methods: Electronic databases (MEDLINE, EMBASE, and the Cochrane Library) were searched up to May 2010 with no language restrictions. Randomized controlled trials in which subcutaneous LMWH were compared to intravenous UFH for the treatment of acute thrombotic events were selected. Two reviewers independently screened studies and extracted data on study design, study quality, incidence of major bleeding, patients’ characteristics, type, dose and number of daily administrations of LMWH, co-treatments, study end points and efficacy outcome. Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated using the random effects model.

Results: Twenty-seven studies were included. A total of 14,002 patients received UFH and 14,635 patients LMWH. Overall, no difference in major bleeding was observed between LMWH patients and UFH (OR = 0.79, 95% CI 0.60–1.04). In patients with VTE LMWH appeared safer than UFH, (OR = 0.68, 95% CI 0.47–1.00).

Conclusion: The results of our systematic review suggest that the use of LMWH in the treatment of VTE might be associated with a reduction in major bleeding compared with UFH. The choice of which heparin to use to minimize bleeding risk must be based on the single patient, taking into account the bleeding profile of different heparins in different settings.

Citation: Costantino G, Ceriani E, Rusconi AM, Podda GM, Montano N, et al. (2012) Bleeding Risk during Treatment of Acute Thrombotic Events with Subcutaneous LMWH Compared to Intravenous Unfractionated Heparin; A Systematic Review. PLoS ONE 7(9): e44553. doi:10.1371/journal.pone.0044553

Editor: Giuseppe Biondi-Zoccai, Sapienza University of Rome, Italy

Received March 8, 2012; Accepted August 6, 2012; Published September 11, 2012

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Funding: The authors have no funding or support to report.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

In daily clinical practice, low molecular weight heparins (LMWH) and unfractionated heparin (UFH) are the most commonly prescribed anticoagulant drugs for the treatment of acute thrombotic conditions, such as venous thromboembolism (VTE) and acute coronary syndromes (ACS).

LMWH have some advantages over UFH, including higher bioavailability and a more predictable anticoagulant effect. These properties allow the use of LMWH at weight-adjusted doses in most patients, without the need for laboratory monitoring. On the other hand, although treatment with UFH needs laboratory monitoring with Activated Partial Thromboplastin Time (aPTT), because its anticoagulant effect is unpredictable, it has the advantage that bleeding complications can be more easily managed, because UFH has a shorter half-life than LMWH, and can be effectively antagonized by protamine [1].

The antithrombotic efficacy of LMWH and UFH in the treatment of VTE and ACS has been evaluated in many randomized clinical trials and analyzed in several meta-analyses. Treatment of VTE with LMWHs is associated with similar or lower rates of recurrences and death as compared to treatment with UFH [2;3]. However, there is no evidence that LMWH are more effective than UFH in patients with ACS [4].

Minimizing the bleeding risk in patients treated with anticoagulants is of utmost clinical relevance, considering that major bleeding, anemia and blood transfusion are powerful and independent predictors of morbidity and mortality in patients with VTE or ACS on treatment with antithrombotic drugs [5–7]. To date, the systematic reviews comparing LMWH and UFH,
focused on drug efficacy as primary end point and considered the incidence of bleeding a secondary end point. This choice could have affected the selection of studies to be included in the analysis, since some studies reporting haemorrhagic events could have been excluded due to the absence of the primary end point considered as inclusion criteria in those meta-analysis.

It has not been established yet whether the incidence of bleeding complications differs between LMWH and UFH.

Aim of our study was to perform a systematic review of randomized clinical trials to compare the incidence of major bleeding associated with the use of subcutaneous LMWH and intravenous UFH for treatment of acute VTE or ACS.

Materials and Methods

Data Sources and Searches

We attempted to identify all relevant published randomized controlled trials (RCT) that compared fixed-dose subcutaneous LMWH with adjusted-dose intravenous UFH in the initial treatment of thrombotic episodes. We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials, using the search terms “randomized controlled trials” and “heparin” in combination with generic and trade names of individual preparations of LMWH. The search was completed in May 2010. We manually searched the references of retrieved publications to look for additional studies. No language restrictions were applied. Two investigators (EC, AMR) independently evaluated the studies for inclusion, and disagreements were resolved by discussion.

Study Selection

In order to be included in this systematic review, published studies had to meet the following criteria: 1) study design: randomized controlled trial; 2) intervention: comparison of subcutaneous weight-adjusted, fixed-dose LMWH with adjusted doses (based on APTT values) intravenous UFH, for the initial treatment of acute thrombotic episodes; 3) availability of outcome data on the incidence of major bleeding. We accepted the definitions of major bleeding that were chosen in each individual trial. Dose-finding studies were excluded. Studies with no events in both LMWH and UFH arms were included in the descriptive analysis, but excluded from the meta-analysis, because calculation of the odds ratio (OR) was not feasible.

Pre-defined subgroup analyses were performed on the basis of the type of disease that was treated (VTE vs ACS), the doses of LMWH that were administered, the number of daily administrations of LMWH (one or two) and the type of LMWH used.

Quality Assessment

In order to evaluate the quality of the included studies, we used the study-quality criteria of Jadad, which take into account proper randomization, allocation of patients and blinding [8].

Data Extraction

Two investigators (EC, AMR) independently extracted the data on study design, study quality, incidence of major bleeding, patients’ characteristics, type, dose and number of daily administrations of LMWH, co-treatments, study end points and efficacy outcome. The data extracted for each trial were confirmed by consensus between the reviewers.

Data Analysis

For each primary study that was included in the meta-analysis, a two-by-two table was constructed and the OR, with their 95% confidence intervals (CI), were calculated to estimate the risk of major bleeding in patients treated with LMWH compared to patients treated with UFH.

Pooled OR and 95% CI were calculated using the random effects model [9]. The homogeneity of the estimates of OR among studies was evaluated using the chi-square statistic test. Given the known difference of clinical settings of primary studies included in our meta-analysis (clinical heterogeneity), random effects analysis was performed for all studies, irrespective of the statistical significance of the heterogeneity chi-square test.

All analyses were performed using STATA 11.0 software [10].

Results

Study Selection

Figure 1 shows the process of study selection. We identified 6513 articles (1498 from Medline, 3205 from Embase, 1810 from the Cochrane Library). Of these, 1515 studies were duplicates, which were therefore eliminated, leaving 4998 articles for consideration. After the exclusion of irrelevant studies, which were identified by reviewing the titles and abstracts of all retrieved articles, 112 publications remained for analysis. We could not obtain the full publication of 19 studies after searching in the British Library and writing to the authors. Fifty-four of the remaining 93 articles were subsequently excluded, based on a more detailed evaluation of the full publications (Fig. 1). No additional studies were identified by reviewing the references from the original studies and other meta-analyses. One study, which operated a double randomization was considered as two data sets [11]. Thus, 37 studies were included in the descriptive analysis [11–47]. In 10 of them, no bleeding events were observed in any treatment group; therefore, 27 studies were included in the meta-analysis [12–15;17–38;47].

Table 1 describes the characteristics of the included studies. Thirty-four studies were published in English, one in French and two in Spanish, in journals of Internal Medicine, Cardiology, Hematology, or, less frequently, Angiology and Pneumology. The years of publication ranged between 1989 and 2006. Twenty-six studies enrolled patients with VTE, 11 studies enrolled patients with ACS (STEMI, NSTEMI, unstable angina). Nine different types of LMWH were used: the most commonly used one was enoxaparin. In all studies, the dose of intravenous UFH was titrated to maintain the APTT ratio between 1.5 and 2.5. The daily doses of subcutaneous LMWH ranged between 90 and 300 anti-Xa U/kg (mean 195 U/kg), in one or two daily administrations (9 and 28 studies respectively); one study allowed both the once daily and the twice daily administration [30]. Treatments lasted between 2 and 28 days (mean, 8 days). Concomitant medications for patients with ACS included Aspirin, Aspirin plus a thienopiridine, Aspirin plus a GPIIb-IIIa inhibitor, or Aspirin plus a thrombolytic agent. Most studies used the TIMI criteria to define major bleeding [48].

A total of 28,637 patients had been enrolled in the studies, 14,635 of whom were treated with LMWH and 14,002 with UFH. The mean number of patients enrolled in each trial was 754 (range 20–9,978 ), their mean age was 62 y (range 49–73), and 63% (range 31–83%) were men.

The aim of the majority of the studies was to evaluate combined end-points; less frequently, a single clinical end-point or an instrumental measure were evaluated. Major bleeding ranged from 0 to 12.5%, (mean, 4.4%) in patients treated with LMWH and from 0 to 11.5% (mean, 4.4%) in patients treated with UFH. The mean incidence of bleeding events were lower in VTE (1.1% with LMWH and 1.9% with UFH), compared to ACS (5.8% with
Figure 1. Study selection progression.
doi:10.1371/journal.pone.0044553.g001
### Table 1. Characteristics of included studies.

| Clinical indication | Patients n. | Major bleeding n. (%) | Mean age (years) | Type and daily dosage of LMWH | Cotreatments |
|---------------------|-------------|-----------------------|-----------------|--------------------------------|--------------|
| **VTE**             |             |                       |                 |                                |              |
| Riess H et al. 2003 | LMWH 627    | 6 (1.0)               | 61              | Certoparin, 8000 IU, bid       | None         |
|                     | UFH 593     | 7 (1.3)               |                 |                                |              |
| Decousus et al. 1998| LMWH 195    | 7 (3.6)               | 72              | Enoxaparin, 100 IU/Kg, bid     | None         |
|                     | UFH 205     | 8 (3.9)               |                 |                                |              |
| Columbus investigators 1997 | LMWH 510 | 10 (2.0)             | 60              | Reviparin, 3500–6300 IU, bid   | None         |
|                     | UFH 511     | 8 (1.6)               |                 |                                |              |
| Zhang Wang et al. 2006 | LMWH 96  | 1 (1.0)               | 66              | Parnaparin, 4250 IU, bid       | ASA, UK      |
|                     | UFH 90      | 3 (3.1)               |                 |                                |              |
| Hull et al. 1992    | LMWH 213    | 1 (0.5)               |                 | Tinzaparin, 175 IU/Kg, qd      | None         |
|                     | UFH 219     | 11 (5.0)              |                 |                                |              |
| Collaborative European Multicentre Study 1991 | LMWH 85  | 2 (2.4)               |                 | Nadroparin, 12500–17500 IU, bid | None         |
|                     | UFH 81      | 4 (4.9)               |                 |                                |              |
| Campos et al. 2002  | ACS 107     | 1 (0.9)               | 60              | Enoxaparin, 80 IU/Kg, bid      | ASA          |
|                     | UFH 96      | 9 (9.4)               |                 |                                |              |
| Goldhaber et al. 1998 | VTE 41  | 1 (2.4)               | 54              | Ardeparin, 130 IU/Kg, bid     | None         |
|                     | UFH 39      | 1 (2.6)               |                 |                                |              |
| Simonneau et al. 1997 | LMWH 304 | 3 (1.0)               | 67              | Tinzaparin, 175 IU/Kg, qd      | None         |
|                     | UFH 308     | 5 (1.6)               |                 |                                |              |
| PRIME CARE Study Investigators Group 2005 | ACS 451 | 2 (0.4)               | 57              | Parnaparin, 6400 IU, qd        | ASA          |
|                     | UFH 446     | 2 (0.4)               |                 |                                |              |
| Goodman et al. 2003 | ACS 380     | 8 (2.1)               | 64              | Enoxaparin, 100 IU/Kg, bid     | ASA, EPF     |
|                     | UFH 366     | 20 (5.5)              |                 |                                |              |
| Kakkar et al. 2003  | VTE 126     | 0 (0)                 |                 | Bepiparin, 115 IU/Kg, qd      | None         |
|                     | UFH 126     | 1 (1.0)               |                 |                                |              |
| Prandoni et al. 1992 | VTE 85  | 1 (1.2)               |                 | Nadroparin, 12500–17500 IU, bid | None         |
|                     | UFH 85      | 3 (3.5)               |                 |                                |              |
| Levine et al. 1996  | VTE 247     | 5 (2.0)               | 58              | Enoxaparin, 100 IU/Kg, bid     | None         |
|                     | UFH 253     | 3 (1.2)               |                 |                                |              |
| Gurfinkei et al. 1995 | ACS 68  | 0 (0)                 | 63              | Nadroparin, 214 IU/Kg, bid     | ASA          |
|                     | UFH 70      | 2 (2.9)               |                 |                                |              |
| Harenberg et al. 2000 | VTE 265 | 4 (1.5)               | 62              | Certoparin, 8000 IU, bid       | None         |
|                     | UFH 273     | 11 (4.0)              |                 |                                |              |
| Cohen et al. 2002   | ACS 315     | 4 (1.3)               | 64              | Enoxaparin, 100 IU/Kg, bid     | ASA, TFB     |
|                     | UFH 210     | 3 (1.4)               |                 |                                |              |
| Blazing et al. 2004 | ACS 2026    | 18 (0.9)              | 61              | Enoxaparin, 100 IU/Kg, bid     | ASA, TFB     |
|                     | UFH 1961    | 8 (0.4)               |                 |                                |              |
| Breddin et al. 2001 | VTE 762     | 2 (0.3)               | 59              | Reviparin, 7000–12600 IU, qd or bid | None         |
|                     | UFH 375     | 2 (0.6)               |                 |                                |              |
| Perez de Llano et al. 2003 | VTE 29 | 1 (3.4)               |                 | Enoxaparin, 100 IU/Kg, bid     | None         |
|                     | UFH 21      | 0 (0)                 |                 |                                |              |
| Fiessinger et al. 1996 | VTE 120 | 0 (0)                 | 61              | Dalteparin, subcutaneous bolus 5000 IU, then 200 IU/kg qd | None         |
|                     | UFH 133     | 2 (1.5)               |                 |                                |              |
| Harenberg et al. 1990 | VTE 24    | 3 (12.5)              | 61              | Certoparin, 150 IU/Kg, bid     | None         |
|                     | UFH 26      | 3 (11.5)              |                 |                                |              |
| Luomanmaki et al. 1996 | VTE 117 | 0 (0)                 | 59              | Dalteparin, subcutaneous bolus 5000 IU, then 200 IU/kg qd | None         |
|                     | UFH 131     | 1 (0.8)               |                 |                                |              |
LMWH and 5.4% with UFH. Considering the efficacy endpoints, 15 studies showed that LMWH were superior to UFH [12;15;17–19;21–23;26;27;29;30;36;40;42], 1 study showed that UFH was superior to LMWH [46], while the remaining 21 showed that there was no statistically significant difference between the two treatments [11;13;14;16;20;24;25;28;31–35;37–39;41;43–45;47].

### Assessment of Study Quality

Based on the study-quality criteria of Jadad [8], 3 studies scored 1 point, 17 scored 2 points, 14 scored 3 points, 1 scored 4 points and 2 scored 5 points. Lack of blindness was the most common flaw in the studies with a low Jadad score.

### Data Synthesis

Pooled estimates of ORs for major bleeding showed a non-statistically significant trend in favor of LMWH compared to UFH (OR = 0.79, 95% CI: 0.60–1.04, p = 0.091; n = 27 primary studies) (Figure 2).

When the analysis was limited to trials that enrolled patients with VTE, pooled estimates of OR was in favor of LMWH (OR = 0.68, 95% CI: 0.47–1.00, p = 0.05) (figure 3).

### Study Characteristics

In contrast, when the analysis was limited to trials that enrolled patients with ACS, no statistically significant differences between LMWH and UFH were found (OR = 0.87, 95% CI: 0.59–1.29; p = 0.493) (figure 4).
Once daily LMWH was significantly safer than UFH, (OR = 0.39, 95% CI: 0.16–0.95, p = 0.039), while, for twice daily LMWH, no statistical difference was observed compared to UFH (OR = 0.86, 95% CI: 0.65–1.14, p = 0.296) (figure S1). When the analysis was limited to the subgroup of VTE trials, once daily LMWH was significantly safer than UFH (OR = 0.31, 95% CI: 0.12–0.84), while no significant differences were found when considering the other subgroups (VTE twice, ACS once and ACS twice) (figure S2).

The exclusion of studies in which LMWH was under-dosed (less than 75% of the recommended daily dose) or overdosed (more than 125% of the recommended dose) did not substantially change the results (OR = 0.79, CI 95% 0.58–1.06, p = 0.121) (figure S3).

No statistically significant differences among different LMWH were observed (figure S4).

The results did not change, after Exclusion of the low quality studies [Jadad score <3] from the analysis (OR = 0.88, 95% CI: 0.67–1.15, p = 0.342) (figure S5).

Based on our a priori defined protocol, we excluded dose-finding studies [49–52], which had been included in other revisions. In particular, in the VTE setting, the study by Merli et al., which used two different LMWH doses, compared to a single UFH group, was excluded despite the large number of patients enrolled. For the sake of completeness, we repeated our analysis including the dose-finding trials and the results did not change (figure S6).

Discussion

Our systematic review shows a trend toward a non-statistically significant lower incidence of major bleeding with LMWH compared to UFH (OR 0.79), in the treatment of acute thrombotic events, such as VTE and ACS. When we analyzed separately the RCT that enrolled VTE patients and those enrolling ACS patients, the reduction in the bleeding risk associated with LMWH (OR = 0.68, p = 0.05) reached statistical significance for VTE. Some reasons might explain the absence of significant difference in bleeding between LMWH and UFH in ACS patients: i) many ACS patients underwent invasive procedures (coronary angiography and PCI), ii) ACS patients were often in co-treatment with antiplatelet agents; iii) LMWH patients are likely to be more often in the therapeutic range compared to dose adjusted UFH.

Somewhat unexpectedly, the incidence of bleeding complications was significantly lower with once daily administrations of LMWH, compared to twice daily administrations, the total daily
doses being similar in the two treatment regimens (figure S1). Although we have not a clear explanation of these results, it could be speculated that bleeding correlates better with the trough drug concentrations (lower in once a day than in twice a day administrations) than with peak concentrations (higher in daily administration).

Anyway, our findings raise the possibility that dosing regimens can be important determinants for bleeding complications. Further studies should clarify this topic.

The use of LMWH and UFH for treatment of VTE and ACS has been evaluated in previous systematic reviews and meta-analyses, which were focused on their antithrombotic efficacy as primary end-point. However, in consideration of the negative impact on mortality and adverse cardiovascular events associated with major bleeding [5–7], it is also important to establish which treatment is safer, in terms of incidence of bleeding complications.

As far as treatment of VTE is concerned, only the meta-analysis of Lim et al on LMWH-associated bleeding is available to date [53], which demonstrated a higher incidence of bleeding complications in patients with renal failure, without comparing LMWH with UFH. Information on the difference in bleeding complications between LMWH and UFH is retrievable from two other meta-analyses, which were mainly focused on evaluating the differences in efficacy between the two treatments [2;3]. Quinlan et al. reported a non-statistically significant trend toward lower frequency of major bleeding associated with LMWH, compared to UFH (1.4% vs 2.3%, OR 0.67, 95% CI 0.36–1.27), in patients with non-massive pulmonary embolism [2]. In the Systematic Review of the Cochrane Collaboration on VTE [3], LMWH were shown to be significantly safer than UFH (incidence of major bleeding, 1% vs 2.1%, OR 0.57; 95% CI 0.39–0.83). While, at a first glance, our review seems to be very similar to the Cochrane review, we think that they are basically different. The recently published Cochrane meta-analysis focused on the comparison between LMWH and unfractionated heparin (UFH in terms of their efficacy for the initial treatment of venous thromboembolism (VTE). In our manuscript we have chosen the safety of these drugs for the initial treatment of acute thrombotic events as primary end point. As a consequence, in our review all the studies reporting haemorrhagic events, irrespective of the efficacy endpoint that was reported, have been included. As a consequence, compared to the Cochrane meta-analysis, 9 additional studies were included in our descriptive analysis [19;23;30;31;33;41;43;46;47], 6 of which were also included in our meta-analysis [31;33;41;43;46;47]. These additional studies account for 1344 more VTE patients included in our analysis.

As far as ACS treatment is concerned, three meta-analysis have recently been published, which gave contrasting results. Magee et al [54], consistently with our data, showed a similar rate of major bleeding in LMWH and UFH-treated patients with ACS (RR = 1), despite the fact that only one of the 7 studies included by Magee met our inclusion criteria. In contrast, Murphy et al [55], who analyzed studies comparing enoxaparin and UFH only, found an excess of major bleeding in the enoxaparin group (OR 1.25,
We have no explanation for the contrasting results of the analysis by Murphy et al, compared to those of the study by Magee et al and of our systematic review. The fact that Murphy et al [55] focused on studies that used enoxaparin only does not apparently account for the differences in results, because, when we restricted our analysis to studies that used enoxaparin only, we found no statistically significant differences in the incidence of major bleeding between the enoxaparin group and the UFH group (figure S4). The inclusion of studies that administered enoxaparin either intravenously or subcutaneously in the meta-analysis by Murphy et al might account for the different results obtained in our meta-analysis, which included those studies that administered LMWHs subcutaneously only. This concept seem to be strengthened by the most recent meta-analysis by Silvain et al [56], that enrolled RCT’s and registers studies and included only patients treated with enoxeparin during percutaneous coronary interventions. While they find an important reduction in major bleeding in patients treated with intravenous Enoxeparin, the risk of bleeding using Enoxeparin by the subcutaneous route was the same as UFH.

The results of our study may have important clinical implications. Patients at high risk for thrombotic events are often also at high risk for bleeding [57;58]. Iron deficiency anemia and/ or hemorrhagic diathesis are common co-morbidities. In this context, the choice of the best anticoagulant treatment should be done taking into account the risk of adverse events more than the therapeutic efficacy. As a matter of fact, minimizing the bleeding risk in patients treated with anticoagulants is of utmost clinical relevance, considering that major bleeding, anemia and blood transfusion are powerful and independent predictors of morbidity and mortality in patients with VTE or ACS on treatment with antithrombotic drugs [5–7]. LMWH has the advantages of subcutaneous administration, more predictable anticoagulant response, lack of the need for laboratory monitoring and probably less risk of major bleeding in the VTE. On the other hand the lack of complete antagonization by antidotes and the long acting profile can be a disadvantage in active bleeding patients. UFH is less easy to handle, but the presence of an antidote and its brief half life could be arguments to consider in choosing the type of heparin to use in high bleeding risk patients who need anticoagulation. The choice must be based on the single patient and on the clinical and practical context, taking into account the bleeding profile of different heparins in different settings.

Limitations

The major limitation of our systematic review is the clinical heterogeneity between studies, especially considering all the trials together. Sources of clinical heterogeneity are several. The primary outcome of our systematic review, major bleeding, was the secondary end-point of the original RCT that we considered in our analysis. As we included all the RCT that compared subcutaneous LMWH with UFH, we considered different clinical scenarios and consequently different study designs, in which heparins were used at different doses and with different co-therapies. However, our results should not be affected by these factors, since we considered randomized studies only. Moreover, trying to take into account clinical heterogeneity, we used a random effect model for the analysis, which is known to be more conservative.
We chose the criteria that had been used in the original studies as criteria for major bleeding and this could account for some of the heterogeneity present in our results. However, most studies considered the following major bleeding events, which are undoubtedly clinically relevant: i) the presence of intracranial or retroperitoneal hemorrhage, ii) hemorrhage that led directly to death, necessitated transfusion or led to the interruption of antithrombotic treatment, iii) a ≥2 g/dl decrease in the haemoglobin concentration.

Finally, in the arterial setting clinical and statistical heterogeneity does not allow to derive definitive conclusions; vice versa, in venous setting the sources of clinical heterogeneity are lower as confirmed by the absence of statistical heterogeneity.

In conclusion, the results of our systematic review suggest that LMWH might have a better safety profile than UFH in the treatment of VTE, while no differences between the two treatments was detected in ACS. The choice of which heparin to use to minimize bleeding risk must be based on the single patient and on the clinical and practical context, taking into account the bleeding profile of different heparins in different settings.

Supporting Information

Figure S1 Subgroup analysis: number of daily LMWH administrations (once daily vs twice daily).

References

1. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, et al. (2006). Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 130:S354–545S.
2. Quinlan DJ, McQuillan A, Elkeboom JvW (2004) Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-analysis of randomized, controlled trials. Ann Intern Med 140: 170–83.
3. Erken PM, Prins MH (2010) Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database Syst Rev CD001100.
4. Harrington RA, Becker RC, Cannon CP, Gutterman D, Lincoff AM, et al. (2008) Antithrombotic therapy for non-ST-segment elevation acute coronary syndromes: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 131: 708–707S.
5. Sabatine MS, Morrow DA, Giugliano RP, Burton PB, Murphy SA, et al. (2005). Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. Circulation 111: 1124–29.
6. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, et al. (2007) Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY Trial. J Am Coll Cardiol 49: 1362–8.
7. Jimenez D, Escobar C, Marti D, Diaz G, Cesar J, et al. (2009) Association of anaemia and mortality in patients with acute pulmonary embolism. Thromb Haemost 102: 133–6.
8. Jadiar AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, et al. (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17: 1–12.
9. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7: 177–88.
10. Stata statistical software: release 8.0 [computer program]. Version; 2003.
11. Kim JH, Jeong MH, Rhew JY, Lim JH, Yun KH, et al. (2005) Long-term clinical outcomes of platelet glycoprotein IIb/IIIa inhibitor combined with low molecular weight heparin in patients with acute coronary syndrome. Circ J 69: 120–4.
12. Ries H, Koppenhagen K, Tolle A, Kemkes-Matthes B, Grave M, et al. (2003) Fixed-dose, body weight-independent subcutaneous low molecular weight heparin Cetorparin compared with adjusted-dose intravenous unfractionated heparin in patients with proximal deep vein thrombosis. Thromb Haemost 90: 252–9.
13. Decousus H, Leizorovicz A, Parent F, Page Y, Tardy B, et al. (1998) A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prevention du Risque d’Embolie Pulmonaire par Interruption Cave Study Group. N Engl J Med 338: 409–15.
14. The Columbus Investigators (1997) Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. N Engl J Med 337: 657–62.
15. Zhang Y, Wang XK, Yang CM, Liu GY (2004) [Use of unfractionated heparin and a low-molecular-weight heparin following thrombolytic therapy for acute ST-segment elevation myocardial infarction]. Di Yi Jun Yi Da Xue Xue Bao 24: 81–4.
16. Hull RD, Raskob GE, Pineo GF, Green D, Trowbridge AA, et al. (1992) Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. N Engl J Med 326: 975–82.
17. (1991) A randomised trial of subcutaneous low molecular weight heparin (CY 216) compared with intravenous unfractionated heparin in the treatment of deep vein thrombosis. A collaborative European multicentre study. Thromb Haemost 65: 251–6.
18. Campos JV, Juarez HU, Rosas PM, Lapique HE, Gonzalez PH, et al. (2002) Decrease of total hemorrhage with reduced doses of enoxaparin in high risk unstable angina. ENHFA1 study. [Enoxaparin vs non-fractionated heparin in unstable angina]. Preliminary report]. Arch Cardiol Mex 72: 209–19.
19. Goldhaber SZ, Morrison RB, Diran LL, Creager MA, Lee TH (1996) Abbreviated hospitalization for deep venous thrombosis with the use of ardeparin. Arch Intern Med 156: 2325–8.
20. Simonneau G, Sors H, Charbonnier B, Page Y, Lauban JP, et al. (1997) A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. The THENE Study Group. Tinzaparin au Heparine Standard: Evaluations dans l’Embolie Pulmonaire. N Engl J Med 337: 663–9.
21. (2005) Comparative efficacy of once daily paremiparin and unfractionated heparin in unstable angiua pectoris: PRIME CARE study. Indian Heart J 57: 649–54.
22. Goodman SG, Fitchett D, Armstrong PW, Tan M, Langer A (2003) Randomized evaluation of the safety and efficacy of enoxaparin versus unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes receiving the glycoprotein IIb/IIIa inhibitor eptifibatide. Circulation 107: 238–44.
23. Kakkar VV, Gehleris M, Kadziola Z, Saha N, Carrasco P (2003) Low-molecular-weight heparin in the acute and long-term treatment of deep vein thrombosis. Thromb Haemost 89: 674–80.
24. Prandoni P, Lensing AW, Buller HR, Carta M, Cogo A, et al. (1992) Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. Lance 339: 441–5.
25. Levine M, Gent M, Hirsch J, Leclerc J, Anderson D, et al. (1996) A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. N Engl J Med 334: 677–81.
26. Gurfinikel EP, Manos EJ, Mejial RI, Cerda MA, Duronto EA, et al. (1995) Low molecular weight heparin versus regular heparin or aspirin in the treatment of unstable angina and silent ischemia. J Am Coll Cardiol 26: 313–8.

27. Harenberg J, Schmidt JA, Koppenagen K, Tolle A, Huisman MV, et al. (2000) Fixed-dose, body weight-independent subcutaneous LMWH heparin versus adjusted dose unfractionated intravenous heparin in the initial treatment of proximal venous thrombosis. EASTERN Investigators. Thromb Haemost 83: 632–6.

28. Cohen M, Théroux P, Borzak S, Frey MJ, White HD, et al. (2002) Randomized double-blind safety study of enoxaparin versus unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes treated with ticlopidin and aspirin: the ACUTE II study. The Antithrombotic Combination Using Ticlopidin and Enoxaparin. Am Heart J 144: 470–9.

29. de Lemos JA, Blazing MA, Wiviott SD, Brady WE, White HD, et al. (2004) Enoxaparin versus unfractionated heparin in patients treated with ticlopidin, aspirin, and an early conservative initial management strategy: results from the A phase of the Astra-Z trial. Eur Heart J 25: 1081–94.

30. Breddin HK, Hach-Wunderle V, Nakos R, Kalkar VV (2001) Effects of a low-molecular-weight heparin on thrombus regression and recurrent thromboembolism in patients with deep vein thrombosis. N Engl J Med 344: 626–31.

31. Perez de Leon LA, Baleira VA, Veres RA, Feiga F, Gópel GR, et al. (2003) [Multicenter, prospective study comparing enoxaparin with unfractionated heparin in the treatment of submassive pulmonary thromboembolism]. Arch Bronconeumol 39: 341–5.

32. Fiesinger JN, Lopez-Fernandez M, Gatterer E, Granquist S, Kher A, et al. (1996) Once-daily subcutaneous dalteparin, a low molecular weight heparin, for the initial treatment of acute deep vein thrombosis. Thromb Haemost 76: 185–9.

33. Harenberg J, Hack K, Bratotch H, Steige G, Demplle CE, et al. (1996) Therapeutic application of subcutaneous low-molecular-weight heparin in acute venous thrombosis. Haemostasis 20 Suppl 1: 205–19.

34. Luomanmaki K, Granqvist S, Hallert C, J. Järvö I, Ketola K, et al. (1996) A multicentre comparison of once-daily subcutaneous daltepin (low molecular weight heparin) and continuous intravenous heparin in the treatment of deep vein thrombosis. J Intern Med 240: 85–92.

35. Koopman MM, Prandoni P, Piovella F, Ockelford PA, Brandjes DP, et al. (2003) Randomized trial to compare the efficacy, safety, cost and platelet aggregation strategy: primary results of the SYNERGY randomized trial. JAMA 292: 45–54.

36. Kirchmaier CM, Wolf H, Schafer H, Ehlers B, Breddin HK (1998) Efficacy of a fixed-dose, body weight-independent subcutaneous LMWH heparin versus adjusted dose unfractionated intravenous heparin in the treatment of proximal venous thrombosis. EASTERN Investigators. Thromb Haemost 83: 632–6.

37. Ferguson JJ, Califf RM, Antman EM, Grines CL, et al. (2004) Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SNXERGY randomized trial. JAMA 292: 45–54.

38. Kirchmaier CM, Wolf H, Schafer H, Ehlers B, Breddin HK (1998) Efficacy of a low molecular weight heparin administered intravenously or subcutaneously in patients with acute pulmonary thromboembolism: Respira 69: 440–4.

39. Loke YK, Price D, Herxheimer A (2007) Systematic reviews of adverse effects: framework for a structured approach. BMC Med Res Methodol 7: 32.

40. Selvakumar N, Ganeshkumar R, Ramasamy M, et al. (1995) Low-molecular-weight heparin fragment versus intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. Ann Intern Med 123: 101–2.

41. Moreno-Palomares JJ, Fisac-Herrero RM, Sánchez-Domingo A, Ferreira-Pasos EM, Graus J, et al. (2001) Low molecular weight heparin versus unfractionated heparin in the treatment of deep vein thrombosis. Am Med Interna 18: 364–6.

42. Simonneau G, Charbonnier B, Decousus H, Planchon B, Ninet J, et al. (1993) Subcutaneous low-molecular-weight heparin fragmin versus intravenous unfractionated heparin in the treatment of acute non massive pulmonary embolism: an open randomized pilot study. Thromb Haemost 74: 1432–5.

43. Stricker H, Marchetti O, Haeberli A, Mombelli G (1999) Hemostatic activation under anticoagulant treatment: a comparison of unfractionated heparin vs. nadroparin in the treatment of proximal deep vein thrombosis. Thromb Haemost 82: 927–31.

44. Stricker H, Marchetti O, Haeberli A, Mombelli G (1999) Hemostatic activation under anticoagulant treatment: a comparison of unfractionated heparin vs. nadroparin in the treatment of proximal deep vein thrombosis. Thromb Haemost 82: 927–31.

45. Aiach M (1989) Treatment of deep venous thrombosis. Comparative study of a fixed dose unfractionated heparin by the subcutaneous route and standard heparin by the continuous intravenous route. A multicenter study. Circulation 83: 1380–1389.

46. Merli G, Sprio T, Olson CG, Abdalaarfi U, Davidson BL, et al. (2001) Subcutaneous Enoxeparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. Ann Intern Med 134: 191–202.

47. Lim W, Dendali F, Eke-Room JW, Crowther MA (2006) Meta-analytic low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. Ann Intern Med 144: 673–84.

48. Magee KD, Secvik W, Moher D, Rowe BH (2005) Low molecular weight heparin versus unfractionated heparin for acute coronary syndromes. Cochrane Database Syst Rev CD002132.

49. Murphy SA, Gibson CM, Morroe DA, Van de Werf F, Menouen IB, et al. (2007) Efficacy and safety of the low-molecular-weight heparin enoxaparin compared with unfractionated heparin across the acute coronary syndrome spectrum: a meta-analysis. Eur Heart J 28: 2077–86.

50. Silvain J, Requini F, Barthely M, Pollarle C, Cohen M, et al. (2012) Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. BMJ 344: e553.

51. Loke YK, Price D, Herxheimer A (2007) Systematic reviews of adverse effects: framework for a structured approach. BMC Med Res Methodol 7: 32.

52. DeGenirow D, Kolman L, DeCaro M, Andrel J, Chervoneva I, et al. (2007) Risk of major bleeding with concomitant dual antiplatelet therapy after percutaneous coronary intervention in patients receiving long-term warfarin therapy. Pharmacotherapy 27: 691–6.