MEDwave

Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
Medwave 2015;15(10):e6320 doi: 10.5867/medwave.2015.6320

Low molecular weight heparin in one or two doses for the initial treatment of venous thromboembolic disease?

Authors: Juan Pablo Albornoz**[1,4]**, Andrés Valenzuela**[1,2,3,4]**, Andrés Aizman**[1,3,4]**

Affiliation:
[1] Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[2] Programa de Salud Basada en Evidencia, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[3] Departamento de Medicina Interna, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[4] Proyecto Epistemonikos, Santiago, Chile

E-mail: andresaizman@gmail.com

Citation: Albornoz JP, Valenzuela A, Aizman A. Low molecular weight heparin in one or two doses for the initial treatment of venous thromboembolic disease?. *Medwave*2015;15(10):e6320 doi: 10.5867/medwave.2015.6320
Publication date: 20/11/2015

Abstract

The preferred dosification for low molecular weight heparins is in two doses for most patients with venous thromboembolic disease. A daily dose would make treatment simpler, less expensive and more comfortable while retaining a similar benefit and safety. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified two systematic reviews including five randomized trials. We combined the evidence using meta-analysis and generated a summary of findings table following the GRADE approach. We concluded it is not clear whether the risk of recurrence differs between the two alternatives because the certainty of the evidence is very low, and that administering low molecular weight heparin in two doses might be associated to little or no difference in the risk of major bleeding and mortality.

Problem

There is wide consensus that low molecular weight heparins are part of the standard treatment for many patients with venous thromboembolic disease. Traditionally they are administered twice daily. However, a single daily dose could increase patient's comfort, reduce costs and facilitate ambulatory treatment. However, it is not clear if this dosification has a similar benefit and safety profile.

Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages
- It is not clear whether a daily dose of low molecular weight heparin modifies the risk of recurrence compared with two daily doses because the certainty of the evidence is very low.
- One daily dose of low molecular weight heparin could result in little or minimal increase in the risk of major bleeding, which would not increase mortality risk.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found two systematic reviews [1],[2] including five randomized controlled trials overall [3],[4],[5],[6],[7].
What types of patients were included	Patients with confirmed thromboembolic event: deep vein thrombosis and/or pulmonary embolism. Four studies included patients with deep vein thrombosis and one [5] included patients with pulmonary embolism or deep vein thrombosis.
What types of interventions were included	All of the studies compared subcutaneous low molecular weight heparin administered once versus twice daily. Two studies used dalteparin [4],[6], one enoxaparin[5], one nadroparin [3] and one logiparin [7]. Four studies used the same daily dose in both arms and one [5] used 75% of the total dose in the once daily dose arm.
What types of outcomes were measured	Symptomatic recurrence, major bleeding (intracranial, retroperitoneal, requiring transfusion, surgery or anticoagulant withdrawal, or as cause of death) during and 48 hours after treatment; total bleeding episodes; global mortality and cause-specific mortality (recurrence, bleeding); clot size increase in venography.

Summary of findings

The information is based on five randomized studies which included 1508 patients. Four studies reported all-cause mortality, three studies reported symptomatic recurrence at 3 months of follow up and five studies presented information on major bleeding during treatment with low molecular weight heparin.

- It is not clear whether a daily dose of low molecular weight heparin modifies the risk of recurrence compared with two daily doses because the certainty of the evidence is very low.
- One daily dose of low molecular weight heparin could result in little or minimal increase in the risk of major bleeding. The certainty of the evidence is low.
- One daily dose of low molecular weight heparin might not increase mortality. The certainty of the evidence is low.

Low molecular weight heparin in one or two doses for venous thromboembolic disease

Patients	Initial treatment of pulmonary embolism and/or deep vein thrombosis
Intervention	Low molecular weight heparin (LMWH) administered once daily
Comparison	Low molecular weight heparin administered twice daily

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITH LMWH twice daily	**WITH LMWH once daily**		
	Difference: patients per 1000			
Recurrence at 3 months	44 per 1000	41 per 1000	RR 0.92 (0.37 to 2.27)	⨁◯◯◯ [1,2] Very low
	Difference: 3 patients less per 1000 (Margin of error: 28 less to 56 more)			
Bleeding	11 per 1000	14 per 1000	RR 1.26 (0.51 to 3.12)	⨁⨁◯◯ [2] Low
	Difference: 3 patients more per 1000 (Margin of error: 28 less to 56 more)			
Mortality	27 per 1000	31 per 1000	RR 1.13 (0.60 to 2.13)	⨁⨁◯◯ [2] Low
	Difference: 4 patients more per 1000 (Margin of error: 11 less to 31 more)			

RR: Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* The risk **WITH two daily doses** is based on the risk in this group of the trials. The risk **WITH one daily dose** (and its margin of error) is calculated from relative effect (and its margin of error).

1- High heterogeneity for this outcome was found (I^2=66%).
2- The certainty of the evidence was decreased in one level for recurrence and two levels for bleeding and mortality due to the wide confidence interval, which includes both a considerable increase and decrease of the event.

Acerca de la certeza de la evidencia (GRADE)*

⨁⨁⨁⨁
Alta: La investigación entrega una muy buena indicación del efecto probable. La probabilidad de que el efecto sea sustancialmente distinto† es baja.

⨁⨁⨁◯
Moderada: La investigación entrega una buena indicación del efecto probable. La probabilidad de que el efecto sea sustancialmente distinto† es moderada.

⨁⨁◯◯
Baja: La investigación entrega alguna indicación del efecto probable. Sin embargo, la probabilidad de que el efecto sea sustancialmente distinto† es alta.

⨁◯◯◯
Muy baja: La investigación no entrega una indicación confiable del efecto probable. La probabilidad de que el efecto sea sustancialmente distinto† es muy alta.

* Esto es también denominado 'calidad de la evidencia' o 'confianza en los estimadores del efecto'.
† Sustancialmente distinto = una diferencia suficientemente grande como para afectar la decisión

Other considerations for decision-making

To whom this evidence does and does not apply

- Applies to patients with venous thromboembolism (pulmonary embolism, deep venous thrombosis or both) who initiate anticoagulation with subcutaneous low molecular weight heparin.
- The majority of the included patients in the randomized studies had deep vein thrombosis, so there is some degree of uncertainty about its applicability to patients with pulmonary embolism. It does not apply to patients with contraindication to low molecular weight heparin, such as massive events or advanced chronic kidney disease.

About the outcomes included in this summary

- This summary includes outcomes that according to the author's criteria are critical for decision making in these patients, and that are also considered in trials and clinical guidelines [8],[9],[10].

Balance between benefits and risks, and certainty of the evidence

- Given the low and very low certainty of the evidence, it is not possible to make an adequate balance between the risks and benefits of the one daily dose scheme over the conventional two daily doses scheme.

What would patients and their doctors think about this intervention

- The use of one daily dose could improve patient's comfort and eventually could facilitate ambulatory treatment, so some patients would prefer this option. It is especially relevant in these cases to warn about the existing uncertainty.

Resource considerations

- It is not possible to make an adequate balance between costs and benefits because there is a high degree of uncertainty about the latter. More information is needed to make an estimation of the costs associated to recurrence, bleeding and mortality.
- The proposed intervention could contribute to decrease the overburden of nursing teams and to reduce supplies needed for the administration.
- The costs could decrease in the case of enoxaparin, since the total daily dose is lower for once daily administration.
- In selected cases, the outpatient treatment would reduce the costs associated to hospitalization for once daily administration.

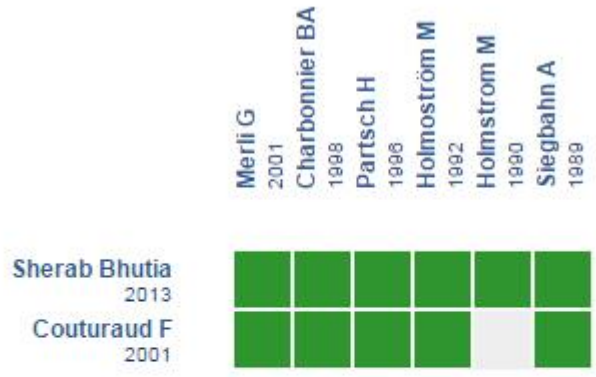
Differences between this summary and other sources

- The conclusions of this summary are consistent with the included systematic reviews.
- Our summary is in partial agreement with the main guidelines. The guideline of the American College of Chest Physicians [8] recommends a single daily dose over two daily doses provided that the total daily dose is not altered. The guidelines of the American Heart Association [9] and the European Society of Cardiology [10], although also supportive of the use of once daily dose, for enoxaparin they recommend a dosification of 1 mg/kg every 12 hours or 1.5 mg/kg every 24 hours (75% of the total daily dose of reference).

Could this evidence change in the future?

- The probability that new studies change the information presented in this summary is high, because the certainty of the evidence is low or very low.

How we conducted this summary
Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Low molecular weight heparin administered once versus twice daily for venous thromboembolism

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

References

1. Bhutia S, Wong PF. Once versus twice daily low molecular weight heparin for the initial treatment of venous thromboembolism. Cochrane Database Syst Rev. 2013 Jul 16;7:CD003074. | CrossRef | PubMed |
2. Couturaud F, Julian JA, Kearon C. Low molecular weight heparin administered once versus twice daily in patients with venous thromboembolism: a meta-analysis. Thromb Haemost. 2001 Oct;86(4):980-4. | PubMed |
3. Charbonnier BA, Fiessinger JN, Banga JD, Wenzel E, d'Azemar P, Sagnard L. Comparison of a once daily with a twice daily subcutaneous low molecular weight heparin regimen in the treatment of deep vein thrombosis. FRAXODI group. Thromb Haemost. 1998 May;79(5):897-901. | PubMed |
4. Holmström M, Berglund MC, Granquist S, Bratt G, Törnebohm E, Lockner D. Fragmin once or twice daily subcutaneously in the treatment of deep venous thrombosis of the leg. Thromb Res. 1992 Jul 1;67(1):49-55. | PubMed |

5. Merli G, Spiro TE, Olsson CG, Abildgaard U, Davidson BL, Eldor A, et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. Ann Intern Med. 2001 Feb 6;134(3):191-202.| PubMed |
6. Partsch H, Kechavarz B, Mostbeck A, Köhn H, Lipp C. Frequency of pulmonary embolism in patients who have iliofemoral deep vein thrombosis and are treated with once- or twice-daily low-molecular-weight heparin. J Vasc Surg. 1996 Nov;24(5):774-82. | PubMed |
7. Siegbahn A, Y-Hassan S, Boberg J, Bylund H, Neerstrand HS, Ostergaard P, Hedner U. Subcutaneous treatment of deep venous thrombosis with low molecular weight heparin. A dose finding study with LMWH-Novo. Thromb Res. 1989 Sep 15;55(6):767-78. | PubMed |
8. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e419S-94S. | CrossRef | PubMed |
9. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation. 2011 Apr 26;123(16):1788-830. | CrossRef| PubMed |
10. Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galiè N, Pruszczyk P, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J. 2008 Sep;29(18):2276-315. | CrossRef | PubMed |

Author address:
[1] Facultad de Medicina
Pontificia Universidad Católica de Chile
Lira 63
Santiago Centro
Chile