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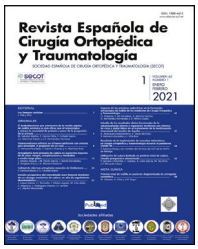

REVIEW ARTICLE

[Translated article] Risk of venous thromboembolism in thromboprophylaxis between aspirin and low molecular weight heparins after total hip arthroplasty or total knee arthroplasty: Systematic review and meta-analysis

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KEYWORDS
Aspirin;
Heparin;
Total knee arthroplasty;
Total hip arthroplasty;
Deep vein thrombosis;
Pulmonary embolism

Abstract
Introduction: The aim of this study was to evaluate the efficacy of aspirin versus low molecular weight heparins (LMWH) for the prophylaxis of venous thromboembolism (VTE), deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing total knee arthroplasty (TKA) and/or total hip arthroplasty (THA).
Materials and methods: Systematic review and meta-analysis. Sixteen studies were selected. The risk of VTE, DVT and PE were analysed. Mortality, risk of bleeding and surgical wound complications was also analysed.
Results: 248,461 patients were included. 176,406 patients with thromboprophylaxis with LMWH and 72,055 patients with aspirin thromboprophylaxis. There were no significant differences in the risk of VTE (OR = 0.93; 95% CI: 0.69–1.26; $p = 0.64$), DVT (OR = 0.72; 95% CI: 0.43–1.20; $p = 0.21$) or PE (OR = 1.13; 95% CI: 0.86–1.49; $p = 0.38$) between both groups. No significant differences were found in mortality ($p = 0.30$), bleeding ($p = 0.22$), or complications in the surgical wound ($p = 0.85$) between both groups. These same findings were found in the sub-analysis of only randomised clinical trials ($p > 0.05$).

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Conclusions: No increased risk of PE, DVT, or VTE was found among patients with aspirin thromboprophylaxis versus patients with LMWH thromboprophylaxis. There was also no greater mortality, greater bleeding, or greater complications in the surgical wound found among patients with aspirin thromboprophylaxis versus patients with LMWH thromboprophylaxis.

PALABRAS CLAVE
Aspirina;
Heparina;
Artroplastia total de rodilla;
Artroplastia total de cadera;
Trombosis venosa profunda;
Tromboembolia pulmonar

Riesgo de tromboembolia venosa en la tromboprofilaxis entre aspirina y heparinas de bajo peso molecular tras una artroplastia total de cadera o artroplastia total de rodilla. Revisión sistemática y metaanálisis

Resumen
Introducción: El objetivo de este estudio fue evaluar la eficacia de la aspirina frente a las heparinas de bajo peso molecular (HBPM) para la profilaxis de la tromboembolia venosa (TEV), trombosis venosa profunda (TVP) y tromboembolia pulmonar (TEP) tras artroplastia total de rodilla (ATR) o artroplastia total de cadera (ATC).
Materiales y métodos: Revisión sistemática y metaanálisis. Se seleccionaron 16 estudios. Se analizaron el riesgo de TEV, TVP y TEP. También se analizó la mortalidad, riesgo de sangrado y complicaciones de la herida quirúrgica.
Resultados: Se incluyó a 248.461 pacientes; 176.406 con tromboprofilaxis con HBPM y 72.055 pacientes con tromboprofilaxis con aspirina. No hubo diferencias significativas en el riesgo del TEV (OR = 0,93; IC 95%: 0,69-1,26; $p = 0,64$), TVP (OR = 0,72; IC 95%: 0,43-1,20; $p = 0,21$) ni TEP (OR = 1,13; IC 95%: 0,86 y,49; $p = 0,38$) entre ambos grupos. Tampoco se hallaron diferencias significativas en la mortalidad ($p = 0,30$), sangrado ($p = 0,22$), ni complicaciones en la herida quirúrgica ($p = 0,85$) entre ambos grupos. Estos mismos hallazgos se encontraron en el subanálisis de solo ensayos clínicos aleatorizados ($p > 0,05$).
Conclusiones: No se halló mayor riesgo de TEP, TVP, ni TEV en los pacientes con tromboprofilaxis con aspirina frente a los pacientes con tromboprofilaxis con HBPM. Tampoco se halló mayor mortalidad, mayor sangrado, ni mayores complicaciones en la herida quirúrgica entre los pacientes con tromboprofilaxis con aspirina y los pacientes con tromboprofilaxis con HBPM.

Introduction

In recent years, there has been a considerable increase in the volume of elective hip and knee arthroplasty cases.[1] Annually, approximately 1.5 million total hip arthroplasties (THA) and total knee arthroplasties (TKA) are performed in the USA. In Spain, more than 40,000 primary THA and 35,000 primary TKAs are reported annually.[2] Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary thromboembolism (PE), remains a severe complication after THA or TKA.[3]

Historically, Johnson et al. in a study of 7959 patients undergoing THA reported a non-fatal PE rate of 7.89% and a fatal PE rate of 1.04% in the first five postoperative weeks; which would make PE the highest cause of mortality after THA in the first postoperative weeks.[4] Stulberg et al. reported in their series of 638 patients undergoing TKA, in which 49 patients were inadvertently not given prophylaxis, that 83% of these patients developed a DVT.[5] These results led to the development of safe and effective strategies for VTE prophylaxis after THA and/or TKA.[3,6] Currently, at one month postoperatively, symptomatic VTE occurs in .6–1.4% of patients undergoing these procedures, even with strategies to prevent VTE.[6]

Drugs used for chemical thromboprophylaxis after TKA and/or THA include oral anticoagulants (OACs), low-molecular-weight heparins (LMWH), and aspirin. LMWHs, such as enoxaparin, dalteparin, bemiparin, etc., have reported DVT rates after THA of 3.4–20.8% and non-fatal PE rates between 0% and .5%, and DVT rates after TKA between 23% and 45% and non-fatal PE rates of 0–.2% at one month post-operatively.[7–9] Currently enoxaparin, an LMWH, is the most widely used pharmacological therapy for thromboprophylaxis after THA and/or TKA in Spain.[10] However, aspirin (ASA) has also been shown to be an effective prophylactic agent after THA and TKA with reported DVT rates of up to 2.6%, and non-fatal PE rates between .14% and .6% at 90 days postoperatively.[11,12]

Due to its low cost, perceived safety, ease of administration, and evidence from observational studies, thromboprophylaxis with ASA has increased in the USA, especially since 2010.[3,13] In their 2012 current trends report among American knee and hip surgeons. Abdel et al. found that aspirin and mechanical measures are the most common measures for VTE prophylaxis after primary THA and TKA (THA: 95% in 2021, 87% in 2018 and 20% in 2009 and TKA: 97% in 2021, 88% in 2018, and 20% in 2009).[13] Similarly, the International Consensus on Venous Thromboembolism (ICM-

VTE), published in 2021, gave a ''strong'' recommendation for the use of aspirin as prophylaxis after THA or TKA.[3]

However, in 2022 the CRISTAL randomised clinical trial (RCT), the largest RCT to date on this topic, with 9711 patients, found that among those undergoing THA or TKA for osteoarthritis, aspirin compared to enoxaparin resulted in a significantly higher rate of symptomatic VTE (defined as below- or above-knee DVT or PE) within 90 days postoperatively.[14] Because in Spain the switch from LMWH to ASA for thromboprophylaxis after TKA or THA is a major change from current protocols,[15] the aim of this study is, through a systematic review and meta-analysis, to evaluate the efficacy of aspirin vs. LMWH for VTE, DVT, and PE prophylaxis in patients undergoing TKA and/or THA, with the hypothesis ''in patients undergoing TKA and/or THA, is the administration of ASA equally effective compared to LMWH for thromboprophylaxis?'' Secondary objectives are to assess the risk for bleeding and complications in surgical wounds.

Material and methods

Literature search strategy

Systematic review with meta-analysis (PROSPERO: ID CRD42023398140). The present systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[16] and the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[17] The electronic search was conducted between February and April 2023. The electronic databases PubMed, Embase, Medline, and Ovid were searched using the following terms: ''total hip arthroplasty'', ''total knee arthroplasty'', ''aspirin'', ''low molecular weight heparin'', ''complications'', ''deep vein thrombosis'', ''pulmonary embolism''; and in Spanish ''*artroplastia total de cadera*'', ''*artroplastia total de rodilla*'', ''*aspirina*'', ''*heparina de bajo peso molecular*'', ''*complicaciones*'', ''*trombosis venosa profunda*'', ''*tromboembolismo de pulmonar*''. The search strategy is presented in Annex 1. Additional strategies to identify studies included consultation with experts and use of the ''related articles'' functions. The literature search was restricted to English and Spanish.

Eligibility criteria

The inclusion criteria for identifying studies were as follows: (1) Studies comparing aspirin vs. LMWH in orthopaedic THA and/or TKA surgery, with a minimum follow-up period of four weeks. The minimum follow-up period of four weeks was taken because most studies recommend prophylactic measures for at least four weeks after surgery, and therefore studies with a follow-up shorter than this period may not provide relevant information on the effectiveness of full prophylactic treatment. (2) Prospective randomised studies, prospective non-randomised studies, and retrospective studies describing patient demographics, and (3) studies reporting postoperative complications using incidence rates, especially risk for deep vein thrombosis and pulmonary thromboembolism. The following were excluded: (1) Animal studies. (2) Studies with a sample size of less than 40 patients. Studies smaller than 40 patients were excluded to increase the precision and reliability of the results, and to reduce bias and variability in the results. (3) Studies that reported complications as a cumulative percentage or ''yes/no''. (4) Studies older than 20 years.

Study selection

Two authors (JN, FM) assessed the eligibility of the search results. A detailed reading of studies that met the inclusion criteria was performed. If there was a conflict between the two reviewers, a third reviewer (JM) was consulted to make a decision.

Data extraction

Data were extracted from the main texts and supplementary annexes of the studies. Data extraction was performed by two reviewers to ensure that data were extracted appropriately. Data extraction from the included studies was performed as follows: (I) general characteristics such as first author, year of publication, study design, study location, number of patients included, and follow-up; (II) demographics of included patients such as age, sex, comorbidities (especially history of DVT or PE); (III) surgery data such as type of surgery (THA or TKA); (IV) type, dose, and duration of thromboprophylaxis; (V) day of mobilisation; and (VI) clinical outcomes. The primary clinical outcome was the risk for DVT or PE. Secondary clinical outcomes included mortality, bleeding events, and wound complications (until last follow-up).

Quality assessment

The quality of the RCTs was assessed according to Review Manager (RevMan) software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014) to assess the risk of bias. The assessment methods consisted of the following: random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting. Scores in these domains are distilled into an overall assessment of the overall risk of bias for a given RCT: (I) ''low risk of bias''; (II) ''some concerns''; or (III) ''high risk of bias''. We also assessed the quality of RCT studies and all other non-randomised studies using the Mixed Methods Appraisal Tool (MMAT), version 2018.[18] The methodological quality criteria and results are presented in Annex 2.

Statistical analysis

Descriptive statistics were mean and standard deviation (SD) for continuous variables, and count and percentage for categorical variables. Meta-analysis was performed with the Review Manager software (version 5.3) of the Cochrane community. For binary variables the odds ratio (OR) was used for assessment, while for continuous variables the standard mean difference (SMD) with a 95% confidence interval (CI) was used. Study heterogeneity was estimated using

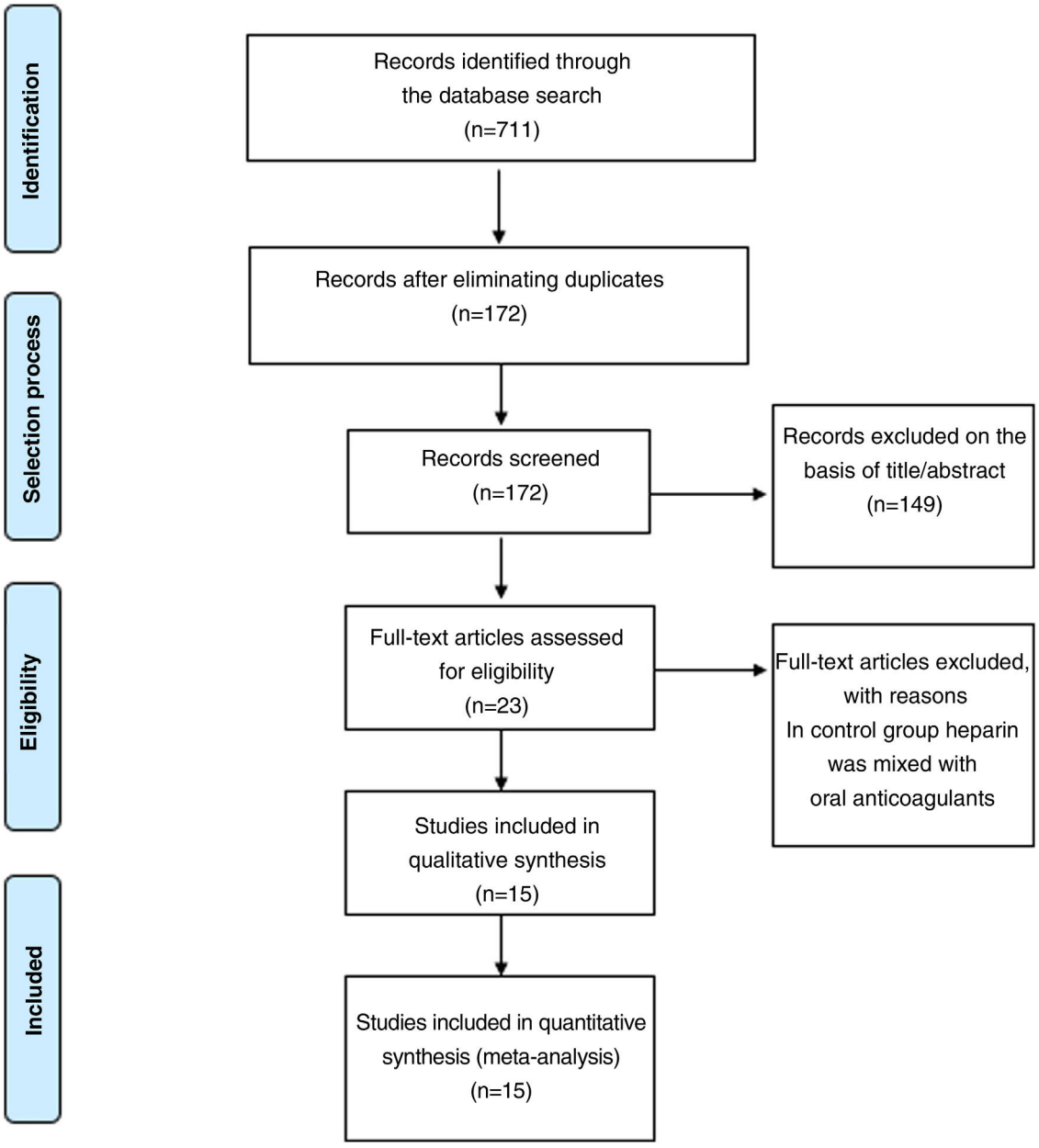


Figure 1 PRISMA flow chart. PRISMA diagram illustrating the number of items excluded at different stages of the selection process.

the I^2 test. The random-effects inverse variance model was applied. Statistical significance was defined as a two-tailed *p*-value of <.05.

Results

Search results and included articles

Our search yielded 711 published articles (PubMed 525, Embase 114, Medline 46, and Ovid 22). After discarding duplicates, selecting inclusion criteria and applying exclusion criteria, 15 articles were selected for analysis (Fig. 1).[14,19–32] Fig. 2 gives the risk of bias summary of the RCTs, and Annex 2 gives the risk summary of all studies included.[14,19–32]

Study characteristics

The general characteristics of each study are shown in Table 1.[14,19–32] Seven included articles were retrospective studies,[19,25,27,31,32] two were prospective non-randomised,[22,23] and six were RCTs.[14,24,26,28–30] The meta-analysis included a total of 248,461 patients, with 176,406 patients on thromboprophylaxis with LMWH and 72,055 patients on thromboprophylaxis with aspirin.[14,19–32] The mean age was 65.3 (SD 3.9) in the LMWH patients and 66.1 (SD 5.4) in the aspirin patients[14,22,24,26,28,29]; 59.6% of the

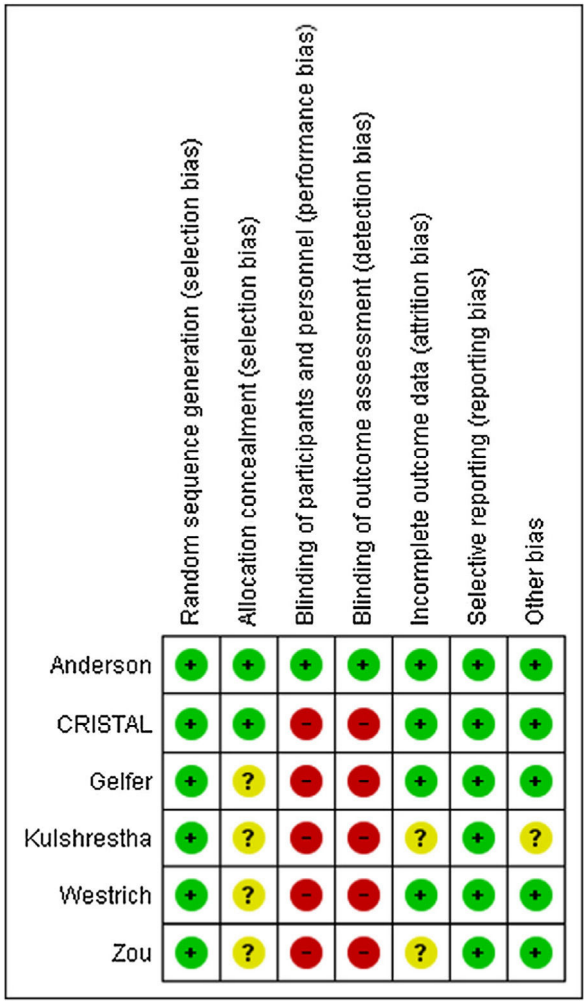


Figure 2 Summary of risk of bias. Randomised clinical trials. The reviewers' judgements on each risk of bias item for each included study: green is ''low risk of bias'', red is ''high risk of bias'', yellow is ''uncertain risk of bias''.

patients were female in the aspirin group and 59.7% in the LMWH group.[14,19,22,24–26,28–30,32]

Risk-of-bias assessment

The results of the risk-of-bias assessment of the RCTs according to Review Manager (RevMan) software version 5.3 are presented in Fig. 2.[14,24,26,28–30] The results of the risk-of-bias assessment of all studies using the MMAT assessment tool are presented in Annex 2.[14,19–32] All six RCTs indicated adequate randomisation methods.[14,24,26,28–30] Only one study blinded both patients and assessors.[28] Age and sex demographics at baseline were similar in both treatment groups in all the RCTs.[14,24,26,28–30] Of the remaining nine non-randomised studies, only one study showed no statistically significant difference in age and gender between the aspirin and LMWH group.[32] Only four studies were funded, with only the study by Westrich et al. being funded by an enoxaparin pharmaceutical.[24] However, no difference was found in this study between enoxaparin and aspirin in the risk for thromboprophylaxis.

Primary results: risk for thromboembolic disease

Fourteen studies assessed the incidences of VTE,[14,19–26,28–32] while 12 studies assessed the incidence of DVT[14,19–26,28–30] and 13 studies assessed the incidence of PE.[14,19–26,28–30,32] There were no significant differences in the risk for VTE (OR = .93; 95% CI: .69–1.26; $p = .64$) (Fig. 3a), TVP (OR = .72; 95% CI: .43–1.20; $p = .21$) (Fig. 3b), or PE (OR = 1.13; 95% CI: .86–1.49; $p = .38$) (Fig. 3c) after THA and/or TKA between aspirin and LMWH. Heterogeneity of $I^2 = 89\%$, $p < .001$; $I^2 = 86\%$, $p < .001$ and $I^2 = 15\%$, $p = .30$, respectively.

In the subgroup analysis, selecting only randomised clinical studies, we also found no significant difference in the risk for VTE (OR = .82; 95% CI: .41–1.65, $p = .59$) (Fig. 4a), DVT (OR = .79; 95% CI: .38–1.67; $p = .54$) (Fig. 4b), and PE (OR = 1.73; 95% CI: 0.96–3.10; $p = .07$) (Fig. 4c) after THA and/or TKA between aspirin and LMWH.[14,24,26,28–30] Heterogeneity of $I^2 = 79\%$, $p < .001$; $I^2 = 77\%$, $p < .001$ and $I^2 = 5\%$, $p = .38$, respectively.

Secondary results: mortality, risk for bleeding, risk for wound complications

There were no significant differences in mortality (OR = 1.10; 95% CI: .92–1.32; $p = .30$) (Fig. 5a),[14,19,22,23,28,29] increased risk for bleeding (OR = .70; 95% CI: .39–1.25; $p = .22$) (Fig. 5b),[14,24–26,28,32] or increased risk for surgical wound complications (OR = .95; 95% CI: .54–1.65; $p = .85$) (Fig. 5c)[14,22,23,25,26,28–30,32] after THA and/or TKA between aspirin and LMWH. Heterogeneity of $I^2 = 0\%$, $p = .87$; $I^2 = 31\%$, $p = .21$ and $I^2 = 56\%$, $p = .02$, respectively.

In the RCT-only subgroup analysis, there were also no significant differences in mortality (OR = 1.37; 95% CI: .37–5.14; $p = .64$) (Fig. 6a),[14,28,29] increased risk for bleeding (OR = .70; 95% CI: .44–1.11; $p = .13$) (Fig. 6b)[14,24,26,28]; or increased risk for surgical wound complications (OR = .70; 95% CI: .32–1.50; $p = .35$) (Fig. 6c)[14,26,28–30] after THA and/or TKA between aspirin and LMWH. Heterogeneity of $I^2 = 0\%$, $p = .55$; $I^2 = 3\%$, $p = .38$ and $I^2 = 57\%$, $p = .05$, respectively.

Discussion

The current study found no significant difference between aspirin and LMWH in the reduction of VTE events, including PE and DVT, in patients undergoing elective THA and TKA surgery. There was also no significant difference in the reduction of mortality, bleeding events, and wound complications between aspirin and LMWH. These same findings were found in the sub-analysis that included only randomised clinical trials.

Although aspirin has been used for several decades in the USA for thromboprophylaxis after THA and/or TKA, in Spain this paradigm shift may be a revolution.[15] Many papers that are consistent with our findings have demonstrated that aspirin is at least as safe and effective for thromboprophylaxis as OACs and LMWH.[3,33–37] In their meta-analysis of randomised studies, Singjie et al. observed no significant differences between aspirin and other anticoagulants (LMWH and OACs) as thromboprophylactic agents in the prevention of VTE in patients undergoing major orthopaedic surgery.[33] Similarly, Haykal et al. in their meta-

Table 1 Baseline characteristics of the studies included in the meta-analysis.

Study	Year	Design	LMWH (dose)	Aspirin (dose)	Number of patients recorded according to type of thromboprophylaxis				Funding
					Number of LMWH patients	Number of aspirin patients	Age of LMWH patients	Age of aspirin patients	
Keays et al.[25]	2003	Retrospective cohort	Enoxaparin 40 mg	ASA 300	75	75	72	72	No
Gelfer et al.[26]	2006	ECA	Enoxaparin 40 mg	ASA 100 mg	60	61	67	68	No
Westrich et al.[24]	2006	ECA	Enoxaparin 40 mg	ASA 650 mg	135	129	68.9	69	Yes[a]
Jameson et al.[19]	2011	Retrospective cohort	LMWH (NM)	ASA (NM)	86,642	22,942	NM	NM	No
Khatod et al.[27]	2011	Retrospective cohort	LMWH (NM)	ASA (NM)	7202	934	NM	NM	No
Anderson et al.[28]	2013	RCT	Dalteparin 5000 U	ASA 81 mg	398	380	57.9	57.6	Yes[b]
Kulshrestha et al.[29]	2013	RCT	Enoxaparin 40 mg	ASA 325 mg	706	194	64.9	62.6	No
Zou et al.[30]	2014	RCT	Enoxaparin 40 mg	ASA 100 mg	112	110	65.7	62.7	No
Yhim et al.[31]	2017	Retrospective cohort	LMWH (NM)	ASA (NM)	68,834	28,266	NM	NM	Yes[c]
Lindquist et al.[32]	2018	Retrospective cohort	Enoxaparin 40 mg	ASA 750 mg	440	366	66.7	65.8	No
Ghosh et al.[20]	2019	Retrospective cohort	Dalteparin 5000 U	ASA 150 mg	995	6078	NM	NM	No
Ní Cheallaigh et al.[21]	2020	Prospective observational	Enoxaparin 40 mg	ASA 150 mg	961	3460	NM	NM	No
Borton et al.[23]	2022	Prospective observational	Enoxaparin 40 mg	ASA 150 mg	1049	2560	NM	NM	No
Hovik et al.[31]	2021	RCT	Dalteparin 5000 U	ASA 75 mg	5010	1084	66	73	No
CRISTAL[14]	2022	Retrospective cohort	Enoxaparin 40 mg	ASA 100 mg	3787	5416	67.2	66.4	Yes[d]

ASA: aspirin; LMWH: low molecular weight heparin; NM: not mentioned; RCT: randomised clinical trial.

[a] Enoxaparin (Lovenox, Aventis, Bridgewater, NJ).

[b] Canadian Institutes of Health Research.

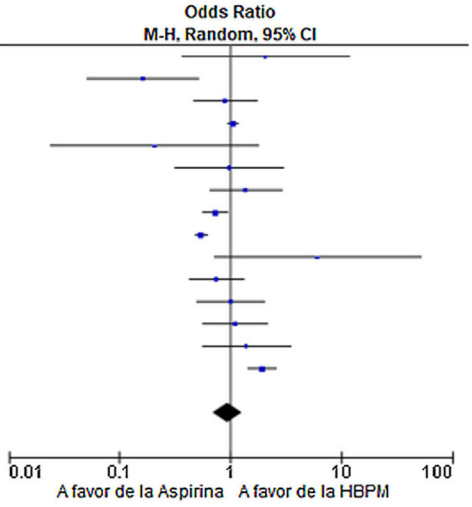
[c] Seoul National University Bundang Hospital.

[d] 4-Year Medical Research Futures Fund grant by the Australian federal government (grant 1152285).

a. Diagrama de bosque del riesgo de tromboembolismo venoso (TEV).

Study or Subgroup	Aspirina Events	Aspirina Total	HBPM Events	HBPM Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Keays	4	75	2	75	2.4%	2.06 [0.37, 11.58]	2003
Gelfer	4	61	18	60	4.3%	0.16 [0.05, 0.52]	2006
Westrich	20	129	23	135	7.4%	0.89 [0.46, 1.72]	2006
Jameson	383	22942	1389	86642	11.2%	1.04 [0.93, 1.17]	2011
Anderson	1	380	5	398	1.7%	0.21 [0.02, 1.78]	2013
Kulshrestha	4	194	15	706	4.5%	0.97 [0.32, 2.96]	2013
Zou	18	110	14	112	6.7%	1.37 [0.64, 2.91]	2014
Yhim	70	3654	355	13653	10.5%	0.73 [0.56, 0.95]	2017
Yhim.	384	24612	1559	55181	11.2%	0.55 [0.49, 0.61]	2017
Lindquist	5	366	1	440	1.7%	6.08 [0.71, 52.28]	2018
Ghost	68	6078	15	995	8.2%	0.74 [0.42, 1.30]	2019
Cheallaigh	36	3460	10	961	7.0%	1.00 [0.49, 2.02]	2020
Borton	32	2560	12	1049	7.3%	1.09 [0.56, 2.13]	2021
Hovik	6	1084	20	5010	5.6%	1.39 [0.56, 3.47]	2021
CRISTAL	187	5416	69	3787	10.4%	1.93 [1.46, 2.55]	2022
Total (95% CI)		**71121**		**169204**	**100.0%**	**0.93 [0.69, 1.26]**	
Total events	1222		3507				

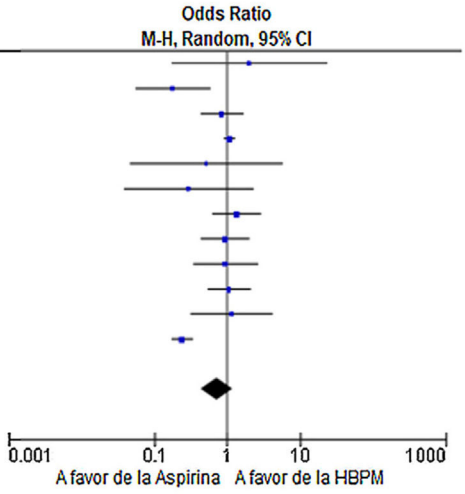
Heterogeneity: Tau² = 0.21; Chi² = 122.04, df = 14 (P < 0.00001); I² = 89%
Test for overall effect: Z = 0.47 (P = 0.64)



b. Diagrama de bosque del riesgo de trombosis venosa profunda (TVP)

Study or Subgroup	Aspirina Events	Aspirina Total	HBPM Events	HBPM Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Keays	2	75	1	75	3.3%	2.03 [0.18, 22.85]	2003
Gelfer	4	61	17	60	7.7%	0.18 [0.06, 0.57]	2006
Westrich	19	129	23	135	10.5%	0.84 [0.43, 1.63]	2006
Jameson	227	22942	806	86642	12.7%	1.06 [0.92, 1.23]	2011
Anderson	1	380	2	398	3.3%	0.52 [0.05, 5.79]	2013
Kulshrestha	1	194	12	706	4.2%	0.30 [0.04, 2.32]	2013
Zou	18	110	14	112	10.0%	1.37 [0.64, 2.91]	2014
Ghost	46	6078	8	995	10.0%	0.94 [0.44, 2.00]	2019
Cheallaigh	17	3460	5	961	8.6%	0.94 [0.35, 2.57]	2020
Borton	31	2560	12	1049	10.5%	1.06 [0.54, 2.07]	2021
Hovik	3	1084	12	5010	7.1%	1.16 [0.33, 4.10]	2021
CRISTAL	50	5416	140	3787	12.2%	0.24 [0.18, 0.34]	2022
Total (95% CI)		**42489**		**99930**	**100.0%**	**0.72 [0.43, 1.20]**	
Total events	419		1052				

Heterogeneity: Tau² = 0.52; Chi² = 77.05, df = 11 (P < 0.00001); I² = 86%
Test for overall effect: Z = 1.26 (P = 0.21)



c. Diagrama de bosque del riesgo de tromboembolismo pulmonar (TEP)

Study or Subgroup	Aspirina Events	Aspirina Total	HBPM Events	HBPM Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Keays	2	75	1	75	1.3%	2.03 [0.18, 22.85]	2003
Gelfer	0	61	1	60	0.7%	0.32 [0.01, 8.07]	2006
Westrich	1	129	0	135	0.7%	3.16 [0.13, 78.36]	2006
Jameson	156	22942	583	86642	47.3%	1.01 [0.85, 1.21]	2011
Khatod	4	934	29	7202	6.2%	1.06 [0.37, 3.03]	2011
Anderson	0	380	3	398	0.9%	0.15 [0.01, 2.88]	2013
Kulshrestha	2	194	3	706	2.3%	2.44 [0.40, 14.71]	2013
Zou	0	110	0	112		Not estimable	2014
Ghost	22	6078	7	995	8.9%	0.51 [0.22, 1.20]	2019
Cheallaigh	19	3460	5	961	6.9%	1.06 [0.39, 2.83]	2020
Borton	1	2560	0	1049	0.7%	1.23 [0.05, 30.22]	2021
Hovik	3	1084	8	5010	4.0%	1.74 [0.46, 6.55]	2021
CRISTAL	58	5416	21	3787	20.0%	1.94 [1.18, 3.20]	2022
Total (95% CI)		**43423**		**107132**	**100.0%**	**1.13 [0.86, 1.49]**	
Total events	268		661				

Heterogeneity: Tau² = 0.03; Chi² = 12.96, df = 11 (P = 0.30); I² = 15%
Test for overall effect: Z = 0.87 (P = 0.38)

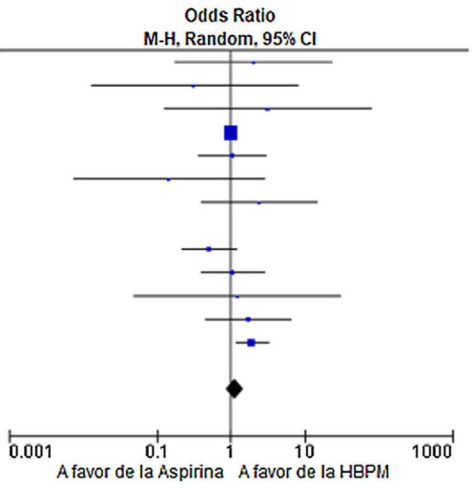


Figure 3 Risk for thromboembolic disease – overall analysis. (a) Forest plot of the risk for venous thromboembolism (VTE). (b) Forest plot of the risk for deep vein thrombosis (DVT). (c) Forest plot of the risk for pulmonary thromboembolism (PE). 95% CI: 95% confidence interval; LMWH: low-molecular-weight heparin; OR = odds ratio.

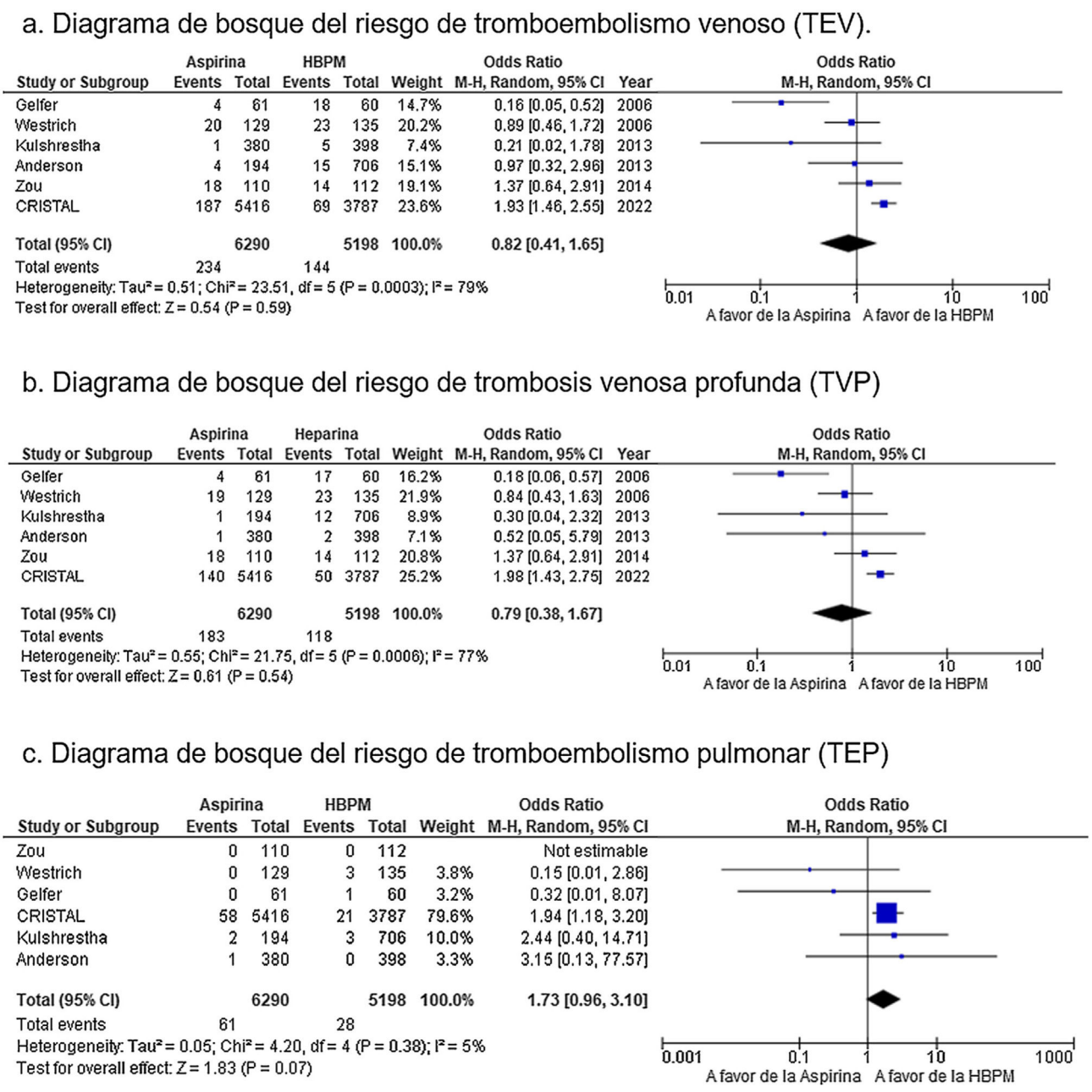


Figure 4 Risk for thromboembolic disease – subanalysis of randomised clinical trials. (a) Forest plot of risk for venous thromboembolism (VTE). (b) Forest plot of risk for deep vein thrombosis (DVT). (c) Forest plot of risk for pulmonary thromboembolism (PE). 95% CI: 95% confidence interval; LMWH: low-molecular-weight heparin; OR: odds ratio.

analysis found no difference between aspirin and LMWH (OR = .76, 95% CI: .37–1.55, $p = .45$), with a heterogeneity of $I^2 = 71\%$, $p = .002$.[34] And although the same results were found, in these meta-analyses all anticoagulants, both LMWH and OACs, were mixed in the same group.[33,34] Given this evidence, the Spanish Society of Orthopaedic Surgery and Traumatology (SECOT) developed a new thromboprophylaxis guideline in Spain in 2022, introducing these new trends. Aspirin and mechanical measures become a first-line option, especially in primary elective THA and TKA surgery.[15]

Aspirin is well tolerated, with its oral administration, and cheaper than other available drugs.[3,38] This gives it unique characteristics that make it a candidate to become the most widely used pharmacological thromboprophylaxis therapy in the coming years.[3,15,39] However there is still controversy.[14] To date, the LMWHs, specifically enoxaparin, constitute the most widely used pharmacological thromboprophylaxis therapy after THK and/or TKA in Spain.[10] The CRISTAL study, the RCT with the largest number of patients, published in 2022, found that among patients undergoing THA and/or TKA for osteoarthritis,

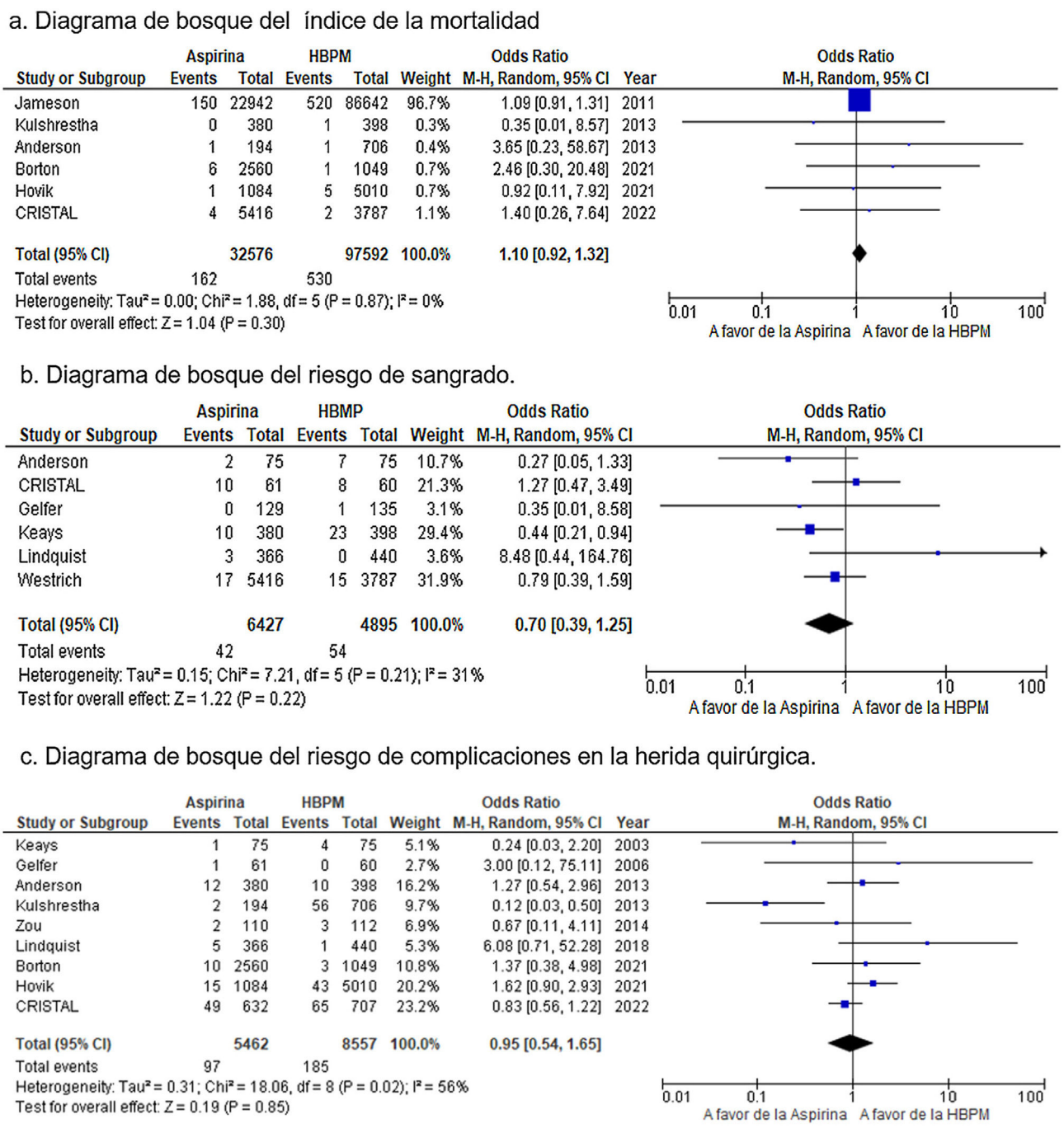


Figure 5 Secondary objectives – overall analysis. (a) Forest plot of mortality rate. (b) Forest plot of risk for bleeding. (c) Forest plot of risk for surgical wound complications. 95% CI: 95% confidence interval; LMWH: low-molecular-weight heparin; OR: odds ratio.

aspirin compared to enoxaparin resulted in a significantly higher rate of symptomatic VTE within the first 90 days (OR: 1.97, 95% CI: .54–3.41, $p = .007$).[14] However, the CRISTAL study, like any other study, has some limitations, the most notable being that the main difference in the incidence of symptomatic VTE was related to the rate of distal (below-knee) DVT, with no difference found in the rate of above-knee DVT, or in the rate of PE.[14,40,41] Below-knee DVT is a clinically less important form of VTE compared to above-knee DVT or PE, and its clinical significance remains unclear.[41,42] Similarly, another large comparative study showed that patients undergoing TKA benefited more from the use of other anticoagulants (LMWH: OR = .47; factor Xa inhibitors: OR = .50; and fondaparinux: OR = .32) than aspirin at the thromboprophylaxis level.[43] However, patients on anticoagulants had higher rates of bleeding-associated complications. This study concluded that the choice of pharmacological prophylaxis should be made based on a balance of the risk/benefit profile of each drug.

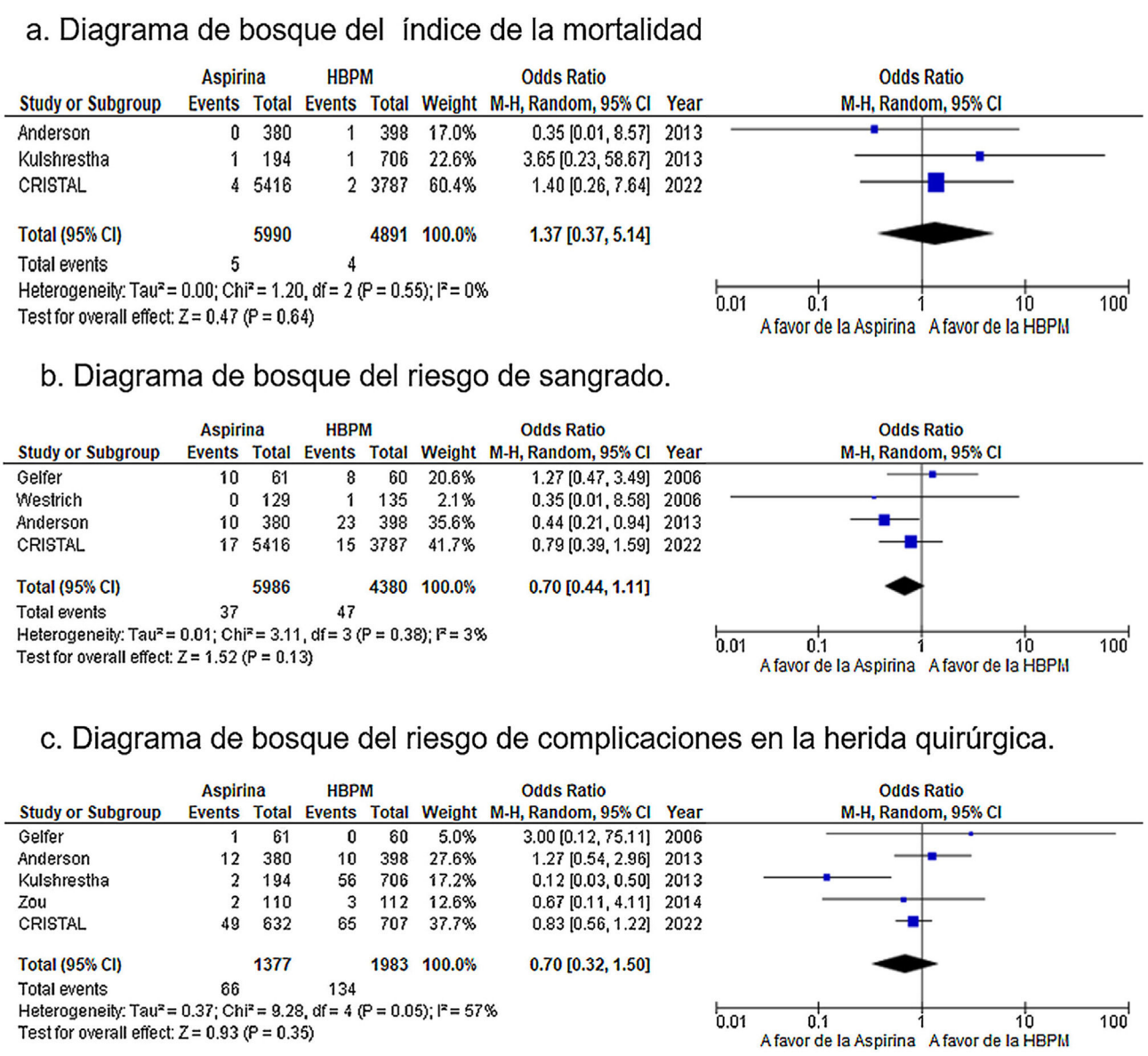


Figure 6 Secondary objectives – sub-analysis of randomised clinical trials. (a) Forest plot of mortality rate. (b) Forest plot of risk for bleeding. (c) Forest plot of risk for surgical wound complications. 95% CI: 95% confidence interval; LMWH: low-molecular-weight heparin; OR: odds ratio.

In terms of secondary outcomes, our results for mortality, bleeding events, and wound complications were similar to those reported by previous studies, which found no significant differences between aspirin and other anticoagulants.[34–37] In a population-based epidemiological study of 261,260 TKAs and 45,652 THAs Yhim et al. found that patients who had aspirin as a thromboprophylactic agent had no increased risk for blood transfusion compared to other anticoagulants (LMWH OR = 1.6, rivaroxaban OR = 1.46, and fondaparinux OR = 1.25).[31]

In short, the selection of a prophylactic VTE regimen is a balance of efficacy and safety that must be individualised for each patient based on their risk for a symptomatic thromboembolic event.[44] VTE can occur in some patients even using the most potent anticoagulant agents.[3,44] Therefore, as Lieberman et al. point out, risk stratification should be optimised because it is the key to selecting the appropriate prophylactic regimen.[45] Currently, based on the recommendations of the new SECOT thromboembolism guidelines,[39] we see no RCT has been conducted that compares ASA 200 mg/day with LMWH (enoxaparin 4000 IU/day or bemiparin 3500 IU/day) for thromboembolic prophylaxis after THA and/or TKA, these being the most widely used heparins in Spain, we believe that such a trial would be important to undertake.

Limitations

Some limitations of the present study should be considered. First, although this study presents an extensive search for data in the four major databases, the study only included six RCTs, which demonstrates the lack of level I evidence on this topic. Second, in the studies included, patients

received different doses and durations of aspirin, and there were also differences in the types, doses, and durations of LMWH used in the control group. Since most of the studies recommend prophylactic measures for at least four weeks after surgery, we took four weeks as the minimum follow-up period, which would assure us of the number of events after full treatment. It should be noted, however, that a strength of this study is that it made a direct comparison between aspirin and LMWH alone, excluding studies where OACs were used, which is present in many meta-analyses where studies comparing aspirin and LMWH, aspirin with OACs, are analysed together. We did this because in Spain, LMWHs are the most widely used pharmacological therapy for thromboprophylaxis after THA and/or TKA.[10] Third, raw data were used for the analysis. In observational studies it is advisable to consider measures adjusted for different covariates of interest. Adjusted measures increase comparability between observational and experimental studies. However, this was not possible due to the lack of multivariate analysis of the primary studies included. Finally, some outcomes have moderate heterogeneity ($I^2 > 40\%$) such as surgical wound complications, and the incidence of VTE, and the incidence of DVT have high heterogeneity ($I^2 > 75\%$), which could introduce bias. Also, at the secondary objective level, we note that the CI for mortality, bleeding, and wound complication analyses could be considered large, which may increase the risk of biased observations and conclusions.

Conclusions

The current meta-analysis showed no difference between aspirin and LMWH as thromboprophylactic agents to prevent VTE in patients undergoing THA and TKA surgery. There was also no significant difference in the reduction of mortality, bleeding events, and wound complications between aspirin and LMWH.

Level of evidence

Level of evidence II.

Funding

No funding was received for this study.

Conflict of interests

The authors have no conflict of interests to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.recot.2024.01.024.

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