LECTURA CRÍTICA DE REVISTAS

UNIDAD ACADÉMICA CLÍNICA MÉDICA ¨B¨
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HOJA DE RUTA

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ARTÍCULO SELECCIONADO

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REVIEW ARTICLE

A systematic review on anti-Xa monitoring in the therapeutic use of low-molecular-weight heparins

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LA REVISTA

- Revista oficial de la Sociedad Internacional de Trombosis y Hemostasia (ISTH).
- Arbitrada
- Indexada en múltiples bases de datos científicas (Scopus, PubMed/MEDLINE, y Web of Science)
- Scimago Journal Rank 2024 1.8
- Índice h 217

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Journal Insights

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7.9 Days to first editorial decision ⓘ	**13.4** Days from acceptance to online publication ⓘ

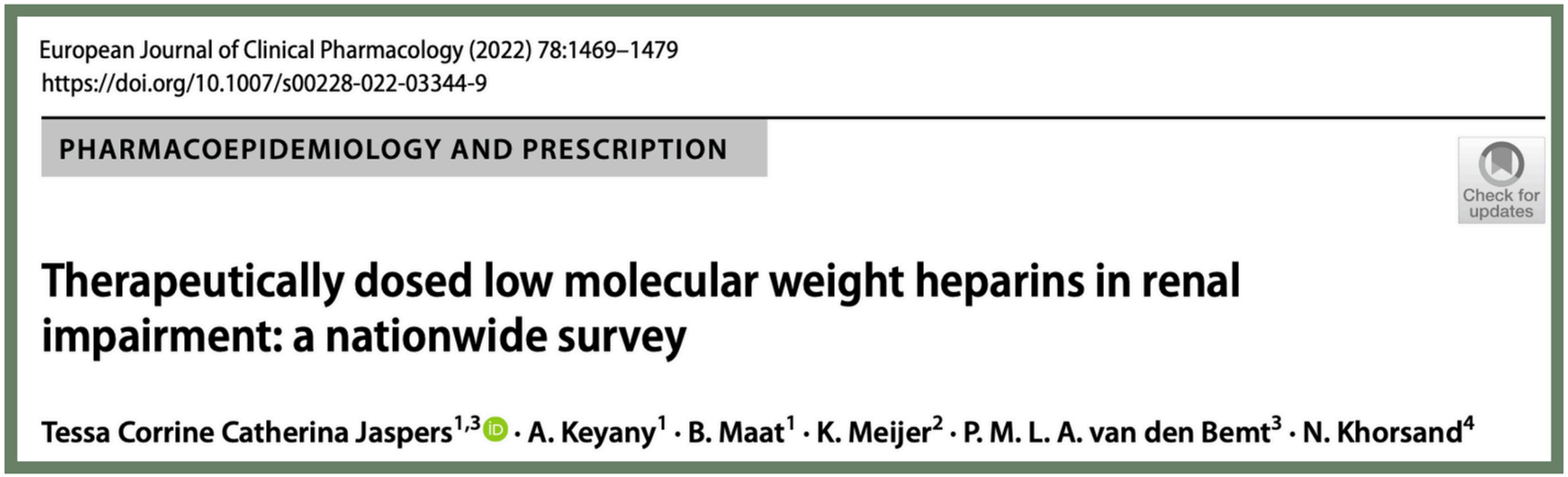
TÍTULO

A systematic review on anti-Xa monitoring in the therapeutic use of low-molecular-weight heparins

- Descriptivo
- 15 palabras, único párrafo
- Describe tipo de estudio
- Menciona tema principal del artículo
- Sin siglas
- No menciona población, tiempo, ni lugar

AUTORES

- Científicos holandeses (2 hematólogos, 3 farmacéuticos de 3 hospitales diferentes)
- Tessa C.C. Jaspers: 8 publicaciones relacionados a trombosis y hemostasia
- Karina Meijer: autora o coautora de más de 100 artículos, múltiples de trombosis y hemostasia
- Nakisa Khorsand >10 publicaciones relacionadas.



European Journal of Clinical Pharmacology (2022) 78:1469–1479
https://doi.org/10.1007/s00228-022-03344-9

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Check for updates

Therapeutically dosed low molecular weight heparins in renal impairment: a nationwide survey

Tessa Corrine Catherina Jaspers[1,3] · A. Keyany[1] · B. Maat[1] · K. Meijer[2] · P. M. L. A. van den Bemt[3] · N. Khorsand[4]

RESUMEN

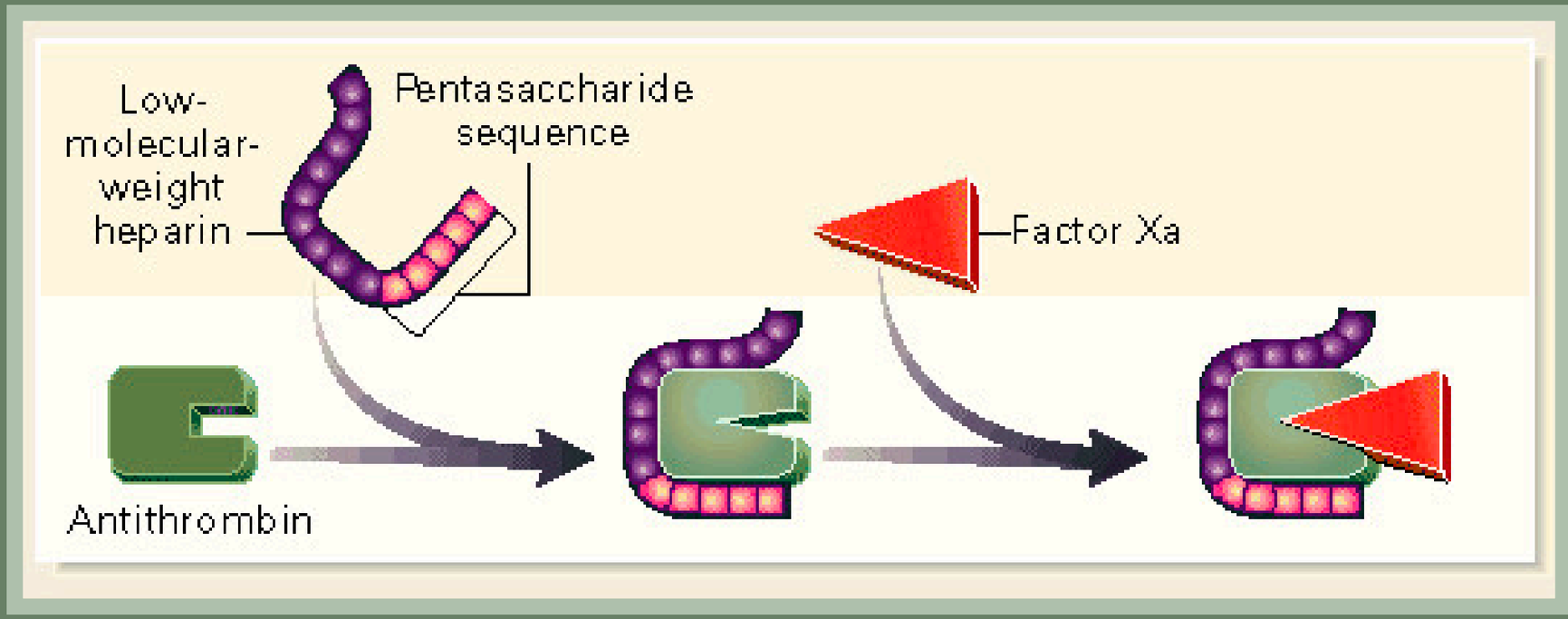
- Narrativo
- 277 palabras
- Describe objetivos
- No menciona aspectos metodológicos
- Fiel al artículo

Abstract

Low-molecular-weight heparins are widely utilized, including in special patient populations (eg, patients with renal impairment, pregnancy, and obesity). Monitoring with anti-Xa measurements is often used, but the effectiveness of anti-Xa—based dose adjustments remains uncertain. This systematic review aimed to provide an informed assessment of the usefulness of anti-Xa monitoring and subsequent dose adjustments in these patients. The primary outcome was the incidence of clinical events, such as major bleeding and venous thromboembolism, compared between patients with and without anti-Xa monitoring. Secondary outcomes were the correlation between anti-Xa levels and bleeding or thromboembolic complications and the frequency of dose adjustments based on anti-Xa levels. A total of 48 studies, both randomized controlled trials and observational studies, were included. All studies had a high risk of bias. Five studies indicated comparable rates of bleeding and thromboembolic complications in anti-Xa–monitored and unmonitored patients. Measurement of anti-Xa levels was associated with frequent dose adjustments. The correlation between anti-Xa levels and both bleeding and thromboembolic complications was weak, if it was present at all. Overall, this review highlights the limited evidence supporting the use of anti-Xa monitoring for dose adjustments in the therapeutic use of low-molecular-weight heparins. Therefore, we conclude that measuring anti-Xa levels is currently not justified. Only new, high-quality, preferably randomized studies could indicate otherwise.

KEYWORDS

drug monitoring, factor Xa, heparin, low-molecular-weight, venous thrombosis


Low-
molecular-
weight
heparin
Pentasaccharide
sequence
Factor Xa
Antithrombin

INTRODUCCIÓN

- Justifica el trabajo, reconoce una brecha en el conocimiento en poblaciones especiales generalmente excluidas en otros estudios.
- Estudios previos y guías internacionales con recomendaciones contradictorias y con escaso nivel de evidencia.
- Necesidad de elaborar un trabajo que ponga a punto el estado del arte en esta temática.
- Autorreferencia estudio previo sobre monitoreo Anti-Xa en pacientes renales.
- Aclara objetivos primarios y secundarios.

OBJETIVOS

Primario

- Comparar la incidencia de desenlaces clínicos entre los pacientes con y sin monitorización de anti-Xa.

Secundarios

- Evaluar la correlación entre los niveles de anti-Xa y las complicaciones hemorrágicas o tromboembólicas.

- Analizar la proporción de pacientes con ajustes de dosis de heparina de bajo peso molecular basados en los niveles de anti-Xa.

PREGUNTA PICO

POBLACIÓN
Pacientes que reciben heparina de bajo peso molecular a dosis terapéuticas.

INTERVENCIÓN
Monitoreo de niveles de anti-Xa con ajustes de dosis basados en esos resultados.

COMPARACIÓN
no realizar monitoreo anti-Xa (mantener dosis estándar)

OUTCOMES
Según objetivos primario y secundarios

METODOLOGÍA

- Revisión sistemática basada en las guías PRISMA.
- Búsqueda en PubMed 03/09/2024. Filtros: artículos en inglés, resumen disponible online.
- Criterios de inclusión y exclusión:
  - Inclusión: ECA o estudio de cohortes revisados por pares en los que se haya dosificado el anti-Xa en pacientes recibiendo dosis terapéuticas de HBPM.
  - Exclusión: reporte de casos, serie de casos o n <10.
- Los artículos fueron revisados por pares de investigadores, discrepancias resueltas en conjunto o mediante consulta a un tercer investigador independiente.
- Los datos relevantes fueron extraídos y corroborados por distintos investigadores.

PRISMA (PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSES)

- Guía internacional que busca mejorar la calidad y transparencia de las revisiones sistemáticas y metaanálisis.
- Pensada para todas las revisiones sistemáticas, con o sin síntesis de resultados.
- Aplicable a revisiones que combinan estudios cuantitativos y cualitativos.
- Puede utilizarse para revisiones sistemáticas originales, revisiones actualizadas, revisiones “vivas”.
- El objetivo NO es orientar la realización de revisiones sistemáticas.
- Elementos principales:
  - Checklist (lista de verificación): guía paso a paso para asegurar que cada sección esté completa.
  - Diagrama de flujo: representa las fases del proceso de revisión.
- Edición 2020 incluye guía para abstract.

Tabla 1
Lista de verificación PRISMA 2020

Sección/tema	Ítem n.°	Ítem de la lista de verificación	Localización del ítem en la publicación
TÍTULO			
Título	1	Identifique la publicación como una revisión sistemática.	
RESUMEN			
Resumen estructurado	2	Vea la lista de verificación para resúmenes estructurados de la declaración PRISMA 2020 (tabla 2).	
INTRODUCCIÓN			
Justificación	3	Describa la justificación de la revisión en el contexto del conocimiento existente.	
Objetivos	4	Proporcione una declaración explícita de los objetivos o las preguntas que aborda la revisión.	
MÉTODOS			
Criterios de elegibilidad	5	Especifique los criterios de inclusión y exclusión de la revisión y cómo se agruparon los estudios para la síntesis.	
Fuentes de información	6	Especifique todas las bases de datos, registros, sitios web, organizaciones, listas de referencias y otros recursos de búsqueda o consulta para identificar los estudios. Especifique la fecha en la que cada recurso se buscó o consultó por última vez.	

EVALUACIÓN DE RIESGO DE SESGO Y CALIDAD

Evaluación riesgo de sesgo y calidad con herramientas validadas:

- Estudios no randomizados
  - MINORS (calidad)
  - RoBANS2 (sesgo)

- ECA
  - RoB 2 (sesgo)

Investigadores determinaron la calidad de los estudios por separado, discrepancias se resolvieron en conjunto.

MINORS

Table 2. The revised and validated version of MINORS

Methodological items for non-randomized studies	Score†
1. **A clearly stated aim:** the question addressed should be precise and relevant in the light of available literature	
2. **Inclusion of consecutive patients**: all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion)	
3. **Prospective collection of data**: data were collected according to a protocol established before the beginning of the study	
4. **Endpoints appropriate to the aim of the study**: unambiguous explanation of the criteria used to evaluate the main outcome which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on an intention-to-treat basis.	
5. **Unbiased assessment of the study endpoint**: blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise the reasons for not blinding should be stated	
6. **Follow-up period appropriate to the aim of the study**: the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events	
7. **Loss to follow up less than 5%**: all patients should be included in the follow up. Otherwise, the proportion lost to follow up should not exceed the proportion experiencing the major endpoint	
8. **Prospective calculation of the study size**: information of the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes	
Additional criteria in the case of comparative study	
9. **An adequate control group**: having a gold standard diagnostic test or therapeutic intervention recognized as the optimal intervention according to the available published data	
10. **Contemporary groups**: control and studied group should be managed during the same time period (no historical comparison)	
11. **Baseline equivalence of groups**: the groups should be similar regarding the criteria other than the studied endpoints. Absence of confounding factors that could bias the interpretation of the results	
12. **Adequate statistical analyses**: whether the statistics were in accordance with the type of study with calculation of confidence intervals or relative risk	

†The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies and 24 for comparative studies.

Extraído de :Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (MINORS): development and validation of a new instrument. *ANZ J Surg.* 2003;73(9):712–716.

ROBANS2

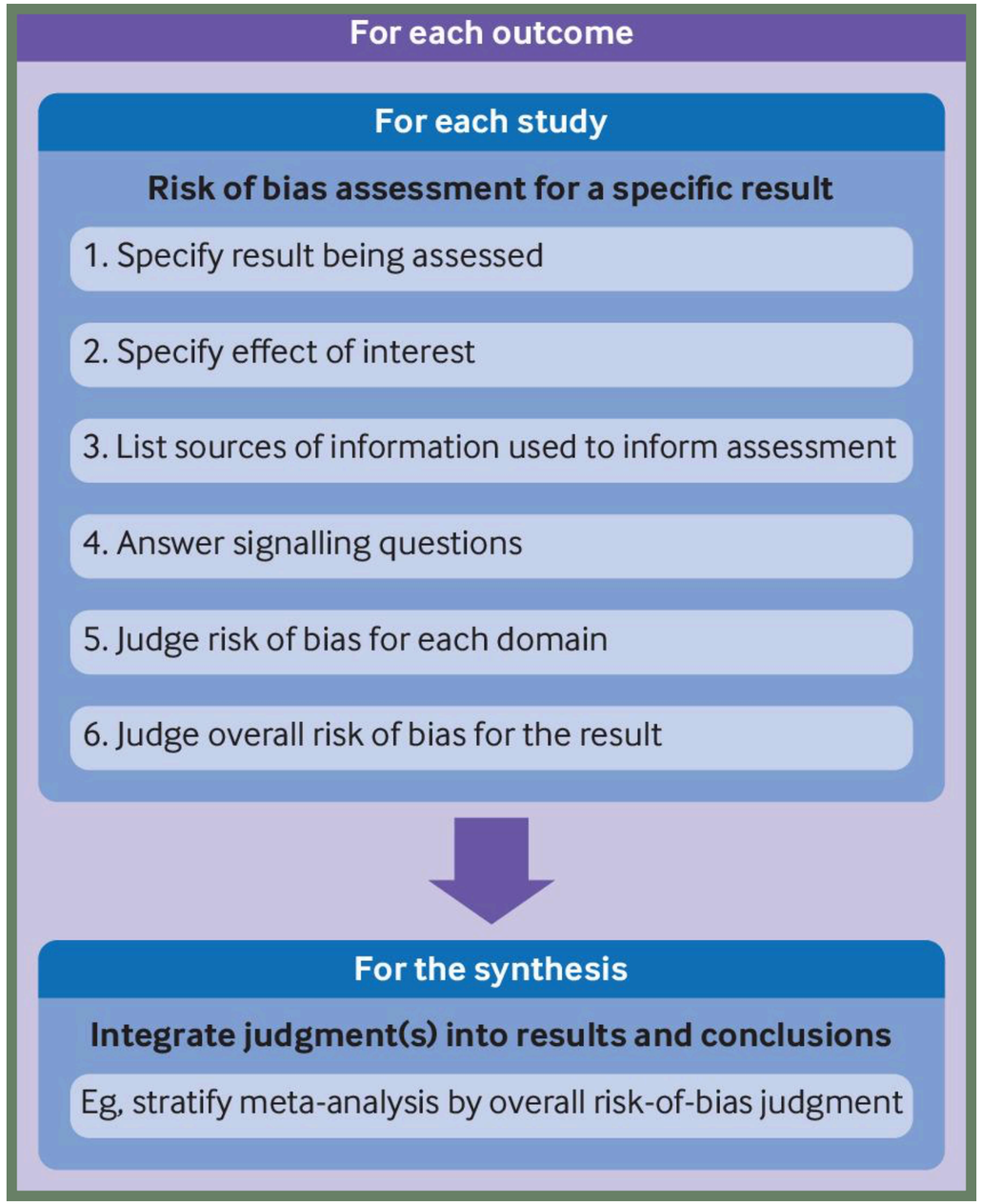
Table 1. Revised version of the risk of bias assessment tool for nonrandomized studies (RoBANS 2)

Domain	Details	Risk of bias
Comparability of the target group	Selection bias due to the selection of an inappropriate comparison target group	☐ Low ☐ High ☐ Unclear
Target group selection	Selection bias due to inappropriate intervention or inappropriate selection of exposure group or patient group	☐ Low ☐ High ☐ Unclear
Confounders	Selection bias due to inappropriate confounder confirmation and consideration	☐ Low ☐ High ☐ Unclear
Measurement of intervention/exposure	Performance bias due to inappropriate intervention or inappropriate exposure measurement	☐ Low ☐ High ☐ Unclear
Blinding of assessors	Detection bias due to inappropriate blinding of assessors	☐ Low ☐ High ☐ Unclear
Outcome assessment	Detection bias due to inappropriate outcome assessment methods	☐ Low ☐ High ☐ Unclear
Incomplete outcome data	Attrition bias due to inappropriate handling of incomplete data	☐ Low ☐ High ☐ Unclear
Selective outcome reporting	Reporting bias due to selective outcome reporting	☐ Low ☐ High ☐ Unclear

RoBANS 2, revised version of Risk of Bias Assessment tool for Nonrandomized Studies.

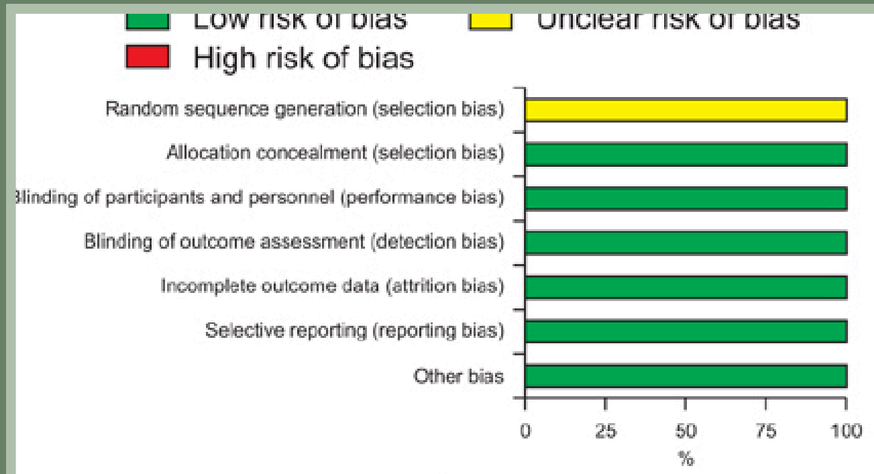
Hyun-Ju Seo, et al.

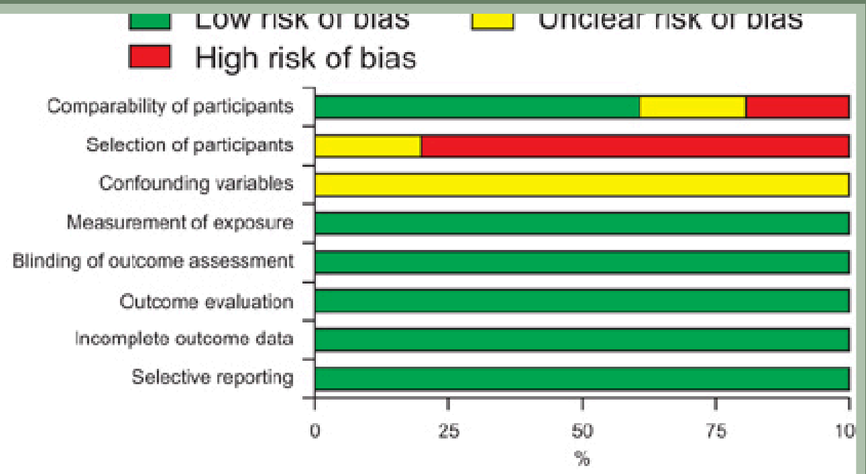
ROB2

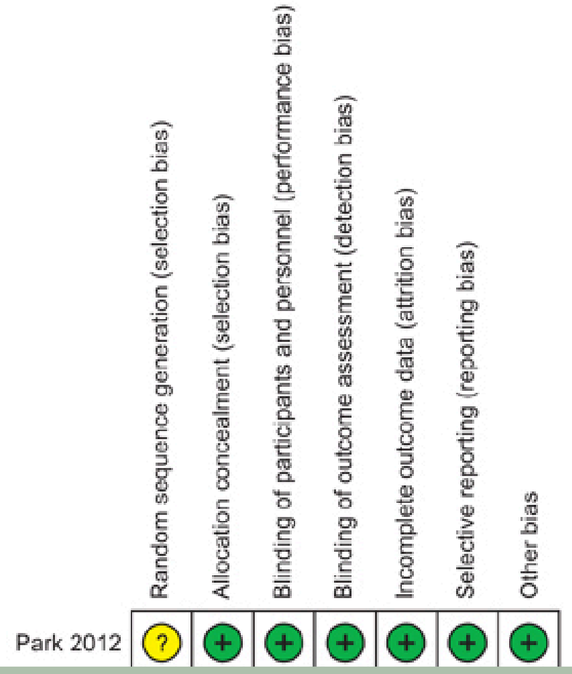


Sterne et al. BMJ 2019;366:l4898

CUADRO INFORMATIVO SESGO







ASPECTOS ÉTICOS

- Una de las autoras recibe financiamiento de varias farmacéuticas, no implicadas en este trabajo

- Resto de autores sin conflictos de interés

RESULTADOS

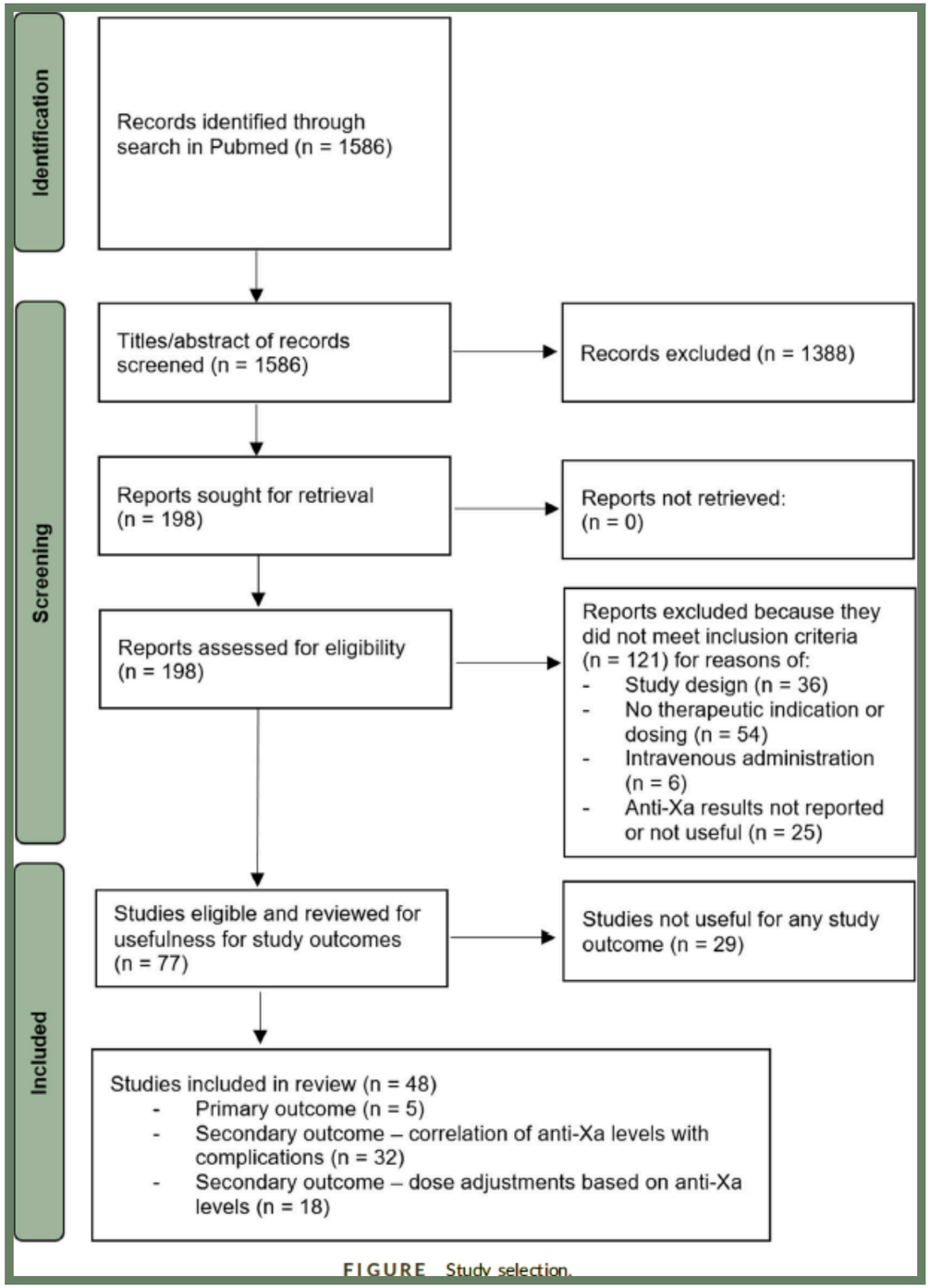


FIGURE Study selection.

CARACTERÍSTICAS DE LOS ESTUDIOS

4 ensayos clínicos aleatorizados

44 observacionales

25 prospectivos

19 retrospectivos

En total 6054 pacientes entre los que se incluye: embarazadas, renales, extremos de peso, añosos.

Se incluyen diferentes tipos de HBPM (75% enoxaparina).

LA MAYORÍA CON ALTO RIESGO DE SESGOS Y BAJA - MEDIA CALIDAD

TABLE 1 Baseline characteristics of included studies.

Reference	Study design	Population[a]	*N* patients	Primary outcome(s)	Type of LMWH	Dosage	Overall quality score[b]	Overall risk of bias[c]
Abdulla et al. (2023) [78]	Retrospective, single-center	VTE	53	Proportion of anti-Xa levels within the therapeutic range	Enoxaparin	Either 1 mg/kg twice daily or 1.5 mg/kg OD	Low	High
Ahuja et al. (2018) [79]	Retrospective, single-center	Either pregnant, creatinine clearance ≤ 50 mL/min, or a body weight ≤ 50 kg or ≥120 kg	31	Percentage of patients with therapeutic anti-Xa levels at the first drawn level	Enoxaparin	Therapeutic dose (not further specified)	Medium	High
Aleidan et al. (2019) [69]	Observational, prospective, single-center	Pregnant and nonpregnant	68	Proportion of anti-Xa levels within the therapeutic range	Enoxaparin	1 mg/kg twice daily	Medium	High
Alhenc-Gelas et al. (1994) [15]	Randomized controlled trial, multicenter	Deep venous thrombosis	122	Treatment efficacy (Marder score), bleeding, VTE[d]	Dalteparin	100 IU/kg twice daily		High

OUTCOME PRIMARIO

- Para su análisis se incluyeron 5 estudios: 1 ECA y 4 observacionales.
- Incidencia similar de hemorragias mayores y ETEV en pacientes con y sin monitorización de anti-Xa.

TABLE 2 The incidence of clinical outcomes between patients with anti-Xa monitoring and those without anti-Xa monitoring.

	Anti-Xa–based dosing cohort *n/N* (%)				Weight-based/unmonitored cohort *n/N* (%)			
Reference	Major bleed	Minor bleed	Unspecified bleed	VTE	Major bleeding	Minor bleeding	Unspecified bleed	VTE
Alhenc-Gelas et al. (1994) [15]	0/64 (0)	3/64 (5)	3/64 (5)	2/64 (3)	1/58 (2)	3/58 (5)	4/58 (7)	1/58 (2)
Appay et al. (2024) [38]	Not reported	Not reported	2/110 (2)	4/110 (4)	Not reported	Not reported	28/652 (4)	13/652 (2)
Hart et al. (2021) [35]	34/283 (12)	Not reported	34/283 (12)	22/283 (8)	37/391 (9)	Not reported	37/391 (9)	18/391 (5)
Petrie et al. (2016) [36]	9/36 (25)	Not reported	9/36 (25)	2/36 (6)	2/8 (25)	Not reported	2/8 (25)	0/8 (0)
Uppuluri et al. (2017) [37]	3/39 (8)	1/39 (3)	4/39 (10)	4/39 (10)	2/47 (4)	3/47 (6)	5/47 (11)	4/47 (9)

VTE, venous thromboembolism.

OUTCOMES SECUNDARIOS

Estudios heterogéneos. Hay evidencia muy débil entre la asociación entre niveles elevados de antiXa y complicaciones hemorrágicas.

TABLE 3 Studies that reported anti-Xa levels in all low-molecular-weight heparin-treated patients and/or patients with a bleed.

Reference	*N* patients	Trough or peak anti-Xa level[a]	Type of LMWH	Dosing regimen	Mean ± SD or median (IQR) anti-Xa (IU/mL) of included patients	Severity of bleeding and frequency	Anti-Xa (IU/mL) in patients with bleeding	Time of anti-Xa measurement in relation to bleeding	Patient category[b]	Anti-Xa assay used
Bazinet et al. (2004) [39]	233	Peak	Enoxaparin	Twice daily	1.14 ± 0.07	Major bleeding (*n* = 3) Significant bleeding (*n* = 20) Minor bleeding (*n* = 2)	All bleeding Mean, 1.13 ± 0.32	Not reported	Obese and renal impairment	Not reported
Montalescot et al.	803	Peak	Enoxaparin	Twice daily	0.91 ± 0.01	Major bleeding (*n* = 8)	0.83 ± 0.01	Not reported	Patients with an	Chromogenic assay
Lee et al. (2020) [51]	241	Peak	Enoxaparin	Twice daily	1.12 ± 0.43	Bleeding of unspecified severity (*n* = 10)	Descriptive: supratherapeutic (*n* = 6) Therapeutic (*n* = 4)	Not applicable	Obese	Chromogenic assay by Diagnostica Stago
N = 30 studies No bleeding events: *n* = 7 studies/ 155 patients	*N* = 3216	N/A	N/A	N/A	N/A	Fatal/major bleed *n* = 43 Minor/moderate bleed *n* = 82 Bleeding of unspecified severity *n* = 59 Total bleeding events = 184	18 studies reported anti-Xa levels numerically 3 studies reported anti-Xa levels descriptively 5 studies: anti-Xa in bleeders > overall group 4 studies: anti-Xa in bleeders < overall group 12 studies: anti-Xa in bleeders is similar to the overall group	6 studies reported the timing of anti-Xa measurement. 3 studies reported peak anti-Xa levels 1 study reported that anti-Xa levels were measured routinely 2 studies reported anti-Xa levels at a time after or before the bleeding event Others: not reported	N/A	N/A

TABLE 4 Studies that reported anti-Xa levels in all low-molecular-weight heparin-treated patients and/or patients with a thromboembolic event.

Reference	*N* patients	Trough or peak level	Type of LMWH	Mean ± SD or median (IQR) anti-Xa (IU/mL) of included patients	Frequency and type of thromboembolic event	Anti-Xa in patients with an event (IU/mL)	Time of anti-Xa measurement in relation to the event	Patient category[a]	Anti-Xa assay used
N = 17 studies No events in *n* = 4 studies/131 patients	*N* = 1749	N/A	N/A	N/A	Total VTE reported: 53	Anti-Xa was numerically reported in 4 studies. Descriptively reported in 3 studies. 3 studies (5 events): anti-Xa in VTE patients < overall group 1 study (6 events): anti-Xa in VTE patients > overall group 3 studies: anti-Xa in VTE patients is similar to the overall group	Timing of anti-Xa reported in 1 study	N/A	N/A

Los autores afirman que no se demostró correlación entre niveles de anti-Xa y complicaciones tromboembólicas.

TABLE 5 The proportion of patients with low-molecular-weight heparin dose adjustments based on anti-Xa levels.

Reference	*n/N* patients with dose adjustments based on anti-Xa levels vs patients with anti-Xa monitoring (%)	*n/N* dose adjustments based on anti-Xa levels vs anti-Xa levels drawn (%)	Patient category[a]
Abdulla et al. (2023) [78]	17/53 (32)	32/95 (34)	VTE
Aleidan et al. (2019) [69] Pregnant cohort Nonpregnant cohort	Not reported/36 Not reported/32	54/108 (50)[c] 24/96 (25)[c]	Pregnant cohort Nonpregnant cohort
Alhenc-Gelas et al. (1994) [15]	24/64 (38)	37/not reported	DVT
Barbour et al. (2004) [70]	11/13 (85)	14/250 (6)	Pregnant
Curry et al. (2018) [43]	6/54 (11)	Not reported	Obese
Hart et al. (2021) [35]	211[b]/283 (74)	Not reported/1584	Oncology
Jacobsen et al. (2003) [71]	10/20 (50)	Not reported	Pregnant
Kruse & Lee (2004) [72]	55/170 (32)	Not reported	Renal impairment
Kufel et al. (2017) [73]	Not reported/59	12/74 (16)	Not specified
Lykke et al. (2008) [74]	18/22 (82)	Not reported/357	Pregnant
Martin et al. (2021) [55]	19/47 (40)	Not reported	Obese
Pautas et al. (2002) [57]	26/200 (13)	Not reported/630	Age > 70 y
Petrie et al. (2016) [36]	22/36 (61)	56/227 (25)	Pregnant
Rey & Rivard (2000)	0/15 (0)	0/34 (0)	Pregnant
Rodie et al. (2002) [59]	3/36 (8)	Not reported	Pregnant
Smith et al. (2004) [76]	1/12 (8)	Not reported	Pregnant
Uppuluri et al. (2017) [37]	Not reported/39	45/183 (25)	Oncology
Yeung et al. (2020) [77]	1/20 (5)	Not reported	Renal impairment
Total	**424/1045 (41)[d]**	**237/1067 (21)[e]**	**All patient categories**
***N* = 8 pregnancy**	**65/154 (42)[f]**	**148/619 (24)[g]**	**Pregnant cohorts**

- Medición de anti-Xa llevó a ajuste de dosis en casi la mitad de los pacientes.
- Aproximadamente la cuarta parte de las mediciones de anti-Xa llevaron a ajuste de dosis.

DISCUSIÓN Y CONCLUSIONES

- Falta evidencia para recomendar el monitoreo rutinario de anti-Xa, por lo cual actualmente no está justificado.
- Se debe determinar el rango terapéutico de anti-Xa para cada centro y cada tipo de HBPM por separado.
- Se requiere un ECA de alta calidad para valorar la utilidad del anti-Xa para la dosificación de HBPM.

LIMITACIONES

- Sesgo de selección por potencial exclusión de estudios secundario a estrategia de búsqueda.
- Estudios incluidos con alto riesgo de sesgo y baja-moderada calidad.
- Gran variabilidad metodológica entre estudios incluídos.

FORTALEZAS

- Diseño metodológico minimiza sesgo de interpretación.
- Única revisión en el tema.
- Alta aplicabilidad, incluye poblaciones diversas y generalmente excluidas.
- Aplicable a nuestro medio, alto porcentaje de uso de enoxaparina.

BIBLIOGRAFÍA

- 82 citas (razonable considerando que se trata de una revisión)
- Variedad de trabajos de últimas 2 décadas
- Autorreferencia a trabajo propio del equipo

MUCHAS GRACIAS