

Low Molecular Weight Heparin: A Review of Clinical Guidelines Across Indications

FINAL COMPREHENSIVE RESEARCH PLAN

September 2015

Study Team: Systematic Review Unit

Objective

To undertake a systematic critical appraisal of evidence-based guidelines to provide a summary of recommendations for the use of low molecular weight heparins for acute treatment and prevention or prophylaxis across a variety of indications .

Research Questions

1. What are the guidelines for the use of low molecular weight heparins (LMWH) for the approved treatment indications in the Province of Ontario?
 - a. Treatment of deep vein thrombosis (non-cancer patients);
 - b. Treatment of deep vein thrombosis in patients in whom treatment with warfarin is not tolerated, or is contraindicated;
 - c. Treatment of deep vein thrombosis in patients who have failed treatment with warfarin;
 - d. Treatment of deep vein thrombosis in pregnant or lactating females; and,
 - e. Treatment of symptomatic acute venous thromboembolism in patients with cancer.
2. What are the guidelines for the use of LMWH for the approved post-operative prophylaxis indications in the Province of Ontario?
 - a. Post-operative prophylaxis of deep vein thrombosis for patients with hip or knee surgery who cannot use warfarin; and,
 - b. Post-operative prophylaxis of venous thromboembolism in patients undergoing orthopedic surgery of the lower limbs (e.g., hip, knee)
3. What are the guidelines for the use of LMWH for:
 - a. Peri-operative bridging in patients who require long-term warfarin and must discontinue due to surgery;
 - b. The prevention of venous thromboembolism in patients with cancer; and,
 - c. The prevention of venous thromboembolism in non-orthopedic surgical patients.

Methods

Literature Search

We will carry out a literature search for relevant national and international treatment guidelines (North America, Europe and Australia) published since 2005 using key resources including MEDLINE, EMBASE, and The Cochrane Library databases, as well as a focused Internet and grey literature search. Additional resources or databases may be utilized if recommended by the medical librarian. No filters will be applied to limit the retrieval by study type.

Clinical experts will also be asked to identify references for the research team to supplement the database and internet search.

Article Selection and Eligibility

All titles and/or abstracts will be reviewed by two independent reviewers to determine eligibility. When citations meet the criteria, the full-text articles will be retrieved and reviewed.

Only guidelines published in English by professional associations, institutions or recognized medical bodies will be included. Guidelines will be included if an evidence-based development process is presented along with the levels of confidence and clinical recommendations (1). Guidelines based on expert opinion and/or consensus activities will be excluded; however, references may be retained for inclusion in the appendix of the final report to supplement higher quality guidelines. If there are updates to guidelines within the search dates employed, only the latest version of the guideline will be included.

Guidelines should report pharmacologic treatment recommendations for the indications of interest (Table 1)(or reference the indication of interest within a more global treatment recommendation).

Table 1. Indications of Interest in the Review of Guidelines
Indications for Treatment or Prevention
Treatment of DVT in non-cancer patients.
Treatment of DVT in patients in whom treatment with warfarin is not tolerated, or is contraindicated.
Treatment of DVT in patients who failed treatment with warfarin.
Treatment of DVT in pregnant or lactating females.
Treatment of symptomatic acute VTE in patients with cancer.
Post-operative prophylaxis of DVT for patients undergoing hip or knee surgery (and who cannot use warfarin).
Post-operative prophylaxis of VTE in patients undergoing orthopedic surgery of the lower limbs (e.g., hip, knee).
Prevention of (prophylaxis) VTE in patients with cancer.
Prevention of (prophylaxis) VTE in non-orthopedic surgical patients.
Peri-operative bridging in patients who require long-term warfarin and must discontinue due to surgery.

VTE=venous thromboembolism, DVT=deep-vein thrombosis, DOAC=direct-acting oral anticoagulant

Included guidelines will be vetted by clinical experts prior to final inclusion and quality appraisal.

Quality Appraisal

The Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool will be used to critique the guidelines. (2) AGREE II is a guideline appraisal tool that has been found to have high construct validity.(3) The tool consists of 23 items arranged into 6 domains: scope and purpose (3 items), stakeholder involvement (3 items), rigor of development (8 items), clarity of presentation (3 items), applicability (4 items), and editorial independence (2 items). Each item is scored between strongly agree (4) and strongly disagree (1). The items scores within a domain will then be added and calculated as a percentage. A domain will be considered effectively addressed if its score was $\geq 60\%$, as has been previously used in critical appraisals of arthritis guidelines.(4, 5)

All members of the research team will complete training on the AGREE II instrument and grading process to ensure consistency and reliability in the review.

Each guideline will be independently assessed by two reviewers. Differences in scoring will be resolved through discussion and consensus with a third independent reviewer.

Based on their overall domain scores, each guideline will be given an overall assessment from the research team based on whether or not the guideline is recommended for clinical use (2).

Summary of Recommendations

Next, guidelines that are recommended for clinical use will be summarized by indication for use by the research team in the development of reimbursement recommendations for the Ontario Ministry of Health and Long-Term Care.

Timeline and Deliverables

Work will commence on acceptance of this protocol. The review and critical appraisal of guidelines will be completed in approximately 12 to 16 weeks. We will provide a draft written report to the ODPRN detailing methods adopted, results and key findings within 16 weeks of study protocol approval. Any revisions or additions identified following completion of the draft report will be available 4 weeks following the receipt of the stakeholder reviews.

References

1. Lim W, Arnold DM, Bachanova V, Haspel RL, Rosovsky RP, Shustov AR, et al. Evidence-based guidelines--an introduction. *Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program*. 2008;26-30.
2. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2010;182(18):E839-42.
3. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. Development of the AGREE II, part 2: assessment of validity of items and tools to support application. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2010;182(10):E472-8.
4. Poitras S, Avouac J, Rossignol M, Avouac B, Cedraschi C, Nordin M, et al. A critical appraisal of guidelines for the management of knee osteoarthritis using Appraisal of Guidelines Research and Evaluation criteria. *Arthritis research & therapy*. 2007;9(6):R126.
5. Hurkmans EJ, Jones A, Li LC, Vliet Vlieland TP. Quality appraisal of clinical practice guidelines on the use of physiotherapy in rheumatoid arthritis: a systematic review. *Rheumatology (Oxford, England)*. 2011;50(10):1879-88.