
DATE: 19 March 2015

CONTEXT AND POLICY ISSUES

There are an estimated 30,000 hip fractures that occur in Canada each year.\(^1\) Approximately 17% of patients requiring surgical repair do not receive surgical treatment within the benchmark of 48 hours from admission to the emergency department.\(^2\) Operative delays may occur when patients are on treatments requiring pre-operative reversal, such as anticoagulation therapy; however, it has been suggested that there is an association between hip fracture surgery delay and adverse outcomes, including mortality.\(^3\)\(^-\)\(^5\) Up to an estimated 62% of hip fracture patients are already receiving anticoagulation or antithrombotic therapy at the time of fracture;\(^6\) therefore, there is uncertainty regarding how to manage a potentially large proportion of patients presenting with hip fractures requiring timely surgical intervention. This is particularly of concern for older patients, who are more likely to be receiving anticoagulation therapy and are also at greater risk of hip fracture.\(^3\)\(^,\)\(^4\)

However, hip fracture surgery itself is high-risk for venous thromboembolism (VTE) for any patient, so initiation of pharmacologic thromboprophylaxis is recommended for patients undergoing this procedure.\(^7\)\(^-\)\(^9\) One option for perioperative thromboprophylaxis is dalteparin, a low-molecular weight heparin (LMWH). There are multiple dosing options for dalteparin in surgical patients, so guidance on the recommended administration to hip fracture patients would clarify clinical practices for the prevention of VTE in this patient population.

The purpose of this report is to identify, summarize, and critically appraise the evidence-based guidelines regarding the management of patients over the age of 50 who require surgery for a hip fracture or other emergency orthopedic surgery, and are either currently on anticoagulation therapy or will receive VTE prophylaxis with dalteparin.
RESEARCH QUESTIONS

1. What are the evidence-based guidelines for discontinuation or modification of anticoagulation therapy for patients requiring emergency orthopedic surgical intervention?

2. What are the evidence-based guidelines for the use of dalteparin pre- and post-hip surgery for patients requiring emergency orthopedic surgical intervention?

KEY FINDINGS

One evidence-based guideline was identified that provides recommendations for pre- and post-surgical doses and frequency of dalteparin administration for VTE prophylaxis in surgical patients; 5000 units of dalteparin subcutaneously were recommended at 12 hours before surgery, followed by 5000 units delivered once daily post-operatively. Potential modifications for high-risk situations were also offered. No evidence-based guidelines were identified regarding treatment of patients on existing anticoagulation therapy requiring emergency orthopedic surgical intervention.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2015, Issue 2), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and February 20, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

<table>
<thead>
<tr>
<th>Table 1: Selection Criteria</th>
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<tbody>
<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td>Q1: Adults aged 50 years and over on anticoagulation therapy requiring emergency orthopedic surgical intervention</td>
</tr>
<tr>
<td>Q2: Adults aged 50 years and over requiring emergency orthopedic surgical intervention</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>Q1: Hip fracture and other emergency orthopedic surgeries performed without a delay to accommodate discontinuation or modification of anticoagulation therapy</td>
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<tr>
<td>Q2: Dalteparin given pre- and post-surgery</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
</tr>
<tr>
<td>No comparators necessary</td>
</tr>
</tbody>
</table>
Outcomes | Management of post-surgical blood clots and bleeding; Guidelines
---|---
Study Designs | Evidence-based guidelines

### Exclusion Criteria

Guidelines were excluded if they did not meet the selection criteria outlined in Table 1, lacked clear methodology, were duplicate publications, or were published prior to 2010.

### Critical Appraisal of Individual Guidelines

Guidelines were assessed for quality using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument.\(^{10}\) A numeric score was not calculated for each guideline. Instead, strengths and limitations of each guideline were summarized and described.

### SUMMARY OF EVIDENCE

#### Quantity of Research Available

A total of 272 citations were identified in the literature search. Following screening of titles and abstracts, 270 citations were excluded and two potentially relevant reports from the electronic search were retrieved for full-text review. Six potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant guidelines, seven publications were excluded for various reasons, while one publication met the inclusion criteria and was included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

#### Summary of Study Characteristics

Details of the included guideline characteristics are provided in Appendix 2.

**Study Design**

One evidence-based guideline,\(^ {11}\) published in 2010, was included in this report. The evidence supporting this guideline was derived from a search of the Cochrane Database for relevant systematic reviews, as well as a search of the journals that published the original studies included in the systematic reviews.

**Country of Origin**

The included guideline was developed in Finland by the Finnish Medical Society Duodecim.\(^ {11}\)

**Patient Population**

The Finnish Medical Society Duodecim guideline\(^ {11}\) addresses patients at risk for VTE in a number of settings, including those undergoing surgery for hip fracture. The age of the target population for the guideline document overall is 19 years and older. Age-specific recommendations for the use of dalteparin were not provided.
Interventions

The use of dalteparin for pharmacologic thromboprophylaxis in surgical patients is the intervention addressed by the guideline that is relevant to this review. This publication also provides guidance on the classification of patient risk level for VTE, recommendations for additional methods of thromboprophylaxis in surgical patients and other patient populations, and strategies for the management of heparin-induced thrombocytopenia and thrombosis.

Grading of Recommendations

The quality of the evidence used to support the recommendations was evaluated with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scheme. However, a grading scheme for the strength of the recommendations was not provided.

Summary of Critical Appraisal

Details of the critical appraisal of the included guidelines are provided in Appendix 3.

The guidelines from the Finnish Medical Society Duodecim\(^1\) had a clear scope and purpose with specific recommendations for particular clinical indications. However, the methodology of the guideline development was somewhat unclear. For example, while the source of the supporting evidence was described, the specific literature search strategy with search terms, study inclusion and exclusion criteria, and number of source documents were not provided. In addition, the group composition and professional affiliations of those involved in both the writing and the peer review process were not described, and conflict of interest disclosures were not provided, which adds uncertainty regarding the level of bias involved in the guideline development. The quality of the evidence was formally evaluated using GRADE; however, neither the methods used to formulate the recommendations nor the strength of the recommendations were provided. Furthermore, the association between the evidence and the recommendations was not always clear, as not every recommendation had a reference and GRADE rating.

Summary of Findings

Details of the included guideline findings and recommendations are provided in Appendix 4.

What are the evidence-based guidelines for discontinuation or modification of anticoagulation therapy for patients with hip fractures requiring surgical intervention?

No relevant evidence-based guidelines were identified regarding the discontinuation or modification of pre-existing anticoagulation treatment regimens of patients with hip fractures who require surgical intervention; therefore, no summary can be provided.

What are the evidence-based guidelines for the use of dalteparin pre- and post-hip surgery for patients with hip fractures requiring surgical intervention?

Guidelines on the prevention of VTE from the Finnish Medical Society Duodecim\(^1\) provide prophylactic regimens for three LMWHs, including dalteparin. They recommend that for VTE prophylaxis in surgical patients, 5000 units of dalteparin can be administered subcutaneously at 12 hours before surgery, followed by 5000 units delivered once daily post-operatively. The post-
operative duration of dalteparin administration is not specified. The dose may be increased or frequency may be increased to twice a day for high-risk, obese patients; however, the recommended dose increase for this patient population is not described. An alternative regimen is 2500 units of dalteparin administered two hours prior to surgery, followed by 2500 to 5000 units once daily post-operatively. Situations in which this alternative may be reasonable or preferable are not provided.

Of note, this dosing regimen was provided for surgical patients in general. However, high-risk patients and indications as defined by this guideline include patients over 40 years of age and major surgery, including hip fracture surgery. Therefore, the recommendations for high-risk situations may be particularly relevant. Though not specific to treatment with dalteparin, another general recommendation for high-risk situations is to continue thromboprophylaxis for four to five weeks.

Limitations

Due to the absence of an explicit link between some recommendations and the corresponding references, it is unclear whether all of the recommendations in this guideline are evidence-based; however, this limitation does not appear to apply to the recommendation for dalteparin regimens reported in this review. Furthermore, the recommendations are not explicitly described for hip fracture patients over the age of 50, introducing uncertainty as to whether there are preferred dalteparin dosing regimens for this specific patient population. A limitation of this review is that it is based on a guideline summary from the National Guidelines Clearinghouse, as the original full text document was unavailable; it is unclear whether additional information is available from the developer that would affect the critical appraisal of the quality of these guidelines.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

One evidence-based guideline\textsuperscript{11} was identified that provides recommendations for pre- and post-operative use of dalteparin for the prevention of VTE in adults undergoing hip fracture surgery. This guideline recommends subcutaneous administration of dalteparin, either 2500 units at two hours before surgery, or 5000 units at 12 hours before surgery. A post-operative daily dose of 5000 units is recommended. The guideline also indicates that modifications to the described regimens can be made based on clinical risk factors. No evidence-based guidelines specific to a Canadian context were identified; however, similar prophylactic regimens for patients undergoing hip fracture surgery were presented in a clinical practice guideline with unclear methodology from Thrombosis Canada.\textsuperscript{12} The American College of Chest Physicians guidelines on the Perioperative Management of Antithrombotic Therapy\textsuperscript{13} recommend anticoagulation bridging in surgical patients with VTE and at high risk for thromboembolism, and provide dalteparin bridging regimens for patients on high- and low-dose heparin for VTE treatment or prophylaxis, respectively. However, these recommendations are not specific to hip fracture surgery patients, but are intended for patients who are having elective surgery. Another guideline from this group on the Prevention of VTE in Orthopedic Surgery Patients\textsuperscript{8} recommends thromboprophylaxis with LMWH for at least 10 to 14 days after hip fracture surgery. In addition, they suggest that for those hip fracture patients who may experience a delay to surgery, LMWH therapy should be initiated after hospital admission but at least 12 hours before surgery. Of note, dalteparin is not referred to specifically in these guidelines.
No evidence-based guidelines regarding the discontinuation or modification of pre-existing anticoagulation therapy in patients who require emergency orthopedic surgical intervention were identified for inclusion in this review. Several guidelines relevant to the prevention of VTE in hip fracture surgical patients provide recommendations for perioperative initiation of pharmacologic thromboprophylaxis, rather than management strategies for patients already on anticoagulation therapy prior to hip fracture. The National Institute for Health and Care Excellence (NICE) recommends the prompt treatment of comorbidities in hip fracture patients in order to avoid surgical delays due to anticoagulation, yet no further specific guidance is provided. It has been reported that no comprehensive, published guidelines exist regarding the management of hip fracture patients on existing anticoagulation therapy, but some review articles discuss this topic and present clinical algorithms for this patient population. Due to the absence of identified evidence-based guidelines, information presented in algorithms for the management of hip fracture patients on existing anticoagulation therapy should be interpreted with caution.

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REFERENCES


APPENDIX 1: Selection of Included Studies

272 citations identified from electronic literature search and screened

270 citations excluded

2 potentially relevant articles retrieved for scrutiny (full text, if available)

6 potentially relevant reports retrieved from other sources (grey literature, hand search)

8 potentially relevant reports

7 reports excluded:
- irrelevant population (2)
- irrelevant intervention (2)
- unclear methodology (2)
- duplicate publication (1)

1 report included in review
APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Guidelines

| Intended users/Target population | Finnish Medical Society Duodecim, 2010

| Intervention and Practice Considered | VTE prophylaxis in surgical patients (e.g., LMWHs, including dalteparin)

| Major Outcomes Considered | Efficacy and safety of thromboprophylactic interventions

| Evidence Collection, Selection and Synthesis | Search of the electronic Cochrane Database of Systematic Reviews; Hand-searches of the Cochrane Library and medical journals for original publications

| Evidence Quality and Strength | Evidence quality weighted according to a provided rating scheme; No rating scheme for the strength of the recommendations

| Recommendations Development and Evaluation | GRADE classification scheme (Code A to D: Quality of evidence High to Very Low)

| Guideline Validation | Peer review, not otherwise described

GRADE = Grading of Recommendations Assessment, Development and Evaluation; LMWH = low molecular weight heparin; VTE = venous thromboembolism
### APPENDIX 3: Critical Appraisal of Included Publications

#### Table A2: Strengths and Limitations of Guidelines using AGREE II\(^\text{10}\)

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
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</thead>
<tbody>
<tr>
<td>- Clearly defined objectives, scope, and target populations</td>
<td>- Composition of the guideline development group not clearly defined</td>
</tr>
<tr>
<td>- Target users of and applicable clinical specialties for the guidelines presented clearly</td>
<td>- Unclear whether patients’ views and preferences were sought</td>
</tr>
<tr>
<td>- Clear presentation of recommendations for defined clinical situations and populations</td>
<td>- One database used for literature search and search terms not provided</td>
</tr>
<tr>
<td>- Evidence quality formally evaluated using GRADE</td>
<td>- Unclear study inclusion and exclusion criteria</td>
</tr>
<tr>
<td>- Benefits and risks of implementing the recommendations were clearly described</td>
<td>- Unclear methods used to formulate the recommendations</td>
</tr>
<tr>
<td>Finnish Medical Society Duodecim, 2010(^\text{11})</td>
<td>- GRADE ratings not provided for every recommendation</td>
</tr>
<tr>
<td></td>
<td>- Unclear methods of peer review</td>
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<tr>
<td></td>
<td>- Unclear procedure for updating the guideline</td>
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<tr>
<td></td>
<td>- Unclear implementation strategy and factors relevant to guideline application not described</td>
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<td></td>
<td>- Conflict of interest declaration not provided</td>
</tr>
</tbody>
</table>

AGREE II = Appraisal of Guidelines for Research & Evaluation II; GRADE = Grading of Recommendations Assessment, Development and Evaluation
APPENDIX 4: Main Recommendations of the Included Guidelines

Table A3: Main Recommendations of the Included Guidelines

<table>
<thead>
<tr>
<th>Main Recommendations</th>
<th>Strength of Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finnish Medical Society Duodecim, 2010(^\text{11})</td>
<td>The strength of recommendations was not described; the quality of the evidence supporting the recommendations was assessed using GRADE.</td>
</tr>
</tbody>
</table>

Prevention of VTE in surgical patients; Implementation:
“Dalteparin by subcutaneous injection 5000 units, 12 hours before surgery and then the same dose once daily. If the patient has a particularly high risk of VTE and is obese, the dose can be increased or 5000 units may be administered twice daily. It is also possible to give 2500 units 2 hours before surgery and then 2500–5000 units once daily.”

The LMWH options and regimens for surgical patients, which included this recommendation for dalteparin, were listed as a whole as GRADE code [A].

Classification of the quality of evidence:
“[A]: High quality of evidence; Further research is very unlikely to change confidence in the estimate of effect.
- Several high-quality studies with consistent results
- In special cases: one large, high-quality multi-centre trial”

GRADE = Grading of Recommendations Assessment, Development and Evaluation; LMWH = low molecular weight heparin; VTE = venous thromboembolism