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Thromboprophylaxis Timing After Blunt Solid Organ Injury: A Systematic Review and Meta-analysis

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ARTICLE INFO

Article history:
Received 13 February 2022
Received in revised form
29 July 2022
Accepted 8 October 2022
Available online 1 November 2022

Keywords:
Abdominal trauma
Blunt organ injury
Nonoperative management
Thromboembolism
Thromboprophylaxis
Timing of treatment

ABSTRACT

Introduction: Trauma patients with blunt abdominal solid organ injuries are at high risk for venous thromboembolism (VTE), but the optimal time to safely administer chemical thromboprophylaxis is controversial, especially for patients who are managed non-operatively due to increased risk of hemorrhage. We sought to compare failure of nonoperative management (NOM) and VTE events based on timing of chemical thromboprophylaxis initiation.

Methods: A systematic review was conducted in PubMed and Embase databases. Studies were included if they evaluated timing of initiation of chemical thromboprophylaxis in trauma patients who underwent NOM of blunt solid organ injuries. Outcomes included failure of NOM and incidence of VTE. A random-effects meta-analysis was performed comparing patients who received late (>48 h) *versus* early thromboprophylaxis initiation.

Results: Twelve retrospective cohort studies, comprising 21,909 patients, were included. Three studies, including 6375 patients, provided data on adjusted outcomes. Pooled adjusted analysis demonstrated no difference in failure of NOM in patients receiving late *versus* early thromboprophylaxis (odds ratio [OR] 0.92, 95% confidence interval [CI]:0.4-2.14). When including all unadjusted studies, even those at high risk of bias, there remained no

PROSPERO Registration: CRD42021240010.

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https://doi.org/10.1016/j.jss.2022.10.003

difference in failure of NOM (OR 1.16, 95% CI:0.72-1.86). In the adjusted analysis for VTE events, which had 6259 patients between two studies, patients receiving late chemical thromboprophylaxis had a higher risk of VTE compared with those who received early thromboprophylaxis (OR 1.89, 95% CI:1.15-3.12).

Conclusions: Based on current observational evidence, initiation of prophylaxis before 48 h is associated with lower VTE rates without higher risk of failure of NOM.

Introduction

Trauma patients are at high risk for venous thromboembolism (VTE).[1-3] Chemical thromboprophylaxis is effective in reducing VTE in the trauma population, and early initiation has been proven to be superior compared with late initiation in several types of traumatic injuries.[4] However, the optimal time to safely initiate chemical thromboprophylaxis in patients following blunt solid abdominal organ injuries remains controversial. This is especially true in those who are managed nonoperatively, resulting in variance of care across trauma centers.[5] The risk of VTE must be balanced against the risk of internal hemorrhage due to organ injury,[6-8] which may lead to failure of nonoperative management (NOM).[9,10]

The Western Trauma Association (WTA) 2020 guidelines recommend that chemical thromboprophylaxis may be initiated within 12-24 h for most patients with solid abdominal organ injury, with caution suggested in patients with high grade injuries (American Association for the Surgery of Trauma injury grades IV and V).[11] The most updated Eastern Association for the Surgery of Trauma guidelines, from 2002, suggest that individual decisions should be made about the safety of chemical prophylaxis in patients with intra-abdominal solid organ injuries undergoing NOM.[12] However, no comment was made on the timing of initiation. In both guidelines, recommendations were based on consensus among experts or anecdotal retrospective cohort studies.

To date, there has been no systematic assessment of data on safety and effectiveness of early *versus* late initiation of VTE prophylaxis in adult patients undergoing NOM of blunt solid abdominal organ injuries. We sought to perform a systematic review and meta-analysis to summarize the available evidence on the timing of initiating chemical thromboprophylaxis in this patient population.

Material and Methods

Study design

A systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA; checklist provided in Supplement S1).[13] The study protocol was registered with PROSPERO, an international prospective register of systematic reviews (ID#CRD42021240010). Minor changes to the original PROPSERO registered study protocol were made only if these were in line with the predetermined main goal of the systematic review and meta-analysis.

Inclusion criteria and search strategy

Studies evaluating the use of early *versus* late chemical thromboprophylaxis in patients aged 16 y or older who underwent nonoperative management of solid organ injury and received chemical thromboprophylaxis in the setting of blunt abdominal trauma were included. Chemical thromboprophylaxis was limited to low molecular weight heparin (LMWH) or unfractionated heparin (UFH). The definition of early and late initiation of VTE prophylaxis was defined by study authors in relation to the hours passed since hospital admission. To the best of our knowledge these definitions were decided arbitrarily and there is no consensus on what defines early, intermediate, or late time points. If there was one time cut-off in the study, we considered before the time early and after the time to be late. Studies of patients with traumatic brain injuries, femoral fractures, pelvic fractures, spinal cord injuries, and penetrating injuries were excluded.

A search strategy was developed in collaboration with an expert librarian researcher for PubMed and Embase with inclusion of all results from inception until the search date of March 24, 2021. Search strategies are reported in supplementary material (Supplement S2). Randomized controlled trials (RCTs) and observational studies were included, while case reports, reviews, expert opinions, and animal studies were excluded. A minimum of two reviewers (among BA, RA, JB, CM, MP, PP) screened each article title and abstract for inclusion and exclusion criteria using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Articles considered for full text review were sourced and reviewed for relevance by a minimum of two reviewers. Any conflicts were resolved by a third reviewer (either BA, RA, JB, CM, MP, or PP depending on original two reviewers). References of included articles were also screened to identify studies that might have been missed.

Data extraction

Extraction of data included year of publication, study type, study period, data source, study location, number of patients, and demographic and clinical factors including age, sex, race, and comorbidities (coronary artery disease, hypertension, diabetes mellitus, chronic kidney disease, respiratory disease, cancer, bleeding disorder). Additionally, definitions for NOM, thromboprophylaxis (type, dose, and timing), type and severity of injury, bleeding incidence, failure of NOM, incidence of VTE, and duration of follow-up were extracted. Statistical analysis methods and adjustment for confounders were noted. We contacted two authors for further information, and they provided data that were not presented in the published

manuscript (Jakob *et al.* and Gaitanidis *et al.*). Correspondence can be found in supplementary material (Supplement S3).

Outcomes

The primary outcome was failure of NOM, as defined by the individual studies. A secondary outcome was VTE, defined by deep vein thrombosis (DVT) or pulmonary embolism (PE).

Assessment of study quality

The quality of evidence of included studies was assessed according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria.[14] GRADE expresses the degree of confidence in quality of evidence and strength of recommendation. In addition, the risk of bias was assessed using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool.[15] Two authors independently (among BA, RA, JB, CM, MP, PP) evaluated each study using the GRADE and ROBINS-I framework, and non-consensus was resolved by a third author.

Statistical analysis

Descriptive statistics were used to assess study characteristics, patient demographics, and intervention details. For the primary analysis, random-effects modeling with DerSimonian-Laird weighting was performed to evaluate the pooled estimates for failure of NOM and VTE, comparing early *versus* late initiation of chemical thromboprophylaxis. The primary pooled analysis was restricted to studies that adjusted for potential confounders between the groups. Sensitivity analyses were performed pooling studies that reported unadjusted estimates and using a Peto's fixed effect model to evaluate VTE due to the presence of zero events in certain studies. Due to variation in the definition of early *versus* late initiation among studies, further analyses were performed to evaluate the impact of 24-h and 72-h time points.

Heterogeneity was evaluated using the I^2 statistic. Funnel plots and Egger test were constructed to assess publication bias. All statistical analyses were performed using STATA software (version 16; Stata-Corp, College Station, TX).

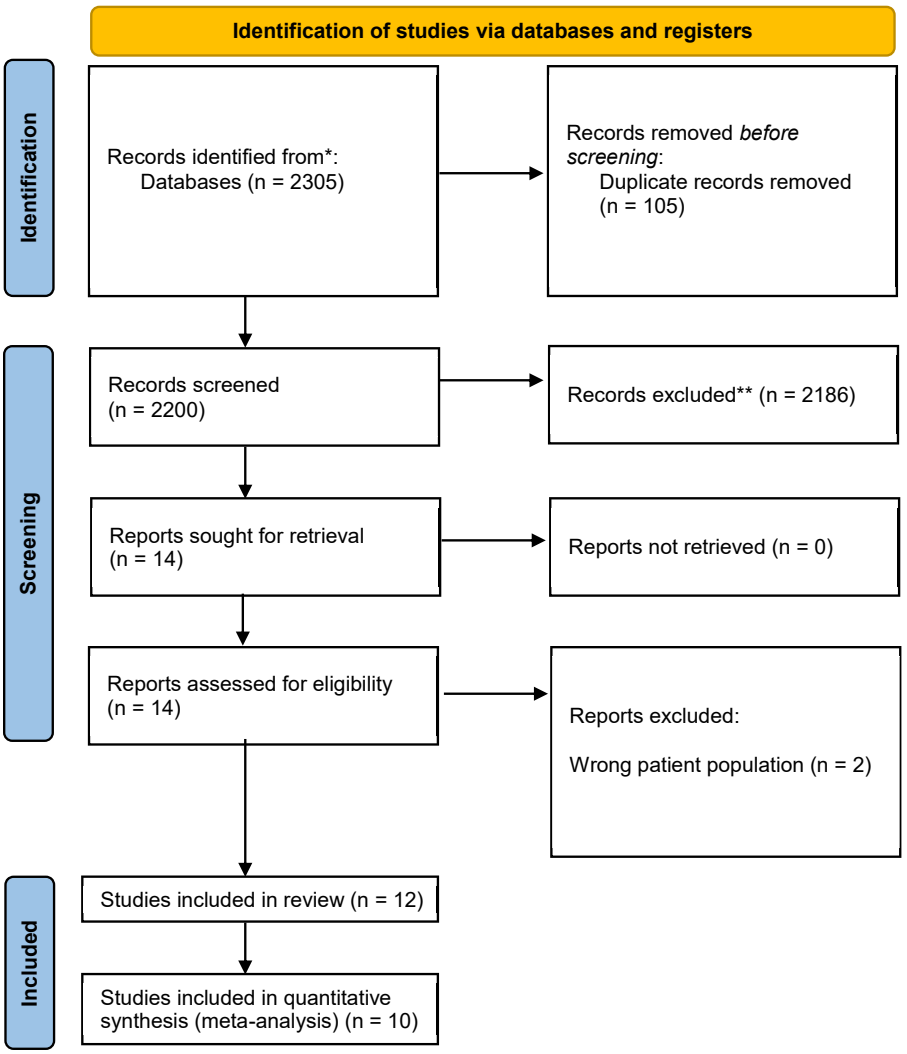

Fig. 1 – PRISMA flow diagram of retrieval and inclusion of studies from systematic literature review.

Table 1 – Characteristics of included studies comparing late *versus* early initiation of thromboprophylaxis following solid organ injury, by publication year.

Author (Year)	Data source*	Time period	Patients†	Organ	Age, mean/ median	Sex, female %	ISS, mean/ median	Prophylaxis	Cohorts‡	Primary outcomes	Secondary outcomes	Adjusted for confounders
Alejandro (2003)[16]	SI	2000-2002	114	Spleen	37-38§	28	NR	LMWH (enoxaparin 30 mg sc q12; dalteparin 2500u sc daily)	<48h ≥48h	FNOM	Mortality; transfusion	No
Datta (2009)[17]	Alberta trauma registry	2000-2004	72	Liver	37	28	24	UFH (NR) LMWH (NR)	≤48h >48h	FNOM	VTE; transfusion	No
Joseph (2015)[18]	SI	2006-2011	116	Spleen Liver Renal	40-45§	31	17	LMWH (enoxaparin 30 mg sc q12)	≤48h 48-72h ≥72h	FNOM; transfusion	VTE; mortality	Yes
Rostas (2015)[19]	MI	2007-2011	328	Spleen Liver	NR	NR	NR	LMWH (enoxaparin 30 mg sc q12 or 40 mg sc daily)	<48h 48-72h >72h	FNOM	VTE; transfusion	No
Kwok (2016)[20]	SI	2007-2015	256	Spleen	40	37	17	UFH (5000u sc q8) LMWH (enoxaparin 30 mg sc q12)	<24h 24-48h 48-72h >72h	FNOM	VTE; transfusion; LOS	No
Murphy (2016)[21]	SI	2010-2014	162	Spleen Liver Renal	42	31	17	LMWH (dalteparin 5000u sc daily)	<48h ≥48h	FNOM	VTE; transfusion; LOS	No
Khatsilous-kaya (2017)[22]	SI	2009-2014	142	Spleen Liver Renal	38	30	21	UFH (10,000u sc daily) LMWH (enoxaparin 30 mg sc q12)	≤72h >72h	FNOM	VTE; mortality	No
Lin (2019)‖,[23]	ACS-TQIP	2013-2014	291	Spleen	34	33	NR	UFH (NR) LMWH (NR)	<48h ≥48h	FNOM	Mortality; LOS	Yes
Skarupa (2019)‖,[24]	ACS-TQIP	2013-2014	13,027	Spleen Liver Renal	50	32	NR	UFH (NR) LMWH (NR)	≤48h >48h	FNOM; transfusion; mortality	VTE; LOS	Yes
Gaitanidis (2020)[10]	ACS-TQIP	2013-2016	3223	Spleen Liver Renal Pancreas	39	35	NR	UFH (NR) LMWH (NR)	<48hh 48-72h >72h	VTE; FNOM or transfusion	DVT	Yes

(*continued*)

Table 1 — (continued)

Author (Year)	Data source*	Time period	Patients†	Organ	Age, mean/ median	Sex, female %	ISS, mean/ median	Prophylaxis	Cohorts‡	Primary outcomes	Secondary outcomes	Adjusted for confounders
Griffard (2020)[25]	SI	2013-2017	104	Spleen	40	33	23	LMWH (NR) UFH (NR)	<24h 24-48h >48h	FNOM		No
Jakob(2021)[26]	ACS-TQIP	2013-2017	4074	Liver	31	47	22	UFH (NR) LMWH (NR)	≤48h >48h	FNOM	VTE; mortality	Yes

SI = single institution; MI = multi institution; ISS = injury severity score; ACS-TQIP = American college of surgeons trauma quality improvement program; UFH = unfractionated heparin; LMWH = low molecular weight heparin; NR = not reported; u = units; mg = milligrams; sc = subcutaneous; qN = every N hours; h = hours; FNOM = failure of nonoperative management; VTE = venous thromboembolism; DVT = deep venous thrombosis; PE = pulmonary embolism; LOS = length of stay; PSM = propensity score matching.

* All included studies were retrospective cohort studies.

† Number of patients includes only those that received thromboprophylaxis, as some studies had three cohorts, including those that received no thromboprophylaxis.

‡ Based on timing of initiation of chemical thromboprophylaxis.

§ Age mean/median in the groups compared.

‖ Study not included in quantitative analysis.

Results

Included studies

Overall, 12 studies out of 2200 fulfilled inclusion criteria. Two studies (Skarupa *et al.* and Lin *et al.*) were excluded from the quantitative meta-analyses due to overlapping patient data sources but were kept in the qualitative description. The selection flow diagram (PRISMA Flowchart) is reported in Figure 1.

Study characteristics

All studies were retrospective cohort studies, published between 2003 and 2021. Six studies (50%) were conducted at a single institution, while one study (Rostas *et al.*) was multi-institution (two institutions), and the remaining ($n = 5$; 42%) used national or regional databases. Most studies evaluated one solid organ, while three studies evaluated three organs (spleen, liver, kidneys), and one study evaluated four organs (spleen, liver, kidney, pancreas). The majority of the studies (11 of 12 studies) compared early *versus* late initiation of chemical thromboprophylaxis as defined by a 48-h time point. Among the studies reporting on failure of NOM, three included adjusted analysis for various patient and treatment facility factors (reporting multivariable analyses or propensity score matched cohorts). Among the studies reporting on VTE, two included an adjusted analysis. Full study characteristics are presented in Table 1.

Patient characteristics

A total of 21,909 patients from the 12 studies were included in the final review. The largest studies were by Skarupa *et al.*, Jakob *et al.*, and Gaitinidis *et al.*, comprising 13,027, 4076, and 3223 patients, respectively. Across all studies, the mean/median patient age ranged from 31 to 50 y old, 28% to 47% of patients were female, and the median Injury Severity Score (ISS) ranged from 17 to 23. Data regarding the injury severity scale or grade of included patients is summarized in Table 2.

Nonoperative management

The pooled adjusted analysis demonstrated no difference in failure of NOM in patients receiving early *versus* late chemical thromboprophylaxis (studies = 3, patients = 6375; odds ratio [OR] 0.92, 95% Confidence Interval [CI]: 0.4-2.14, $P = 0.85$; Fig. 2A). The statistical heterogeneity was high ($I^2 = 79\%$) across studies. We aimed to examine publication bias using funnel plots and Egger tests, but as none of the analyses included more than 10 studies, the results are not presented as these tests are underpowered.

Three studies looked at differences in angioembolization rates among groups. Gaitinidis *et al.* found that intermediate and late VTE prophylaxis is associated with a higher percentage of angioembolization rates (6.3% and 6.5%) compared to early thromboprophylaxis (3.2%, *P*-value < 0.001). Lin *et al.* found no statistically significant differences (7.6% in the no prophylaxis group, compared to 8.3% and 13.6% in the early

Table 2 – Injury severity of patients in studies reporting on venous thromboembolism prophylaxis following blunt abdominal trauma. Only six studies (50%) reported the injury scale or grade.

Author (year)	Patients	Splenic injury AIS ≥3 % (*n*)	Splenic AAST grade score (mean)	Hepatic injury AIS ≥3 (*n*)	Hepatic AAST grade score (mean)	Renal injury AIS ≥3 % (*n*)	Pancreatic injury AIS ≥3 % (*n*)
Rostas (2015)[19]	328	NR	0.86-1.00	NR	0.85-1.28	8% (261)	1% (26)
Kwok (2016)[20]	256	32% (83)	NR	NR	NR	NR	NR
Murphy (2016)[21]	162	23% (38)	NR	12% (19)	NR	4% (7)	NR
Jakob (2021)[26]	4074	NR	NR	100% (4074)	NR	NR	NR
Gaitanidis (2020)[10]	3223	34% (1080)	NR	32% (1038)	NR	NR	NR
Griffard (2020)[25]	104	NR	3.37	NR	NR	NR	NR

AIS = abbreviated injury scale (range 1-6); AAST = American association for the surgery of trauma grade of solid organ injury (range 1-5, in reported studies); *n* = number; NOM = nonoperative management; VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary emboli; NR = nonreported.

and late prophylaxis groups, respectively; $P = 0.08$). Kwok *et al.* also found no significant difference in angioembolization rates (3% in the no prophylaxis and 4% in the prophylaxis group; $P = 0.41$).

Timing of initiation

In studies that compared initiation of chemical thromboprophylaxis >24 h *versus* <24 h, pooling of the data demonstrated no differences in failure of NOM between the timepoints (OR 0.59, 95% CI 0.17-2.13, $P = 0.42$; Supplement S6). Only two studies were included in this analysis due to availability of data (Kwok *et al.* and Griffard *et al.*).[20,25] Only one of these studies (Kwok *et al.*) reported on VTE,[20] precluding a pooled analysis for the primary outcome in these subgroups.

In studies that compared initiation of chemical thromboprophylaxis >72 h *versus* <72 h, pooling of the data demonstrated no difference in failure of NOM between the timepoints (studies = 4; OR 0.91, 95% CI 0.47-1.73, $P = 0.76$) and no difference in VTE (studies = 4; OR 1.29, 95% CI 0.86-1.93, $P = 0.21$) (Supplement S7).

Venous thromboembolism

In the adjusted analysis for risk of VTE (studies = 2, patients = 6259), patients receiving late chemical thromboprophylaxis had a higher risk of VTE compared with those who received early thromboprophylaxis (OR 1.89, 95%CI: 1.15-3.12, $P = 0.01$; Fig. 2B). The statistical heterogeneity was moderate ($I^2 = 58\%$). Table 3 summarizes the percentage of VTE in the included studies.

Sensitivity analyses

Nonoperative management

In a sensitivity analysis of all studies reporting on failure of NOM (studies = 7), there remained no difference in failure of NOM between early and late initiation of chemical thromboprophylaxis (OR 1.16, 95%CI: 0.72-1.86, $P = 0.54$; $I^2 = 60\%$;

Table 3 – Reported percentage and number of venous thromboembolism (VTE) in observational studies comparing late *versus* early initiation, the time point of which was defined by the individual study, of VTE chemical prophylaxis.

Author (year)	Patients	Failure of NOM (*n*)	VTE (*n*)	DVT (*n*)	PE (*n*)
Alejandro (2003)[16]	114	5% (6)	NR	NR	NR
Datta (2009)[17]	72	0% (0)	13% (9)	11% (8)	1% (1)
Joseph (2014)[18]	116	3% (3)	2% (2)	NR	NR
Rostas (2015)[19]	328	0% (0)	2% (7)	1% (3)	1% (4)
Kwok (2016)[20]	256	7% (19)	2% (5)	0% (1)	2% (4)
Murphy (2016)[21]	162	4% (3)	4% (3)	0% (1)	1% (2)
Khatsilouskaya (2017)[22]	142	1% (2)	3% (4)	0% (0)	3% (4)
Gaitanidis (2020)[10]	3223	2% (55)	3% (90)	2% (62)	1% (33)
Griffard (2020)[25]	104	6% (6)	NR	NR	NR
Jakob (2021)[26]	4074	2% (60)	3% (125)	2% (80)	1% (45)
Lin (2019)[23]	291	3% (10)	2.7-2.8% (NR)	1.4-2.1% (NR)	0.7-2% (NR)
Skarupa (2019)[24]	13,027	4% (565)	1% (143)	1% (95)	0% (53)

n = number; NOM = nonoperative management; VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary emboli; NR = nonreported.

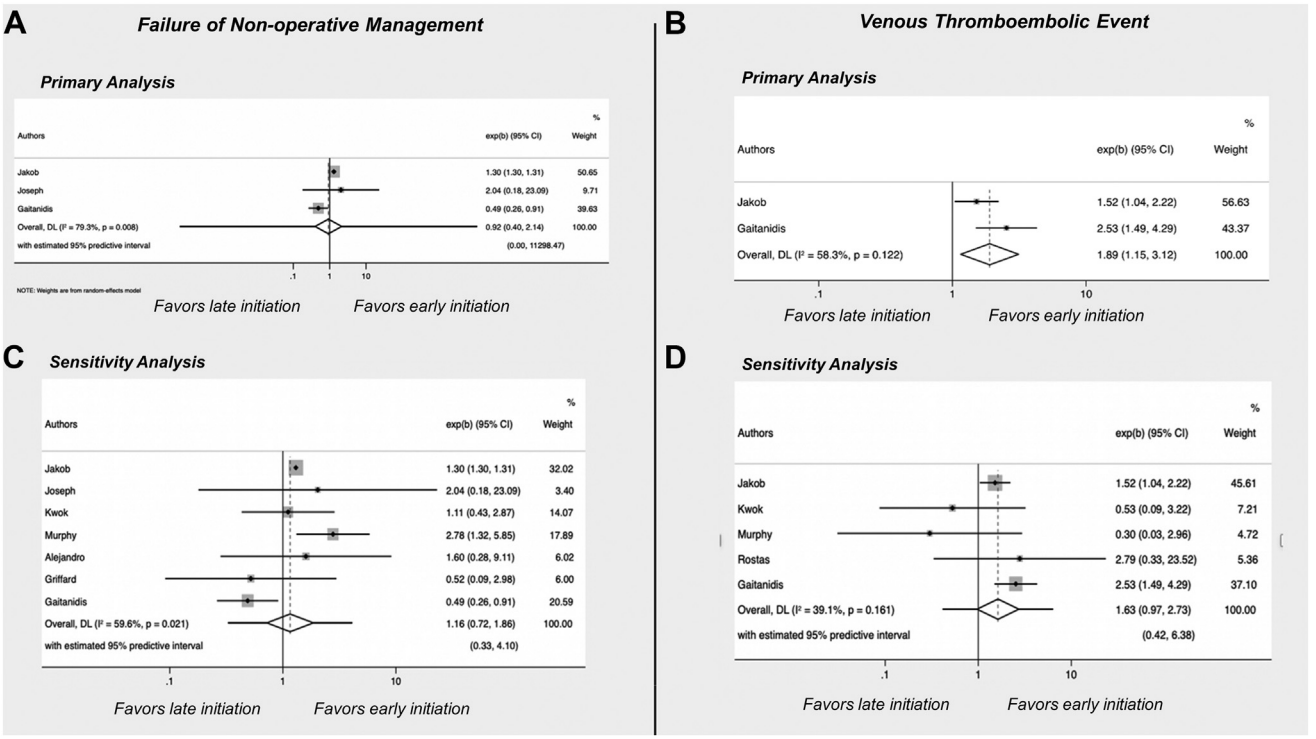

Fig. 2 – Forest plots showing the difference in the risks of failure of nonoperative management and venous thromboemboliism comparing late (>48 h after admission) *versus* early (<48 h) chemical thromboprophylaxis initiation. Primary analysis was restricted to studies that adjusted for possible confounders. A sensitivity analysis was conducted with additional inclusion of studies that did not adjust for possible confounders.

Fig. 2C). This analysis included four studies presenting only unadjusted outcomes and three studies presenting adjusted outcomes.[10,18,26]

Venous thromboembolism

In a sensitivity analysis including all studies reporting on VTE, the association between late initiation of chemical thromboprophylaxis and VTE was attenuated and no longer statistically significant (studies = 5; OR 1.63; 95%CI: 0.97-2.73, $P = 0.07$; $I^2 = 39\%$; Fig. 2D). This analysis included three studies presenting unadjusted outcomes and two studies that adjusted for potential confounders. A secondary pooled analysis using Peto's fixed effect model that included the crude results of seven studies (i.e., including only unadjusted data) did show an association between late initiation of chemical thromboprophylaxis and VTE (OR 1.98; 95%CI: 1.53-2.56, $P < 0.001$; $I^2 = 49\%$; Supplement S5).

Quality of evidence and risk of bias assessments

The quality of evidence assessment and risk of bias of all the included studies is summarized in Table 4. Based on the GRADE criteria, the quality of evidence was "very low" in six studies, "low" in one study, "moderate" in two studies, and "high" in three studies. Based on the ROBINS-I tool, the risk of bias was "low" in two studies, "moderate" in three studies, and "serious" in seven studies. Detailed scoring for the ROBINS-I grading system is located in the supplemental material (Supplement S4).

Discussion

Studies on the association of timing of VTE prophylaxis and patient outcomes following NOM after blunt abdominal solid organ injury are all observational. Our search strategy identified 12 retrospective cohort studies published between 2003 and 2021, with substantial heterogeneity in the methodological quality, definitions of early *versus* late initiation, and evaluation of bleeding and VTE outcomes. At present, this is the most updated systematic review with a quality assessment and meta-analysis on the evidence of timing of chemical thromboprophylaxis in blunt abdominal solid organ injury. A meta-analysis restricted to a small number of studies that adjusted for possible confounders demonstrated no difference in failure of NOM when comparing early (<48 h) *versus* late initiation of thromboprophylaxis in this patient population. Based on two observational studies, early use of thromboprophylaxis is associated with lower risk of developing VTE compared with delayed initiation. However, these results should be interpreted with caution as the confidence intervals were relatively wide due to the small number of studies included in each analysis.

Table 4 – Quality assessments of included studies.

Author (year)	Certainty of the evidence (GRADE)[14,†]	Risk of bias assessment (ROBINS-I)[15,‡]
Alejandro (2003)[16]	Very low	Serious
	Due to risk of bias and imprecision	
Datta (2009)[17]	Very low	Serious
	Due to risk of bias and imprecision	
Joseph (2014)[18]	Moderate	Moderate
	Due to risk of bias	
Rostas (2015)[19]	Very low	Serious
	Due to risk of bias and imprecision	
Kwok (2016)[20]	Very low	Serious
	Due to risk of bias and imprecision	
Murphy (2016)[21]	Very low	Serious
	Due to risk of bias and imprecision	
Khatsilouskaya (2017)[22]	Very low	Serious
	Due to risk of bias and imprecision	
Gaitanidis (2020)[10]	High	Low
	Not applicable	
Griffard (2020)[25]	Low	Serious
	Due to risk of bias	
Jakob (2021)[26]	High	Low
	Not applicable	
Lin (2019)[*,23]	Moderate	Moderate
	Due to imprecision	
Skarupa (2019)[*,24]	High	Moderate
	Not applicable	

[*] Study not included in quantitative analysis due to overlapping database.
[†] Grade certainty meanings: Very low = The true effect is probably markedly different from the estimated effect; Low = The true effect might be markedly different from the estimated effect; Moderate = The authors believe that the true effect is probably close to the estimated effect; High = The authors have a lot of confidence that the true effect is similar to the estimated effect.
[‡] Detailed Grading of ROBINS-I Found in the Supplemental Material.

The management of blunt abdominal solid organ injuries has evolved over the past decade with a trend toward NOM among hemodynamically stable patients. While careful observation for signs of bleeding remains of high importance in these patients, navigating the risk of VTE remains relevant. A study of 898 trauma patients evaluated with serial thromboelastography (TEG) found that approximately half of all patients show signs of hypercoagulability by 120 h after injury.[27] A smaller study, focused specifically on patients with abdominal solid organ injuries admitted to the intensive care unit (ICU), found that the entire cohort was hypercoagulable by TEG at the time of admission with nearly all patients remaining hypercoagulable for the duration of the study.[3] These findings suggest that prophylaxis in the hypercoagulable trauma patient may be critical to avoid clinically significant VTE such as DVT or PE. In most of the studies we identified, the percentage of patients developing VTE ranged from 0 to 3% (0-2% for DVT, and 1%-3% for PE). These percentages are likely lower than reality given the screening bias inherent in study designs and clinical care. Due to the variability of institutional VTE protocols, these retrospective studies varied with regards to follow-up time, VTE presentation (clinically significant *versus* asymptomatic), and indications for ordering diagnostic studies (protocoled screening *versus* surgeon discretion). Recently, a meta-analysis investigating a similar research question had comparable conclusions.[28] However, that meta-analysis included both adjusted and unadjusted studies in their primary analysis without a sensitivity analysis, which made lead to more biased estimated due to a significant risk of selection bias among patients. Our meta-analysis included adjustment for confounding, as well as a more recent review of the literature with inclusion of one of the largest and best quality of evidence studies (Gaitianidis *et al.* with 3223 patients).

Our pooled analyses suggest that initiation of chemical thromboprophylaxis in the first 48 h after admission is not associated with higher odds of NOM failure. Our primary analysis of this outcome included three observational retrospective studies with low to moderate risk of bias. Sensitivity analysis with additional studies with higher risk of bias, mainly due to lack of adjustment for possible confounders, resulted in a similar pooled association. These results affirm the 2020 WTA guidelines suggesting that early pharmacologic prophylaxis is safe across moderate injury grade patients. These recent guidelines recommended initiation within 12-24 h, based on two studies that compared initiation before or after 48 h and the single arm study that analyzed serial TEGs demonstrating hypercoagulability on ICU admission.[3,24,29] Of note, one of these studies, a small single center analysis of 118 patients, was

excluded from our analysis due to inclusion of traumatic brain injuries in the study population.[29] On account of the limited number of studies, a more nuanced investigation was not possible. Importantly, there was insufficient data to thoroughly compare very early initiation (<24 h) and intermediate initiation (24-48 h) to late initiation (>48 h). Gaitanidis *et al.* reported that very early thromboprophylaxis was independently associated with a higher likelihood of bleeding (OR 2.05, 95% CI 1.1-2.18) compared with late initiation, whereas intermediate (24-48 h) thromboprophylaxis was not associated with higher likelihood of bleeding (OR 0.99, 95% CI 0.45-3.81).

The association between delayed initiation of VTE prophylaxis and higher risk of VTE found in our analysis is based on two studies utilizing the same national database (The American College of Surgeons Trauma Quality Improvement Program database) in overlapping years (2013-2016/7).[10,26] Gaitanidis *et al.* agreed to our request to perform an additional adjusted multivariable analysis (see supplemental material), excluding patients that were included in the Jacobs *et al.* paper, allowing for a pooled analysis of the two cohorts. In both studies, initiation of chemical thromboprophylaxis after 48 h was associated with a higher risk for subsequent VTE, yet with a higher odds ratio reported by Gaitanidis *et al.* compared to that reported by Jacobs *et al.* (OR 2.53 *versus* 1.52, respectively). The difference in the magnitude of the point estimates can be explained by the dissimilar study populations. Jacobs *et al.* focused on patients with high grade liver injury, whereas Gaitanidis *et al.* combined patients with varying organ injuries (spleen, liver, kidney, and/or pancreas) and injury grades. Furthermore, the authors did not adjust for the exact same variables. In the reviewed studies, subgroup analysis stratified by high grade injuries was not routinely conducted. Thus, analyzing a pooled impact of early chemoprophylaxis initiation in patients with higher *versus* lower grade injuries was not possible. Of note, Datta *et al.* reported that in patients with higher hepatic injury grades (III, IV, V), the group of patients that received delayed administration of chemoprophylaxis had higher rates of failure of nonoperative treatment (6% compared to 0) and higher incidence of VTE (23% compared to 0). These observations were based on a small set of patients ($n = 43$), not statistically significant, and possibly influenced by selection bias. In addition, Gaitandis *et al.* highlighted how higher grade (grades 3-5) pancreatic injuries were associated with higher VTE rates after multivariable adjustment, but this finding was not separated by early *versus* late thromboprophylaxis and thus could not be used in a pooled meta-analysis.

Most of the reviewed studies lacked data on the results of nonoperative interventional management after blunt solid organ injury. Only three studies (Gaitanidis, Lin, Kwok) reported the need for angiography, with or without embolization, according to the timing of VTE prophylaxis. However, they did not further report in what percentage did angioembolization fail and subsequent operative management was attempted. Granular reporting on the outcomes of different interventional management techniques is important as cessation of hemorrhage following such interventions may affect the surgeon's decision to start chemoprophylaxis.

There are limitations to this study which warrant additional discussion. The level of evidence ranges from very low to moderate due to potential risk of bias, inconsistency, and imprecision (Table 4). This variability among the certainty of the available evidence and risk of biases within the studies suggests that the true effect might be markedly different from the estimated pooled effects. With the majority of papers at high risk of bias, readers should be cautious when interpreting results to general clinical guidelines. However, our decision to exclude studies with low or very low evidence from the primary pooled analysis strengthens our main conclusions. Further, the relatively low number of included studies in the subgroup analyses may have resulted in underpowered analyses precluding meaningful interpretations. The primary adjusted analysis was also mostly based on studies utilizing national databases, thus limiting the benefit of the pooled analysis. Another limitation to our conclusions is the heterogeneity within the type and dosing of prophylactic medication (UFH *versus* LMWH) among the studies (described further in Table 1) as well as the lack of description of the rates of missed doses. The reviewed studies lacked the required data granularity to address these questions. Of note, the use of angiography was varied among studies and data regarding its use was unreported in some of the reviewed studies. Future research should account for residual confounding due to variance in angiography intervention utilization. With these caveats in mind, our results offer generalized safety guidance to surgeons as they make individualized decisions about thromboprophylaxis. Our findings underscore the necessity for further research, preferably randomized controlled trials or multi-institutional observational studies with proper adjustment for possible confounders.

Conclusions

No randomized controlled trial exists that examines the timing of initiation of chemical thromboprophylaxis in blunt abdominal solid organ injuries that are managed nonoperatively. Based on low quality evidence of retrospective observational studies, initiation of chemical VTE prophylaxis less than 48 h after admission is associated with a lower risk for developing VTE, without an associated higher risk NOM failure. Future studies are needed to generate more robust, less biased data and to determine specific subgroups of patients for whom tailored thromboprophylaxis timing may be most beneficial.

Author Contributions

R.A., B.A., J.B., P.P., C.M., M.P., S.P designed this study. R.A., B.A., J.B., P.P., C.M., M.P. searched the literature, selected the studies, and collected the data. R.A., P.P, C.M., analyzed the data. All authors participated in data interpretation. R.A., B.A., J.B, and M.P wrote the initial draft and all authors participated in critical revisions.

Acknowledgments

We would like to thank Harvard Countway Librarian Paul Bain, PhD MLIS, for his bibliographic and search term support for this project.

Disclosures

None declared.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Meeting Presentations

This project was presented as an Oral Presentation at the 17th Annual Academic Surgical Congress in Orlando, FL.

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